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Microwave assisted organic synthesis

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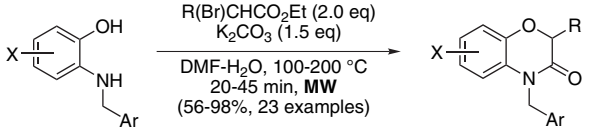

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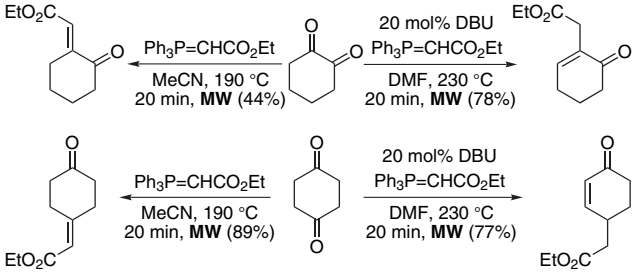

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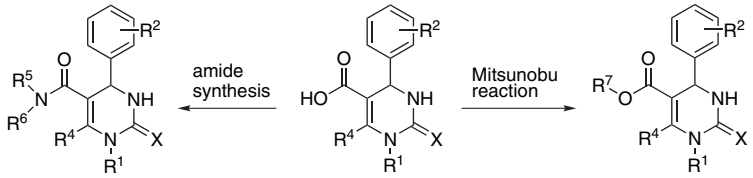

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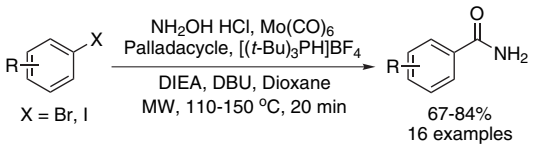

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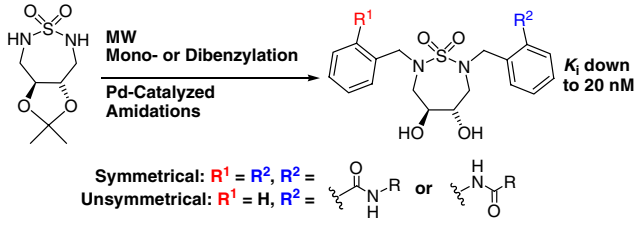

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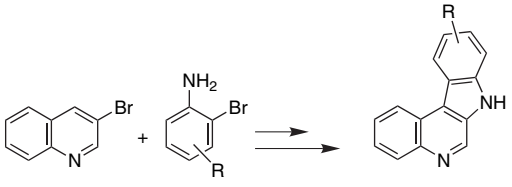

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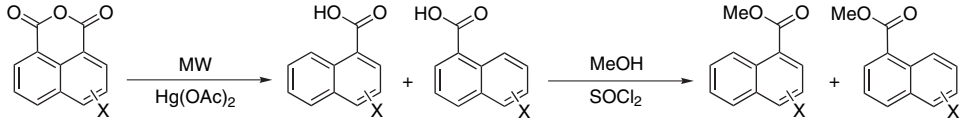

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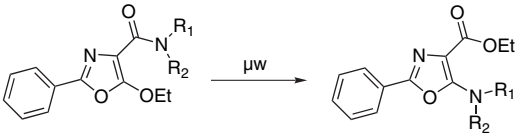

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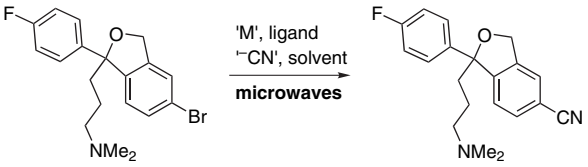
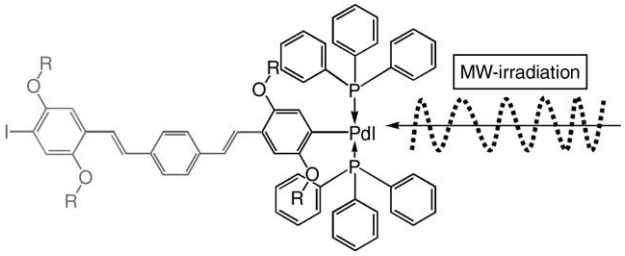


A microwave enhanced palladium catalysed cyanation procedure was optimised for citalopram. The method was demonstrated on multigram batch scale for the synthesis of escitalopram and in a stop-flow continuous process for citalopram.

Microwave-assisted polymer chemistry: Heck-reaction, transesterification, Baeyer–Villiger oxidation, oxazoline polymerization, acrylamides, and porous materials pp 4709–4714
Carsten Koopmans, Mauro Iannelli, Patrick Kerep, Michael Klink, Sarah Schmitz, Sebastian Sinnwell and Helmut Ritter*

In this paper we report the first MW assisted synthesis of poly(2,5-dibutoxy-1,4-phenylenvinylene) via Heck polycondensation. The facile synthesis of the higher lactones via Baeyer–Villiger reaction offers indeed an example for the MW-accelerating effect. A survey of our recent work is also given to provide examples for what we term special MW effects.



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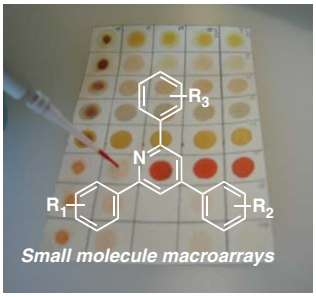
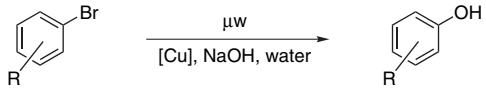


Direct conversion of aryl halides to phenols using high-temperature or near-critical water and microwave heating pp 4728–4732
Chad M. Kormos and Nicholas E. Leadbeater*



The direct conversion of aryl halides to the corresponding phenols has been achieved using microwave heating. High-temperature or near-critical water is used as the solvent in conjunction with a copper catalyst and a mineral base.

*Corresponding author
Supplementary data available via ScienceDirect

COVER

The cover art is a collage bringing together some concepts of microwave-promoted synthesis. Microwaves, like all electromagnetic radiation, travel at the speed of light. They are of relatively low energy and cannot break chemical bonds, they can only make molecules rotate. They cause heating on a molecular level and can accelerate reactions, leading to a significant time saving and often improving product yields. The reaction shown is a Suzuki coupling. Using microwave heating, the Suzuki coupling can be performed in water using as little as 50 ppb palladium.

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Tetrahedron Symposia-in-Print comprise collections of original research papers covering timely areas of organic chemistry.

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Preface

Microwaves in organic chemistry

At the start of 2006, it is hard not to find an example of a microwave-promoted transformation when looking through the contents of a new issue of a synthetic organic chemistry journal like Tetrahedron. This shows how the technique has caught on within the community and is finding applications in topics as diverse as natural product synthesis, peptide synthesis and nanoparticle preparation. Chemists are finding that, by using microwave heating, it is possible to reduce reaction times from hours to minutes and, in many cases, increase product yields. In addition, and very excitingly, it is becoming an enabling technology, opening up new avenues for synthesis.

Alongside development of new synthetic procedures, the field of microwave-promoted synthesis also relies on equipment development. While much of the early work was performed using domestic microwave ovens, today there is apparatus designed for use in preparative chemistry. This has improved reproducibility, safety and allows for a wide range of different chemistries to be performed.

It is fitting that this Symposium-in-Print comes in the 20th anniversary of the publication of the first reports of microwave heating as a tool for synthetic organic chemistry. It brings together articles written by diverse groups from across the world and highlights some of the areas at the forefront of modern microwave-promoted synthesis. In addition to papers from research groups in academia, there are contributions from industry. Topics presented include medicinal chemistry, microarray synthesis, reaction scale-up, chemistry in hot water, transition-metal catalysis and polymer synthesis.

I would like to thank all the authors in this Symposium-in-Print for their contributions and the reviewers for their helpful comments. I also thank Professor Harry Wasserman for the kind invitation to edit this issue and for his advise and comments along the way. Rich Davis from CEM Microwave Technology is acknowledged for the cover art. Finally, I hope that the papers here will stimulate further development of microwave-promoted synthesis. With the interest from academic and industrial sectors, together with the inherent advantages they bring, it is not difficult to imagine the day when every chemist will have a microwave at their bench rather than a hotplate or oil bath.

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One-pot regioselective annulation toward 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds under controlled microwave heating☆

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Abstract—An efficient and general synthesis of 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines under controlled microwave heating has been established. It consists of a microwave-assisted reductive N-arylmethylation of substituted 2-aminophenols with aromatic aldehydes followed by a one-pot base-mediated regioselective O-alkylation of the *N*-arylmethyl-2-aminophenols with 2-bromoalkanoates to give the acyclic intermediates, which cyclize spontaneously to furnish the benzoxazine scaffolds in good to excellent yields. It was found that microwave heating over 180 °C was necessary for ring closure of the acyclic intermediates possessing an electron-withdrawing group.

1. Introduction

A variety of naturally occurring and synthetic bioactive compounds are known to possess the 2*H*-1,4-benzoxazine scalffold.[1] For instance, the enediyne antitumor antibiotic, C-1027,[2] consists of a 2-methylene-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine moiety in the chromophore subunit. Many derivatives of 2*H*-1,4-benzoxazine have been reported as plant resistance factors against microbial disease and insects,[3] serotonin-3 (5-HT_3) receptor antagonists,[4] potassium channel modulators,[5] antirheumatic agents,[6] antihypertensive agents,[7] inotropic vasodilator agents,[8] cannabinoid receptor agonists,[9] intracellular calcium antagonists,[10] neuroprotective antioxidants,[11] and others.[12a,b] 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazine skeleton is also considered as the bioisoster of 2(3*H*)-benzoxazolone[12c] and can be used as the privileged scaffold in drug design. From the synthetic point of view, 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine **1** presents a heterocycle system with three points of structural diversity (X, Y, and Z) on the aromatic ring, the nitrogen, and the C2 carbon (Fig. 1). 2-Aminophenols **2** and 2-nitrophenols **3** are the common building blocks for the synthesis of **1**.[1b] Normally, stepwise synthetic sequences were adopted, for example, 2-nitrophenols underwent an O-alkylation followed by nitro reduction and subsequent intramolecular *N*-substitution.[6,9,13] In the case of 2-aminophenols, protection and deprotection manipulations were used to achieve the desired regioselectivity.[14] When treating 2-aminophenols with 2-haloalkanoyl chlorides or bromides N-acylation took place to give 2-(*N*-2′-haloacylamino)phenols, which underwent an intramolecular O-alkylation on heating at ca. 70 °C in the presence of a base to afford 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines.[4c,5a–c,8,13a] Microwave heating up to 80 °C was used in a recent synthesis.[5c] However, for the electron-deficient 2-(*N*-2′-haloacylamino)phenols, higher temperatures were required for complete cyclization.[15] Moreover, various annulation methods including Pd-catalyzed reactions have been reported for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines.[7,10,14a,16] In connection with our previous studies on synthesis of indoles,[17,18] benzofurans,[19a] and benzoxazines[19b] from substituted 2-aminophenols, we report here a regioselective annulation approach

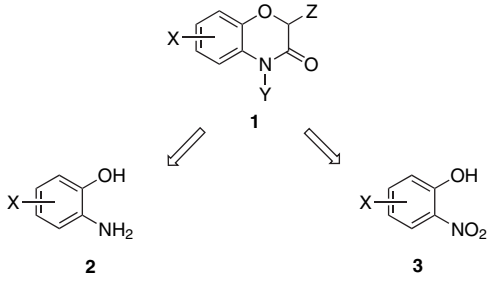

Figure 1. Common building blocks for 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds **1**.

☆ Part 6 of Chemistry of Aminophenols. For Part 5, see Ref. 19b.
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for rapidly accessing 4-arylmethyl-3,4-dihydro-2-alkyl-3-oxo-2*H*-1,4-benzoxazines in aqueous DMF under controlled microwave heating.[20]

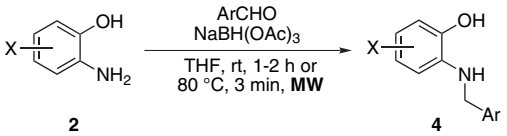
2. Results and discussion

In order to avoid the nitro reduction step in the synthesis starting from 2-nitrophenols **3**, we selected 2-aminophenols **2** as the building blocks in the current work. Although 2-haloalkanoyl halides were found to give an excellent regioselectivity in reactions with **2**,[4c,5a–c,8,13a,15] a recent study reported that reactions of 2-aminophenols with acyl chlorides at 210 °C under microwave irradiation for 15 min afforded benzoxazoles.[21] We preferred to use mild and easily handling 2-bromoalkanoates[4d] as the annulation agents, which are also suitable for running reactions in aqueous media. In our previous study,[19b] we found that heating a mixture of 2-aminophenol **2** (X=H) with ethyl 2-bromopropionate in NMP at 180 °C in the absence of a base resulted in almost exclusive formation of 3-methyl-3,4-dihydro-2-oxo-2*H*-1,4-benzoxazine along with some N,O-bisalkylation byproduct. It was found that a base such as DBU could preferentially remove the phenolic proton and promote O-alkylation of 2-aminophenols with 2-bromoalkanoates, leading to the formation of acyclic intermediates, which then underwent in situ intramolecular amidation at high temperatures under controlled microwave heating to furnish the scaffolds **1** (Y=H). By heating a mixture of 2-aminophenols **2**, ethyl 2-bromopropionate, and DBU in NMP at 180 °C for 3 min, we prepared a number of 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazines in 44–82% yields. However, with bulky 2-bromoalkanoates, significantly reduced yields were obtained for the desired benzoxazine products.[19b] Moreover, the reactions of *N*-substituted 2-aminophenols have not been generally investigated for the one-pot synthesis except for one report where ethyl bromoacetate was reacted with *N*-methyl 2-aminophenols in refluxing MeOH in the presence of 10% aqueous NaOH.[4d] It is the purpose of our current study to establish a reliable, general, and efficient procedure for synthesis of the 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds **1** with three points of diversity at X, Y, and Z.

We prepared a variety of *N*-arylmethylated 2-aminophenols **4a–i**[22] from **2** and four representative electron-rich and electron-deficient aromatic aldehydes (Table 1) under microwave heating (80 °C, 3 min).[23] The yields of **4a–i** were comparable to those obtained from the reactions at room temperature (1–2 h), despite that direct reduction of aldehydes by $NaBH(OAc)_3$ is a known competitive side-reaction, especially for strongly electron-deficient aldehydes.[24] An improved yield for the microwave-assisted reaction was achieved for compound **4d** (58%), which was accompanied by bis-arylmethylation byproduct (20%) at room temperature. The high-throughput rate is a unique strength of the microwave-assisted reactions.

The annulation of **4a–c** with ethyl 2-bromoalkanoates was examined using microwave heating in a mixture of DMF–H_2O (2:1) with dissolved K_2CO_3 as the base for avoiding generation of 'hot spots', which may damage the reaction vial (Table 2). On the basis of the results we can conclude

Table 1. Reductive N-alkylation of **2** at room temperature and under controlled microwave heating[a]



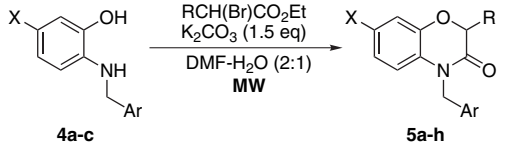
2 **4**

Entry	**2**: X	**4**	Yield (%)[b]
1	H	**4a**: X=H, Ar=2-furyl	73 (95)
2	5-Me	**4b**: X=5-Me, Ar=Ph	79 (97)
3	5-Me	**4c**: X=5-Me, Ar=2-furyl	75 (90)
4	4,5-$(CH_2)_4$–	**4d**: X=4,5-$(CH_2)_4$–, Ar=2-furyl	58 (48)[c]
5	4-NO_2	**4e**: X=4-NO_2, Ar=2-furyl	81 (98)
6	4-Cl	**4f**: X=4-Cl, Ar=2-furyl	86 (99)
7	4-Cl	**4g**: X=4-Cl, Ar=Ph	91 (99)
8	4-Cl	**4h**: X=4-Cl, Ar=4-$MeOC_6H_4$	80
9	4-Cl	**4i**: X=4-Cl, Ar=3-pyridinyl	87

[a] Compound **2** (1 equiv), 1.1 equiv of ArCHO, and 3 equiv of $NaBH(OAc)_3$ were used. All reactions with microwave heating were carried out on a commercial technical microwave reactor with temperature and pressure controlling capacity.
[b] Isolated yields of **4**. The numbers given in the parentheses are the yields for the room temperature reactions.
[c] The bisalkylation byproduct was isolated in 20% yield.

the following points: (a) use of 2 equiv of 2-bromoalkanoates gave slightly higher yields (Table 2, entry 2 vs entry 1); (b) N,O-bisalkylation byproducts were not observed even using excess 2-bromoalkanoates with R≠H; (c) annulations using 2-bromoacetate (R=H) always formed N,O-bisalkylation byproducts and lower temperatures afforded higher yields of the desired products (Table 2, entry 6 vs entry 5 and entry 7 vs entry 10); and (d) for the reactions of bulky 2-bromoalkanoates, excellent yields were obtained at high reaction temperatures (Table 2, entries 11–13 vs entries 8 and 9). Moreover, we found that the microwave-assisted annulation reactions of bulky bromo esters at 180 °C gave comparable chemical yields as to those obtained from

Table 2. One-pot annulation of **4a–c** under microwave heating[a]

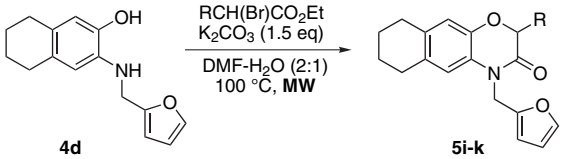


4a-c **5a-h**

Entry	*T* (°C), *t* (min)	**5**	Yield (%)[c]
1	100, 20[b]	**5a**: X=R=H, Ar=2-furyl	64[d]
2	100, 20	**5a**: X=R=H, Ar=2-furyl	68[d]
3	100, 20	**5b**: X=H, R=Et, Ar=2-furyl	75
4	100, 25	**5c**: X=H, R=*n*-Pr, Ar=2-furyl	74
5	120, 15[b]	**5d**: X=Me, R=H, Ar=Ph	51[d]
6	100, 20[b]	**5d**: X=Me, R=H, Ar=Ph	60[d]
7	80, 15[b]	**5e**: X=Me, R=H, Ar=2-furyl	74[d] (80)
8	100, 20[b]	**5g**: X=Me, R=Et, Ar=2-furyl	68
9	100, 20[b]	**5h**: X=Me, R=*n*-Pr, Ar=2-furyl	67
10	180, 20	**5e**: X=Me, R=H, Ar=2-furyl	62[d]
11	180, 20	**5f**: X=Me, R=Me, Ar=2-furyl	85
12	180, 20	**5g**: X=Me, R=Et, Ar=2-furyl	81 (92)
13	180, 20	**5h**: X=Me, R=*n*-Pr, Ar=2-furyl	80 (74)

[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] $RCH(Br)CO_2Et$ (1.5 equiv) was used.
[c] Isolated yields of **5**. The numbers given in the parentheses are the yields for the room temperature reactions (DMF, 3–4.5 h).
[d] Various amounts of N,O-bisalkylation byproducts were detected.

Table 3. One-pot annulation of **4d** under microwave heating[a]



4d **5i-k**

Entry	*t* (min)	**5**	Yield (%)[b]
1	25	**5i**: R=H	67[c]
2	35	**5j**: R=Et	75
3	35	**5k**: R=*n*-Pr	75

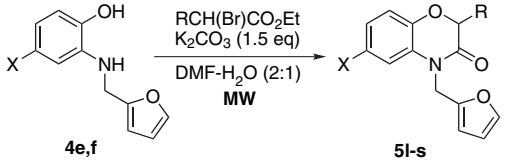
[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] Isolated yields of **5**.
[c] The N,O-bisalkylation byproduct was detected.

reactions of **4a–c** at room temperature but with greatly shortened reaction times (Table 2, entries 12 and 13 vs entries 8 and 9).

Table 3 shows the reactions of the bicyclic 2-aminophenol **4d** at 100 °C under microwave irradiation. Good yields were obtained for **5i–k** and the N,O-bisalkylation byproduct was also detected in the reaction of 2-bromoacetate (Table 3, entry 1).

The reactions of 2-aminophenols **4e**,**f** possessing an electron-withdrawing group are very different from those described in Tables 2 and 3. When **4e** was treated with ethyl 2-bromoacetate and K_2CO_3 in DMF at room temperature, the O-alkylation intermediate[25] was isolated in 99% yield without formation of the expected **5l**, which was formed in 56% yield by heating at 200 °C for 40 min (Table 4, entry 1). Also, the annulation of **4f** with ethyl 2-bromovalerate at 100 °C for 30 min produced a mixture of the acyclic O-alkylation intermediate and **5s** in 20% and 68% yields, respectively (Table 4, entry 8). The one-pot reactions of **4f** with 2-bromoalkanoates at 180 °C furnished the products **5q–s** in 81–96% yields (Table 4, entries 5–7 and 9). On the other hand, annulation reactions of **4e** with 2-bromoalkanoates required heating at 190 °C for 40–45 min to give

Table 4. One-pot annulation of **4e**,**f** under microwave heating[a]

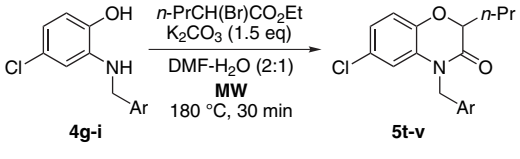


4e,f **5l-s**

Entry	*T* (°C), *t* (min)	**5**	Yield (%)[b]
1	200, 40	**5l**: X=NO_2, R=H	56
2	190, 40	**5m**: X=NO_2, R=Me	74
3	190, 45	**5n**: X=NO_2, R=Et	71
4	190, 40	**5o**: X=NO_2, R=*n*-Pr	85
5	180, 30	**5p**: X=Cl, R=H	81
6	180, 30	**5q**: X=Cl, R=Me	88
7	180, 30	**5r**: X=Cl, R=Et	90
8	100, 30	**5s**: X=Cl, R=*n*-Pr	68[c]
9	180, 30	**5s**: X=Cl, R=*n*-Pr	96

[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] Isolated yields of **5**.
[c] The O-alkylation intermediate was obtained in 20% yield.

Table 5. One-pot annulation of **4g–i** under microwave heating[a]



4g-i **5t-v**

Entry	**5**	Yield (%)[b]
1	**5t**: Ar=Ph	91
2	**5u**: Ar=4-$MeOC_6H_4$	98
3	**5v**: Ar=3-pyridinyl	70

[a] $RCH(Br)CO_2Et$ (2 equiv) was used.
[b] Isolated yields of **5**.

2-alkyl-3,4-dihydro-6-nitro-3-oxo-2*H*-1,4-benzoxazines **5m–o** in 71–85% yields (Table 4, entries 2–4).

Finally, we evaluated the one-pot annulation of **4g–i** bearing different arylmethyl groups on the nitrogen atom (Table 5). By heating at 180 °C for 30 min, the products **5t** and **5u** possessing *N*-benzyl and *N*-4-methoxybenzyl (PMB) groups were formed in 91% and 98% yields, respectively. The 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine **5v** was isolated in 70% yield presumably due to the influence of the 3-pyridinylmethyl group.

3. Conclusion

In summary, we have established a high-throughput synthesis for access to a variety of 2-alkyl-4-arylmethyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine scaffolds starting from readily available substituted 2-aminophenols. The synthesis takes advantage of microwave-assisted fast reductive N-arylmethylation (80 °C, 3 min) of 2-aminophenols, followed by microwave-assisted one-pot regioselective annulation with 2-bromoalkanoates in aqueous DMF in the presence of K_2CO_3 (100–200 °C, 20–45 min). In particular, microwave heating at 180 °C or above is necessary for high yielding of the 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines possessing an electron-withdrawing NO_2 or Cl group at the C6 position.

4. Experimental

4.1. General information and the microwave reactor

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6, or DMSO-d_6 (500 or 400 MHz for ^1H and 125 or 100 MHz for ^{13}C, respectively) with $CHCl_3$, acetone, or DMSO as the internal reference. IR spectra were taken on an FTIR spectrophotometer. Mass spectra (MS) were measured by the ESI method. Elemental analyses were performed at Zhejiang University. All reactions were carried out on an Emrys creator from Personal Chemistry AB (now under Biotage AB, Uppsala Sweden) with temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature. The reaction mixture was checked by thin-layer chromatography on silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Flash column chromatography over silica gel was used for

purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received.

4.2. General procedure for reductive N-alkylation of 2-aminophenols under microwave irradiation

A 10 mL pressurized process vial was charged with a mixture of an aldehyde (0.74 mmol), 2-aminophenol **2** (0.66 mmol), and $NaBH(OAc)_3$ (424.0 mg, 2 mmol) in THF (5 mL) and was tightly sealed with a cap containing a silicon septum. The loaded vial was then placed into the microwave reactor cavity and heated at the final temperature of 80 °C for 3 min. After cooling to room temperature the reaction mixture was diluted with water and the resultant mixture was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel to provide the product **4**. The yields are listed in Table 1.

4.2.1. 2-(2′-Furylmethyl)aminophenol (4a). Prepared in 73% yield. *Compound* **4a**. A pale yellow gum; R_f=0.40 (20% EtOAc in hexane); IR (film) 3406, 3327, 3120, 1609, 1509, 1449, 1265, 1195 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.89–6.67 (m, 4H), 6.33 (br s, 1H), 6.25 (br s, 1H), 5.50–4.50 (br s, 2H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 144.2, 141.9, 136.2, 121.4, 118.9, 114.7, 113.4, 110.3, 107.1, 41.9; MS (−ESI) *m*/*z* 188 (M−H$^+$, 100). HRMS (+ESI) calcd for $C_{11}H_{11}NO_2Na$ 212.0683 (M+Na$^+$), found 212.0680.

4.2.2. 2-Benzylamino-5-methylphenol (4b). Prepared in 79% yield. *Compound* **4b**. A white crystalline solid; mp 98–102 °C (EtOAc–hexane); R_f=0.46 (20% EtOAc in hexane); IR (KBr) 3422 (br), 3314, 3033, 2918, 1527, 1474, 1451, 1420, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H), 6.59 (s, 2H), 6.44 (s, 1H), 4.71 (br s, 2H), 4.25 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 139.4, 134.1, 128.6 (×2), 128.5, 127.7 (×2), 127.2, 121.6, 115.6, 113.6, 49.3, 20.6; MS (+ESI) *m*/*z* 235 (M+Na$^+$, 81), 213 (M$^+$, 100). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.92; H, 7.16; N, 6.65%.

4.2.3. 2-(2′-Furylmethyl)amino-5-methylphenol (4c). Prepared in 75% yield. *Compound* **4c**. A white crystalline solid; mp 80–82 °C (EtOAc–hexane); R_f=0.42 (20% EtOAc in hexane); IR (KBr) 3429 (br), 3350, 3339, 2919, 1529, 1451, 1419, 1125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=1.6 Hz, 1H), 6.71 (d, *J*=8.0 Hz, 1H), 6.67 (d, *J*=8.4 Hz, 1H), 6.46 (s, 1H), 6.33 (dd, *J*=1.6, 3.2 Hz, 1H), 6.23 (d, *J*=3.2 Hz, 1H), 5.16 (br s, 2H), 4.29 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 145.0, 141.9, 133.3, 129.5, 121.4, 115.8, 114.5, 110.3, 107.2, 42.5, 20.6; MS (−ESI) *m*/*z* 202 (M−H$^+$, 100). Anal. Calcd for $C_{12}H_{13}NO_2 \cdot 1/8\ H_2O$: C, 70.14; H, 6.50; N, 6.82. Found: C, 70.31; H, 6.67; N, 5.62%.

4.2.4. 3-(2′-Furylmethyl)amino-5,6,7,8-tetrahydro-2-naphthol (4d). Prepared in 58% yield. *Compound* **4d**. A white crystalline solid; mp 76–78 °C (CH_2Cl_2–hexane); R_f=0.44 (20% EtOAc in hexane); IR (KBr) 3456 (br), 3339, 2921, 1527, 1448, 1258, 1188, 1146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.48 (s, 1H), 6.40 (s, 1H), 6.33 (dd, *J*=1.2, 3.2 Hz, 1H), 6.24 (d, *J*=3.2 Hz, 1H), 4.63 (br s, 2H), 4.27 (s, 2H), 2.66–2.60 (m, 4H), 1.75 (br s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6, recorded at 80 °C) δ 154.0, 142.6, 141.7, 135.0, 127.1, 124.4, 114.4, 111.2, 110.3, 106.5, 40.9, 28.6, 28.2, 23.3, 23.3; MS (−ESI) *m*/*z* 242 (M−H$^+$, 100). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.73; H, 6.94; N, 4.88%.

4.2.5. 2-(2′-Furylmethyl)amino-4-nitrophenol (4e). Prepared in 81% yield. *Compound* **4e**. A red crystalline solid; mp 118–120 °C (EtOAc–hexane); R_f=0.17 (20% EtOAc in hexane); IR (KBr) 3407, 1527, 1468, 1335, 1275, 1245, 1101 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (br s, 1H), 7.58 (d, *J*=1.6 Hz, 1H), 7.46 (dd, *J*=2.8, 8.4 Hz, 1H), 7.34 (d, *J*=2.8 Hz, 1H), 6.80 (d, *J*=8.4 Hz, 1H), 6.39 (dd, *J*=1.6, 3.2 Hz, 1H), 6.29 (d, *J*=3.2 Hz, 1H), 5.81 (br s, 1H), 4.39 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.0, 151.4, 142.5, 140.7, 137.6, 113.8, 112.6, 110.8, 107.4, 104.0, 31.1; MS (−ESI) *m*/*z* 233 (M−H$^+$, 100). Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.29; H, 4.37; N, 12.31%.

4.2.6. 4-Chloro-2-(2′-furylmethyl)aminophenol (4f). Prepared in 86% yield. *Compound* **4f**. A white crystalline solid; mp 84–87 °C (CH_2Cl_2–hexane); R_f=0.31 (20% EtOAc in hexane); IR (KBr) 3407, 1611, 1512, 1445, 1419, 1190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.69 (s, 1H), 6.60–6.55 (m, 2H), 6.34 (dd, *J*=1.6, 3.2 Hz, 1H), 6.25 (d, *J*=3.2 Hz, 1H), 4.76 (br s, 2H), 4.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 142.1, 142.0, 137.4, 126.5, 117.4, 115.1, 112.3, 110.4, 107.4, 41.3; MS (−ESI) *m*/*z* 222 (M−H$^+$, 61.5), 224 (M+2−H$^+$, 19.7), 445 (2M−H$^+$, 100). Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.82; H, 4.64; N, 5.95%.

4.2.7. 2-Benzylamino-4-chlorophenol (4g). Prepared in 91% yield. *Compound* **4g**. A pale yellow crystalline solid; mp 118–120 °C (EtOAc–hexane); R_f=0.36 (20% EtOAc in hexane); IR (KBr) 3505, 3403, 1609, 1514, 1154, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 6.63 (d, *J*=8.0 Hz, 1H), 6.62 (d, *J*=2.0 Hz, 1H), 6.56 (dd, *J*=2.0, 8.0 Hz, 1H), 4.32 (s, 2H) (signals for OH and NH were not found); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.4, 137.9, 128.7 (×2), 127.6 (×2), 127.5, 126.6, 116.8, 114.9, 111.8, 48.2; MS (−ESI) *m*/*z* 232 (M−H$^+$, 100), 234 (M+2−H$^+$, 31). Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.87; H, 5.19; N, 6.00%.

4.2.8. 4-Chloro-2-((4′-methoxyphenyl)methyl)aminophenol (4h). Prepared in 80% yield. *Compound* **4h**. A white crystalline solid; mp 148–151 °C (EtOAc–hexane); R_f=0.34 (20% EtOAc in hexane); IR (KBr) 3497, 3409, 1608, 1513, 1415, 1253, 1116 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.59 (s, 1H), 7.33 (d, *J*=8.4 Hz, 2H), 6.90 (d, *J*=8.4 Hz, 2H), 6.70 (d, *J*=8.4 Hz, 1H), 6.48 (d, *J*=2.4 Hz, 1H), 6.42 (dd, *J*=2.4, 8.4 Hz, 1H), 5.11 (br s, 1H), 4.34 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 158.8, 142.7, 138.8, 131.5, 128.3 (×2), 124.6, 114.9, 113.9, 113.7 (×2), 109.8, 54.5, 46.3; MS (−ESI) *m*/*z* 262 (M−H$^+$, 72), 264 (M+2−H$^+$, 23), 525.3 (2M−H$^+$, 100). Anal. Calcd for

$C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.52; H, 5.52; N, 3.51%.

4.2.9. 4-Chloro-2-(3′-pyridinylmethyl)aminophenol (4i). Prepared in 87% yield. *Compound* **4i**. A pale green crystalline solid; mp 168–174 °C (MeOH); R_f=0.19 (67% EtOAc in hexane); IR (KBr) 3435, 2931, 1609, 1582, 1519, 1428, 1251, 1206 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.56 (s, 1H), 8.43 (d, J=4.8 Hz, 1H), 7.72 (d, J=7.6 Hz, 1H), 7.33 (dd, J=4.8, 7.6 Hz, 1H), 6.63 (d, J=8.4 Hz, 1H), 6.39 (dd, J=2.0, 8.4 Hz, 1H), 6.35 (d, J=2.0 Hz, 1H), 5.77 (br s, 1H), 4.35 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.1, 148.3, 143.5, 138.6, 135.8, 135.3, 123.9, 123.6, 115.3, 114.5, 109.7, 43.9; MS (−ESI) m/z 233 (M−H$^+$, 100), 235 (M+2−H$^+$, 32). Anal. Calcd for $C_{12}H_{11}ClN_2O\cdot 1/8\ H_2O$: C, 60.83; H, 4.79; N, 11.82. Found: C, 60.74; H, 4.96; N, 11.08%.

4.3. General procedure for microwave-assisted one-pot synthesis of 5

A 10 mL pressurized process vial was charged with a mixture of the aminophenol **4** (0.30 mmol), ethyl 2-bromo ester (0.60 mmol), and K_2CO_3 (62.8 mg, 0.45 mmol) in water (1 mL) and DMF (2 mL) and was tightly sealed with a cap containing a silicon septum. The loaded vial was then placed into the microwave reactor cavity and was heated at the final temperature for the specified time (see Tables 2–5 for details). After cooling to room temperature the reaction mixture was diluted with water (5 mL) and the resultant mixture was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to furnish the product **5**. The yields are listed in Tables 2–5.

4.3.1. 3,4-Dihydro-4-(2′-furylmethyl)-3-oxo-2*H*-1,4-benzoxazine (5a). Prepared in 68% yield. *Compound* **5a**. A yellow oil; R_f=0.41 (11% EtOAc in hexane); IR (film) 3120, 2890, 1690, 1502, 1400, 1281, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=1.6, 1.2 Hz, 1H), 7.24–7.21 (m, 1H), 7.03–6.97 (m, 3H), 6.33–6.31 (m, 2H), 5.08 (s, 2H), 4.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 149.6, 145.3, 142.2, 128.7, 124.1, 122.8, 117.0, 115.5, 110.6, 108.8, 67.7, 38.3; MS (+ESI) m/z 481 (2M+Na$^+$, 100), 252 (M+Na$^+$, 98). HRMS (+ESI) calcd for $C_{13}H_{11}NO_3Na$ 252.0631 (M+Na$^+$), found 252.0629.

4.3.2. 2-Ethyl-3,4-dihydro-4-(2′-furylmethyl)-3-oxo-2*H*-1,4-benzoxazine (5b). Prepared in 75% yield. *Compound* **5b**. A yellowish crystalline solid; mp 54–55 °C (EtOAc–hexane); R_f=0.53 (11% EtOAc in hexane); IR (KBr) 2972, 1687, 1502, 1401, 1278, 1141, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=2.0, 0.8 Hz, 1H), 7.19–7.15 (m, 1H), 7.01–6.98 (m, 3H), 6.31 (dd, J=3.2, 2.0 Hz, 1H), 6.29 (dd, J=3.2, 0.8 Hz, 1H), 5.10 and 5.04 (ABq, J=16.2 Hz, 2H), 4.50 (dd, J=8.8, 4.8 Hz, 1H), 1.99–1.83 (m, 2H), 1.08 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.9, 144.2, 142.1, 128.9, 124.0, 122.5, 117.3, 115.1, 110.6, 108.4, 78.2, 38.6, 23.7, 9.4; MS (+ESI) m/z 537 (2M+Na$^+$, 100), 280 (M+Na$^+$, 41). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.05; H, 6.07; N, 5.48%.

4.3.3. 3,4-Dihydro-4-(2′-furylmethyl)-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5c). Prepared in 74% yield. *Compound* **5c**. A white amorphous solid; R_f=0.65 (11% EtOAc in hexane); IR (KBr) 2962, 1688, 1502, 1401, 1279, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=1.6, 0.8 Hz, 1H), 7.18–7.16 (m, 1H), 7.01–6.97 (m, 3H), 6.31 (dd, J=2.8, 1.6 Hz, 1H), 6.28 (dd, J=2.8, 0.8 Hz, 1H), 5.11 and 5.03 (ABq, J=16.2 Hz, 2H), 4.59 (dd, J=8.4, 5.2 Hz, 1H), 1.88–1.81 (m, 2H), 1.64–1.49 (m, 2H), 0.96 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 149.9, 144.1, 142.1, 128.9, 124.0, 122.5, 117.4, 115.1, 110.6, 108.4, 76.9, 38.6, 32.2, 18.3, 13.7; MS (+ESI) m/z 565 (2M+Na$^+$, 100), 294 (M+Na$^+$, 29). HRMS (+ESI) calcd for $C_{16}H_{17}NO_3Na$ 294.1101 (M+Na$^+$), found 294.1108.

4.3.4. 4-Benzyl-3,4-dihydro-7-methyl-3-oxo-2*H*-1,4-benzoxazine (5d). Prepared in 60% yield. *Compound* **5d**. A white crystalline solid; mp 87–89 °C (EtOAc–hexane); R_f=0.53 (20% EtOAc in hexane); IR (KBr) 1683, 1513, 1405, 1296, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H), 6.82 (s, 1H), 6.76 (d, J=8.0 Hz, 1H), 6.70 (d, J=8.0 Hz, 1H), 5.15 (s, 2H), 4.71 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 145.2, 136.1, 134.1, 128.9 (×2), 127.5, 126.7 (×2), 126.3, 123.3, 117.6, 115.5, 67.8, 45.0, 20.7; MS (+ESI) m/z 529 (2M+Na$^+$, 100), 276 (M+Na$^+$, 85). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.75; H, 5.94; N, 5.52%.

4.3.5. 3,4-Dihydro-4-(2′-furylmethyl)-7-methyl-3-oxo-2*H*-1,4-benzoxazine (5e). Prepared in 74% yield. *Compound* **5e**. A yellowish crystalline solid; mp 75–76 °C (EtOAc–hexane); R_f=0.38 (11% EtOAc in hexane); IR (KBr) 1679, 1514, 1407, 1152, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.08 (d, J=8.0 Hz, 1H), 6.81 (d, J=8.0 Hz, 1H), 6.81 (s, 1H), 6.31 (s, 1H), 6.30 (s, 1H), 5.06 (s, 2H), 4.61 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 149.6, 145.0, 142.1, 134.1, 126.2, 123.2, 117.5, 115.1, 110.5, 108.6, 67.7, 38.2, 20.7; MS (+ESI) m/z 509 (2M+Na$^+$, 100), 266 (M+Na$^+$, 46). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.26; H, 5.46; N, 5.68%.

4.3.6. 3,4-Dihydro-4-(2′-furylmethyl)-2,7-dimethyl-3-oxo-2*H*-1,4-benzoxazine (5f). Prepared in 85% yield. *Compound* **5f**. A yellowish crystalline solid; mp 67–68 °C (EtOAc–hexane); R_f=0.48 (11% EtOAc in hexane); IR (KBr) 2981, 1513, 1399, 1158, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.06 (d, J=8.4 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 6.80 (s, 1H), 6.30 (dd, J=3.2, 2.0 Hz, 1H), 6.28 (d, J=3.2 Hz, 1H), 5.12 and 4.97 (ABq, J=15.8 Hz, 2H), 4.62 (q, J=6.8 Hz, 1H), 2.28 (s, 3H), 1.56 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 149.9, 144.3, 142.1, 134.0, 126.5, 123.1, 117.8, 114.9, 110.5, 108.4, 73.5, 38.7, 20.7, 16.2; MS (+ESI) m/z 537 (2M+Na$^+$, 100), 280 (M+Na$^+$, 44). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.16; H, 6.10; N, 5.46%.

4.3.7. 2-Ethyl-3,4-dihydro-4-(2′-furylmethyl)-7-methyl-3-oxo-2*H*-1,4-benzoxazine (5g). Prepared in 81% yield. *Compound* **5g**. A yellowish oil; R_f=0.56 (11% EtOAc in hexane); IR (film) 2971, 1686, 1514, 1403, 1149 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=2.0 Hz, 1H), 7.03 (d, J=7.6 Hz, 1H), 6.81 (s, 1H), 6.79 (d, J=8.0 Hz, 1H), 6.30 (dd, J=3.2, 2.0 Hz, 1H), 6.27 (d, J=3.2 Hz, 1H), 5.09 and 5.02 (ABq, J=16.0 Hz, 2H), 4.48 (dd, J=8.4, 4.4 Hz, 1H), 2.28 (s, 3H), 1.95–1.82 (m, 2H), 1.07 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 149.9, 143.9, 142.0, 134.0, 126.3, 122.9, 117.8, 114.8, 110.5, 108.2, 78.2, 38.5, 23.6, 20.7, 9.4; MS (+ESI) m/z 565 (2M+Na$^+$, 100), 294 (M+Na$^+$, 41). HRMS (+ESI) calcd for $C_{16}H_{17}NO_3Na$ 294.1101 (M+Na$^+$), found 294.1102.

4.3.8. 3,4-Dihydro-4-(2′-furylmethyl)-7-methyl-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5h). Prepared in 80% yield. *Compound* **5h**. A yellow amorphous solid; R_f=0.62 (11% EtOAc in hexane); IR (KBr) 2961, 1686, 1514, 1401, 1292, 1149 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=1.2 Hz, 1H), 7.03 (d, J=8.4 Hz, 1H), 6.80 (s, 1H), 6.79 (d, J=8.4 Hz, 1H), 6.30 (dd, J=2.8, 1.2 Hz, 1H), 6.26 (d, J=2.8 Hz, 1H), 5.09 and 5.00 (ABq, J=15.8 Hz, 2H), 4.56 (dd, J=8.0, 4.8 Hz, 1H), 2.28 (s, 3H), 1.86–1.80 (m, 2H), 1.61–1.48 (m, 2H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 149.9, 143.8, 142.0, 134.0, 126.3, 122.9, 117.9, 114.8, 110.5, 108.2, 76.9, 38.5, 32.1, 20.7, 18.3, 13.6; MS (+ESI) m/z 593 (2M+Na$^+$, 100), 308 (M+Na$^+$, 32). HRMS (+ESI) calcd for $C_{17}H_{19}NO_3Na$ 308.1257 (M+Na$^+$), found 308.1256.

4.3.9. 6,7,8,9-Tetrahydro-4-(2′-furylmethyl)-3-oxo-2*H*-naphtho[2,3,*b*][1,4]oxazine (5i). Prepared in 67% yield. *Compound* **5i**. A white crystalline solid; mp 104–106 °C (EtOAc–hexane); R_f=0.39 (11% EtOAc in hexane); IR (KBr) 2926, 1701, 1679, 1515, 1389, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J=1.6, 0.8 Hz, 1H), 6.88 (s, 1H), 6.69 (s, 1H), 6.32 (dd, J=3.2, 1.6 Hz, 1H), 6.30 (dd, J=3.2, 0.8 Hz, 1H), 5.06 (s, 2H), 4.58 (s, 2H), 2.71–2.68 (m, 4H), 1.79–1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 149.8, 143.2, 142.1, 133.0, 131.4, 126.4, 116.9, 115.6, 110.6, 108.6, 67.8, 38.3, 29.1, 28.8, 23.1, 23.0; MS (+ESI) m/z 589 (2M+Na$^+$, 100), 306 (M+Na$^+$, 34). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.08; H, 6.30; N, 5.15%.

4.3.10. 2-Ethyl-6,7,8,9-tetrahydro-4-(2′-furylmethyl)-3-oxo-2*H*-naphtho[2,3,*b*][1,4]oxazine (5j). Prepared in 75% yield. *Compound* **5j**. A white crystalline solid; mp 79–80 °C (EtOAc–hexane); R_f=0.53 (11% EtOAc in hexane); IR (KBr) 2936, 1680, 1514, 1262 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=2.0, 0.4 Hz, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 6.31 (dd, J=2.8, 2.0 Hz, 1H), 6.30 (dd, J=2.8, 0.4 Hz, 1H), 5.08 and 5.00 (ABq, J=15.8 Hz, 2H), 4.45 (dd, J=8.4, 4.4 Hz, 1H), 2.71–2.67 (m, 4H), 1.94–1.82 (m, 2H), 1.78–1.73 (m, 4H), 1.06 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 150.0, 142.0, 141.7, 132.9, 131.0, 126.4, 117.2, 115.2, 110.5, 108.2, 78.3, 38.5, 29.1, 28.8, 23.6, 23.2, 23.0, 9.5; MS (+ESI) m/z 645 (2M+Na$^+$, 100), 334 (M+Na$^+$, 86). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.31; H, 7.36; N, 4.74%.

4.3.11. 6,7,8,9-Tetrahydro-4-(2′-furylmethyl)-3-oxo-2-propyl-2*H*-naphtho[2,3,*b*][1,4]oxazine (5k). Prepared in 75% yield. *Compound* **5k**. A white crystalline solid; mp 96–97 °C (EtOAc–hexane); R_f=0.58 (11% EtOAc in hexane); IR (KBr) 2958, 1682, 1509, 1395, 1146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J=2.0 Hz, 1H), 6.82 (s, 1H), 6.68 (s, 1H), 6.31 (dd, J=3.2, 2.0 Hz, 1H), 6.27 (d, J=3.2 Hz, 1H), 5.09 and 4.99 (ABq, J=16.0 Hz, 2H), 4.54 (dd, J=7.2, 6.0 Hz, 1H), 2.71–2.68 (m, 4H), 1.85–1.78 (m, 2H), 1.77–1.75 (m, 4H), 1.61–1.47 (m, 2H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 150.0, 142.0, 141.7, 132.9, 131.0, 126.4, 117.2, 115.2, 110.5, 108.2, 76.9, 38.5, 32.1, 29.1, 28.8, 23.2, 23.0, 18.3, 13.6; MS (+ESI) m/z 673 (2M+Na$^+$, 100), 348 (M+Na$^+$, 45). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.79; H, 7.67; N, 4.41%.

4.3.12. 3,4-Dihydro-4-(2′-furylmethyl)-6-nitro-3-oxo-2*H*-1,4-benzoxazine (5l). Prepared in 56% yield. *Compound* **5l**. A yellow crystalline solid; mp 125–126 °C (CH_2Cl_2–hexane); R_f=0.14 (11% EtOAc in hexane); IR (KBr) 1705, 1519, 1341, 1276 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J=2.4 Hz, 1H), 7.93 (dd, J=8.8, 2.4 Hz, 1H), 7.38 (dd, J=2.0, 0.8 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 6.43 (dd, J=3.6, 0.8 Hz, 1H), 6.34 (dd, J=3.6, 2.0 Hz, 1H), 5.16 (s, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 150.0, 148.3, 143.0, 142.8, 128.7, 120.0, 117.1, 111.3, 110.7, 109.8, 67.3, 38.2; MS (+ESI) m/z 571 (2M+Na$^+$, 43), 297 (M+Na$^+$, 100). Anal. Calcd for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22. Found: C, 56.84; H, 3.66; N, 10.25%.

4.3.13. 3,4-Dihydro-4-(2′-furylmethyl)-2-methyl-6-nitro-3-oxo-2*H*-1,4-benzoxazine (5m). Prepared in 74% yield. *Compound* **5m**. A yellow crystalline solid; mp 146–147 °C (CH_2Cl_2–hexane); R_f=0.24 (11% EtOAc in hexane); IR (KBr) 1685, 1522, 1341, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J=2.4 Hz, 1H), 7.93 (dd, J=8.8, 2.4 Hz, 1H), 7.37 (d, J=1.6 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 6.40 (d, J=3.2 Hz, 1H), 6.33 (dd, J=3.2, 1.6 Hz, 1H), 5.20 and 5.07 (ABq, J=16.2 Hz, 2H), 4.78 (q, J=6.8 Hz, 1H), 1.61 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 149.6, 148.5, 143.0, 142.8, 129.0, 120.0, 117.4, 111.1, 110.6, 109.5, 73.9, 38.6, 16.9; MS (+ESI) m/z 311 (M+Na$^+$, 100). Anal. Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.32; H, 4.36; N, 9.88%.

4.3.14. 2-Ethyl-3,4-dihydro-4-(2′-furylmethyl)-6-nitro-3-oxo-2*H*-1,4-benzoxazine (5n). Prepared in 71% yield. *Compound* **5n**. A yellow crystalline solid; mp 77–78 °C (CH_2Cl_2–hexane); R_f=0.32 (11% EtOAc in hexane); IR (KBr) 2976, 1689, 1523, 1243, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=2.4 Hz, 1H), 7.91 (dd, J=2.4, 2.8 Hz, 1H), 7.35 (d, J=2.0 Hz, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.39 (d, J=3.2 Hz, 1H), 6.32 (dd, J=3.2, 2.0 Hz, 1H), 5.17 and 5.09 (ABq, J=15.8 Hz, 2H), 4.72 (dd, J=8.8, 4.8 Hz, 1H), 1.91–1.82 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 149.4, 148.5, 142.8, 142.7, 128.8, 120.0, 117.3, 110.9, 110.6, 109.4, 78.5, 38.4, 24.3, 9.1; MS (+ESI) m/z 325 (M+Na$^+$, 100). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.65; H, 4.81; N, 9.47%.

4.3.15. 3,4-Dihydro-4-(2′-furylmethyl)-6-nitro-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5o). Prepared in 85% yield.

Compound **5o**. A yellow crystalline solid; mp 62–64 °C (EtOAc–hexane); R_f=0.40 (11% EtOAc in hexane); IR (KBr) 2966, 1692, 1525, 1340, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=2.4 Hz, 1H), 7.91 (dd, J=8.8, 2.8 Hz, 1H), 7.35 (d, J=1.6 Hz, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.38 (d, J=3.2 Hz, 1H), 6.32 (dd, J=3.2, 1.6 Hz, 1H), 5.17 and 5.09 (ABq, J=15.8 Hz, 2H), 4.72 (dd, J=8.8, 4.8 Hz, 1H), 1.91–1.82 (m, 2H), 1.58–1.48 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 149.3, 148.5, 142.8, 142.7, 128.8, 120.0, 117.4, 110.1, 110.6, 109.4, 77.3, 38.4, 32.8, 18.0, 13.5; MS (+ESI) m/z 339 (M+Na^+, 100). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.80; H, 5.21; N, 8.87%.

4.3.16. 6-Chloro-3,4-dihydro-4-(2′-furylmethyl)-3-oxo-2*H*-1,4-benzoxazine (5p). Prepared in 81% yield. *Compound* **5p**. A white crystalline solid; mp 88–90 °C (CH_2Cl_2–hexane); R_f=0.39 (11% EtOAc in hexane); IR (KBr) 1687, 1498, 1373, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J=0.8 Hz, 1H), 7.23 (d, J=2.0 Hz, 1H), 6.96 (dd, J=8.4, 2.0 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 6.35–6.32 (m, 2H), 5.05 (s, 2H), 4.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 149.0, 143.8, 142.4, 129.7, 127.8, 123.7, 117.9, 115.6, 110.6, 109.1, 67.5, 38.3; MS (+ESI) m/z 286 (M+Na^+, 100), 288 (M+2+Na^+, 32). Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.12; H, 3.80; N, 5.22%.

4.3.17. 6-Chloro-3,4-dihydro-4-(2′-furylmethyl)-2-methyl-3-oxo-2*H*-1,4-benzoxazine (5q). Prepared in 88% yield. *Compound* **5q**. A white crystalline solid; mp 96–97 °C (CH_2Cl_2–hexane); R_f=0.50 (11% EtOAc in hexane); IR (KBr) 2938, 1672, 1499, 1374, 1264, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.21 (d, J=2.0 Hz, 1H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 6.33 (s, 2H), 5.11 and 4.94 (ABq, J=15.8 Hz, 2H), 4.62 (q, J=6.4 Hz, 1H), 1.56 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.2, 143.1, 142.4, 130.1, 127.6, 123.6, 118.2, 115.4, 110.6, 108.9, 73.5, 38.8, 16.1; MS (+ESI) m/z 300 (M+Na^+, 100), 302 (M+2+Na^+, 32). Anal. Calcd for $C_{14}H_{12}ClNO_3$: C, 60.55; H, 4.36; N, 5.04. Found: C, 60.53; H, 4.46; N, 5.19%.

4.3.18. 6-Chloro-2-ethyl-3,4-dihydro-4-(2′-furylmethyl)-3-oxo-2*H*-1,4-benzoxazine (5r). Prepared in 90% yield. *Compound* **5r**. A white crystalline solid; mp 98–100 °C (EtOAc–hexane); R_f=0.56 (11% EtOAc in hexane); IR (KBr) 2975, 1667, 1499, 1375, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J=0.8 Hz, 1H), 7.18 (d, J=2.0 Hz, 1H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 6.33–6.30 (m, 2H), 5.06 and 5.00 (ABq, J=16.0 Hz, 2H), 4.48 (dd, J=8.4, 4.4 Hz, 1H), 1.96–1.81 (m, 2H), 1.06 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 149.2, 142.7, 142.3, 129.8, 127.5, 123.6, 118.2, 115.3, 110.6, 108.8, 78.2, 38.6, 23.6, 9.3; MS (+ESI) m/z 314 (M+Na^+, 100), 316 (M+2+Na^+, 31). Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.76; H, 4.84; N, 4.80. Found: C, 61.86; H, 5.10; N, 5.05%.

4.3.19. 6-Chloro-3,4-dihydro-4-(2′-furylmethyl)-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5s). Prepared in 96% yield. *Compound* **5s**. A white crystalline solid; mp 46–47 °C (EtOAc–hexane); R_f=0.63 (11% EtOAc in hexane); IR (KBr) 2964, 1679, 1500, 1437, 1366, 1273, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J=2.0, 0.8 Hz, 1H), 7.18 (d, J=2.0 Hz, 1H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 6.89 (d, J=8.4 Hz, 1H), 6.32 (dd, J=3.2, 2.0 Hz, 1H), 6.31 (dd, J=3.2, 0.8 Hz, 1H), 5.07 and 4.98 (ABq, J=16.0 Hz, 2H), 4.56 (dd, J=8.8, 4.8 Hz, 1H), 1.86–1.78 (m, 2H), 1.58–1.49 (m, 2H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 149.2, 142.7, 142.3, 129.9, 127.5, 123.6, 118.2, 115.3, 110.6, 108.8, 76.9, 38.6, 32.1, 18.2, 13.6; MS (+ESI) m/z 328 (M+Na^+, 100), 331 (M+2+Na^+, 32). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 63.01; H, 5.64; N, 4.82%.

4.3.20. 4-Benzyl-6-chloro-3,4-dihydro-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5t). Prepared in 91% yield. *Compound* **5t**. A white crystalline solid; mp 70–73 °C (EtOAc–hexane); R_f=0.71 (20% EtOAc in hexane); IR (KBr) 2962, 1688, 1497, 1439, 1377, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 6.87 (s, 2H), 6.80 (s, 1H), 5.15 and 4.96 (ABq, J=16.4 Hz, 2H), 4.63 (dd, J=8.4, 5.6 Hz, 1H), 1.89–1.82 (m, 2H), 1.62–1.47 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 142.5, 135.5, 129.9, 128.9 (×2), 127.6, 127.4, 126.4 (×2), 123.6, 118.3, 115.4, 76.9, 45.1, 32.2, 18.2, 13.6; MS (+ESI) m/z 338 (M+Na^+, 100), 340 (M+2+Na^+, 31). HRMS (+ESI) calcd for $C_{18}H_{20}ClNO_2Na$ 338.0919 (M+Na^+), found 338.0920.

4.3.21. 6-Chloro-3,4-dihydro-4-(4′-methoxybenzyl)-3-oxo-2-propyl-2*H*-1,4-benzoxazine (5u). Prepared in 98% yield. *Compound* **5u**. A white crystalline solid; mp 74–75 °C (EtOAc–hexane); R_f=0.63 (20% EtOAc in hexane); IR (KBr) 2963, 1685, 1513, 1498, 1439, 1382, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J=8.8 Hz, 2H), 6.90–6.85 (m, 5H), 5.12 and 4.94 (ABq, J=16.0 Hz, 2H), 4.65 (dd, J=8.4, 5.2 Hz, 1H), 3.78 (s, 3H), 1.91–1.84 (m, 2H), 1.63–1.52 (m, 2H), 0.98 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 159.0, 142.6, 129.9, 127.9 (×2), 127.6, 127.3, 123.5, 118.2, 115.4, 114.3 (×2), 76.9, 55.2, 44.6, 32.2, 18.2, 13.6; MS (+ESI) m/z 368 (M+Na^+, 100), 370 (M+2+Na^+, 32). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.72; H, 6.01; N, 3.35.

4.3.22. 6-Chloro-3,4-dihydro-3-oxo-2-propyl-4-(3′-pyridinylmethyl)-2*H*-1,4-benzoxazine (5v). Prepared in 70% yield. *Compound* **5v**. A white crystalline solid; mp 80–81 °C (EtOAc–hexane); R_f=0.11 (20% EtOAc in hexane); IR (KBr) 2963, 1685, 1498, 1437, 1382, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.51 (d, J=4.8 Hz, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.25 (dd, J=8.0, 4.8 Hz, 1H), 6.93–6.88 (m, 2H), 6.78 (s, 1H), 5.17 and 5.01 (ABq, J=16.4 Hz, 2H), 4.63 (dd, J=8.0, 5.2 Hz, 1H), 1.88–1.82 (m, 2H), 1.58–1.49 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 149.1, 148.3, 142.6, 134.4, 131.3, 129.4, 127.5, 123.9, 123.8, 118.5, 114.9, 76.9, 42.8, 32.1, 18.2, 13.6; MS (+ESI) m/z 339 (M+Na^+, 100), 341 (M+2+Na^+, 31). Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; N, 8.84. Found: C, 64.51; H, 5.47; N, 8.83.

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Microwave-assisted regioselective olefinations of cyclic mono- and di-ketones with a stabilized phosphorus ylide

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Abstract—A number of cyclic mono- and di-ketones underwent regioselective olefination with (carbethoxyethylidene)triphenylphospharane under controlled microwave heating. The Wittig reaction of 4-substituted cyclohexanones or 1,2- and 1,4-cyclohexanediones with the ylide at 190 °C for 20 min in MeCN afforded the exocyclic olefins in >94:6 isomer ratios. On the other hand, the same reactions carried out at 230 °C for 20 min in the presence of 20 mol % DBU furnished the endocyclic olefins in >83:17 isomer ratios. The base-mediated isomerization of the exocyclic olefins into the endocyclic isomers was primarily driven by thermodynamic stability of the products and the effect of ring structures on deconjugation was examined.

1. Introduction

Cycloalkylideneacetic acids have been reported to exhibit anticonvulsant activity[1] and to act as novel effectors of Ras/Raf interaction.[2] In the area of chemical synthesis cycloalkylideneacetic acids and their endocyclic deconjugative analogs have been used as the precursors of bromomethylenecycloalkanes[3] and the substrates for vinylogous Wolff rearrangment.[4] Various cycloalkylideneacetates and (4-oxocyclohexylidene)acetate were used for total synthesis of several natural products.[5] The unsaturated esters of 4-*tert*-amylcyclohexanone were used for the synthesis of [4-*tert*-pentylcyclohexyl]acetaldehyde, which was described as strong lilial-like and bourgeonal-like for use in perfumery.[6] Similarly, the *exo*- and *endo*-unsaturated esters of bicyclo-[3.3.0]octane-3,7-diones have been used as the key intermediates in synthesis of prostacyclin analogs[7] and as the chiroptical trigger for a liquid-crystal-based optical switch.[8] The Wittig reaction[9] and the Horner–Wadsworth–Emmons (HWE) olefination are the most popular methods of choice for preparation of cycloalkylideneacetates from cyclic mono- and di-ketones. For the reactions of the stabilized phosphorus ylides such as (carbethoxyethylidene)triphenylphospharane (**2**), high temperatures are required. Microwave irradiation[10] has been introduced to improve the efficiency of olefination using stabilized phosphorus ylides and the substrates have been extended to aldehydes,[11] ketones,[12] lactones,[13] and amides.[13a] Formation of phosphonium salts under microwave heating was also reported.[14] However, all these early studies except for the work of Westman[11h] were carried out on domestic microwave ovens, which are lacking temperature controlling capability. In some cases, isomerization of olefin products was observed under solvent-free conditions or in dry media presumably due to uncontrolled high reaction temperature.[12a,d] In connection with our interest in performing the Wittig reaction in aqueous media[15] and the asymmetric versions based on chiral stabilized arsonium ylides,[16] we have established a set of reaction conditions for achieving regioselective Wittig reaction of 4-substituted cyclohexanones under controlled microwave heating.[17–19] We report here the full details of an expanded study covering a number of cyclic mono- and di-ketones and provide an example that illustrates efficient control over regiochemistry at high temperatures under microwave dielectric heating.

2. Results and discussion

Ethyl cycloalkylideneacetates have been prepared via HWE reaction using triethyl phosphonoacetate in excellent yields.[3–5b,6,20] An alternative route is based on the Wittig reaction of cycloalkanones with (carbethoxyethylidene)triphenylphospharane (**2**) (Scheme 1) at high temperatures[21] including use of microwave irradiation.[12d,17] Recently, olefination of cycloalkanones with ethyl diazoacetate was reported to proceed at 80 °C in the presence of benzoic acid and a catalytic iron(III) porphyrin complex Fe(TPP)Cl.[22] Stepwise approaches to ethyl cycloalkylideneacetates were

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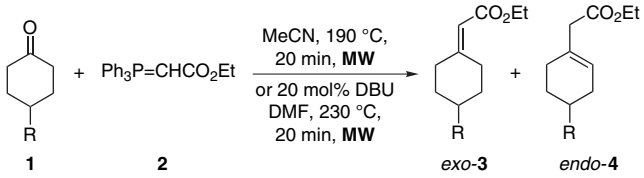
known and consist of formation of 1-[(ethoxycarbonyl)-methyl]cycloalkanols by addition of lithio ethyl acetate[23] or by the Reformatsky reaction[24] followed by acidic dehydration. However, mixtures of exocyclic (conjugated) and endocyclic (deconjugated) isomers were obtained in the stepwise synthesis and the isomer ratios were found to be ring size-dependent. The endocyclic isomers became much more favorable for the rings larger than seven primarily due to increased thermodynamic stability of the products.[24b] Deconjugation of ethyl cycloalkylideneacetates could be achieved by deprotonation and protonation operations[4,24c,25] or via photochemical process[26] to form ethyl cycloalken-1-ylacetates. The latter endocyclic olefines were also prepared selectively from the carbonation reactions of the allylic lithium reagents possessing two sp^2 carbons within the ring system.[27] In our preliminary studies,[12d,17] we found that the Wittig reactions of 4-substituted cyclohexanones **1** with the ylide **2** gave a mixture of the olefins *exo*-**3** and *endo*-**4** under microwave heating (Scheme 1). Isomerization of *exo*-**3** into *endo*-**4** was accelerated by high temperature, polar solvents, and base.[17] We established reaction conditions for regioselective formation of ethyl cyclohexylideneacetates *exo*-**3** and ethyl cyclohexen-1-ylacetates *endo*-**4**. The results are summarized in Table 1. Under controlled microwave heating at 190 °C for 20 min in MeCN, the conjugated olefins *exo*-**3a**–**h** were obtained in 33–66% yields and in 99:1 isomer ratios. Due to volatile nature of the products, the yields were not optimized. At reaction temperatures higher than 190 °C or using DMF and NMP as the solvent, deconjugation of *exo*-**3** was observed.[17] In order to promote in situ deconjugation, we carried out the Wittig reactions at 230 °C for 20 min in DMF in the presence of 20 mol % DBU, resulting in isolation of *endo*-**4a**–**h** as the major isomers in >84:16 ratios and in 52–82% combined yields (Table 1). Use of less amount of DBU or other bases such as 4-dimethylaminopyridine (DMAP) and 1,1,3,3-tetramethylguanidine (TMG) gave partial deconjugation. The esters *exo*-**3** and *endo*-**4** are not separable by column chromatography over silica gel and their ratios were estimated by ^{1}H NMR analyses.



Scheme 1. Microwave-assisted olefinations of 4-substituted cyclohexanones **1** with the stabilized phosphorus ylide **2**.

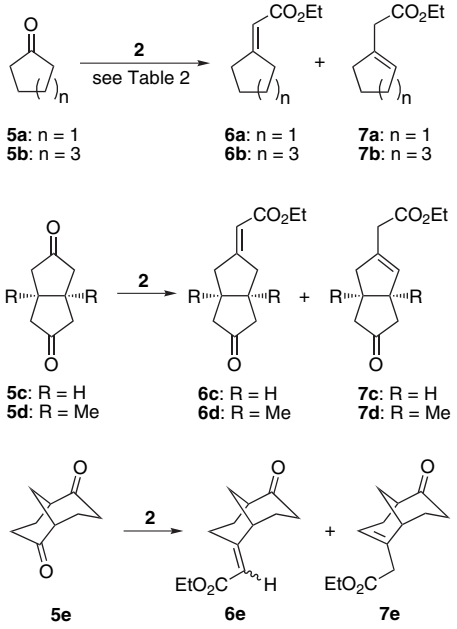
We then applied the reaction conditions for the olefinations of other cyclic mono- and di-ketones **5a**–**e** (Scheme 2 and Table 2). The reaction of cyclopentanone (**5a**) with **2** at 190 °C for 20 min gave similar result as that of cyclohexanone (**1a**), the exocyclic product **6a** was obtained in 60% yield and in 99:1 isomer ratio. But the endocyclic product **7a** was formed only in a very small amount at 230 °C for 20 min in the presence of DBU (Table 2, entry 1). On the other hand, the olefination of cycloheptanone (**5b**) afforded the products in significantly reduced yields under both reaction conditions. Although an excellent ratio of 99:1 was achieved for the reaction at 190 °C, a 57:43 mixture of **6b**:**7b** was formed for the reaction at 230 °C (Table 2, entry 2).

Table 1. Olefination of cyclohexanones **1** with **2** under controlled microwave heating[a]

Entry	**1**: R	190 °C, 20 min	230 °C, 20 min, 20 mol % DBU
		Yield (%);[b] **3**:**4**[c]	Yield (%);[b] **3**:**4**[c]
1	**a**: H	62; 99:1	78; 16:84
2	**b**: Me	60; 99:1	70; 14:86
3	**c**: *t*-Bu	61; 99:1	76; 13:87
4	**d**: Ph	66; 99:1	82; 13:87
5	**e**: Et	33; 99:1	59; 13:87
6	**f**: *n*-Pr	45; 99:1	63; 13:87
7	**g**: *i*-Pr	40; 99:1	52; 15:85
8	**h**: *t*-Amy	52; 99:1	74; 13:87

[a] Carried out with 3:1 ratio of **1** and **2** on a commercial technical microwave reactor. MeCN and DMF were used for reactions at 190 °C and 230 °C, respectively.
[b] Combined isolated yields of *exo*-**3** and *endo*-**4**.
[c] Determined by ^{1}H NMR.

This observation is quite different from the dehydration of 1-[(ethoxycarbonyl)methyl]cycloheptanol, which gave a 22.6:77.4 mixture of **6b**:**7b**.[24b] The diminished reactivity of the stabilized ylide **2** toward **5b** may be attributed to the cyclic transition state of the Wittig reaction.[9] The effect of ketone ring structures on the olefin product distribution was also observed in the reactions of bicyclic ketones **5c**–**e** (Scheme 2). The olefinations of *cis*-bicyclo[3.3.0]octane-3,7-dione (**5c**) and *cis*-1,5-dimethylbicyclo[3.3.0]octane-3,7-dione (**5d**) at both 190 °C and 230 °C provided good yields (Table 2, entries 3 and 4) but in a less regioselective manner. The isomer ratio of **6d**:**7d** could be improved to 94:6 by carrying out the reaction at 170 °C for 40 min at the expense of a reduced yield (Table 2, entry 5). The reaction of (±)-bicyclo[3.3.1]nonane-2,6-dione (**5e**), being a much more flexible bicyclic di-ketone, furnished the deconjugative olefin **7e** as the sole isomer at 230 °C in 77% yield (Table 2, entry 6). The olefination of **5e** with **2** at 190 °C for 20 min produced the exocyclic product **6e** as an inseparable 71:29 mixture of *E*- and *Z*-isomers, contaminating by ca. 5% of **7e**. The major isomer of **6e** was tentatively assigned as the *E* configuration.



Scheme 2. Microwave-assisted olefinations of ketones **5a**–**e**.

Table 2. Effect of ring structures on olefination[a]

Entry	Ketone	190 °C, 20 min	230 °C, 20 min, 20 mol % DBU
		Yield (%);[b] **6**:**7**[c]	Yield (%);[b] **6**:**7**[c]
1	**5a**: n=1	60; 99:1	72; 90:10
2	**5b**: n=3	27; 99:1	38; 57:43
3	**5c**: R=H	61; 88:12	78; 32:68
4	**5d**: R=Me	63; 88:12	78; 45:55
5	**5d**: R=Me	47; 94:6[d]	—
6	**5e**	64; 95:5[e]	70; 0:100

[a] Carried out with 3:1 ratio of the ketone and **2** on a commercial technical microwave reactor. MeCN and DMF were used for reactions at 190 °C and 230 °C, respectively.
[b] Combined isolated yields of *exo*- and *endo*-olefins.
[c] Determined by ^{1}H NMR.
[d] Carried out at 170 °C for 40 min.
[e] The *E*:*Z* ratio of **6e** is 71:29.

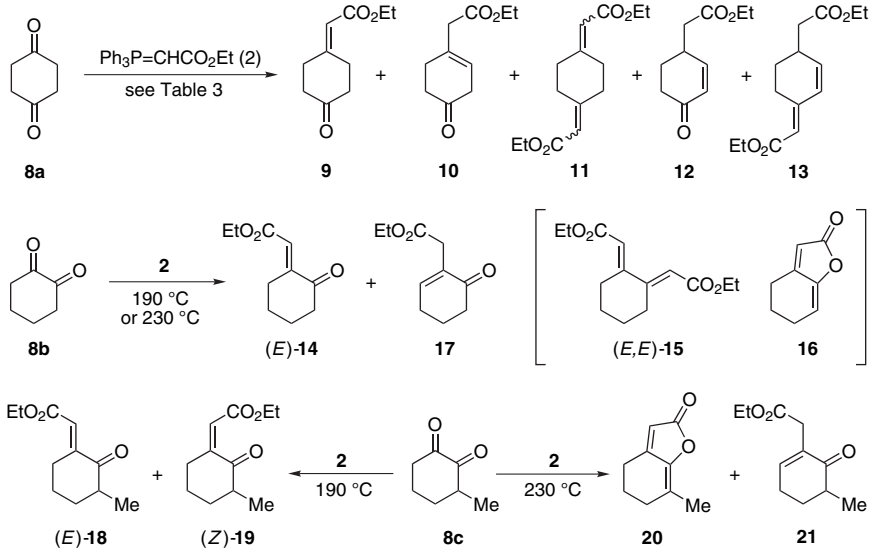
Table 3. Olefinations of 1,4- and 1,2-cyclohexanediones **8a–c**[a]

Entry	Ketone	190 °C, 20 min	230 °C, 20 min, 20 mol % DBU
		Yield (%);[b] ratio[c]	Yield (%);[b] ratio[c]
1	**8a**	**9**+**10**: 89; 94:6; **11**: 8 (*E*:*Z*=60:40)	**10**+**12**+**13**: 77; 9:83:8
2	**8b**	**14**: 44; uncharacterized byproducts[d]	**17**: 78; uncharacterized byproducts[d]
3	**8c**	(*E*)-**18**+(*Z*)-**19**: 63; 87:13	**20**+**21**: 73; 45:55

[a] Carried out with 3:1 ratio of the ketone and **2** on a commercial technical microwave reactor. MeCN and DMF were used for reactions at 190 °C and 230 °C, respectively.
[b] Combined isolated yields of *exo*- and *endo*-olefins.
[c] Determined by ^{1}H NMR.
[d] See text for details. Much more mass of the uncharacterized byproducts was formed at 190 °C than at 230 °C.

The Wittig reactions of 1,4-cyclohexanedione (**8a**) and 1,2-cyclohexanedione (**8b**) with the ylide **2** have been investigated by others[28a] with conventional thermal heating and a solvent effect on product distribution was observed. For the reaction of **8a** in DMF at refluxing for 7 h followed by stirring at room temperature for 1 day, the mono-olefination product **9**, and the bis-olefination products **11** were obtained in 83% yield and in a ratio of 91:5:4 for **9**:(*E*)-**11**:(*Z*)-**11** (see Scheme 3 for the structures).[28a] For the reaction of **8b** with **2** in DMF at refluxing for 6 h followed by stirring at room temperature for another 2 days, the exocyclic olefins (*E*)-**14** and (*Z*)-**14** and the rearranged enone **17** were isolated in 83% yield and in a 59:7:34 ratio for (*E*)-**14**:(*Z*)-**14**:**17**.[28a] Formation of **17** in EtOH was observed but to a very lower level of 4% of the total product mass.[28a] When the reaction of **8b** with **2** was carried out in refluxing PhH for 7 h, (*E*)-**14** was obtained in 76% yield as the sole product.[28b] Treatment of (*E*)-**14** with the sodium salt of triethyl phosphonoacetate in PhH at room temperature for 30 min afforded the bis-olefination product (*E*,*E*)-**15** and the (*E*,*Z*)-**15** in 41% and 11% yields, respectively (see Scheme 3 for the structures).[28b] The compounds **10**, **12**, (*E*)-**14**, and **17** have been prepared by non-Wittig type olefination procedures as well.[29] We investigated the microwave-assisted olefination of 1,4-cyclohexanedione (**8a**), 1,2-cyclohexanedione (**8b**), and 3-methyl-1,2-cyclohexanedione (**8c**) with the ylide **2** as shown in Scheme 3 and Table 3. The reaction of **8a** with **2** at 190 °C afforded the mono-olefination product **9**[5c–f] in 89% yield as a 94:6 inseparable mixture with **10**[29b] together with about 8% of the bis-olefination product **11**[30] in a ca. 60:40 ratio of *E*- and *Z*-isomers.[28a,30] The conjugated enone **12**[29a,b] was not detected in the reaction at 190 °C but it could be obtained as the major component by heating **8a** with **2** at 230 °C for 20 min in DMF in the presence of 20 mol % DBU (Table 3, entry 1). The enone **12** was isolated in 77% yield as an inseparable mixture[29b] with **10** and **13** and the ratio of **10**:**12**:**13** was estimated to be 9:83:8 by ^{1}H NMR analysis. The byproduct **13** seems not being reported in literature and the exocyclic double bond configuration is tentatively assigned. It could be formed by either isomerization of **11** or via a second Wittig reaction of **12**. On one occasion, we obtained pure **12** in 56% yield. It seems that a slight variation in reaction conditions resulted in different product distribution.

The ^{1}H NMR spectrum of **9** recorded on a 500 MHz instrument in $CDCl_3$ features a singlet peak at 5.85 ppm for the



Scheme 3. Microwave-assisted olefinations of di-ketones **8a–c** with the ylide **2**.

vinyl proton, which is consistent with the reported value of 5.82 ppm (t, J=1.4 Hz measured on a 200 MHz instrument in $CDCl_3$).[5d] The minor product **10** gives characteristic signals at 3.10 (s, 2H) and 5.64 (br s, 1H) ppm, the latter is consistent with the known value of 5.60 (m)[29b] for the vinyl proton. The *E*- and *Z*-isomers of **11** show the vinyl protons at 5.70 (s, major) and 5.78 (s, minor) ppm, which are in accord with the reported chemical shifts of 5.64 (s, *E*-) and 5.80 (s, *Z*-) ppm.[30a] The vinyl protons of the conjugated enone **12** are found at 6.84 (d, J=10.4 Hz) and 5.99 (dd, J=10.4, 2.0 Hz) ppm and agree well with the reported values of 6.82 (ddd, J=10, 3, 1 Hz) and 5.95 (dd, J=10, 2 Hz) ppm.[29b] The structure of **13** was tentatively assigned on the basis of the characteristic signals at 7.11 (d, J=8.4 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.25 (br s, 1H), and 3.50 (s, 2H) ppm. The significant downfield shifts of these signals are indicative of the extended conjugation system.

The Wittig reactions of 1,2-cyclohexanedione (**8b**) with the ylide **2** were complicated by the formation of byproducts (Scheme 3). The reaction carried out at 190 °C gave the exocyclic olefin (*E*)-**14**[28] isomer in a pure form in 44% isolated yield. The majority of the remaining mass was an inseparable mixture of more than two components and the structures could not be fully characterized (Table 3, entry 2). The compounds (*E*,*E*)-**15**,[28b] (*E*,*Z*)-**15**[28b] and **16**[31] are known in literature. Chemical shifts of 5.87 (s) and 5.67 (m) ppm recorded on a 60 MHz instrument were reported for the vinyl protons of (*E*,*E*)-**15**[28b] and (*E*,*Z*)-**15**,[28b] respectively. For our mixture mentioned above, a vinyl proton appears at 6.16 (t, J=4.8 Hz on a 400 MHz instrument) ppm and its splitting pattern is similar to that of the vinyl proton of (*E*)-**14**, being a triplet (J=2 or 2.3 Hz) at 6.42 or 6.43 ppm in two independent reports[28a,b,32] and at 6.47 (t, J=2.2 Hz) ppm obtained in our study. Therefore, we are not sure whether (*E*,*E*)-**15** was formed in the reaction of **8b** with **2**. Also, the butenolide **16**, having chemical shifts of 1.57–2.92 (m, 6H) and 5.66–6.01 (m, 2H) ppm, was prepared from an intramolecular Wittig reaction of an adduct formed from **8b** and $Ph_3P{=}C{=}C(OEt)_2$ followed by acidic hydrolysis.[31] We only observed a singlet peak at 5.69 ppm (possibly for the vinyl proton of the butenolide ring) in the above mixture but the other enolic vinyl proton was not found. At this stage, no conclusion can be made about the formation of **16** although a similar analog **20** was formed in the reaction of **8c** with **2** (vide infra).

When the reaction of **8b** with **2** was carried out at 230 °C, the amount of the byproducts was significantly reduced to afford the endocyclic enone **17**[29b,c] in 78% isolated yield. The typical proton signals for **17** are found at 6.85 (t, J=4.0 Hz, 1H) and 3.17 (s, 2H) ppm, being consistent with the reported values of 6.83 (t, J=4.0) and 3.16 (d, J=0.5 Hz, 2H),[28a] 6.85 (t, J=4.0) and 3.28 (br s, 2H),[29b] or 6.86 (t, J=3.8 Hz) and 3.20 (s, 2H)[29c] ppm in three independent reports. Therefore, our microwave-assisted Wittig reactions of **8b** with **2** furnished only the exocyclic (at 190 °C in MeCN) and endocyclic (at 230 °C in DMF with DBU) olefins, respectively, being different from the reaction carried out in refluxing DMF with conventional thermal heating.[28a] Our reactions completed within 20 min but were accompanied by the formation of byproducts due to high reaction temperatures.

Finally, we carried out the Wittig reactions of 3-methyl-1,2-cyclohexanedione (**8c**) with the ylide **2** in order to examine the influence of the methyl group on reactivity and regiochemistry. Under controlled microwave heating at 190 °C for 20 min, the reaction gave only the exocyclic olefins (*E*)-**18** and (*Z*)-**19** in 63% isolated yield as an 87:13 ratio of inseparable mixture. The vinyl protons having chemical shift at 6.33 (t, J=1.2 Hz) and 6.26 (s) ppm are assigned for (*E*)-**18** and (*Z*)-**19**, respectively. This is in accord with the upfield chemical shift of 5.63 ppm reported for (*Z*)-**14**.[28a,32] When the olefination of **8c** was performed at 230 °C, the butenolide **20** was formed together with the expected endocyclic enone **21** (Table 3, entry 3). Compounds **20** and **21** were isolated in 73% yield as an inseparable mixture of 45:55 ratio. Compound **20** features a vinyl proton at 5.65 (s) ppm while the enone **21** has the vinyl proton appearing at 6.77 (t, J=4.4 Hz) and the CH_2CO_2 protons at 3.15 (ABq, J=15.4 Hz, 2H) ppm.

3. Conclusion

In summary, we have investigated the Wittig reactions of a number of cyclic mono- and di-ketones under controlled microwave heating. By selecting suitable reaction temperature, solvent, and base, we are able to demonstrate high regioselective olefinations of 4-substituted cyclohexanones (**1a–h**) and the bicyclic di-ketone **5e** to selectively form either the exocyclic olefins (MeCN, 190 °C, 20 min) or the deconjugated olefins (DMF, DBU, 230 °C, 20 min). We found that the ring structures have a major effect on isomerization of the initially formed olefins and poor results in deconjugation were observed for the substrates **5a–d**. Reactions of the cyclohexanediones **8a–c** were somewhat complicated due to the formation of inseparable byproducts, but good regioselectivity was obtained for the products **9**, **12**, (*E*)-**14**, **17**, (*E*)-**18**, and (*Z*)-**19**. These results clearly demonstrate the importance of temperature regulation in microwave-assisted organic synthesis. Therefore, use of controlled microwave heating is the direction of future advancement in this rapidly growing area of chemical synthesis.

4. Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (500, 400, or 300 MHz for ^1H and 75 MHz for ^{13}C) with $CHCl_3$ as the internal reference. IR spectra were taken on an FTIR spectrophotometer. Mass spectra (MS) were measured by the +CI or ESI method. All reactions were carried out on an Emrys creator from Personal Chemistry AB (now under Biotage AB, Uppsala, Sweden) with temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature. The reaction mixture was checked by thin-layer chromatography on silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Flash column chromatography over silica gel was used for purification. Yields refer to chromatographically and

spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received.

4.1. Representative procedure for Wittig reactions of 2 with cyclic mono- and di-ketones under controlled microwave heating at 190 °C in MeCN

4.1.1. Ethyl (4-phenylcyclohexylidene)acetate [(*exo*)-3d].[22] A 10 mL pressurized process vial containing a magnetic stirring bar was charged with 4-phenylcyclohexanone (214.5 mg, 1.23 mmol), (carbethoxymethylene)triphenylphosphorane (**2**, 142.6 mg, 0.41 mmol) and MeCN (3 mL) and then the vial was sealed with a cap containing a silicon septum. The loaded vial was placed into the cavity of the microwave reactor and heated at 190 °C for 20 min. The reaction mixture was diluted with diethyl ether and washed with aqueous NH_4Cl. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. (Caution: it is essential to control the pressure carefully to avoid removal of the volatile products.) The residue was purified by flash column chromatography (5% EtOAc–hexane) to give *exo*-**3d** (66 mg, 66%) as a 99:1 inseparable mixture with *endo*-**4d** (Table 1, entry 4). The ratio of regioisomers was determined by ^{1}H NMR. Other results are listed in Tables 1–3. *Compound exo*-**3d**: IR (film) 2931, 1713, 1651, 1144, 1178 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.18 (m, 5H), 5.71 (s, 1H), 4.18 (q, J=7.1 Hz, 2H), 4.02–3.97 (m, 1H), 2.81–2.78 (m, 1H), 2.41–2.35 (m, 2H), 2.11–2.06 (m, 3H), 1.69–1.62 (m, 2H), 1.31 (t, J=7.1 Hz, 3H); MS (ESI) m/z 245 (M+H$^+$).

4.1.2. Ethyl cyclohexylideneacetate [(*exo*)-3a].[3,22,24b] *Compound exo*-**3a**: IR (film) 2928, 1722, 1648, 1266 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.15 (q, J=7.1 Hz, 2H), 2.85–2.81 (m, 2H), 2.35–2.17 (m, 8H), 1.28 (t, J=7.1 Hz, 3H); MS (+CI) m/z 167 (M−H$^+$).

4.1.3. Ethyl (4-methylcyclohexylidene)acetate [(*exo*)-3b].[21b,22] *Compound exo*-**3b**: IR (film) 2926, 1714, 1651, 1191, 1153 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.75–3.70 (m, 1H), 2.24–2.16 (m, 2H), 1.94–1.81 (m, 3H), 1.75–1.53 (m, 1H), 1.27 (t, J=7.1 Hz, 3H), 1.14–1.05 (m, 2H), 0.91 (d, J=6.5 Hz, 3H); MS (+CI) m/z 167 (M−Me$^+$).

4.1.4. Ethyl (4-*tert*-butylcyclohexylidene)acetate [(*exo*)-3c].[20e,22,24b] *Compound exo*-**3c**: IR (film) 2959, 1716, 1652, 1185 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.95–3.82 (m, 1H), 2.28–1.98 (m, 8H), 1.27 (t, J=7.1 Hz, 3H), 0.87 (s, 9H); MS (+CI) m/z 225 (M+H$^+$).

4.1.5. Ethyl (4-ethylcyclohexylidene)acetate [(*exo*)-3e].[21b] *Compound exo*-**3e**: IR (film) 2931, 1719, 1654, 1186 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.77–3.71 (m, 1H), 2.30–2.10 (m, 2H), 2.03–1.84 (m, 3H), 1.50–1.35 (m, 1H), 1.30–1.20 (m, 5H), 1.17–0.95 (m, 2H), 0.88 (d, J=7.4 Hz, 3H); MS (+CI) m/z 197 (M+H$^+$).

4.1.6. Ethyl (4-propylcyclohexylidene)acetate [(*exo*)-3f]. *Compound exo*-**3f**: IR (film) 2928, 1713, 1649, 1185, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.80–3.68 (m, 1H), 2.32–2.10 (m, 2H), 2.00–1.82 (m, 3H), 1.58–1.42 (m, 1H), 1.38–0.95 (m, 9H), 0.88 (d, J=7.1 Hz, 3H); MS (+CI) m/z 211 (M+H$^+$).

4.1.7. Ethyl (4-*iso*-propylcyclohexylidene)acetate [(*exo*)-3g]. *Compound exo*-**3g**: IR (film) 2958, 1717, 1649, 1189, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (s, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.86–3.75 (m, 1H), 2.37–2.10 (m, 2H), 1.96–1.82 (m, 3H), 1.55–1.42 (m, 1H), 1.38–1.05 (m, 6H), 0.86 (d, J=6.8 Hz, 6H); MS (+CI) m/z 209 (M−H$^+$).

4.1.8. Ethyl (4-*tert*-amylcyclohexylidene)acetate [(*exo*)-3h].[6] *Compound exo*-**3h**: IR (film) 2963, 1716, 1651, 1181, 1144 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.16 (q, J=7.1 Hz, 2H), 3.95–3.86 (m, 1H), 2.38–1.80 (m, 8H), 1.38–1.10 (m, 5H), 0.83 (t, J=7.5 Hz, 3H), 0.81 (s, 6H); MS (+CI) m/z 239 (M+H$^+$).

4.1.9. Ethyl cyclopentylideneacetate (6a).[3,22,24b] *Compound* **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (br s, 1H), 4.14 (q, J=7.2 Hz, 2H), 2.76 (t, J=7.0 Hz, 2H), 2.43 (t, J=7.0 Hz, 2H), 1.77–1.62 (m, 4H), 1.27 (t, J=7.2 Hz, 3H).

4.1.10. Ethyl cycloheptylideneacetate (6b).[3,22,24b] *Compound* **6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (t, J=1.2 Hz, 1H), 4.14 (q, J=7.2 Hz, 2H), 2.86 (td, J=6.2, 1.4 Hz, 2H), 2.39 (t, J=6.0 Hz, 2H), 1.73–1.47 (m, 8H), 1.27 (t, J=7.2 Hz, 3H).

4.1.11. 7-[(Ethoxycarbonyl)methylene]-*cis*-bicyclo-[3.3.0]octan-3-one (6c).[8] *Compound* **6c**: IR (film) 2939, 1741, 1709, 1654, 1207, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78–5.76 (m, 1H), 4.08 (q, J=7.2 Hz, 2H), 3.20–3.05 (m, 1H), 2.80–2.60 (m, 4H), 2.45–2.30 (m, 3H), 2.08–1.90 (m, 2H), 1.21 (t, J=7.2 Hz, 3H); MS (+CI) m/z 209 (M+H$^+$).

4.1.12. 7-[(Ethoxycarbonyl)methylene]-*cis*-1,5-dimethylbicyclo[3.3.0]octan-3-one (6d).[8] *Compound* **6d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81–5.78 (m, 1H), 4.13 (q, J=7.2 Hz, 2H), 2.97 and 2.90 (ABq, J=21.4 Hz, 2H), 2.57 (s, 2H), 2.35–2.15 (m, 4H), 1.26 (t, J=7.2 Hz, 3H), 1.09 (s, 3H), 1.07 (s, 3H); MS (ESI) m/z 259 (M+Na$^+$).

4.1.13. (±)-6-[(Ethoxycarbonyl)methylene]bicyclo-[3.3.1]nonan-2-one (6e). *Compound* **6e**: For (*E*)-isomer (major): IR (film) 2933, 1710 (br), 1641, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, J=1.6 Hz, 1H), 4.15 (q, J=7.2 Hz, 2H), 3.81 (dd, J=16.6, 5.8 Hz, 1H), 2.75–1.60 (m, 11H), 1.26 (t, J=7.2 Hz, 3H); MS (+CI) m/z 223 (M+H$^+$). For (*Z*)-isomer (minor): ^{1}H NMR (400 MHz, $CDCl_3$) δ 568 (br s, 1H), 4.30 (br s, 1H).

4.1.14. Ethyl (4-oxocyclohexylidene)acetate (9).[5c–f,28a] *Compound* **9**: IR (KBr) 2963, 1709 (br), 1646, 1167 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (s, 1H), 4.17 (q, J=7.0 Hz, 2H), 3.21 (t, J=6.5 Hz, 2H), 2.67 (t, J=6.5 Hz, 2H), 2.52–2.40 (m, 4H), 1.29 (t, J=7.0 Hz, 3H); MS (+CI) m/z 183 (M+H$^+$).

4.1.15. Ethyl (2-oxocyclohexylidene)acetate [(*E*)-14].[28a,b,29c,32] *Compound* **14**: IR (film) 2940, 1719 (br), 1697, 1187 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 4.21 (q, J=7.0 Hz, 2H), 3.11–3.07 (m, 2H), 2.53

(t, J=6.6 Hz, 2H), 1.94–1.90 (m, 2H), 1.83–1.78 (m, 2H), 1.30 (t, J=7.0 Hz, 3H); MS (+CI) m/z 183 ($M+H^+$).

4.1.16. Ethyl (3-methyl-2-oxocyclohexylidene)acetate [(*E*)-18]. *Compound* (*E*)-**18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34–6.32 (m, 1H), 4.17 (q, J=7.2 Hz, 2H), 3.70–3.57 (m, 1H), 2.70–2.32 (m, 2H), 2.20–2.02 (m, 1H), 2.00–1.80 (m, 1H), 1.77–1.50 (m, 2H), 1.27 (t, J=7.2 Hz, 3H), 1.13 (d, J=6.4 Hz, 3H); MS (ESI) m/z 219 ($M+Na^+$).

4.2. Representative procedure for Wittig reactions of 2 with cyclic mono- and di-ketones under controlled microwave heating at 230 °C in DMF in the presence of 20 mol % DBU

4.2.1. Ethyl (4-phenylcyclohexen-1-yl)acetate [(*endo*)-4d]. A 10 mL pressurized process vial containing a magnetic stirring bar was charged with 4-phenylcyclohexanone (214.5 mg, 1.23 mmol), (carbethoxymethylene)triphenylphosphorane (**2**, 142.6 mg, 0.41 mmol), DBU (13 μL), and DMF (3 mL) and then the vial was sealed with a cap containing a silicon septum. The loaded vial was placed into the cavity of the microwave reactor and heated at 230 °C for 20 min. The reaction mixture was diluted with diethyl ether and washed with aqueous NH_4Cl. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. (Caution: control the pressure carefully to avoid removal of the volatile products.) The residue was purified by flash column chromatography (5% EtOAc–hexane) to give *endo*-**4d** (82 mg, 82%) as an 87:13 inseparable mixture with *exo*-**3d** (Table 1, entry 4). The ratio of regioisomers was determined by ^{1}H NMR. Other results are listed in Tables 1–3. *Compound endo*-**4d**: IR (film) 2918, 1738, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H), 5.72–5.67 (m, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.04 (s, 2H), 2.89–2.74 (m, 1H), 2.45–1.80 (m, 6H), 1.32 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 147.4, 131.7, 129.0 (×2), 127.5 (×2), 126.6, 125.9, 61.3, 44.0, 40.4, 34.3, 30.6, 29.8, 15.1; MS (+CI) m/z 245 ($M+H^+$).

4.2.2. Ethyl cyclohexen-1-ylacetate [(*endo*)-4a].[4,24c,27] *Compound endo*-**4a**: IR (film) 2933, 1728, 1275, 1121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (br s, 1H), 4.14 (q, J=7.1 Hz, 2H), 2.94 (s, 2H), 2.11–1.95 (m, 4H), 1.75–1.53 (m, 4H), 1.27 (t, J=7.1 Hz, 3H); MS (+CI) m/z 167 ($M-H^+$).

4.2.3. Ethyl (4-methylcyclohexen-1-yl)acetate [(*endo*)-4b]. *Compound endo*-**4b**: IR (film) 2928, 1728, 1274, 1121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (br s, 1H), 4.13 (q, J=7.1 Hz, 2H), 2.95 (s, 2H), 2.38–1.56 (m, 7H), 1.26 (t, J=7.1 Hz, 3H), 0.95 (d, J=5.9 Hz, 3H); MS (+CI) m/z 183 ($M+H^+$).

4.2.4. Ethyl (4-*tert*-butylcyclohexen-1-yl)acetate [(*endo*)-4c].[4,27] *Compound endo*-**4c**: IR (film) 2961, 1736, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (br s, 1H), 4.14 (q, J=7.1 Hz, 2H), 2.95 (s, 2H), 2.32–1.75 (m, 7H), 1.27 (t, J=7.1 Hz, 3H), 0.86 (s, 9H); MS (+CI) m/z 225 ($M+H^+$).

4.2.5. Ethyl (4-ethylcyclohexen-1-yl)acetate [(*endo*)-4e]. *Compound endo*-**4e**: IR (film) 2962, 2932, 1732, 1187 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (br s, 1H), 4.12 (q, J=7.1 Hz, 2H), 2.93 (s, 2H), 2.22–1.25 (m, 11H), 0.88 (t, J=7.3 Hz, 3H); MS (+CI) m/z 195 ($M-H^+$).

4.2.6. Ethyl (4-propylcyclohexen-1-yl)acetate [(*endo*)-4f]. *Compound endo*-**4f**: IR (film) 2925, 1738, 1181, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (br s, 1H), 4.12 (q, J=7.1 Hz, 2H), 2.93 (s, 2H), 2.20–1.14 (m, 13H), 0.88 (t, J=6.9 Hz, 3H); MS (+CI) m/z 211 ($M+H^+$).

4.2.7. Ethyl (4-*iso*-propylcyclohexen-1-yl)acetate [(*endo*)-4g]. *Compound endo*-**4g**: IR (film) 2926, 1729, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (br s, 1H), 4.13 (q, J=7.1 Hz, 2H), 2.94 (s, 2H), 2.40–1.40 (m, 8H), 1.27 (t, J=7.1 Hz, 3H), 0.91 (d, J=7.4 Hz, 3H), 0.87 (d, J=7.3 Hz, 3H); MS (+CI) m/z 211 ($M+H^+$).

4.2.8. Ethyl (4-amylcyclohexen-1-yl)acetate [(*endo*)-4h]. *Compound endo*-**4h**: IR (film) 2964, 1736, 1162 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60–5.56 (m, 1H), 4.14 (q, J=7.1 Hz, 2H), 2.96 (s, 2H), 2.47–1.70 (m, 7H), 1.45–1.14 (m, 5H), 0.87–0.75 (m, 9H); MS (+CI) m/z 239 ($M+H^+$).

4.2.9. Ethyl cyclohepten-1-ylacetate (7b).[24c,27] As a 57:43 inseparable mixture of **6b**:**7b**. *Compound* **7b**: Partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (t, J=6.5 Hz, 1H), 2.97 (s, 2H).

4.2.10. 3-Ethoxycarbonylmethyl-*cis*-bicyclo[3.3.0]oct-2-en-7-one (7c). As a 32:68 inseparable mixture of **6c**:**7c**. *Compound* **7c**: IR 2933, 1739, 1206, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (br s, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.45–3.33 (m, 1H), 3.08 (s, 2H), 3.05–1.85 (m, 7H), 1.23 (t, J=7.2 Hz, 3H); MS (+CI) m/z 209 ($M+H^+$).

4.2.11. 3-Ethoxycarbonylmethyl-*cis*-1,5-dimethyl-bicyclo[3.3.0]oct-2-en-7-one (7d). As a 45:55 inseparable mixture of **6d**:**7d**. *Compound* **7d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (br s, 1H), 4.14 (q, J=7.2 Hz, 2H), 3.11 and 3.04 (ABq, J=16.2 Hz, 2H), 2.50–2.15 (m, 6H), 1.26 (t, J=7.2 Hz, 3H), 1.13 (s, 3H), 1.08 (s, 3H); MS (+CI) m/z 237 ($M+H^+$).

4.2.12. (±)-3-[(Ethoxycarbonyl)methyl]bicyclo[3.3.1]-nonan-2-en-6-one (7e). *Compound* **7e**: IR (film) 2931, 1731, 1709, 1158 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (br s, 1H), 4.14 (q, J=7.0 Hz, 2H), 3.08 and 3.01 (ABq, J=15.0 Hz, 2H), 2.69 (br s, 1H), 2.49–2.34 (m, 3H), 2.27 (dd, J=15.5, 5.0 Hz, 1H), 2.03–1.81 (m, 5H), 1.26 (t, J=7.0 Hz, 3H); MS (+CI) m/z 223 ($M+H^+$).

4.2.13. Ethyl (4-oxo-cyclohexen-2-yl)acetate (12).[29a,b] *Compound* **12**: IR (film) 2981, 1732, 1680, 1182, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, J=10.4 Hz, 1H), 5.99 (dd, J=10.4, 2.0 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 3.00–2.80 (m, 1H), 2.55–2.32 (m, 4H), 2.24–2.15 (m, 1H), 1.80–1.67 (m, 1H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 172.2, 153.5, 130.3, 61.5, 39.6, 37.4, 33.6, 29.4, 14.9; MS (+CI) m/z 183 ($M+H^+$).

4.2.14. Ethyl (6-oxo-cyclohexen-1-yl)acetate (17).[28a,29b,c] *Compound* **17**: IR (film) 2937, 1737, 1675, 1179 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (t, J=4.0 Hz, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.17 (s, 2H), 2.47–2.36 (m, 4H), 2.04–1.99 (m, 2H), 1.23 (t, J=7.2 Hz, 3H); MS (+CI) m/z 183 ($M+H^+$).

4.2.15. 5,6-Dihydro-7-methylbenzofuran-2(4*H*)-one (20). As a 45:55 inseparable mixture of **20**:**21**. *Compound* **20**: IR (film) 1770, 1189 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (s, 1H), 2.62 (t, J=6.4 Hz, 2H), 2.44–1.60 (m, 4H), 1.93 (s, 3H); MS (+CI) m/z 151 ($M+H^+$).

4.2.16. Ethyl (5-methyl-6-oxo-cyclohexen-1-yl)acetate (21). As a 45:55 inseparable mixture of **20**:**21**. *Compound* **21**: IR (film) 2931, 1739, 1675, 1179 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (t, J=4.4 Hz, 1H), 4.09 (q, J=7.6 Hz, 2H), 3.19 and 3.11 (ABq, J=15.4 Hz, 2H), 2.44–1.60 (m, 5H), 1.21 (t, J=7.6 Hz, 3H), 1.11 (d, J=6.8 Hz, 3H); MS (+CI) m/z 197 ($M+H^+$).

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Microwave-assisted solution phase synthesis of dihydropyrimidine C5 amides and esters

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Abstract—Multifunctionalized dihydropyrimidine-5-carboxylic amides and esters are generated in a multistep sequence integrating a variety of enabling and high throughput technologies such as automated or parallel microwave synthesis, the use of polymer-supported reagents, fluorous synthesis and purification strategies, and a continuous flow hydrogenation system. The key dihydropyrimidine-5-carboxylic acid intermediates are obtained in two steps by Biginelli multicomponent condensation of benzyl or allyl β-ketoesters with aldehydes and urea/thioureas, followed by suitable benzyl or allyl deprotection strategies. Further functionalization of the acid cores with amines using polymer-supported coupling reagents or with alcohols utilizing Mitsunobu chemistry provides the desired amides or esters, respectively.

1. Introduction

Modern drug discovery steadily relies on high speed organic synthesis and combinatorial chemistry techniques for the rapid generation of compound libraries. Microwave-assisted organic synthesis[1,2] and combinatorial chemistry together with high throughput screening (HTS) methods are being instrumental for the rapid synthesis, screening, and identification of compounds with new and improved biological activities.[3]

Over the years, research interest in multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs), viz. the Biginelli scaffold, has surged rapidly, owing to the pharmacological properties associated with many derivatives of this privileged heterocyclic core.[4–7] Reports describe several DHPMs that have been identified, for example, calcium channel modulators,[5] or small molecules targeting the mitotic machinery.[6] Notably, 4-aryldihydropyrimidinone heterocycles attached to an aminopropyl-4-piperidine moiety via a C5 amide linkage (see Chart 1) have proven to be excellent templates for selective α_{1a} receptor subtype antagonists to warrant further consideration for the treatment of Benign Prostatic Hyperplasia (BPH).[7] In the synthesis of these DHPM-5-carboxamides, amide bond formation between the requisite amines and the corresponding DHPM acids was performed using standard solution phase amide coupling chemistry involving carbodiimide coupling reagents.[7,8]

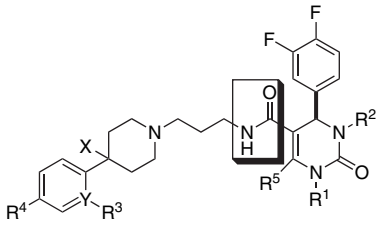

Chart 1.

This approach of introducing structural diversity appealed to our ongoing interest in the microwave-induced high speed synthesis[9] and decoration[10] of the Biginelli scaffold. In the present work we describe a rapid microwave-induced polymer-assisted solution phase synthesis (PASP) and high throughput purification of diverse DHPM C5 amides starting from a corresponding set of structurally diverse DHPM C5 acid cores and selected amines (see Scheme 1). With a high diversity of commercially available amines but limited availability of β-ketoamides, the synthesis of amides via the acid precursors has been chosen. In addition, the acid cores generated would also serve as excellent precursors for other interesting chemistries.

To introduce more diversity at the C5 position, we also synthesized a set of DHPM C5 esters **7** starting from the acids using Mitsunobu chemistry (Scheme 1). Via this protocol more diverse and novel ester-functionalities could be established by using the corresponding alcohols. Besides the standard Mitsunobu conditions, a fluorous Mitsunobu protocol was employed to facilitate the product isolation and purification.

Keywords: Microwave synthesis; Continuous flow techniques; Pyrimidines; Amide couplings; Fluorous synthesis; Mitsunobu reaction.
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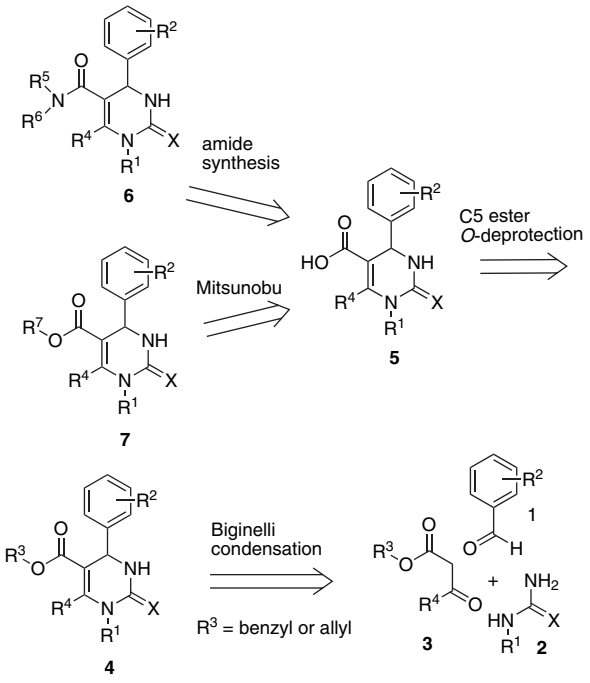


Scheme 1. Retrosynthetic strategy toward DHPM amide and ester libraries.

A microwave-induced combinatorial set and a parallel scale-up synthesis of structurally diverse DHPM C5 benzyl and allyl ester form the starting point in the synthesis of the DHPM C5 acid cores (Scheme 1).

2. Results and discussion

2.1. Microwave-assisted synthesis of DHPM esters 4

The Lewis acid-catalyzed multicomponent cyclocondensation of an aldehyde **1**, urea **2**, and a β-ketoester **3** (Biginelli condensation) constitutes the most elegant synthesis of multifunctionalized 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) of type **4** and has been extensively reported in the literature.[11,12] By far, library generation through automated sequential microwave-assisted Biginelli multicomponent condensation is most attractive in combining speed, diversity, and efficiency.[9] Improvements in the classical Biginelli multicomponent protocol have favored the more tolerant Lewis acids over a mineral acid viz. conc. HCl as the catalyst for yield improvements.[13] The use of solvents such as ethanol, acetic acid, THF, dioxane, acetonitrile, environmentally benign ionic liquids or solvent-free protocols has also been reported.[12]

As a starting point in our study, we have generated a small set (11 examples) of 4-aryl-DHPM C5 benzyl (Bn) and allyl (All) esters **4** using six different aldehydes **1A–F**, three urea/thiourea **2a–c**, and three CH-acidic carbonyl **3α–γ** building blocks (Figs. 1 and 2). This set of esters were synthesized in order to conveniently prepare DHPM acids **5**. In the synthesis of DHPM benzyl/allyl esters **4**, $Yb(OTf)_3$ as the Lewis acid catalyst and acetonitrile as the reaction solvent were chosen based on previous optimization studies on a larger and more diverse set of microwave-induced Biginelli multicomponent cyclocondensations.[9,10] Synthesis of both the DHPM C5 benzyl and allyl esters was performed to allow for a subsequent C5 O-deprotection using classical debenzylation and deallylation strategies (see below). The microwave-assisted sequential synthesis of DHPM esters **4** (4 mmol scale) utilized an excess (6 mmol) of the CH-acidic carbonyl building blocks **3**, which has led to improved yields in other Biginelli condensations.[12] In our case, the cyclocondensation has also been translated to 40 mmol scale using microwave-assisted parallel synthesis under nearly identical reaction conditions. For this scale-up synthesis (40 mmol) in a multimode cavity, the reaction mixtures were irradiated in parallel at preset conditions to afford the structurally diverse set of DHPM benzyl/allyl esters **4**.[14] The small scale (4 mmol) synthesis of the 4-aryl-DHPM C5 benzyl/allyl esters **4** involved sequential heating (120 °C for 20 min) of the corresponding reaction mixtures in a single-mode microwave reactor. The isolated yields obtained from each of the microwave (MW) heating runs are described in Table 1.

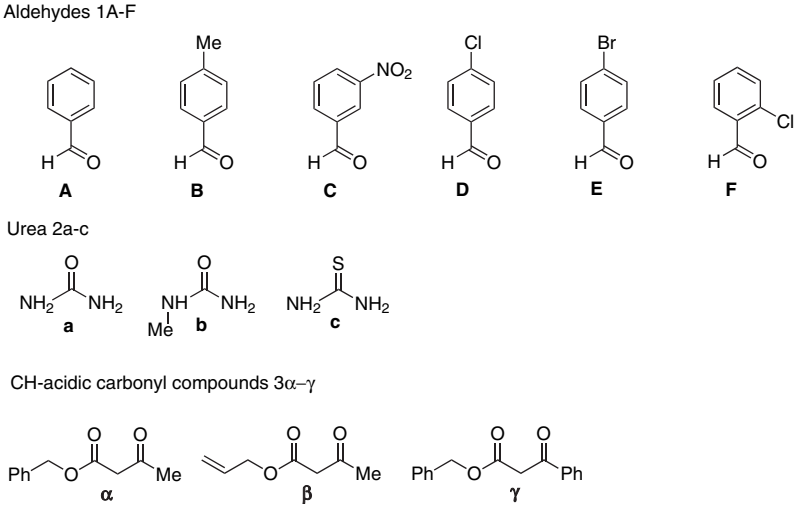


Figure 1. Aldehyde, urea, and β-ketoester building blocks.

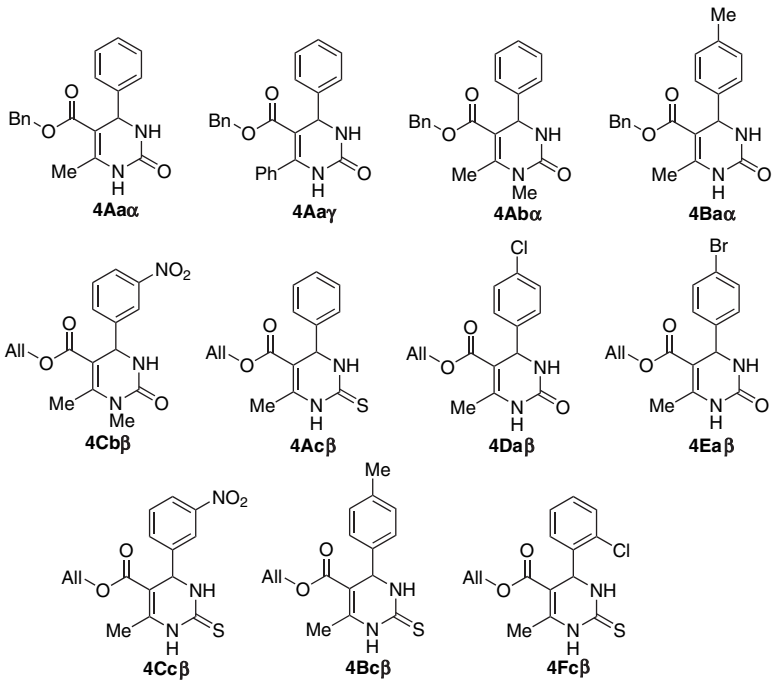
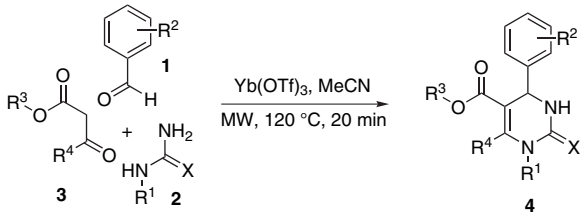


Figure 2. Dihydropyrimidine esters generated by Biginelli multicomponent condensations.

Reaction mixtures with **3α** and **3γ** as the CH-acidic carbonyl component (R^3=benzyl) provided easy access to the desired DHPMs **4Aaα**, **4Aaγ**, **4Abα**, and **4Baα** in 24–62% isolated yields. In each of these cases, the reaction mixture becomes completely homogeneous over 20 min of microwave heating at the optimized temperature of 120 °C. A low solubility of the resulting cyclocondensed DHPMs upon overnight standing under refrigeration (4 °C) afforded complete precipitation of the desired corresponding DHPM benzyl esters in >95% HPLC purity. We also undertook a scale-up synthesis (4 mmol–40 mmol) of DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα**, and **4Bbα**, switching from a single-mode microwave to a multimode microwave reactor capable of parallel synthesis.[14] Maintaining identical reaction conditions (catalyst, solvent and ratio of building blocks) in each of the cases provided the target compounds in multigram quantities and in similar yields (see Section 4 for details).

Table 1. Microwave-assisted synthesis of dihydropyrimidine benzyl/allyl esters **4**[a]



Entry	DHPM	R^1	R^2	R^3	R^4	X	Yield (%)[b]
1	**4Aaα**	H	H	Bn	Me	O	62
2	**4Aaγ**	H	H	Bn	Ph	O	17
3	**4Abα**	Me	H	Bn	Me	O	28
4	**4Baα**	H	4-Me	Bn	Me	O	43
5	**4Cbβ**	Me	3-NO_2	Allyl	Me	O	35
6	**4Acβ**	H	H	Allyl	Me	S	46
7	**4Daβ**	H	4-Cl	Allyl	Me	O	74
8	**4Eaβ**	H	4-Br	Allyl	Me	O	48
9	**4Ccβ**	H	3-NO_2	Allyl	Me	S	61
10	**4Bcβ**	H	4-Me	Allyl	Me	S	67
11	**4Fcβ**	H	2-Cl	Allyl	Me	S	37

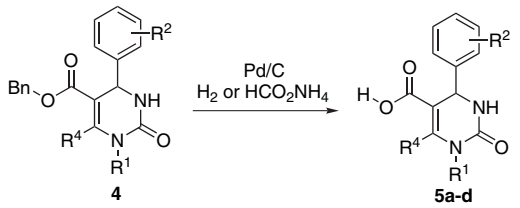
[a] Single-mode microwave on a 4 mmol scale.
[b] Isolated yield of pure compounds (>95% purity by HPLC at 215 nm).

The above generated DHPM benzyl esters exemplify a relative simplicity in terms of overall core diversity. The C6 phenyl substituent in **4Aaγ** and *N*1-methyl substituent in **4Abα** posed as robust diversity factors on the heterocyclic core. The synthesis of other DHPM C5 benzyl esters is similarly feasible by introducing diversity also in C2 (X=O or S) and the phenyl ring on C4 positions of the DHPM core. However, under identical deprotecting conditions this does not ensure to selectively carry out O-debenzylations without inadvertently affecting some of the other diversity points (the functional group substituents like NO_2, Cl, Br on the phenyl ring C4 position). The synthesis of DHPM allyl esters **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, **4Bcβ**, and **4Fcβ** became imperative for some of the structurally diverse building blocks, in particular with the aldehydes **1C–F** and/or thiourea **2c**, to retain the diversity in the resulting DHPM cores whilst selectively affording O-deprotections (deallylation) on the DHPM esters **4** under non-reducing conditions. The microwave-assisted synthesis (4 mmol and 40 mmol scale) was afforded under identical conditions as in the case of the 4-aryl-DHPM C5 benzyl esters, described in Table 1. In some cases, the relatively low yields of the DHPM allyl esters (e.g., for **4Fcβ**) may be attributed to the higher solubility of the DHPMs rendered by the allyl functionality.

2.2. Synthesis of DHPM acids 5a–d by catalytic transfer hydrogenation of DHPM benzyl esters 4

The next stage in our study was to gain access to compounds **5a–d** by devising a facile catalytic transfer hydrogenation of DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα** and **4Baα**,

Table 2. Deprotection of DHPM benzyl esters **4**[a]



4 **5a-d**

DHPM	R^1	R^2	R^4	Conditions[a]	Yield (%)[b]	Product
4Aaα	H	H	Me	rt	66	**5a**
				MW	62	
				CF	95	
4Aaγ	H	H	Ph	rt	65	**5b**
				MW	60	
				CF	80	
4Abα	Me	H	Me	rt	57	**5c**
				MW	55	
				CF	85	
4Baα	H	4-Me	Me	rt	56	**5d**
				MW	53	
				CF	85	

[a] Conditions: rt: room temperature catalytic transfer hydrogenation ($HCOONH_4$, 25 °C, 8–10 h; 5 mmol); MW: microwave-assisted catalytic transfer hydrogenation ($HCOONH_4$, 120 °C, 20 min; 0.5 mmol); CF: continuous flow hydrogenation. For details see text.
[b] Yields are isolated yields of pure product.

respectively, in the presence of a suitable catalyst. So far, the synthesis of DHPM C5 carboxylic acids has been reported both in solution[15] and on solid phase.[16] The solution phase studies have involved Pd-catalyzed hydrogenation of benzyl esters using hydrogen or allyl deprotection. In our approach the DHPM benzyl esters were easily transfer hydrogenated in the presence of catalytic 5% Pd/C using ammonium formate as the in situ hydrogen source and methanol as the solvent. Within 20 min of microwave heating at 120 °C, the catalytic transfer hydrogenations afforded quantitative conversions and good to moderate isolated yields of the corresponding DHPM acids (Table 2). Similar results were obtained by carrying out the same reaction at room temperature in a sealed vessel for 8–10 h.

2.3. Hydrogenation of DHPM benzyl esters 4 in a flow manner

The hydrogenation for *O*-benzyl deprotection on DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα**, and **4Baα** has additionally been carried out in a continuous flow manner using a continuous flow hydrogenation apparatus.[17]

This hydrogenation technology consists of a compact device capable to generate hydrogen gas in situ (up to 100 bars of H_2 pressure and 100 °C system temperature) and enabling catalytic hydrogenations in a flow mode. The electrolytic decomposition of water within the flow reactor (H-Cube™) generates hydrogen in the required quantity. The hydrogenation takes places within a heterogeneous catalyst (CatCart™) column. The exchangeable heterogeneous catalyst cartridges are advantageous for the final purification and isolation of the desired product over the conventional batch catalytic heterogeneous hydrogenations. Only homogeneous reaction mixtures are entered into the H-Cube via an HPLC injector (with up to 10 mL/min flow rate), allowing a continuous monitoring of reaction progress by sampling and also large scale hydrogenations in flow under optimized conditions.[18]

The *O*-benzyl deprotection of DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα**, and **4Baα** was afforded in a flow manner in the H-Cube™ using a 5% Pd/C catalyst (CatCart™) column by preparing 0.025 M stock solutions using 30% AcOH in EtOH as solvent (25 mL). A continuous flow (1 mL/min flow rate) of 30% AcOH in EtOH is set through the H-Cube™ while maintaining a low (atmospheric) hydrogen pressure at 40–45 °C system temperature. After equilibrating the H-Cube™ with the above conditions of H_2 pressure and system temperature, the stock solution of substrate **4Aaα** was injected at 1 mL/min flow rate. A continuous sampling (reaction monitoring) enabled to identify quantitative conversion (by HPLC) to the desired corresponding DHPM acid **5a**. An entire cycle of 25 mL reaction mixture (**4Aaα**) extended for 25–30 min to provide a complete and clean conversion with 95% isolated yield of the desired product **5a** (Table 2). Similar conditions were applied to carry out transfer hydrogenations on DHPM benzyl esters **4Aaγ**, **4Abα**, and **4Baα** to afford quantitative conversions (by HPLC) to the corresponding DHPM C5 acids **5b**, **5c**, and **5d** (80%, 85%, and 85% isolated yields, respectively). The activity of 5% Pd/C catalyst column was retained for several cycles of similar and/or different chemistries (for a new example/substrate, the catalyst bed is rinsed with the reaction solvent prior to initiating a hydrogenation).

It was evident that transfer hydrogenation of DHPM benzyl esters **4Aaγ**, **4Abα**, and **4Baα** in the H-Cube™ flow system has a clear advantage to afford excellent yields of the desired acids **5a–d** by simple evaporation of the collected mixture after exposure of the reaction mixture to hydrogenation conditions. This makes the flow reactor an ideal candidate for automated generation of compound libraries from a library of its corresponding precursors.[18]

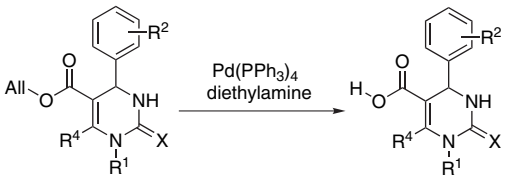
2.4. Microwave-assisted synthesis of DHPM acids 5e–k by Pd(0) catalyzed O-deallylation

The mild and selective method of Pd(0) catalyzed removal of allyl protecting groups[19] using 5 mol % of $Pd(PPh_3)_4$ as a catalyst and diethyl amine as a base formed the basis of transforming DHPM allyl esters **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, **4Bcβ**, and **4Fcβ** (ca. 0.5 mmol scale) to the corresponding DHPM acids **5e–k** under non-reducing conditions (Table 3).

Within 20 min of microwave heating at 100 °C in THF, a smooth and selective *O*-allyl deprotection was possible in the presence of the Pd(0) catalyst and the nucleophilic amine. Under these conditions, the nucleophile selectively scavenges the allyl group to afford the desired DHPM acids **5e–k**. The *O*-allyl deprotections have also been performed at room temperature under otherwise similar conditions (Table 3), and on a ca. 5 mmol scale in parallel (rt) providing similar yields.

In summary, a set of 11 DHPM C5 carboxylic acids has been prepared on a multigram scale by either a Pd-catalyzed

Table 3. Microwave-assisted O-deallylation of DHPM allyl esters **4**



4 **5e-k**

DHPM	R^1	R^2	R^4	X	Conditions[a]	Yield (%)[b]	Product
4Cbβ	Me	3-NO_2	Me	O	rt	82	**5e**
					MW	49	
4Acβ	H	H	Me	S	rt	64	**5f**
					MW	59	
4Daβ	H	4-Cl	Me	O	rt	73	**5g**
					MW	60	
4Eaβ	H	4-Br	Me	O	rt	73	**5h**
					MW	58	
4Ccβ	H	3-NO_2	Me	S	rt	57	**5i**
					MW	56	
4Bcβ	H	4-Me	Me	S	rt	56	**5j**
					MW	61	
4Fcβ	H	2-Cl	Me	S	rt	63	**5k**
					MW	59	

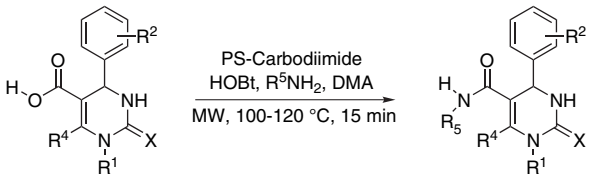
[a] Conditions: rt: room temperature deallylation with 5 mol % $Pd(PPh_3)_4$ in THF (ca. 5 mmol, 25 °C, 4–5 h); MW: microwave-assisted deallylation with 5 mol % $Pd(PPh_3)_4$ in THF (0.6–0.7 mmol, 100 °C, 20 min). See Section 4 for details.
[b] Yields are isolated yields of pure product.

debenzylation or a deallylation strategy. The acid cores **5a–k** were used as starting materials in a subsequent microwave-assisted decoration procedure to synthesize libraries of DHPM C5 amides.

2.5. Microwave-induced polymer-assisted solution phase synthesis of DHPM C5 amides from diverse DHPM acids 5 and selected amines

The multifunctionalized DHPM C5 carboxylic acids **5a–j** prepared by conventional and microwave-induced debenzylation and deallylation strategies were subsequently utilized as platforms to introduce structural diversity on the C5 position of the DHPM heterocycle. We subjected the DHPM acids **5a–j** to an existing rapid analoging amidation protocol[20] involving a polymer-assisted solution phase microwave-assisted synthesis and purification by solid-phase extraction (SPE). A simple representative set of amides was prepared in moderate to high yields, using benzylamine and propylamine as the starting amines. The polymer-assisted solution phase (PASP) microwave synthesis of the corresponding DHPM C5 amides was best afforded using DMA (*N*,*N*-dimethylacetamide) as the solvent. The highly polar DMA as the solvent ensured complete homogeneity of the reaction mixture (excluding the polymer-supported carbodiimide resin) and effective microwave heating of the reaction mixture. On the other hand, the use of solvents such as acetonitrile gave compromising yields, and at instances showed uncharacterizable by-products and/or incomplete conversions (by HPLC). In case of DMA as the solvent, 15 min of microwave heating was found sufficient to completely consume the starting DHPM acids (**5a–j**) and

Table 4. Microwave-assisted DHPM C5 amide synthesis[a]



5e-k **6a-j**

DHPM amides	R^1	R^2	R^4	R^5	X	Yields (%)[b]
6a	H	H	Me	Bn	O	84
6b	H	H	Ph	Bn	O	88
6c	Me	H	Me	Pr	O	89
6d	H	Me	Me	Bn	O	87
6e	H	2-Cl	Me	Bn	S	60
6f	H	4-Me	Me	Bn	S	51
6g	H	4-Br	Me	Pr	O	37
6h	H	3-NO_2	Me	Pr	S	57
6i	H	H	Me	Pr	S	52
6j	Me	3-NO_2	Me	Bn	O	54

[a] For conditions, see Section 4.
[b] Yields are isolated yields of pure product.

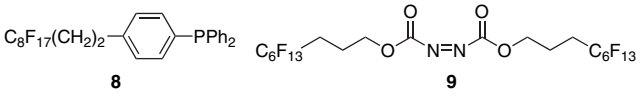
the amine component from the reaction mixture, affording a clean conversion to the corresponding DHPM amides (**6a–j**) (by HPLC monitoring). It was also evident that short term microwave heating (5 min) of the reaction mixture resulted mostly in the formation of the corresponding DHPM hydroxybenzotriazole active ester, retaining the unreacted starting amine (monitored by HPLC). The integration of a polymer-supported carbodiimide as an acid activating reagent (readily removed by simple post-reaction filtration) and a subsequent purification of the filtrate by filtering through a pre-packed Si-carbonate SPE cartridge,[20] aided a high throughput delivery of the corresponding DHPM amides **6a–j** (see Table 4) in high purity after solvent evaporation.[21]

2.6. Microwave-assisted Mitsunobu esterifications of DHPM C5 acids using fluorous synthesis and purification strategies

For the synthesis of DHPMs with more diverse and novel C5 ester moieties we wanted to perform esterification reactions employing a Mitsunobu protocol. The Mitsunobu reaction is a versatile method for the condensation of alcohols with various acidic nucleophiles promoted by triphenylphosphine (TPP) and diethyl- or diisopropyl azodicarboxylate (DEAD or DIAD) as the classical set of Mitsunobu reagents.[22] Since there are considerably more alcohols commercially available compared to β-ketoesters, diversity can potentially very rapidly be introduced at this position starting from DHPM C5 acids **5**. Nevertheless, the drawback of Mitsunobu protocol is the purification step, which usually requires a careful chromatography to separate the product from many by-products of this transformation (triphenylphosphine oxide, hydrazide, and excess alcohol) and therefore limits this reaction in the context of combinatorial/high throughput synthesis. Therefore, several strategies have been investigated to facilitate the purification step, employing, for example, polymer-bound or fluorous Mitsunobu reagents.[23–26]

For the esterification of DHPM C5 acids **5** we decided initially upon a protocol using a combination of the fluorous

Mitsunobu (F-Mitsunobu) reagents diphenyl-[4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl]phosphine **8** (F-TPP) and bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorononyl) azodicarboxylate **9** (F-DIAD, Chart 2). Compared to polymer-bound reagents, which cannot be employed concurrently in this process and create heterogeneous reaction mixtures (therefore leading to slower reactions), fluorous reagents enable classical solution phase reaction conditions. They are soluble in most organic solvents like THF, DCM or MeOH, creating homogeneous reaction conditions, and due to the fluorous tag, product isolation can be easily performed by a fluorous solid-phase extraction (F-SPE) through fluorous silica gel.[27]



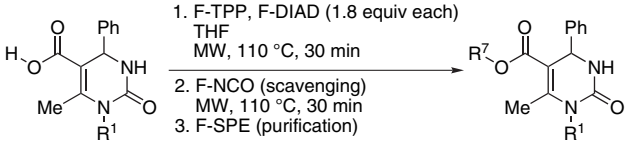
8 9

Chart 2.

For our initial optimization experiments we utilized the DHPM acid **5a** (R^1=H) and *n*-butanol as primary alcohol and made investigations on appropriate solvents, temperature, time, and molar ratios of the reaction partners. The best conditions turned out to be THF as solvent, 1.8 equiv each of the alcohol, F-TPP, and F-DIAD, and microwave irradiation at 110 °C for 10 min. With this set of conditions a conversion of 80% (HPLC) could be achieved. Reducing or increasing the temperature did not improve the conversion. By adding more equivalents of the reagents a slight increase in product concentration could be established by HPLC analysis, but due to the rather high cost of the fluorous reagents we decided to limit the amount of reagents to 1.8 equiv. Although it is known for Mitsunobu chemistry that the sequence of adding individual reagents can be crucial for the success of the reaction,[22,25] in our case a different order of reagent addition did not improve the conversion (for more details on the reaction conditions, see Section 4). After the completion of the reaction the F-reagents and F-by-products were removed by F-SPE. By eluting the reaction mixture with 80% MeOH in H_2O the F-reagents are retained on the F-silica and the 'organic' compounds can be easily separated. Since in our case only an 80% conversion was reached, some unreacted acid **5a** remained in the reaction mixture. For the removal of unreacted acid the mixture was subsequently passed through a cartridge filled with basic ion exchange Amberlite IRA-900 resin in carbonate form.[28] After evaporation of the solvent, the DHPM C5 ester **7a** was obtained in 95% purity. Unfortunately isolated product yields remained in the 30% region and could not be improved (Table 5). For secondary or other primary alcohols (like 3-fluorobenzyl alcohol), unsatisfactory conversion and very low isolated product yields were obtained. We assumed that perhaps the free *N*1–H moiety could somehow interfere with the reactivity of the acid, although no N1-alkylation was observed. In a previous publication we have shown that for the N1-alkylation of the DHPMs the more reactive Mitsunobu reagents tributylphosphine (TBP) in combination with *N*,*N*,*N*′,*N*′-tetramethyl azodicarboxamide (TMAD) have to be used since the pK_a of the nucleophilic NH was too high.[29]

Since the results for the esterification of the *N*1–H DHPM C5 acid **5a** have been rather disappointing, we turned our attention to the *N*1-substituted DHPM C5 acid **5c** (R^1=Me). The same reaction conditions have been employed for the reaction with 3-fluorobenzyl alcohol (Table 5). The only issue that had to be considered for this non-volatile alcohol was the removal of excess alcohol after the reaction, since 1.8 equiv of the alcohol were used. Therefore, we wanted to introduce a scavenging step by again using a fluorous reagent. We selected fluorous isocyanate **10** (F-NCO, 2-(perfluorooctyl)ethyl isocyanate, Chart 3) as electrophilic scavenger, which has been previously employed as scavenger for amines.[30] After some scavenging optimizations, we found that 3.2 equiv of the F-NCO reagent and 4 equiv of Et_3N (in relation to the DHPM C5 acid) were necessary to remove all the remaining acid. The scavenging step was best performed under microwave irradiation at 110 °C for 30 min. Note that the scavenging step for this particular reaction with 3-fluorobenzyl alcohol could be performed within 15 min, furnishing full conversion. In other cases (entry 5, Table 5) the time for scavenging of excess alcohol was prolonged to 30 min. Subsequent F-SPE and acid removal by filtration through a cartridge filled with Amberlite IRA-900 resin provided product **7b** in 69% isolated yield and 96% purity.

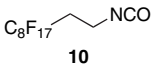
Table 5. Synthesis of C5-esters using a fluorous Mitsunobu protocol



5a,c **7a-e**

Entry	DHPM esters	R^1	R^7	Yield (%)[a]
1	**7a**	H	*n*-Bu	30[b,c]
2	**7b**	Me	3-F-PhCH$_2$	69[b]
3	**7c**	Me	*n*-Pr	44[c]
4	**7d**	Me	*i*-Pr	46[c]
5	**7e**	Me	Cyclohexyl	43

[a] Yields are isolated yields.
[b] Mitsunobu reaction at 110 °C for 10 min.
[c] No scavenging step.



10

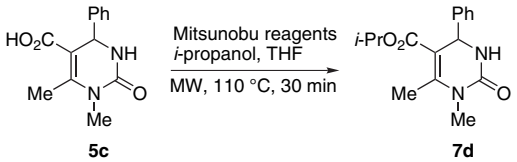
Chart 3.

For DHPM acid precursor **5c**, reasonable yields and purities≥94% could also be achieved for secondary alcohols such as *i*-propanol (46%) and cyclohexanol (43%) (Table 5), requiring an increased reaction time of 30 min at 110 °C as compared to 10 min for primary alcohols. However, the above mentioned fluorous protocol failed for more complex alcohols such as 1-butynol or longer chained alcohols like hexanol.

2.7. Reactivity studies of the fluorous Mitsunobu reagents F-TPP and F-DIAD

In summary, rather unsatisfactory results were obtained by applying the F-Mitsunobu protocol. Since full conversion could only be reached in a single case (entry 2, Table 5) and the subsequent purification steps turned out to be more

Table 6. Reactivities of F-TPP and F-DIAD



5c **7d**

Entry	Mitsunobu reagents	Yield (%)[a]
1	TPP/DIAD	75
2	F-TPP/DIAD	71
3	TPP/F-DIAD	49
4	TPP/F-DIAD	36[b]

[a] Yields are isolated yields.
[b] rt, overnight.

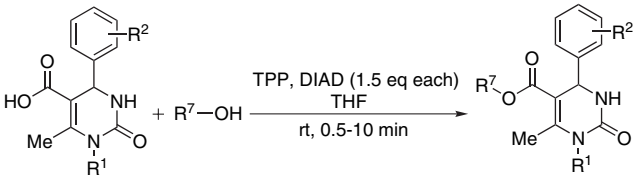
troublesome than expected, we performed reactivity studies on the F-Mitsunobu reagents. For these investigations, we examined Mitsunobu esterification of the *N*1-methyl-DHPM acid **5c** with *i*-propanol under several different conditions (Table 6). Initial experiments were performed with the classical Mitsunobu tandem TPP/DIAD using the optimized conditions of the F-Mitsunobu protocol for secondary alcohols (MW, 110 °C, 30 min). After column chromatography, product **7d** could be isolated in 75% yield with 99% purity, which was an improvement of 30% in yield compared to the F-Mitsunobu procedure. In a direct comparison experiment the combinations F-TPP/DIAD and TPP/F-DIAD were subsequently compared. By using the F-TPP/DIAD tandem nearly the same isolated yield (71%) was obtained after column chromatography compared to the 'all non-fluorous' TPP/DIAD combination (75% yield). Applying the TPP/F-DIAD combination, an isolated yield of only 49% after column chromatography could be achieved. We therefore conclude that F-DIAD has considerably lower reactivity in these esterifications as compared to standard DIAD. Longer reaction times did not lead to higher conversions. Similarly, performing the reaction at room temperature over night also did not increase the yield (entry 4, Table 6). As these studies indicate, it is the lower reactivity of the F-DIAD reagent, which limits the reaction progress.

2.8. Mitsunobu esterifications of DHPM C5 acids using classical reaction conditions

Since we could not achieve satisfactory results for the esterification of the DHPM acids **5** via the F-Mitsunobu reaction, we therefore decided to use the classical Mitsunobu conditions (TPP/DIAD), which have shown to be superior in yield (see Table 6).

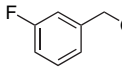
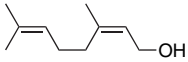
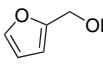
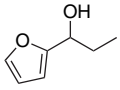
Further optimizations with respect to temperature, time, and molar equivalents of reagents with both *N*1–H (**5a**) and *N*1-methyl (**5c**) DHPM acids were performed with *n*-propanol and *i*-propanol using the TPP/DIAD reagent couple. Ultimately, we discovered that only 1.5 equiv each of propanol, TPP, and DIAD were sufficient at room temperature to obtain full conversion according to HPLC analysis. The reaction times for both **5a** and **5c** were surprisingly very short: 5 min for the *N*1–H analog **5a** and only 30 s for the *N*1-methyl DHPM acid **5c**. For the reaction with *i*-propanol 1.8 equiv each of alcohol, TPP, and DIAD were necessary for 10 min at room temperature for achieving 78% conversion in the case of *N*1-methyl (**5c**) and 50% for the *N*1-unsubstituted acid (**5a**). Longer reaction times or more equivalents of reagents did not improve the conversion.

Table 7. Synthesis of C5-esters via a classical Mitsunobu protocol



5a,c,e **7b-r**

17 examples

Entry	DHPM acid	Alcohol	*t* (min)	Yield (%)[a]	Product
1	**5a**		5	80	**7f**
2	**5c**		0.5	96	**7c**
3	**5a**		10	26[b]	**7g**
4	**5c**		10	75[b]	**7d**
5	**5a**		5	82	**7h**
6	**5c**		0.5	86	**7i**
7	**5a**		5	92	**7j**
8	**5c**		0.5	98	**7b**
9	**5a**		5	79	**7k**
10	**5c**		0.5	89	**7l**
11	**5a**		5	70	**7m**
12	**5c**		0.5	99	**7n**
13	**5a**		5	63	**7o**
14	**5c**		0.5	83	**7p**
15	**5c**		10	43[b]	**7e**
16	**5c**		10	56[b]	**7q**
17	**5e**		10	86	**7r**

[a] Yields are isolated yields.
[b] Alcohol, TPP, and DIAD, each of 1.8 equiv.

With these optimized protocols for primary and secondary alcohols we now prepared a set of 17 examples of DHPM C5 esters (Table 7). After purification by standard column chromatography, the products **7b–7r** could be obtained in moderate to excellent yields (26–99%) and in purities≥97%. The yields for the *N*1–H DHPM esters are in general somewhat lower than those for the *N*1-methyl products, especially if a secondary alcohol such as *i*-propanol is used (26% yield compared to 75%, see Table 7). If more hindered secondary alcohols, like cyclohexanol (entry 15) or the racemic 1-2(furyl)-1-propanol (entry 16) are employed in the reaction with *N*1-methyl DHPM acid, yields are moderate and in the case of cyclohexanol identical to that of the F-Mitsunobu protocol (43%, see also Table 5).

3. Conclusion

In conclusion, the efficiency of high speed sequential batch and parallel microwave synthesis has been applied to

generate a set of multifunctionalized dihydropyrimidinone esters. An easy access to the valuable carboxylic acid platform on the multifunctionalized DHPM heterocycle was found by microwave-assisted ester deprotections. The scope of flow methodology for high purity and throughput delivery of DHPM acid precursors have also been demonstrated. A rapid microwave-induced polymer-assisted solution phase (PASP) analoging protocol has been instrumental to introduce structural diversity, in the form of DHPM C5 amides. By applying a standard Mitsunobu protocol we were able to synthesize DHPM C5 esters with novel functionalities at the C5 position in excellent yields and in very short reaction times.

4. Experimental

4.1. General

Fluorous reagents were obtained from Fluorous Technologies Inc. (F-TPP: F017039, F-DIAD: F026100, F-NCO: F017032, F-Silica: 801-0100B). Amberlite IRA-900 Cl ion exchange resin was obtained from Acros (202315000). THF used for Mitsunobu reaction was obtained from Aldrich (puriss; over molecular sieve, 87371). Solvents for column chromatography have been distilled prior to use. TLC analysis was performed on Merck precoated 60 F_{254} plates. Melting points were obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX360 and 500 instruments in $CDCl_3$ or DMSO-d_6. IR spectra were taken on a Perkin–Elmer 298 spectrophotometer in KBr pellets. Mass spectra were taken on a Hewlett-Packard LC/MSD 1100 series instrument in the atmospheric pressure chemical ionization (negative or positive APCI) mode. HPLC analysis was carried out on two different Shimadzu systems. The Shimadzu LC-10 includes LC10-AT (VP) pumps, an autosampler (S-10AXL), and a dual wavelength UV detector. The separations were carried out using a C18 reversed phase analytical column, LiChrospher 100 (E. Merck, 100×3 mm, particle size 5 μm) at 25 °C and a mobile phase from (A) 0.1% TFA in 90:10 water/MeCN and (B) 0.1% TFA acid in MeCN (all solvents were HPLC grade, Acros; TFA was analytical reagent grade, Aldrich). The following gradient was applied: linear increase from solution 30% B to 100% B in 7 min, hold at 100% solution B for 2 min. The Shimadzu LC-20 system includes an LC-20AD pump, an SIL-20A autosampler, a diode array detector (SPD-M20A), a column oven (CTO-20A), and a degasser (DGU-20A5). The separations were carried out using a Pathfinder®AS100 reversed phase analytical column (150× 4.6 mm, particle size 5 μm) at 25 °C and a mobile phase from (A) 0.1% TFA in 90:10 water/MeCN and (B) 0.1% TFA acid in MeCN (all solvents were HPLC grade, Acros; TFA was analytical reagent grade, Aldrich). The following gradient was applied: linear increase from solution 20% B to 100% B in 7 min, hold at 100% solution B for 1 min.

4.2. Microwave irradiation experiments

Small scale microwave-assisted synthesis was carried out in an Emrys™ Synthesizer or Initiator 8 single-mode microwave instrument producing controlled irradiation at 2.450 GHz (Biotage AB, Uppsala).[9] Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel.

All microwave scale-up synthesis has been performed in a Synthos 3000 multimode batch reactor (Anton Paar GmbH).[14] The instrument is equipped with two magnetrons, operating at a frequency of 2.45 GHz with continuous microwave output power from 0 to 1400 W. The reactor cavity encompasses a 16-vessel rotor and its protection lid. The rotor carries 16 reaction vessels, which are 100 mL PTFE–TFM (maximum filling volume 60 mL) made, equipped with a pressure release valve on its seal and individually resting inside ceramic jackets, to enable reactions under high pressure (maximum pressure 40 bars). The temperature is monitored using an internal gas balloon thermometer placed in one reference vessel and additionally by exterior IR thermography.

4.3. Continuous flow hydrogenations

All hydrogenations (*O*-benzyl deprotections) were conducted in a flow manner using the H-Cube™ (Thales Nanotechnology Inc.)[18] operating at 0–100 bars of in situ H_2 pressure and up to 100 °C of maximum temperature with an HPLC-like platform and a maximum flow rate of 9 mL/min. The benzyl deprotections were catalyzed by 10% Pd/C (average particle size: 32–40 microns) catalyst beds (CatCart™), used as available from Thales and were deactivated after usage by introduction into sodium bisulfite solution.

4.4. General procedure for microwave-assisted synthesis of DHPM benzyl/allyl esters 4 (4 mmol)

A microwave process vial (2–5 mL) equipped with a magnetic stirrer bead was charged with the aldehyde **1A–F** (4 mmol), β-ketoester **3α–γ** (6 mmol), urea/thiourea **2a–c** (4 mmol), and $Yb(OTf)_3$ (248 mg, 10 mol %) as the catalyst in acetonitrile (3 mL). The process vial was sealed using an aluminum crimp equipped with a Teflon septum. The sealed vial was introduced in the microwave cavity using a robotic gripper and microwave irradiated at a set temperature of 120 °C for 20 min. After completion of irradiation time, the reaction mixture was cooled to room temperature through rapid gas-jet cooling and the desired DHPM was isolated (Fig. 2). In most instances the DHPM products precipitated from the reaction mixture upon cooling to room temperature. In the synthesis of compounds **4Abα**, **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, and **4Fcβ** the reaction mixture was poured over crushed ice after the irradiation to induce complete precipitation of product. The precipitates were filtered and washed with crushed ice–ethanol mixture to yield HPLC pure products. For isolated yields see Table 1.

4.5. General procedure for microwave-assisted synthesis of DHPM benzyl/allyl esters 4 (40 mmol)

Scale-up synthesis has been performed in a Synthos 3000 multimode batch reactor. The PTFE–TFM reaction vessels are charged with Teflon coated stirrer bars. Reaction mixtures were prepared in individual vessels with a set of corresponding aldehydes **1A–F** (40 mmol), urea/thiourea **2a–c** (40 mmol), and β-diketoester **3α–γ** (60 mmol) components

in 20 mL of acetonitrile (see Fig. 1 for building blocks). The PTFE vessels were introduced in ceramic jackets, appropriately sealed, and fitted into the rotor positions. The rotor fitted with the sealed reaction vessels is equipped with its protection lid and introduced in the reactor cavity. The reaction mixtures are then irradiated at a preset temperature of 120 °C for 20 min (with 3 min programmed ramp). After completion of the reaction, the mixture is allowed to cool to 40 °C by a built-in fan-assisted cooling. The reaction mixtures are worked up individually and the product yields evaluated upon isolation.

Isolated yields: **4Aaα** (48%), **4Aaγ** (25%), **4Abα** (36%), **4Baα** (39%), **4Cbβ** (59%), **4Acβ** (60%), **4Daβ** (59%), **4Eaβ** (66%), **4Ccβ** (47%), **4Bcβ** (76%), and **4Fcβ** (17%).

4.5.1. Benzyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Aaα). Mp 166 °C (lit.[15d] 168 °C). ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 5.01–5.03 (m, 2H), 5.15 (d, J=2.8 Hz, 1H), 7.13–7.29 (m, 10H), 7.75 (br s, 1H), 9.26 (br s, 1H). MS (ES$^+$) m/z 323.1 (M+1).

4.5.2. Benzyl 4,6-diphenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Aaγ). Mp 210 °C (lit.[15d] 209 °C). ^{1}H NMR (DMSO-d_6) δ 4.79 (m, 2H), 5.26 (d, J=3.6 Hz), 6.79–7.38 (m, 15H), 7.88 (br s, 1H), 9.33 (s, 1H). MS (ES$^+$) m/z 385.2 (M+1).

4.5.3. Benzyl 1,6-dimethyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Abα). Mp 119–120 °C (lit.[15d] 118 °C). ^{1}H NMR (DMSO-d_6) δ 2.51 (s, 3H), 3.10 (s, 3H), 5.03–5.11 (m, 2H), 5.17 (d, J=3.6 Hz, 1H), 7.16–7.29 (m, 10H), 7.96 (d, J=3.8 Hz, 1H). MS (ES$^+$) m/z 337.2 (M+1).

4.5.4. Benzyl 6-methyl-4-tolyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Baα). Mp 170–171 °C. ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.26 (s, 3H), 3.32 (s, 3H), 4.97–5.06 (m, 2H), 5.12 (d, J=3.2 Hz, 1H), 7.06–7.28 (m, 9H), 7.69 (br s, 1H), 9.22 (br s, 1H). MS (ES$^+$) m/z 337.2 (M+1).

4.5.5. Allyl 1,6-dimethyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Cbβ). Mp 125–126 °C (lit.[9a] 122–123). ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H), 3.11 (s, 3H), 4.53 (m, 2H), 5.08–5.13 (m, 2H), 5.31 (d, J=3.9 Hz, 1H), 5.81–5.88 (m, 1H), 7.64–7.67 (m, 2H), 8.06 (br s, 1H), 8.12–8.18 (m, 2H). MS (ES$^+$) m/z 332.1 (M+1).

4.5.6. Allyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Acβ). Mp 154–155 °C. ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H), 4.50 (br, 2H), 5.05–5.10 (m, 2H), 5.19 (br, 1H), 5.78–5.86 (m, 1H), 7.20–7.34 (m, 5H), 9.67 (s, 1H), 10.37 (s, 1H). MS (ES$^+$) m/z 288.9 (M+).

4.5.7. Allyl 6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Daβ). Mp 174–176 °C. ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 4.48 (m, 2H), 5.06–5.11 (m, 2H), 5.15–5.16 (d, J=3.2 Hz, 1H), 5.77–5.88 (m, 1H), 7.23–7.40 (m, 4H), 7.79 (br s, 1H), 9.30 (br s, 1H). MS (ES$^+$) m/z 306.9 (M+1).

4.5.8. Allyl 6-methyl-4-(4-bromophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Eaβ). Mp 195–196 °C. ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 4.48 (m, 2H), 5.07–5.12 (m, 2H), 5.13–5.14 (d, J=3 Hz, 1H), 5.77–5.88 (m, 1H), 7.17–7.53 (m, 4H), 7.79 (br s, 1H), 9.30 (br s, 1H). MS (ES$^+$) m/z 351 (M+1).

4.5.9. Allyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Ccβ). Mp 182–183 °C. ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H), 4.51 (m, 2H), 5.07–5.12 (m, 2H), 5.34 (d, J=3.6 Hz, 1H), 5.77–5.88 (m, 1H), 7.67–8.18 (m, 4H), 9.97 (br s, 1H), 10.55 (br s, 1H). MS (ES$^+$) m/z 333.9 (M+1).

4.5.10. Allyl 6-methyl-4-tolyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Bcβ). Mp 161–162 °C. ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 2.29 (s, 3H), 2.49 (s, 3H), 4.49 (m, 2H), 5.08–5.13 (m, 2H), 5.14–5.15 (d, J=3.9 Hz, 1H), 5.78–5.88 (m, 1H), 7.08–7.15 (m, 4H), 9.64 (br s, 1H), 10.34 (br s, 1H). MS (ES$^+$) m/z 303 (M+1).

4.5.11. Allyl 6-methyl-4-(2-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Fcβ). Mp 107–108 °C. ^{1}H NMR (DMSO-d_6) δ 2.340 (s, 3H), 4.43 (m, 2H), 4.93–5.05 (m, 2H), 5.65 (d, J=3.2 Hz, 1H), 5.68–5.79 (m, 1H), 7.27–7.42 (m, 4H), 9.61 (br s, 1H), 10.41 (br s, 1H). MS (ES$^+$) m/z 323.1 (M+1).

4.6. General procedure for the microwave-assisted synthesis of DHPM acids 5a–d by catalytic transfer hydrogenation

A microwave process vial (2–5 mL) equipped with a magnetic stirrer bead was charged with 0.60 mmol of the appropriate DHPM C5 benzyl ester **4Aaα**, **4Aaγ**, **4Abα** or **4Baα**, 5% Pd/C (10% w/w), and ammonium formate (0.37 mg, 10 equiv) in methanol (3 mL). The process vial was sealed with an aluminum crimp equipped with a Teflon septum. The sealed vial was introduced in the microwave cavity using a robotic gripper and microwave irradiated at a set temperature of 120 °C for 20 min. After completion of the irradiation, the reaction mixture was cooled to room temperature, the contents transferred to a round bottom flask, and evaporated to dryness. The residue was treated with 0.5 M KOH solution (5–8 mL), stirred vigorously, and filtered under gravity. The filtrate was acidified with 2 M HCl to pH 4–5 and the resulting precipitates of the corresponding 4-aryl-DHPM C5 acids **5a–d** were collected by suction filtration and recrystallized from ethanol. For yields refer to Table 2.

4.7. General procedure for the continuous flow hydrogenation of DHPM C5 benzyl esters 4

A hydrogenation flow apparatus (H-Cube™) capable of generating hydrogen gas in situ (100 bars and 100 °C system temperature) has been utilized for the synthesis of the DHPM C5 carboxylic acids **5a–d** by a continuous flow *O*-benzyl deprotection of DHPM C5 benzyl esters **4** (Table 2). Stock solutions (0.60 mmol, 0.025 M) of the DHPM benzyl esters (**4Aaα**, **4Aaγ**, **4Abα**, **4Baα**, Fig. 2) were prepared in 30% AcOH in EtOH (25 mL). The H-Cube™ was equipped with a fresh 5% Pd/C catalyst (CatCart™) column and then purged with the solvent mixture (30% AcOH in

EtOH). Initially, the solvent flow is regulated to 1 mL/min while maintaining a low hydrogen pressure (ca. atmospheric pressure) and the system temperature set to 40–45 °C. The solvent flow is allowed to equilibrate with the set conditions. Thereafter, the reaction mixture stock solution is injected at 1 mL/min flow rate and exposed to the preset hydrogenation conditions. The injected mixture is analyzed by continuous sampling and the progress of the reaction is monitored by HPLC. The entire cycle of 25 mL stock solution is completed in 25–30 min. The corresponding DHPM carboxylic acids **5a–d** were isolated in ca.100 mg quantities and yields determined after evaporating the solvent from the collected mixture after exposure to the hydrogenation conditions in the H-Cube™ (Table 2).

4.8. General procedure for the room temperature synthesis of DHPM acids 5a–d by catalytic transfer hydrogenation

In 50 mL single neck round bottom flasks equipped with magnetic stirrer beads, individual reaction mixtures of 6.0 mmol of the corresponding DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα**, and **4Baα**, 5% Pd/C (10% w/w) and ammonium formate (3.78 g, 10 equiv) are suspended in 15 mL of methanol. The reaction flask is sealed with a rubber septum and a balloon maintained on it. After allowing the reaction mixture to stir at room temperature for 8–10 h to enable complete reaction, the solvent is completely evaporated under reduced pressure. The solid residue is treated with 0.5 M KOH solution (10–15 mL), vigorously stirred, and filtered under gravity. The filtrate is acidified by 2 M HCl till pH 4–5 and the resulting precipitates of the corresponding DHPM carboxylic acids **5a–d** are collected by suction filtration and recrystallized from ethanol. For yields, see Table 2.

4.9. General procedure for the microwave-assisted synthesis of DHPM acids 5e–k by palladium-catalyzed O-deallylation

A microwave process vial (2–5 mL) equipped with a magnetic stirrer bead was charged with 0.60 mmol of the corresponding DHPM allyl esters **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, **4Bcβ**, and **4Fcβ**, 5 mol % of $Pd(PPh_3)_4$ (0.034 g), and diethyl amine (0.438 mg, 10 equiv) in THF (3 mL) as the solvent. The process vial was sealed using an aluminum crimp equipped with a Teflon septum. The sealed vial was introduced in the microwave cavity using a robotic gripper and microwave irradiated at a set temperature of 100 °C for 20 min. After completion of irradiation time, the reaction mixture is cooled to room temperature through rapid gas-jet cooling and the reaction mixture is transferred into a round bottom flask and evaporated to dryness. To this residue 0.5 M KOH (5–8 mL) is added, vigorously stirred, and filtered under gravity. The filtrate is acidified with 2 M HCl to pH 4–5 and the resulting DHPM C5 carboxylic acid precipitates are filtered under suction and recrystallized from ethanol. For yields, see Table 3.

4.10. General procedure for the room temperature synthesis of DHPM acids 5e–k by palladium-catalyzed O-deallylation

In 50 mL single neck round bottom flasks equipped with a magnetic stirrer bead, individual reaction mixtures containing 6.0 mmol of the corresponding DHPM allyl esters **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, **4Bcβ**, and **4Fcβ**, 5 mol % of $Pd(PPh_3)_4$ (0.346 mg), and diethyl amine (4.38 g, 10 equiv) are prepared in 15 mL THF. The reaction mixture is stoppered and allowed to stir at room temperature for 4–5 h to enable complete conversion. Thereafter, the reaction mixture is evaporated to dryness under reduced pressure and the solid residue is treated with 0.5 M KOH solution (10–15 mL), vigorously stirred, and filtered under gravity. The filtrate is acidified by 2 M HCl till pH 4–5 and the resulting precipitates of the corresponding 4-aryl-DHPM C5 carboxylic acids **5e–k** are collected by suction filtration and recrystallized from ethanol. For yields, see Table 3.

4.10.1. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylic acid (5a). Mp 210 °C (lit.[15d] 210–213 °C). ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H), 5.09 (br s, 1H), 7.22–7.66 (m, 5H), 7.66 (br s, 1H), 9.07 (br s, 1H), 11.88 (br s, 1H). MS (ES$^+$) *m*/*z* 233.2 (M+1).

4.10.2. 1,2,3,4-Tetrahydro-2-oxo-4,6-diphenylpyrimidine-5-carboxylic acid (5b). Mp 160 °C (lit.[15d] 163 °C). ^{1}H NMR (DMSO-d_6) δ 5.22 (d, J=3.6 Hz, 1H), 7.30–7.39 (m, 10H), 7.89 (br s, 1H), 9.13 (s, 1H). MS (ES$^+$) *m*/*z* 295 (M+1).

4.10.3. 1,2,3,4-Tetrahydro-1,6-dimethyl-2-oxo-4-phenylpyrimidine-5-carboxylic acid (5c). Mp 235 °C (lit.[15d] 237 °C). ^{1}H NMR (DMSO-d_6) δ 2.48 (s, 3H), 3.07 (s, 3H), 5.12 (d, J=3.9 Hz, 1H), 7.20–7.30 (m, 5H), 7.89 (d, J=3.2 Hz, 1H). MS (ES$^+$) *m*/*z* 247 (M+1).

4.10.4. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-*p*-tolylpyrimidine-5-carboxylic acid (5d). Mp 220–223 °C. ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H), 2.25 (s, 3H), 5.14 (d, J=3.6 Hz, 1H), 7.11–7.12 (m, 4H), 7.62 (br s, 1H), 9.04 (br s, 1H), 11.84 (s, 1H). MS (ES$^+$) *m*/*z* 247 (M+1).

4.10.5. 1,2,3,4-Tetrahydro-1,6-dimethyl-4-(3-nitrophenyl)-2-oxopyrimidine-5-carboxylic acid (5e). Mp 200–201 °C. ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H), 3.08 (s, 3H), 5.26 (d, J=3.9 Hz, 1H), 7.62–8.10 (m, 4H), 8.13 (br s, 1H), 12.34 (br s, 1H). MS (ES$^+$) *m*/*z* 292.2 (M+1).

4.10.6. 1,2,3,4-Tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylic acid (5f). Mp 209–210 °C. ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H), 5.14 (d, J=3.6 Hz, 1H), 7.20–7.34 (m, 5H), 9.72 (br s, 1H), 10.24 (br s, 1H). MS (ES$^+$) *m*/*z* 249.1 (M+1).

4.10.7. 4-(4-Chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylic acid (5g). Mp 199–200 °C. ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3H), 5.13 (d, J=3.4 Hz, 1H), 7.23–7.39 (m, 4H), 7.71 (br s, 1H), 9.16 (br s, 1H), 11.92 (br s, 1H). MS (ES$^+$) *m*/*z* 267 (M+1).

4.10.8. 4-(4-Bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylic acid (5h). Mp 174–175 °C. ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H), 5.08 (d, J=3.2 Hz, 1H), 7.17–7.53 (m, 4H), 7.70 (br s, 1H), 9.13 (br s, 1H), 11.92 (br s, 1H). MS (ES$^+$) *m*/*z* 311.1 (M+1).

4.10.9. 1,2,3,4-Tetrahydro-6-methyl-4-(3-nitrophenyl)-2-thioxopyrimidine-5-carboxylic acid (5i). Mp 204–205 °C. ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H), 5.30 (d, J=3.6 Hz, 1H), 7.16–8.16 (m, 4H), 9.72 (br s, 1H), 10.42 (br s, 1H), 12.39 (br s, 1H). MS (ES$^+$) m/z 294.1 (M+1).

4.10.10. 1,2,3,4-Tetrahydro-6-methyl-2-thioxo-4-*p*-tolyl-pyrimidine-5-carboxylic acid (5j). Mp 208–209 °C. ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.26 (s, 3H), 2.49 (s, 3H), 5.09 (d, J=3.6 Hz, 1H), 7.08–7.15 (m, 4H), 9.54 (br s, 1H), 10.20 (br s, 1H), 12.14 (br s, 1H). MS (ES$^+$) m/z 262.9 (M+1).

4.10.11. 4-(2-Chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylic acid (5k). Mp 206–208 °C. ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H), 5.58 (d, J=3.4 Hz, 1H), 7.25–7.43 (m, 5H), 9.49 (br s, 1H), 10.29 (br s, 1H), 12.12 (br s, 1H). MS (ES$^+$) m/z 283 (M+1).

4.11. General procedure for the amidation of acids to DHPM amides

In a small microwave process vial (0.5–2.5 mL), a mixture of the corresponding DHPM acids **2a**–**d** (0.050 mmol), polymer-supported carbodiimide (PS-carbodiimide, 1.29 mequiv/g loading, Argonaut part no. 800370) (150 mg, 0.1 mmol, 2.0 equiv), 1-hydroxybenzotriazole (7 mg, 0.051 mmol), and benzylamine or *n*-propylamine (0.050 mmol) was suspended in *N*,*N*-dimethylacetamide (DMA) (2 mL). The process vial was sealed appropriately, introduced into the single-mode microwave cavity, and microwave irradiated at 100 °C for 15 min. After completion of the irradiation time, the reaction vial was rapidly cooled to room temperature by compressed air (gas-jet cooling) and the mixture was diluted with MeOH (2 mL). The reaction mixture was filtered through a pre-packed column of Si-carbonate (1 g, 0.8 mmol/g loading, Silicycle Inc.) and washed with several aliquots of MeOH (3×3 mL) under gravity. The filtrate collected was evaporated under reduced pressure to yield the corresponding DHPM amides as colorless solids in 37–89% yield. The purity of those compounds was >95% by HPLC (215 nm) and ^{1}H NMR analysis.

4.11.1. *N*-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl-pyrimidine-5-carboxamide (6a). Mp 210–212 °C (MeCN). ^{1}H NMR (DMSO-d_6) δ 2.02 (s, 3H), 4.22 (br, 2H), 5.30 (br, 1H), 6.96–7.31 (m, 10H), 7.49 (s, 1H), 8.10 (br, 1H), 8.56 (s, 1H); ^{13}C NMR δ 17.4, 42.5, 55.5, 105.2, 126.9, 127.0, 127.4, 127.7, 128.5, 128.8, 138.0, 140.2, 144.7, 153.0, 166.8. MS (pos. APCI) m/z 322.3 (M+1). Anal. Calcd ($C_{19}H_{19}N_3O_2$): C, 71.01; H, 5.96; N, 13.08. Found: C, 70.83; H, 5.96; N, 12.97.

4.11.2. *N*-Benzyl-1,2,3,4-tetrahydro-2-oxo-4,6-diphenyl-pyrimidine-5-carboxamide (6b). Mp 175–177 °C (MeCN). ^{1}H NMR (DMSO-d_6) 3.83–3.89 (dd, J=5.07, 5.42 Hz, 1H), 3.98–4.04 (dd, J=6.21, 6.00 Hz, 1H), 5.26 (br, 1H), 6.67 (br, 2H), 7.10 (br, 3H), 7.34–7.36 (m, 10H), 7.49 (br, 1H), 7.55 (s, 1H), 8.68 (s, 1H); ^{13}C NMR δ 42.6, 56.5, 107.4, 126.8, 127.3, 127.3, 127.9, 128.4, 128.5, 128.8, 128.9, 129.4, 134.5, 144.1, 153.2, 166.9. MS (pos. APCI) m/z 384.6 (M+1).

4.11.3. *N*-Propyl-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxo-4-phenyl-pyrimidine-5-carboxamide (6c). Mp 239–241 °C (MeCN). Anal. Calcd ($C_{16}H_{21}N_3O_2$) C, 66.88; H, 7.37; N, 14.62. Found: C, 66.85; H, 7.44; N, 14.62. ^{1}H NMR (DMSO-d_6) δ 0.74 (br, 3H), 1.33 (m, 2H), 2.09 (s, 3H), 3.02 (br, 5H), 5.15 (s, 1H), 7.18–7.30 (m, 5H), 7.60 (s, 1H), 7.81 (br, 1H); ^{13}C NMR δ 11.8, 16.8, 22.7, 29.7, 41.0, 54.3, 110.0, 126.5, 127.7, 128.8, 138.0, 144.2, 154.6, 167.3. MS (pos. APCI) m/z 288.2 (M+1).

4.11.4. *N*-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-*p*-tolylpyrimidine-5-carboxamide (6d). Mp 223–226 °C (MeCN). Anal. Calcd ($C_{20}H_{21}N_3O_2$): C, 71.62; H, 6.31; N, 12.53. Found: C, 71.04; H, 6.22; N, 12.22. ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3H), 2.28 (s, 3H), 4.21 (br, 2H), 5.25 (br, 1H), 6.97–7.17 (m, 9H), 7.43 (s, 1H), 8.06 (br, 1H), 8.53 (s, 1H); ^{13}C NMR δ 17.4, 21.1, 42.2, 55.2, 105.4, 126.9, 127.4, 128.4, 129.3, 136.8, 137.8, 140.2, 141.8, 153.0, 166.8. MS (pos. APCI) m/z 336.4 (M+1).

4.11.5. *N*-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-(2-chlorophenyl)-pyrimidine-5-carboxamide (6e). Mp 235–237 °C. ^{1}H NMR (DMSO-d_6) δ 1.98 (s, 3H), 4.13 (br, 1H), 4.26 (br, 1H), 5.68 (1H), 6.92–7.40 (m, 9H), 8.29 (s, 1H), 9.17(br, 1H), 9.86 (br, 1H); ^{13}C NMR δ 16.6, 42.5, 53.6, 106.6, 126.9, 127.2, 128.0, 128.5, 130.0, 132.2, 134.2, 139.7, 140.2, 166.2, 174.3. MS (pos. APCI) m/z 372.6 (M+1).

4.11.6. *N*-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-*p*-tolyl-pyrimidine-5-carboxamide (6f). Mp 216–217 °C. ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3H), 2.28 (s, 3H), 4.17–4.28 (m, 2H), 5.27 (s, 1H), 6.98–7.19 (m, 9H), 8.26 (m, 1H), 9.30 (br, 1H), 9.81 (s, 1H); ^{13}C NMR δ 16.8, 21.1, 42.5, 55.2, 107.2, 126.9, 127.0, 127.4, 128.4, 129.4, 135.0, 137.3, 139.9, 140.5, 166.4, 174.2. MS (pos. APCI) m/z 352.5 (M+1).

4.11.7. *N*-Propyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(4-bromophenyl)-pyrimidine-5-carboxamide (6g). Mp 234–236 °C. Anal. Calcd ($C_{15}H_{18}BrN_3O_2$): C, 51.15; H, 5.15; N, 11.93. Found: C, 50.67; H, 4.95; N, 11.45. ^{1}H NMR (DMSO-d_6) δ 0.70 (t, J=7.2 Hz, 3H), 1.32 (m, 2H), 1.97 (s, 3H), 2.90 (m, 2H), 5.21 (s, H), 7.15–7.18 (d, 2H), 7.49–7.52 (br, 2H), 7.55 (br, 1H), 7.57 (t, J=5 Hz, 1H), 8.55 (s, 1H); ^{13}C NMR δ 11.7, 17.2, 22.7, 54.9, 105.3, 120.7, 129.0, 131.6, 134.4, 144.1, 153.0, 166.5. MS (pos. APCI) m/z 352.5 (M+1).

4.11.8. *N*-Propyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-(3-nitrophenyl)-pyrimidine-5-carboxamide (6h). Mp 240–241 °C. ^{1}H NMR (DMSO-d_6) δ 0.68 (t, J=7.5 Hz, 3H), 1.30 (m, 2H), 2.03 (s, 3H), 2.96 (m, 2H), 5.40 (s, 1H), 7.65–7.70 (m, 2H), 7.81 (t, J=5.2 Hz, 1H), 8.07 (s, 1H), 8.14 (d, J=7.2 Hz, 1H), 9.45 (br, 1H), 10.0 (s, 1H); ^{13}C NMR δ 11.7, 16.8, 22.6, 54.7, 106.6, 121.6, 123.0, 130.7, 133.5, 135.6, 145.5, 148.2, 165.9, 174.7. MS (pos. APCI) m/z 335.4 (M+1).

4.11.9. *N*-Propyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-phenyl-pyrimidine-5-carboxamide (6i). Mp 174–176 °C. ^{1}H NMR (DMSO-d_6) δ 0.71 (t, J=7.2 Hz, 3H), 1.31 (m, 2H), 1.99 (s, 3H), 2.49–2.99 (m, 2H), 5.25 (s, 1H),

7.18–7.35 (m, 5H), 7.75 (t, J=5.2 Hz, 1H), 9.30 (br, 1H), 9.81 (s, 1H); ^{13}C NMR δ 11.7, 16.7, 22.6, 55.9, 107.6, 108.4, 126.8, 128.0, 128.9, 139.4, 166.3. MS (pos. APCI) m/z 290.4 (M+1).

4.11.10. *N*-Benzyl-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxo-4-(3-nitrophenyl)-pyrimidine-5-carboxamide (6j). Mp 241–242 °C. ^{1}H NMR (DMSO-d_6) δ 2.16 (s, 3H), 3.05 (s, 3H), 4.17–4.23 (dd, J=5.7, 5.7 Hz, 1H), 4.25–4.31 (dd, J=6.12, 6.12 Hz, 1H), 5.35 (s, 1H), 6.99–7.01 (m, 1H), 7.16–7.18 (m, 3H), 7.59–7.67 (m, 2H), 7.82 (d, J=2.5 Hz, 1H), 8.06 (br, 1H), 8.13–8.15 (m, 1H), 8.38–8.42 (m, 1H); ^{13}C NMR δ 17.0, 29.8, 53.9, 108.0, 121.5, 122.8, 127.0, 127.4, 128.5, 130.5, 133.6, 139.8, 140.0, 146.2, 148.2, 153.5, 167.0. MS (pos. APCI) m/z 381.6 (M+1).

4.12. General procedure for the synthesis of DHPM C5 esters using a fluorous Mitsunobu protocol

A small microwave vial (0.5–2 mL) was charged with 0.07 mmol of the corresponding DHPM acid **5a** or **c**, F-TPP (89 mg, 1.8 equiv), and anhydrous THF (0.5 mL). After stirring for a few seconds, the corresponding alcohol (1.8 equiv) and F-DIAD (106 mg, 1.8 equiv) were added, the vial was capped, flushed with argon, and heated at 110 °C for the times given in Table 5. After cooling to 50 °C, F-NCO reagent (110 mg, 3.2 equiv, 0.22 mmol) and Et_3N (39 μL, 4 equiv, 0.28 mmol) were added and the vial was again heated in the microwave reactor at 110 °C for 30 min (entries 2 and 5, Table 5). Subsequently, the solvent was evaporated, the mixture dissolved in ca. 300–400 μL MeOH, and passed through a cartridge filled with 2.5 g of F-silica, which was pre-conditioned with 5 mL THF and 15 mL H_2O, with 8 mL of 80% MeOH in H_2O. The solvent was evaporated then the residue was dissolved in 0.5 mL of THF and passed through a cartridge filled with 700 mg Amberlite IRA-900 resin in carbonate form (1.5 g for entries 3–5), which was pre-conditioned with 8 mL MeOH and 10–20 mL THF, with 10 mL THF. The solvent was evaporated and the residue was washed two times with toluene, which was also removed by evaporation. For yields and purities see text and Table 5.

4.12.1. Butyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7a). ^{1}H NMR (DMSO-d_6) δ 0.78 (t, J=7.3 Hz, 3H), 1.09–1.19 (m, 2H), 1.39–1.47 (m, 2H), 2.25 (s, 3H), 3.86–3.99 (m, 2H), 5.13 (d, J=3.0 Hz, 1H), 7.21–7.35 (m, 5H), 7.73 (br s, 1H), 9.20 (br s, 1H). MS (ES$^+$) m/z 289.1 (M+1).

4.13. General procedure for the synthesis of DHPM C5 esters under classical Mitsunobu conditions

A small microwave vial (0.5–2 mL) was charged with 0.1 mmol of the corresponding DHPM acid **5a**, **5c** or **5e**, triphenylphosphine (TPP, 39 mg, 1.5 equiv), and anhydrous THF (0.7 mL). After stirring for a few seconds, the corresponding alcohol (1.5 equiv) and diisopropyl azodicarboxylate (DIAD, 29.5 μL, 1.5 equiv) were added and the mixture was stirred for the time given in Table 7. For secondary alcohols, 1.8 equiv each of alcohol, TPP, and DIAD was used. Subsequently, the solvent was evaporated and the reaction mixture was purified by column chromatography using DCM/EtOAc for *N*1-methyl substituted and $CHCl_3$/acetone for *N*1-unsubstituted products. For the products **7k** and **7l** a mixture of hexane/THF and for **7p** hexanes/EtOAc were used. For yields and purities see text and Table 7.

4.13.1. 3-Fluorobenzyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7b). ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 3.26 (s, 3H), 5.01–5.05 and 5.09–5.13 (2m, 2H), 5.40 (d, J=2.9 Hz, 1H), 5.58 (br s, 1H), 6.79 (d, J=9.5 Hz, 1H), 6.91–7.01 (m, 2H), 7.19–7.31 (m, 6H). MS (ES$^+$) m/z 355.5 (M+1).

4.13.2. Propyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7c). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J=7.4 Hz, 3H), 1.54–1.64 (m, 2H), 2.54 (s, 3H), 3.25 (s, 3H), 4.02 (t, J=6.6 Hz, 2H), 5.39 (d, J=2.9 Hz, 1H), 5.58 (br s, 1H), 7.25–7.33 (m, 5H). MS (ES$^+$) m/z 289.5 (M+1).

4.13.3. *i*-Propyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7d). ^{1}H NMR ($CDCl_3$) δ 1.06 (d, J=6.2 Hz, 3H), 1.24 (d, J=6.2 Hz, 3H), 2.52 (s, 3H), 3.25 (s, 3H), 4.94–5.04 (m, 1H), 5.38 (d, J=2.7 Hz, 1H), 5.55 (br s, 1H), 7.25–7.33 (m, 5H). MS (ES$^+$) m/z 289.5 (M+1).

4.13.4. Cyclohexyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7e). ^{1}H NMR ($CDCl_3$) δ 1.22–1.54 (m, 9H), 1.82–1.85 (m, 1H), 2.54 (s, 3H), 3.24 (s, 3H), 4.74–4.79 (m, 1H), 5.40 (d, J=2.8 Hz, 1H), 5.57 (br s, 1H), 7.25–7.33 (m, 5H). MS (ES$^+$) m/z 329.4 (M+1).

4.13.5. Propyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7f). ^{1}H NMR (DMSO-d_6) δ 0.74 (t, J=7.4 Hz, 3H), 1.47 (sex, J_1=6.9 Hz, J_2=7.1 Hz, 2H), 2.26 (s, 3H), 3.83–3.94 (m, 2H), 5.14 (d, J=3.0 Hz, 1H), 7.22–7.34 (m, 5H), 7.73 (br s, 1H), 9.19 (br s, 1H). MS (ES$^+$) m/z 275.7 (M+1).

4.13.6. *i*-Propyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7g). ^{1}H NMR (DMSO-d_6) δ 0.98 (d, J=6.2 Hz, 3H), 1.15 (d, J=6.2 Hz, 3H), 2.24 (s, 3H), 4.75–4.86 (m, 1H), 5.12 (d, J=2.8 Hz, 1H), 7.22–7.34 (m, 5H), 7.72 (br s, 1H), 9.16 (br s, 1H). MS (ES$^+$) m/z 275.3 (M+1).

4.13.7. 3-Butynyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7h). ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.42–2.45 (m, 2H), 2.85 (br s, 1H), 3.95–4.07 (m, 2H), 5.14 (d, J=2.8 Hz, 1H), 7.21–7.33 (m, 5H), 7.77 (br s, 1H), 9.24 (br s, 1H). MS (ES$^+$) m/z 285.3 (M+1).

4.13.8. 3-Butynyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7i). ^{1}H NMR ($CDCl_3$) δ 1.97 (t, J=2.5 Hz, 1H), 2.43–2.47 (m, 2H), 2.54 (s, 3H), 3.26 (s, 3H), 4.17 (t, J=6.6 Hz, 2H), 5.40 (d, J=3.0 Hz, 1H), 5.59 (br s, 1H), 7.26–7.33 (m, 5H). MS (ES$^+$) m/z 299.4 (M+1).

4.13.9. 3-Fluorobenzyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7j). ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 4.97–5.00 and 5.07–5.11 (2m,

2H), 5.19 (d, J=3.0 Hz, 1H), 6.88 (d, J=10.0 Hz, 1H), 6.96 (d, J=7.6 Hz, 1H), 7.06–7.11 (m, 1H), 7.20–7.34 (m, 6H), 7.77 (br s, 1H), 9.30 (br s, 1H). MS (ES^+) m/z 341.4 (M+1).

4.13.10. *cis*-3,7-Dimethyl-2,6-octadien-1-yl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7k). ^1H NMR (DMSO-d_6) δ 1.52 (s, 3H), 1.60 (s, 3H), 1.67 (s, 3H), 1.99 (br s, 4H), 2.23 (s, 3H), 4.44 (d, J=7.0 Hz, 2H), 5.03 (br s, 1H), 5.12 (d, J=2.6 Hz, 1H), 5.21 (t, J=7.0 Hz, 1H), 7.20–7.31 (m, 5H), 7.73 (br s, 1H), 9.19 (br s, 1H). MS (ES^+) m/z 369.3 (M+1).

4.13.11. *cis*-3,7-Dimethyl-2,6-octadien-1-yl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7l). ^1H NMR (DMSO-d_6) δ 1.52 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 2.00 (br s, 4H), 2.46 (s, 3H), 3.08 (s, 3H), 4.43–4.53 (m, 2H), 5.04–5.05 (m, 1H), 5.13 (d, J=3.5 Hz, 1H), 5.23 (t, J=6.8 Hz, 1H), 7.17–7.31 (m, 5H), 7.96 (br d, J=3.6 Hz, 1H). MS (ES^+) m/z 383.4 (M+1).

4.13.12. Furfuryl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7m). ^1H NMR (DMSO-d_6) δ 2.22 (s, 3H), 5.00 (s, 2H), 5.11 (d, J=3.1 Hz, 1H), 6.39–6.43 (m, 2H), 7.15–7.29 (m, 5H), 7.65 (d, J=0.8 Hz, 1H), 7.76 (br s, 1H), 9.28 (br s, 1H). MS (ES^+) m/z 313.5 (M+1).

4.13.13. Furfuryl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7n). ^1H NMR (DMSO-d_6) δ 2.47 (s, 3H), 3.09 (s, 3H), 5.06 (s, 2H), 5.12 (d, J=3.7 Hz, 1H), 6.43 (s, 2H), 7.12–7.29 (m, 5H), 7.67 (s, 1H), 7.98 (br d, J=3.8 Hz, 1H). MS (ES^+) m/z 327.2 (M+1).

4.13.14. (*R*)-(+)-Oxirane-2-methyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7o). ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H), 2.50 (br s, 1H), 2.70 (t, J=4.5 Hz, 1H), 3.07–3.15 (m, 1H), 3.76–3.83 (m, 1H), 4.28–4.32 (m, 1H), 5.16 (d, J=2.7 Hz, 1H), 7.24–7.35 (m, 5H), 7.79 (br s, 1H), 9.29 (br s, 1H). MS (ES^+) m/z 289.0 (M+1).

4.13.15. (*R*)-(+)-Oxirane-2-methyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7p). ^1H NMR (DMSO-d_6) δ 2.50 (br s, 4H), 2.71–2.73 (m, 1H), 3.11–3.20 (m, 4H), 3.78–3.87 (m, 1H), 4.33–4.38 (m, 1H), 5.17 (d, J=2.6 Hz, 1H), 7.22–7.34 (m, 5H), 8.02 (br d, J=2.1 Hz, 1H). MS (ES^+) m/z 303.1 (M+1).

4.13.16. 1-(2-Furyl)-1-propyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7q). ^1H NMR ($CDCl_3$), mixture of diastereoisomers, δ 0.60 (t, J=7.3 Hz, 3H), 0.90 (t, J=7.3 Hz, 3H), 1.71–1.84 (m, 2H), 1.94–2.02 (m, 2H), 2.49 (s, 3H), 2.56 (s, 3H), 3.23+3.24 (2s, 6H), 4.94–5.01 (m, 2H), 5.36+5.41 (2s, 2H), 5.56+5.58 (2br s, 2H), 6.04 (d, J=2.4 Hz, 1H), 6.25+6.29+6.34 (3s, 3H), 7.13–7.30 (m, 11H), 7.39 (s, 1H). MS (ES^+) m/z 355.5 (M+1).

4.13.17. *i*-Propyl 1-methyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7r). ^1H NMR (DMSO-d_6) δ 1.01 (d, J=6.2 Hz, 3H), 1.19 (d, J=6.2 Hz, 3H), 2.50 (s, 3H), 3.11 (s, 3H), 4.82–4.93 (m, 1H), 5.28 (d, J=3.5 Hz, 1H), 7.63–7.69 (m, 2H), 8.06 (br s, 1H), 8.12–8.14 (m, 2H). MS (ES^+) m/z 334.5 (M+1).

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Hydroxylamine as an ammonia equivalent in microwave-enhanced aminocarbonylations

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Abstract—A novel palladium-catalyzed and $Mo(CO)_6$ promoted aminocarbonylation protocol was developed for rapid generation of primary aromatic amides from aryl bromides and iodides. Employing controlled microwave heating, hydroxylamine was first reduced in situ to ammonia, which thereafter reacted with carbon monoxide and the aryl halide substrate, delivering the benzamide product in less than 20 min. Based on this in situ carbonylation, a facile preparation of a novel HIV-1 protease inhibitor was achieved.

1. Introduction

Microwave heating has now been used in organic chemistry for 20 years with a steadily increasing number of reported examples every year.[1] In particular, applications in early stages of drug discovery have increased dramatically during the last 5-year period. It is the highly controlled, facile, and rapid in situ heating that makes controlled high-density microwave heating ideal, not only for promoting traditional laboratory-scale reactions, but also for automated organic and medicinal syntheses.[2,3] Despite the impressive advantages, additional robust and selective microwave protocols must be identified to accelerate lead identification and optimization work in the pharmaceutical industry.[4]

The greatest advantage of carbonylative reactions mediated by solid or liquid carbon monoxide sources is that they can be performed without equipment for introduction of gaseous carbon monoxide.[5] Handling in small-scale experiments is also more straightforward and much safer compared to protocols using free carbon monoxide gas. We have previously reported the exploitation of formamides or $Mo(CO)_6$ as robust carbon monoxide releasing reagents in palladium-catalyzed amino-,[6–8] alkoxy-,[9] sulfonamido-[10] and hydrazidocarbonylations.[11] Other research groups have presented alternative methods for carbon monoxide-free carbonylative chemistry.[5] One of our initial forays into $Mo(CO)_6$ promoted aminocarbonylations included the investigation of intermolecular reactions to form secondary and tertiary aromatic amides, and subsequent work has allowed for the extension of this chemistry into intramolecular examples.[12] However, the preparation of primary benzamides by aminocarbonylation of aryl halides with ammonia as the nucleophile is recognized as considerably more troublesome, since the reaction requires two toxic gaseous reactants, ammonia and carbon monoxide. In addition, the nucleophilicity of ammonia is limited and the Pd(II) coordination strength is high.[13] Thus, Indolese's recently reported synthesis of primary benzamides under pressurized carbon monoxide (5 bar) using a nucleophilic Lewis base (imidazole or 4-(dimethylamino)pyridine) as promoter, represented a major improvement.[14] In order to avoid using free carbon monoxide and to speed up the reaction rate, we further developed the protocol from Indolese by applying high-density microwave radiation. Under these high temperature conditions and in the presence of KO*t*-Bu, formamide served not only as the solvent, but also as a combined ammonia and carbon monoxide source.[15] Unfortunately, the strong basic reaction medium prevented utilization of the methodology for preparation of easily racemized and sensitive target structures. Therefore, a mild and rapid method for carbonylative preparation of primary benzamides appeared attractive and of high value for demanding medicinal chemistry applications. Stimulated by reports on $Mo(CO)_6$ mediated reductive cleavage of N–O bonds,[16] we decided to investigate hydroxylamine hydrochloride (**1**) as a convenient solid ammonia equivalent. Herein, we report the development of a rapid palladium-catalyzed procedure for benzamide (**3**) synthesis from hydroxylamine and aryl bromides (**2**) or iodides (**4**) by the reductive and carbon monoxide releasing actions of $Mo(CO)_6$. The methodology was further applied to the synthesis of a complex HIV-1 protease inhibitor.

Keywords: Carbonylation; Microwave; Palladium catalysis; Inhibitors.
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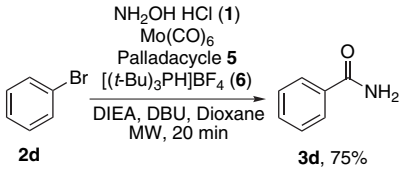
2. Results and discussion

2.1. Aryl bromides as coupling partners

To establish the viability of the carbonylation, we first undertook a small screening of a variety of palladium sources, ligands, solvents, and reaction variables (temperature and irradiation time) employing bromobenzene (**2d**) as substrate and **1** as pronucleophile (Eq. 1). The reactions were performed with 0.5 equiv of $Mo(CO)_6$ in sealed microwave transparent vessels under air. An excess of DBU was used in all attempts both to release free hydroxylamine and to serve as an efficient base in the reaction along with diisopropylethylamine (DIEA). We quickly found that using 5% Herrmann's palladacycle (**5**), 10% $[(t\text{-Bu})_3PH]BF_4$ (**6**) as an additional ligand source, and with 1,4-dioxane as solvent, microwave heating at 150 °C for 20 min furnished a generally successful reaction protocol (Eq. 1). Product **3d** was obtained in 75% isolated yield and importantly, no phenylhydroxamic acid product from a direct carbonylation with **1** was observed. Based on this result, the method was tested on seven additional model aryl bromides.



(1)

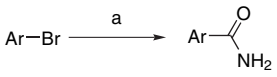
The results are summarized in Table 1. It was quickly proven that both electron-rich and electron-poor aryl bromides worked for this transformation, providing 71–81% yield of **3a–g** without traces of potentially competing hydroxamic acid. In addition, the heterocyclic 3-thiophene amide **3h** was isolated in 70% yield (entry 8). To compare **1** with the perhaps more obvious ammonia source ammonium chloride, two additional carbonylations were performed. Interestingly, ammonium chloride delivered lower yields compared with **1** in both reactions due to the formation of nitriles as side products, indicating a true advantage of hydroxylamine hydrochloride (Table 1, entries 4 and 7).

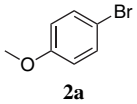
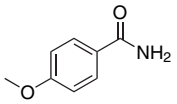
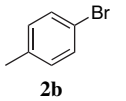
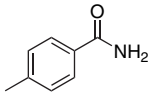
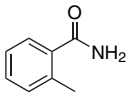
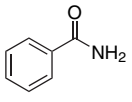
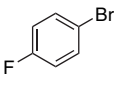
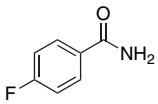
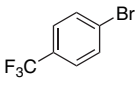
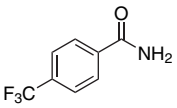
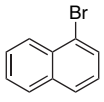
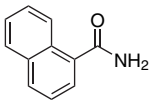
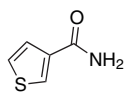
2.2. Aryl iodides as coupling partners

We chose the aminocarbonylation of *o*-tolyl iodide (**4c**) with hydroxylamine hydrochloride as the standard reaction to investigate suitable reaction conditions for both the amidation of electronically diverse model aryl iodides **4a,b,d–h** and for subsequent decoration of the HIV-1 inhibitor *ortho*-bromo precursors **7** and **9**. Although the original ligand-free aminocarbonylative conditions developed by our laboratory for generation of secondary and tertiary benzamides from aryl iodides[8] delivered significant amounts of product, the reactions failed to reach full conversion of **4c**. It was however found that addition of phosphine ligands, especially $[(t\text{-Bu})_3PH]BF_4$ and the bidentate ligand dppf, dramatically improved both conversion and yield (Table 2).

This finding was unexpected since aryl iodides normally do not need sophisticated phosphines to undergo activation by palladium(0) catalysts. Thus, by employing lower reaction temperatures (110–130 °C) but with an otherwise identical reaction system as the corresponding aryl bromides, we could isolate the primary amide **3c** in 69–84% yield (Table 2,

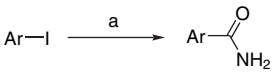
Table 1. Preparation of benzamides from aryl bromides by in situ carbonylation

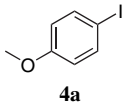
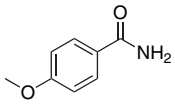
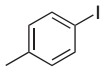
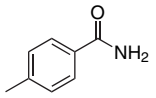
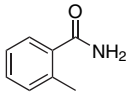
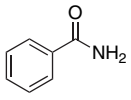
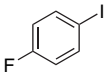
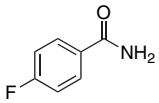
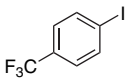
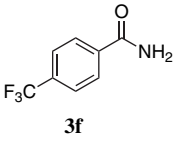
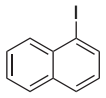
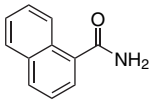
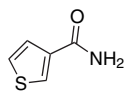


Entry	Ar-Br	Benzamide	Isolated yield (%)
1	 **2a**	 **3a**	71
2	 **2b**	 **3b**	81
3	 **2c**	 **3c**	78
4	 **2d**	 **3d**	75 69[b]
5	 **2e**	 **3e**	81
6	 **2f**	 **3f**	80
7	 **2g**	 **3g**	71 55[b]
8	 **2h**	 **3h**	70

[a] Aryl bromide (0.8 mmol), $Mo(CO)_6$ (0.4 mmol), NH_2OH HCl (1.6 mmol), Herrmann's palladacycle **5** (5 mol %), $[(t\text{-Bu})_3PH]BF_4$ (10 mol %), DBU (0.8 mmol), DIEA (1.6 mmol), dioxane (2.0 mL), microwave irradiation at 150 °C for 20 min in a sealed vial.
[b] NH_4Cl as ammonia source.

Table 2. Preparation of benzamides from aryl iodides by in situ carbonylation



Entry	Ar-I	Benzamide	Temp (°C)	Isolated yield (%)
1	 **4a**	 **3a**	130 110	67 78
2	 **4b**	 **3b**	130 110	74 80
3	 **4c**	 **3c**	130 110	69 84
4	 **4d**	 **3d**	130 110	74 77
5	 **4e**	 **3e**	110	76
6	 **4f**	 **3f**	130 110	73 76
7	 **4g**	 **3g**	110	83
8	 **4h**	 **3h**	110	80

[a] Aryl iodide (0.8 mmol), $Mo(CO)_6$ (0.4 mmol), NH_2OH HCl (1.6 mmol), Herrmann's palladacycle **5** (5 mol %), $[(t\text{-}Bu)_3PH]BF_4$ (10 mol %), DBU (0.8 mmol), DIEA (1.6 mmol), dioxane (2.0 mL), microwave irradiation for 20 min in a sealed vial.

entry 3). Furthermore, from Table 2 it is clear that this is a general microwave method that tolerates electronically diverse coupling partners **4**. This trend also held true with electron-rich thiophene **4h**. It is noteworthy that in all cases a reaction time of 20 min was sufficient for complete consumption of the aryl iodide and that an increase of the reaction temperature to 130 °C afforded reduced yields (Table 2).

2.3. Synthesis of HIV-1 protease inhibitors

The 1,2-dihydroxyethylene structure derived from L-mannitol and depicted in Figure 1 has been shown to be an effective transition-state mimic in inhibitors of aspartic proteases. By using this C_2-symmetric core scaffold, compounds inhibiting the HIV-1 protease enzyme at low nanomolar or even sub-nanomolar concentrations have been reported.[17,18]

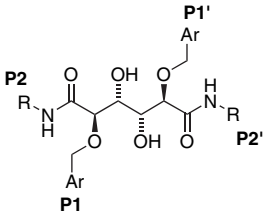


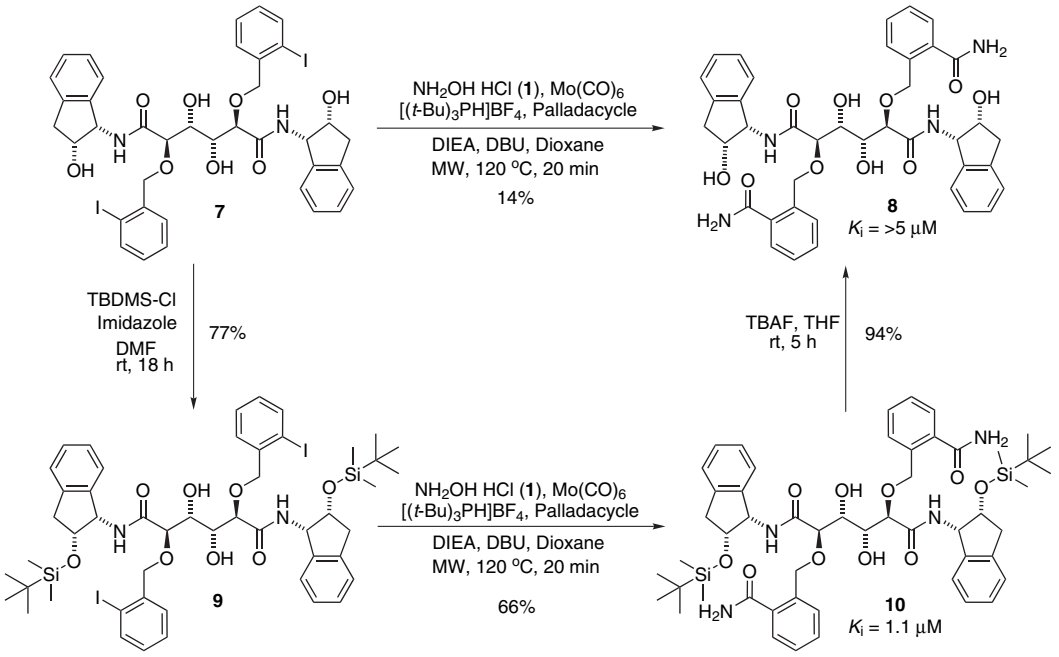
Figure 1.

The benzylic P1/P1′ side chains of these inhibitors have also been previously decorated in the 2-, 3-, and 4-positions by palladium(0)-catalyzed couplings and aminocarbonylation reactions.[17,19] Up to this point, however, synthesis of inhibitors including a primary benzamide functionality in the P1/P1′ positions has not been accomplished.

After preparing **7** according to the literature procedure,[18] we attempted the first carbonylation using **1** as the ammonia surrogate (Scheme 1). The conditions for aryl iodides identified above furnished complete conversion at 120 °C but in a complex product mixture. The purification of the product was further hampered by the poor solubility and high retention of **8** on silica. We then decided to protect the hydroxyl groups of compound **7** in an attempt to block the possibility of intramolecular alkoxycarbonylation and to improve the solubility of the product.[20] Standard conditions for TBDMS protection of alcohols produced the bis-protected compound **9** as the main product.[21] Carbonylation of **9** proceeded smoothly using slightly modified conditions and product **10** could be isolated in a satisfying 66% yield. Compound **10** was subsequently deprotected with TBAF to deliver inhibitor **8** (Scheme 1). Even though biological testing of compounds **8** and **10** showed that only **10** was a full inhibitor at 5 μM, the synthesis of **8** and **10** exemplifies the usefulness of the developed method also when dealing with more complex substrates.

2.4. Discussion

We propose that the investigated palladium(0)-catalyzed carbonylation follows the same general pathway as the analogous reaction with gaseous carbon monoxide and ammonia.[22] To examine the hypothesis that ammonia, and not hydroxylamine, acts as the principal nucleophile in the aminocarbonylation, we decided to conduct a series of control reactions. First, benzohydroxamic acid was cleanly reduced to benzamide **3d** under aryl bromide carbonylation conditions without the palladium catalyst and **1**. At room temperature, no benzamide formation was detected. These



Scheme 1.

two experiments established that hydroxylamine might operate as the nucleophile attacking the intermediate palladium acyl complex, affording **3d** after reduction at 150 °C. The next step was to study the reduction of hydroxylamine hydrochloride (**1**) to ammonia. A complete aminocarbonylation cocktail (entry 4, Table 1) was stirred for 20 min at room temperature with subsequent addition of benzoyl chloride to trap all free amines and revealed that only benzamide **3d** was formed without any trace of benzohydroxamic acid. Increase of the reaction temperature afforded an identical outcome, strongly supporting the suggestion that hydroxylamine is directly reduced to ammonia in the presence of $Mo(CO)_6$. Thus, in summary we believe benzamide products **3a**–**h** are formed as a result of a carbonylation process with free ammonia, and not hydroxylamine, as the reactive nucleophile.

3. Conclusion

A new $Mo(CO)_6$ promoted and microwave-accelerated route to primary benzamides from aryl bromides or iodides has been developed utilizing hydroxylamine hydrochloride as the solid source of ammonia. Consequently, no cumbersome handling of gases is needed following this in situ carbonylation protocol. The synthetic method is rapid, efficient, and quite practical and we envision that the procedure may find applications as a valuable amidation reaction. Employing this in situ ammoniacarbonylation approach, we successfully prepared a novel HIV-1 protease inhibitor in a straightforward manner.

4. Experimental

4.1. General

All microwave-assisted reactions were carried out using a single-mode microwave cavity (Smith Synthesizer, Biotage AB, Uppsala, Sweden) producing controlled irradiation at 2450 MHz. Reaction temperatures were determined and controlled via the built-in, on-line IR-sensor. Thin-layer chromatography was performed using aluminum or glass supported Merck Silica gel 60 F_{254} TLC plates and visualized with UV light. Flash column chromatography was performed using Merck Silica gel 60 (0.040–0.063 mm). Mass spectra (EI, 70 eV) of compounds **3a**–**h** were recorded with a mass-selective detector interfaced with a gas chromatograph equipped with a 30 m×0.25 mm CP-Sil 8 CB capillary column. RPLC–MS analysis of compounds **7**–**10** were performed using a Gilson HPLC system with a Chromolith SpeedROD RP-18e column (50×4.6 mm) and a Finnigan AQA quadropole mass spectrometer using a 4 mL/min CH_3CN/H_2O gradient (0.05% HCOOH) and detection by both UV (DAD, 190–350 nm) and MS (ESI+). ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer at 400 and 100.5 MHz, respectively. Chemical shifts were referenced to internal tetramethylsilane when using $CDCl_3/CD_3OD$ mixtures and indirectly to tetramethylsilane via the residual solvent signal when using pure solvents.

All starting materials and reagents were commercially available and used as received. Herrmann's palladacycle, *trans*-di(μ-acetato)bis[*o*-tolylphosphino)benzyl]dipalladium (II) **5** was purchased from Strem. $Mo(CO)_6$ was obtained from Acros. Products **3a**,[15] **3b**,[15] **3c**,[15] **3d**,[15] **3f**,[15] **3g**,[15] **3e**,[23] and **3h**[24] are known compounds and analytical data were consistent with literature values.

4.2. General procedure for aminocarbonylation with hydroxylamine hydrochloride salt (1)

A 2–5 mL process vial was charged with **1** (112 mg, 1.60 mmol) or NH_4Cl (86 mg, 1.60 mmol), $Mo(CO)_6$ (106 mg, 0.40 mmol), palladacycle **5** (38 mg, 0.040 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (22 mg, 0.080 mmol), DBU (0.120 mL, 0.80 mmol), DIEA (0.277 mL, 1.6 mmol), aryl bromides **2**

(0.80 mmol) or iodides **4** (0.80 mmol), and dioxane 2.0 mL. The vessel was sealed under air and exposed to microwave heating for 20 min at 150 °C (for bromides) or 110–130 °C (for iodides). The reaction tube was thereafter cooled to room temperature and the mixture was diluted with 5.0 mL CH_2Cl_2 and purified on silica gel (30:70 to 100:0 EtOAc/hexane) to give the corresponding benzamides **3a**–**h**.

4.3. Synthesis of HIV-1 protease inhibitors

4.3.1. *N*1,*N*6-Bis[(1*S*,2*R*)-2-hydroxy-1-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(2-iodobenzyloxy)-3,4-dihydroxyhexane-1,6-diamide (7). Synthesized according to the procedure in Ref. 18. MS (ESI+) *m*/*z*=905.3 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, *J*=7.9, 1.2 Hz, 2H), 7.44–7.37 (m, 4H), 7.31 (ddd, *J*=7.9, 7.6, 1.2 Hz, 2H), 7.26–7.18 (m, 8H), 6.99 (ddd, *J*=7.9, 7.4, 1.7 Hz, 2H), 5.31 (dd, *J*=8.8, 5.2 Hz, 2H), 4.74 (d, *J*=11.8 Hz, 2H), 4.70 (d, *J*=11.8 Hz, 2H), 4.63 (app. dt, *J*=5.4, 2.5 Hz, 2H), 4.34 (AA′ part of AA′BB′, 2H), 4.26 (BB′ part of AA′BB′, 2H), 3.08 (dd, *J*=16.6, 5.6 Hz, 2H), 2.88 (dd, *J*=16.6, 2.5 Hz, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.4, 141.0, 139.8, 139.7, 139.2, 130.2, 128.7, 128.5, 127.2, 125.5, 124.5, 99.0, 82.3, 72.7, 71.5, 58.0, 39.4. Anal. Calcd (%) for $C_{38}H_{38}I_2N_2O_8$+H_2O: C, 49.47; H, 4.37; N, 3.04. Found: C, 49.3; H, 4.6; N, 3.1.

4.3.2. *N*1,*N*6-Bis[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyl-oxy)-indan-1-yl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(2-iodobenzyl-oxy)-3,4-dihydroxyhexane-1,6-diamide (9). Imidazole (272 mg, 4.00 mmol), TBDMSCl (301 mg, 2.00 mmol), and DMAP (10 mg, catalyst) were added sequentially to a solution of **7** (181 mg, 0.200 mmol) in 2 mL of DMF. After stirring at room temperature for 18 h, the reaction mixture was quenched with MeOH, diluted with ethyl acetate (40 mL), washed with water (3×30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Hexanes/EtOAc gradient). A side product consistent with tris-protected **7** was isolated (43.6 mg, 18%) but the main product was identified as **9** (176 mg, 77%). MS (ESI+) *m*/*z*=1133.6 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, *J*=7.9, 1.3 Hz, 2H), 7.65 (d, *J*=9.1 Hz, 2H), 7.39 (dd, *J*=7.6, 1.8 Hz, 2H), 7.28–7.12 (m, 10H), 6.97 (dt, *J*=7.6, 1.8 Hz, 2H), 5.44 (dd, *J*=9.1, 5.4 Hz, 2H), 4.82 (d, *J*=11.7 Hz, 2H), 4.76 (d, *J*=11.7 Hz, 2H), 4.68–4.66 (m, 2H), 4.63 (app. dt, *J*=5.3, 2.4 Hz, 2H), 4.29 (d, *J*=7.9 Hz, 2H), 4.16–4.09 (m, 2H), 3.11 (dd, *J*=16.2, 5.3 Hz, 2H), 2.91 (dd, *J*=16.2, 2.5 Hz, 2H), 0.76 (s, 18H), 0.04 (s, 6H), 0.01 (s, 6H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 173.0, 140.9, 140.1, 139.6, 139.4, 130.5, 130.0, 128.5, 128.1, 127.0, 125.04, 124.99, 99.4, 77.92, 77.87, 74.1, 71.3, 56.4, 40.8, 26.0, 18.2, −4.6. Anal. Calcd (%) for $C_{50}H_{66}I_2N_2O_8Si_2$: C, 53.00; H, 5.87; N, 2.47. Found: C, 53.29; H, 6.04; N, 2.33.

4.3.3. *N*1,*N*6-Bis[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyl-oxy)-indan-1-yl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(2-carbamoyl-benzyloxy)-3,4-dihydroxyhexane-1,6-diamide (10). A 0.5–2 mL microwave vial was charged with **9** (170 mg, 0.150 mmol), $Mo(CO)_6$ (106 mg, 0.40 mmol), palladacycle **5** (19 mg, 0.020 mmol), [(*t*-Bu)$_3$PH]BF_4 (11 mg, 0.040 mmol), hydroxylamine hydrochloride (112 mg, 1.60 mmol), dioxane (2 mL), and DIEA (0.247 mL, 1.40 mmol). Finally DBU (0.120 mL, 0.80 mmol) was added and the vial was capped with a Teflon septum and irradiated with microwaves to 120 °C for 20 min. After cooling to room temperature the reaction mixture was filtered through a short Celite pad and the solvent was evaporated. The residue was purified by silica column flash chromatography (EtOAc/MeOH gradient) to give **10** (98.6 mg, 66%) as a light yellow solid. MS (ESI+) *m*/*z*=967.7 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, *J*=5.6, 3.4 Hz, 2H), 7.43 (d, *J*=8.6 Hz, 2H), 7.38–7.19 (m, 14H), 6.65 (s, 2H), 6.52 (s, 2H), 5.42 (dd, *J*=8.6, 5.3 Hz, 2H), 5.00–4.73 (m, 2H), 4.68 (d, *J*=10.2 Hz, 2H), 4.60 (app. dt, *J*=5.2, 2.2 Hz, 2H), 4.16 (app. s, 4H), 3.10 (dd, *J*=16.2, 5.2 Hz, 2H), 2.90 (dd, *J*=16.2, 2.3 Hz, 2H), 0.76 (s, 18H), 0.05 (s, 6H), 0.00 (s, 6H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 172.04, 172.02, 141.3, 140.0, 135.7, 134.6, 131.3, 130.8, 128.9, 128.4, 128.1, 127.2, 125.0, 124.9, 80.6, 74.2, 71.9, 70.9, 56.8, 40.7, 25.8, 18.2, −4.7. Anal. Calcd (%) for $C_{52}H_{70}N_4O_{10}Si_2$: C, 64.57; H, 7.29; N, 5.79. Found: C, 64.30; H, 7.39; N, 5.65.

4.3.4. *N*1,*N*6-Bis[(1*S*,2*R*)-2-hydroxy-1-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(2-carbamoyl-benzyloxy)-3,4-dihydroxyhexane-1,6-diamide (8).

4.3.4.1. Carbonylation of 7. A 0.5–2 mL microwave vial was charged with **7** (136 mg, 0.150 mmol), $Mo(CO)_6$ (106 mg, 0.40 mmol), palladacycle **5** (19 mg, 0.020 mmol), [(*t*-Bu)$_3$PH]BF_4 (11 mg, 0.040 mmol), hydroxylamine hydrochloride (112 mg, 1.60 mmol), dioxane (2 mL), and DIEA (0.247 mL, 1.40 mmol). Finally DBU (0.120 mL, 0.80 mmol) was added and the vial was capped with a Teflon septum and irradiated with microwaves to 120 °C for 20 min. After cooling to room temperature the reaction mixture was filtered through a short Celite pad and the solvent was evaporated. The residue was purified by silica column flash chromatography (10% MeOH in $CHCl_3$) to give **8** (15.5 mg, 14%) as a white solid.

4.3.4.2. Deprotection of 10. To a solution of **10** (61.1 mg, 0.063 mmol) in THF (2 mL) was added tetrabutylammoniumfluoride (TBAF, 1 M in THF, 0.14 mL, 0.14 mmol) and the mixture was stirred at room temperature. After 5 h the solvent was evaporated and the solid residue suspended in 10 mL of water and stirred for 15 min. The water was decanted off and the water wash was repeated once. The suspension was then filtered and the solid was washed with 10 mL of ether and thereafter dried to give **8** (43.8 mg, 94%) as a white solid. MS (ESI+) *m*/*z*=739.5 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD, 1:1): δ 7.53–7.48 (m, 2H), 7.44–7.35 (m, 6H), 7.31–7.19 (m, 8H), 5.41 (d, *J*=5.3 Hz, 2H), 4.85 (d, *J*=11.1 Hz, 2H), 4.81 (d, *J*=11.1 Hz, 2H), 4.66–4.61 (m, 2H), 4.19–4.12 (m, 4H), 3.19 (dd, *J*=16.6, 5.3 Hz, 2H), 2.98 (dd, *J*=16.6, 2.3 Hz, 2H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 171.1, 170.5, 142.0, 140.6, 136.3, 135.0, 129.7, 128.1, 127.3, 127.2, 127.1, 126.3, 124.7, 124.3, 79.7, 72.3, 70.0, 69.1, 56.8, 39.9. Anal. Calcd (%) for $C_{40}H_{42}N_4O_{10}$+H_2O: C, 63.48; H, 5.86; N, 7.40. Found: C, 63.38; H, 5.94; N, 7.27.

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Fast and selective synthesis of novel cyclic sulfamide HIV-1 protease inhibitors under controlled microwave heating

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Abstract—A novel and highly selective silver-promoted monobenzylation method was developed to promote synthesis of nonsymmetrical sulfamide-based HIV-1 inhibitors. Microwave-accelerated palladium-catalyzed *N*-amide arylation- and aminocarbonylation reactions were employed for rapid and reliable compound generation. With this class of inhibitory agents, six active inhibitors were identified, the most potent inhibitor possessing a K_i-value of 20 nM.

1. Introduction

Since the mid-1980s, a large number of studies have demonstrated that an acceleration of chemical rates can be achieved by employing high-density microwave irradiation instead of traditional sources of heat.[1–4] Although high yields and clean reactions are commonly obtained with microwave heating, reduced selectivities have been reported at high temperatures.[5,6] Hence, development of fast and highly selective reaction protocols, remains a challenge.

The recent development of palladium-catalyzed gas-free aminocarbonylations[7] and *N*-amide arylations[8] has enabled direct attachment of amide functionalities to sp^2-carbons that were previously difficult to accomplish. However, the commonly tedious fine-tuning of the appropriate reaction parameters, and the requirement for inert conditions and long reaction times, has limited the usage of these direct transformations in medicinal chemistry.

A large number of very potent urea-based cyclic HIV-1 protease inhibitors carrying four-side chains has been prepared and evaluated following the pioneering work by Lam and coworkers.[9] Interestingly, by switching the water-mimicking group from urea to sulfamide, an unanticipated flipped binding mode was obtained according to X-ray crystal structures of inhibitors in complex with the HIV-1 protease.[10,11] The preparative route to these inhibitors was complex and the inhibitors were lipophilic and of high-molecular weight. To investigate if properly functionalized benzylic side-chains could span from *P*2/*P*2′ to *P*1/*P*1′ and thus simplify the otherwise cumbersome synthetic pathway, a set of C_2-symmetric *ortho*-functionalized sulfamide derivatives were synthesized and evaluated. The most potent inhibitor from this series (K_i=0.53 μM), substituted with two benzofuran moieties, was identified as a lead structure for further optimization (Fig. 1).[12] Thus, based on isosteric replacement and modeling, it was hypothesized that an amide function (–CONH) might be of interest to incorporate in the two *ortho*-positions (R-) of the dibenzylated cyclic sulfamide **5** to act as a mimic for the furan ring (Fig. 1, Scheme 1). In addition, we decided to investigate the inverted amides (–NHCO). Reactants were selected in order to vary flexibility and size of the *ortho*-substituents. With the aim to reduce

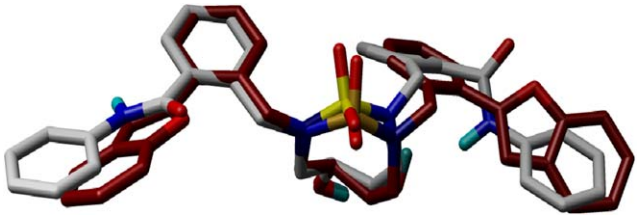

Figure 1. Superposition of benzofuran and anilide (**5a**) *o*-substituted *N*,*N*′-dibenzylic seven-membered sulfamide structures. The molecular graphics image was produced using the UCSF program Chimera.[13]

Keywords: Microwave; Aminocarbonylation; Goldberg; HIV-1 protease inhibitor.
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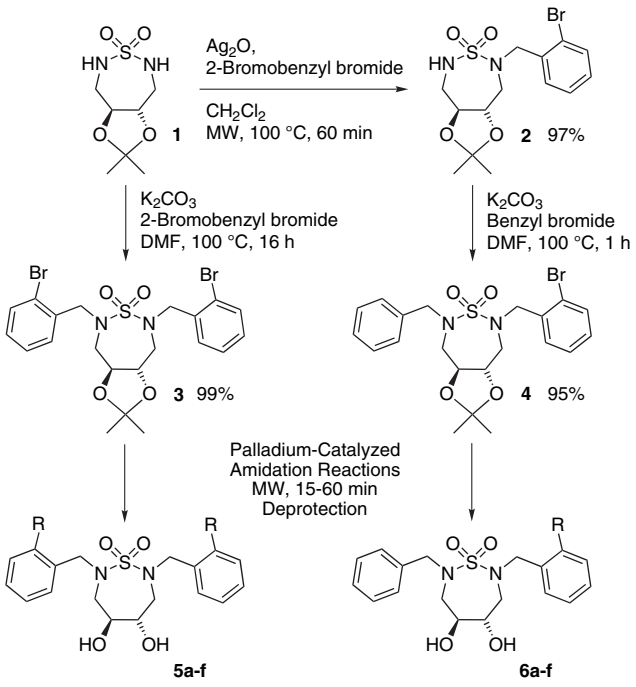


Scheme 1.

the size of the inhibitors and to produce nonsymmetrically decorated dibenzyl sulfamides, precursor **2** was much desired.

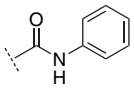
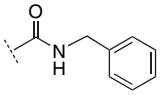
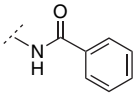
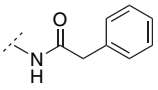
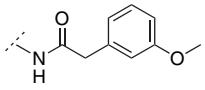
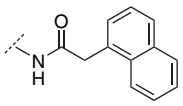
In this communication, a microwave promoted and chemoselective procedure for monoalkylation of the sulfamide scaffold **1** is reported (Scheme 1). Furthermore, a number of direct palladium-catalyzed *ortho*-amidations of the *P*2/*P*2′ benzyl groups have been conducted, delivering 12 new HIV-1 protease inhibitors.

2. Results and discussion

2.1. Synthetic strategies

The core structure **1** served as the precursor to provide the symmetric and nonsymmetric aryl bromide derivatives **3** and **4**, respectively (Scheme 1). Compound **3** was obtained, as previously reported, in 99% yield after N,N-dibenzylation with 2-bromobenzyl bromide in the presence of K_2CO_3.[10] Double *ortho*-amidations of **3** by palladium-catalyzed coupling reactions and deprotection, provided the symmetrical inhibitors in good yields (Table 1). More specifically, the aminocarbonylation products **5a**,**b** were obtained in 59 and 80% yield after 60 min of heating at 150 °C, respectively.[14] The corresponding *N*-amide arylations delivered the inverted amides **5c–f** in 53–72% yields after only 15 min of irradiation (160 °C). Early attempts to prepare unsymmetrical **4** from **1** showed an increased reactivity of the monoalkylated product **2** towards concomitant dialkylation, resulting in unwanted **3**. Fortunately, by initial addition of 1.5 equiv Ag_2O, subsequent microwave-assisted benzylation afforded pure aryl bromide **2** with excellent selectivity (**2**/**3**=99:1, Scheme 1). The yield of **2** was 97% despite the high-reaction temperature (100 °C). Related monoalkylations of symmetrical diols have been performed in presence of Ag_2O.[15]

Table 1. Microwave-heated palladium-catalyzed coupling reactions on symmetric and nonsymmetric cyclic sulfamides **3** and **4**

Reactant[a], route[b]	R-group	Symmetric (yield)[c], K_i (nM)	Nonsymmetric (yield)[c], K_i (nM)
a, A		**5a** (59%), >20,000	**6a** (77%), >20,000
b, A		**5b** (80%), 8600	**6b** (74%), >20,000
c, B		**5c** (72%), >20,000	**6c** (77%), >20,000
d, B		**5d** (53%), 1200	**6d** (51%), >20,000
e, B		**5e** (54%), 1300	**6e** (68%), 7700
f, B		**5f** (57%), 20	**6f** (66%), 140

[a] a: Aniline, b: Benzylamine, c: Benzamide, d: 2-Phenylacetamide, e: 2-(3-Methoxyphenyl)acetamide, f: 2-(2-Naphthyl)acetamide.
[b] A: Aminocarbonylation, B: *N*-amide arylation.
[c] Isolated yields after deprotection.

Aminocarbonylations of parent **4** with $Mo(CO)_6$ as the CO-source smoothly produced the monofunctionalized products **6a**,**b** (74 and 77%, Table 1). Similarly, **6c–f** were prepared as reported for the symmetric analogs **5c–f** in 51–77% yields after deprotection. The K_i-values for the synthesized compounds were determined as previously described.[16,17]

2.2. Discussion

Six active inhibitors were identified. Apparently, incorporation of the amide function alone was not sufficient, and an extra methylene spacer was required in order to yield active symmetrical compounds (**5b**, **5d–f**). The most potent compound **5f** possessed low nanomolar activity with a K_i-value of 20 nM. The high activity of **5f** was obtained by steric replacement of phenylacetamide for 1-naphthylacetamide. To our satisfaction, the smaller nonsymmetric compounds, occupying only three subsites, also proved to be active (**6e**, **6f**). With these structures, both the extra methylene spacer and further enlargement of the R-group was essential for activity.

3. Conclusion

In conclusion, the concept of *ortho*-extension from benzylic *P*2/*P*2′ side-chains to reach the *P*1/*P*1′ binding sites provided highly active HIV-1 protease inhibitors. With regard to inhibition potency, improved K_i-values were achieved using mono- and di-*ortho*-elongated structures with flexible three-atom spacers between the aromatic moieties.

Furthermore, single-mode microwave heating at 100 °C for 60 min was exploited without compromising the selectivity in the key monobenzylation step.

4. Experimental

4.1. General

The microwave-assisted reactions were performed in a single-mode microwave cavity (Smith Synthesizer, Biotage AB, Uppsala, Sweden) producing controlled irradiation at 2450 MHz. Reaction temperatures were determined and controlled via the built-in, on-line IR-sensor. Flash column chromatography was performed using Merck Silica gel 60 (0.040–0.063 mm). Analytical HPLC–MS analyses were performed using a Gilson HPLC system with a Chromolith SpeedROD RP-18e column (50×4.6 mm) and a Finnigan AQA quadropole mass spectrometer using a 4 mL/min CH_3CN/H_2O gradient (0.05% HCOOH), employing UV-detection (214 and 254 nm) and mass selective detector (ESI+). ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer at 399.8 and 100.6 MHz, respectively. All starting materials and reagents were commercially available and used as received. Xantphos, (4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene) was purchased from Aldrich. Herrmann's palladacycle, *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium (II) was purchased from Strem and $Mo(CO)_6$ was obtained from Acros.

4.2. Method for monobenzylation of cyclic sulfamides

Cyclic sulfamide **1** (0.45 mmol, 100 mg) and Ag_2O (0.67 mmol, 156 mg) were mixed in a Smith process vial for 5 min in 2 mL of CH_2Cl_2. After addition of *o*-bromobenzyl bromide (0.47 mmol, 117 mg) and another 3 mL of CH_2Cl_2, the vial was capped with a septum. The microwave synthesizer was set to 100 °C for 1 h. After cooling, the reaction mixture was filtered through a plug of Celite and immediately transferred to a short flash column and **2** was easily purified using 9:1 *iso*-hexane/EtOAc as the eluent (>95% purity by ^1H NMR and GC–MS). In a subsequent benzylation, **2** (0.68 mmol, 266 mg), benzyl bromide (1.36 mmol, 232 mg) and K_2CO_3 (3.33 mmol, 460 mg) were mixed in a process vial with 5 mL DMF. Reaction was heated in a heating block at 60 °C overnight. The reaction mixture was concentrated in vacuo and purified over silica, using 2:1–1:1 *iso*-hexane/CH_2Cl_2 as the eluent.

4.2.1. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-bromobenzyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (2). White solid. LC–MS, m/z=392 [M+H$^+$]. ^1H NMR (400 MHz, acetone-d_6): δ=7.62 (dd, 1H, J=1.2, 8.0 Hz), 7.56 (dd, 1H, J=1.7, 7.8 Hz), 7.44 (ddd, 1H, J=1.2, 7.4, 7.8 Hz), 7.26 (ddd, 1H, J=1.7, 7.4, 8.0 Hz), 6.72 (br m, 1H), 4.51 (d, 1H, J=16.0 Hz), 4.46 (d, 1H, J=16.0 Hz), 4.32–4.22 (m, 2H), 3.59 (ddd, 1H, J=3.9, 4.7, 12.8 Hz), 3.50 (dd, 1H, J=4.2, 13.6 Hz), 3.15 (ddd, 1H, J=0.6, 9.4, 13.6 Hz), 3.08 (ddd, 1H, J=7.0, 9.5, 12.8 Hz), 1.37 (m, 3H), 1.36 (m, 3H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=136.5, 132.9, 1230.0, 129.6, 128.3, 128.2, 109.2, 78.7, 77.8, 54.0, 49.4, 43.5, 26.6, 26.5. Anal. Calcd (%) for $C_{14}H_{19}BrN_2O_4S$: C, 42.98; H, 4.89; N, 7.16. Found: C, 43.30; H, 5.04; N, 7.19.

4.2.2. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-bromobenzyl)-7-benzyl-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (4). White solid. LC–MS, m/z=482 [M+H$^+$]. ^1H NMR (400 MHz, $CDCl_3$): δ=7.57 (m, 1H), 7.54 (m, 1H), 7.40–7.29 (m, 6H), 7.18 (m, 1H), 4.58 (d, 1H, J=15.4 Hz), 4.50 (d, 1H, J=15.4 Hz), 4.49 (d, 1H, J=14.6 Hz), 4.36 (d, 1H, J=14.6 Hz), 4.31–4.18 (m, 2H), 3.50 (dd, 1H, J=4.5, 13.0 Hz), 3.46 (dd, 1H, J=4.6, 12.8 Hz), 3.11 (dd, 1H, J=9.2, 13.0 Hz), 3.02 (dd, 1H, J=9.3, 12.8 Hz), 1.38 (d, 1H, J=0.6 Hz), 1.37 (d, 1H, J=0.6 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=136.1, 135.5, 133.2, 130.3, 129.7, 129.0, 128.7, 128.4, 128.2, 123.8, 110.1, 77.9, 77.7, 55.4, 54.8, 49.3, 48.6, 27.1. Anal. Calcd (%) for $C_{21}H_{25}N_2O_4S$: C, 52.39; H, 5.23; N, 5.82. Found: C, 52.46; H, 5.29; N, 5.79.

4.3. General method for aminocarbonylation of both symmetrical (3) and nonsymmetrical (4) sulfamide scaffolds

Cyclic sulfamide (0.083 mmol), Herrmann's catalyst (8.3 μmol, 7.8 mg), $Mo(CO)_6$ (0.017 mmol, 47 mg), DBU (0.83 mmol, 136 mg) and amine (2.5 mmol) were put in a 2–5 mL Smith process vial. THF (2.5 mL) was added and the reaction was run at 150 °C for 60 min. After cooling the reaction mixture was filtered through a plug of Celite and the organic solvent was evaporated under reduced pressure. Flash column chromatography and removal of the protective group using 1 mL 2.2 M HCl/ether and 2 mL methanol at rt for 45 min, followed by a second rapid flash column chromatography yielded pure products in all cases.

4.3.1. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis(*N*-phenyl-2-amido-benzyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5a). White solid. LC–MS, m/z=601 [M+H$^+$]. ^1H NMR (400 MHz, $CDCl_3$): δ=8.09 (s, 2H), 7.62–7.54 (m, 6H), 7.46–7.40 (m, 4H), 7.36–7.24 (m, 6H), 7.15 (tt, 2H, J=7.4, 1.2 Hz), 4.64 (d, 2H, J=15.8 Hz), 4.58 (d, 2H, J=15.8 Hz), 3.61–3.56 (m, 2H), 3.35 (d, 1H, J=15.4 Hz), 3.34 (d, 1H, J=15.4 Hz), 3.22 (d, 1H, J=15.4 Hz), 3.20 (d, 1H, J=15.4 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=168.3, 137.9, 136.2, 136.0, 131.3, 130.2, 129.4, 128.2, 127.1, 125.2, 120.5, 72.4, 50.6, 48.9.

4.3.2. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis(*N*-benzyl-2-amido-benzyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5b). White solid. LC–MS, m/z=629 [M+H$^+$]. ^1H NMR (400 MHz, $CDCl_3$): δ=7.68 (ddd, 2H, J=7.8, 1.2, 0.6 Hz), 7.49 (ddd, 2H, J=7.8, 7.3, 1.5 Hz), 7.42–7.27 (m, 14H), 6.34 (br t, 2H, J=5.8 Hz), 4.78 (d, 2H, J=15.4 Hz), 4.73 (d, 2H, J=15.4 Hz), 4.64 (dd, 2H, J=14.7, 5.8 Hz), 4.59 (dd, 2H, J=14.7, 5.8 Hz), 3.76–3.72 (m, 2H), 3.58–3.54 (m, 2H), 3.53–3.47 (m, 2H), 327–3.20 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=169.9, 137.8, 136.2, 135.8, 131.3, 130.9, 129.2, 128.22, 128.18, 128.1, 126.9, 72.5, 49.9, 47.2, 44.5.

4.3.3. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(*N*-phenyl-2-amido-benzyl)-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6a). White solid. LC–MS, m/z=482 [M+H$^+$]. ^1H NMR (400 MHz, acetone-d_6): δ=9.57 (br s, 1H),

7.87–7.82 (m, 2H), 7.70 (m, 1H), 7.62 (m, 1H), 7.55 (m, 1H), 7.46–7.27 (m, 8H), 7.13 (m, 1H), 4.97 (d, 1H, J=16.8 Hz), 4.82 (d, 1H, J=16.8 Hz), 4.68 (d, 1H, J=15.8 Hz), 4.55 (d, 1H, J=15.8 Hz), 4.26 (d, 1H, J=3.9 Hz), 4.22 (d, 1H, J=4.3 Hz), 3.42–3.23 (m, 3H), 3.15 (dd, 1H, J=15.2, 3.2 Hz). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=168.2, 140.3, 138.5, 137.3, 137.3, 131.2, 129.6, 129.4, 129.2, 128.8, 128.34, 128.30, 128.0, 124.7, 120.8, 73.1, 73.0, 53.2, 50.9, 49.3, 48.5. Anal. Calcd (%) for $C_{25}H_{27}N_3O_5S$: C, 62.35; H, 5.65; N, 8.73. Found: C, 62.21; H, 5.80; N, 8.61.

4.3.4. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(*N*-benzyl-2-amidobenzyl)-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6b). White solid. LC–MS, m/z=496 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.13 (br t, 1H), 7.67 (ddd, 1H, J=7.8, 1.2, 0.6 Hz), 7.57–7.22 (m, 13H), 4.89 (d, 1H, J=16.6 Hz), 4.78 (d, 1H, J=16.6 Hz), 4.70 (d, 1H, J=15.8 Hz), 4.61 (d, 2H, J=6.0 Hz), 4.56 (d, 1H, J=15.8 Hz), 4.29 (d, 1H, J=3.8 Hz), 4.26 (d, 1H, J=4.2 Hz), 3.67–3.56 (m, 2H), 3.40–3.12 (m, 4H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=169.7, 140.3, 138.6, 137.2, 137.1, 131.0, 129.42, 129.40, 129.3, 128.9, 128.4, 128.3, 128.1, 128.1, 127.8, 73.1, 73.0, 53.2, 50.6, 49.0, 48.5, 43.9. Anal. Calcd (%) for $C_{26}H_{29}N_3O_5S$: C, 63.01; H, 5.90; N, 8.48. Found: C, 62.89; H, 6.06; N, 8.43.

4.4. General method for *N*-amide arylation of both symmetrical (3) and nonsymmetrical (4) sulfamide scaffolds

Cyclic sulfamide (0.083 mmol), Pd(dba)$_2$ (4 μmol, 2.4 mg), Xantphos (6.2 μmol, 3.6 mg), Cs_2CO_3 (0.4 mmol, 135 mg) and amide (0.8 mmol) were put in a Smith process vial, with 2.5 mL 10% NMP in dioxane as the solvent. The reaction mixture was heated in the microwave at 160 °C for 15 min. After cooling the reaction mixture was filtered through a plug of Celite and the organic solvent was evaporated under reduced pressure. Flash column chromatography and removal of the protecting group using 1 mL of 2.2 M HCl/ether and 2 mL methanol at rt for 45 min followed by a second rapid flash column chromatography yielded pure products in all cases.

4.4.1. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis(2-benzamidobenzyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5c). White solid. LC–MS, m/z=601 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=9.31 (br s, 2H), 8.05 (dd, 4H, J=1.4, 8.4 Hz), 7.80 (dd, 2H, J=1.4, 8.0 Hz), 7.61–7.56 (m, 2H), 7.55–7.47 (m, 6H), 7.38 (ddd, 2H, J=1.6, 7.5, 7.7 Hz), 7.26 (ddd, 2H, J=1.4, 7.5, 7.5 Hz), 4.72 (d, 2H, J=16.2 Hz), 4.68 (d, 2H, J=16.2 Hz), 4.32 (br d, 2H, J=4.1 Hz), 3.54–3.45 (m, 2H), 3.30 (dd, 2H, J=9.2, 15.1 Hz), 3.18 (dd, 2H, J=2.9, 15.1 Hz). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=166.15, 137.0, 135.0, 131.9, 130.6, 129.7, 128.6, 128.5, 127.9, 125.9, 125.7, 72.6, 49.5, 48.3.

4.4.2. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis[2-(2-phenylacetamido)-benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5d). White solid. LC–MS, m/z=629 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.92 (s, 2H), 7.94 (dm, 2H, J=8.1 Hz), 7.49 (dm, 2H, J=7.5 Hz), 7.42 (dm, 4H, J=7.5 Hz), 7.37–7.26 (m, 6H), 7.25–7.15 (m, 4H), 4.68 (d, 2H, J=15.5 Hz), 4.52 (d, 2H, J=15.5 Hz), 4.23 (br s, 2H), 3.76 (s, 4H), 3.30–3.17 (m, 4H), 3.16–3.02 (m, 2H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=169.6, 137.5, 136.2, 130.1, 129.5, 128.9, 128.6, 128.0, 126.9, 124.9, 123.7, 72.5, 49.5, 48.5, 43.9.

4.4.3. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis{2-[2-(3-methoxy-phenyl)-acetamido]-benzyl}-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5e). White solid. LC–MS, m/z=689 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.88 (s, 2H), 7.93 (dm, 2H, J=8.1 Hz), 7.48 (dd, 2H, J=1.6, 7.6 Hz), 7.34 (ddd, 2H, J=1.6, 7.6, 7.6 Hz), 7.23–7.15 (m, 4H), 7.02 (m, 2H), 6.99 (dm, 2H, J=7.6 Hz), 6.80 (ddd, 2H, J=1.0, 2.6, 8.2 Hz), 4.68 (d, 2H, J=15.5 Hz), 4.52 (d, 2H, J=15.5 Hz), 4.21 (br s, 2H), 3.77 (s, 6H), 3.73 (s, 4H), 3.32–3.18 (m, 4H), 3.17–3.08 (m, 2H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=167.8, 146.2, 138.7, 138.2, 137.9, 130.1, 129.8, 129.7, 129.3, 128.8, 126.9, 73.1, 50.9, 49.0, 46.2, 44.1.

4.4.4. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis{2-[2-(2-naphthyl)-acetamido]-benzyl}-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5f). White solid. LC–MS, m/z=729 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.91 (s, 2H), 8.25 (ddd, 2H, J=0.9, 2.1, 8.5 Hz), 7.90 (dm, 2H, J=8.2 Hz), 7.83 (dd, 2H, J=1.2, 8.0 Hz), 7.82 (dm, 2H, J=8.2 Hz), 7.60–7.39 (m, 10H), 7.31 (ddd, 2H, J=1.6, 7.5, 7.7 Hz), 7.16 (ddd, 2H, J=1.3, 7.5, 7.5 Hz), 4.63 (d, 2H, J=15.6 Hz), 4.51 (d, 2H, J=15.6 Hz), 4.27 (s, 4H), 4.22 (br s, 2H), 3.32–3.22 (m, 4H), 3.20–3.08 (m, 2H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=170.2, 138.0, 134.9, 133.4, 133.1, 130.6, 129.43, 129.39, 129.3, 129.0, 128.5, 127.1, 126.6, 126.4, 125.8, 125.3, 124.9, 73.2, 50.1, 49.2, 42.1. Anal. Calcd (%) for $C_{42}H_{40}N_4O_6S$: C, 69.2; H, 5.53; N, 7.69. Found: C, 68.95; H, 5.66; N, 7.50.

4.4.5. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-benzamidobenzyl)-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6c). White solid. LC–MS, m/z=482 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.73 (br s, 1H), 7.93 (dd, 2H, J=1.3, 8.4 Hz), 7.86 (dm, 1H, J=8.1 Hz), 7.55 (m, 2H), 7.49–7.42 (m, 2H), 7.39–7.23 (m, 7H), 7.20 (m, 1H), 4.60 (d, 1H, J=14.8 Hz), 4.58 (d, 1H, J=15.5 Hz), 4.34 (d, 1H, J=14.8 Hz), 4.30 (d, 1H, J=15.5 Hz), 3.42 (m, 1H), 3.30 (dd, 1H, J=9.2, 14.6 Hz), 3.26–3.08 (m, 4H), 3.03 (dd, 1H, J=3.9, 15.2 Hz), 2.84 (br s, 1H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=167.7, 136.5, 136.2, 134.0, 132.5, 131.1, 129.7, 129.1, 128.9, 128.44, 128.43, 128.2, 127.9, 126.4, 125.7, 73.2, 72.4, 53.2, 50.0, 48.7, 47.9. Anal. Calcd (%) for $C_{25}H_{27}N_3O_5S$: C, 62.35; H, 5.65; N, 8.73. Found: C, 62.51; H, 5.79; N, 8.64.

4.4.6. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-phenylacetamidobenzyl)-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6d). White solid. LC–MS, m/z=496 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.93 (s, 1H), 8.06 (dd, 1H, J=1.2, 8.1 Hz), 7.51–7.39 (m, 7H), 7.37–7.30 (m, 2H), 7.29–7.18 (m, 3H), 7.14 (ddd, 1H, J=1.3, 7.5, 7.5 Hz), 4.78 (d, 1H, J=15.7 Hz), 4.70 (d, 1H, J=15.3 Hz), 4.54 (d, 1H, J=15.7 Hz), 4.42 (d, 1H, J=15.3 Hz), 4.21–4.19 (m, 2H), 3.74 (s, 1H), 3.57 (m, 1H), 3.44–3.04 (m, 5H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=169.5, 137.7, 137.5, 136.2, 130.5, 129.5, 128.9,

128.6, 128.3, 127.9, 127.4, 126.9, 125.4, 124.5, 123.0, 73.1, 71.9, 52.4, 49.6, 48.8, 48.1, 43.9. Anal. Calcd (%) for $C_{26}H_{29}N_3O_5S$: C, 63.01; H, 5.90; N, 8.48. Found: C, 63.23; H, 6.23; N, 8.13.

4.4.7. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-[2-(3-methoxyphenyl-acetamido)-benzyl]-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6e). White solid. LC–MS, m/z=526 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.90 (br s, 1H), 8.02 (dd, 1H, J=1.3, 8.2 Hz), 7.50–7.29 (m, 7H), 7.20–7.12 (m, 2H), 7.03 (m, 1H), 6.98 (dm, 1H, J=7.5 Hz), 6.97 (ddd, 1H, J=1.0, 2.6, 8.3 Hz), 4.76 (d, 1H, J=15.7 Hz), 4.68 (d, 1H, J=15.3 Hz), 4.55 (d, 1H, J=15.7 Hz), 4.43 (d, 1H, J=15.3 Hz), 4.22–4.19 (m, 2H), 3.76 (s, 3H), 3.71 (s, 2H), 3.58 (m, 1H), 3.40–3.06 (m, 5H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=170.1, 160.7, 138.3, 138.2, 138.1, 131.1, 130.2, 129.6, 129.5, 128.9, 128.6, 125.3, 123.9, 122.4, 115.7, 113.1, 73.7, 72.6, 55.4, 53.1, 50.3, 49.4, 48.8, 44.7.

4.4.8. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-{2-[2-(2-naphthyl)-acetamido]-benzyl}-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6f). White solid. LC–MS, m/z=546 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.98 (s, 1H), 8.27 (dm, 1H, J=8.4 Hz), 7.90 (m, 2H), 7.82 (dm, 1H, J=8.2 Hz), 7.61–7.27 (m, 11H), 7.15 (ddd, 1H, J=1.2, 7.5, 7.5 Hz), 4.75 (d, 1H, J=15.8 Hz), 4.66 (d, 1H, J=15.4 Hz), 4.55 (d, 1H, J=15.8 Hz), 4.46 (d, 1H, J=15.4 Hz), 4.27 (s, 1H), 4.26 (d, 1H, J=4.4 Hz), 4.24 (d, 1H, J=4.2 Hz), 3.60 (m, 1H), 3.40–3.10 (m, 5H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=169.5, 137.6, 137.5, 134.2, 132.8, 132.5, 130.2, 128.9, 128.74, 128.73, 128.4, 128.2, 127.9, 127.8, 126.4, 125.9, 125.8, 124.8, 124.7, 123.7, 72.9, 72.0, 52.5, 49.5, 48.7, 48.1, 41.4. Anal. Calcd (%) for $C_{30}H_{31}N_3O_5S$: C, 66.04; H, 5.73; N, 7.70. Found: C, 66.05; H, 5.85; N, 7.68.

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Synthesis of 7*H*-indolo[2,3-*c*]quinolines: study of the Pd-catalyzed intramolecular arylation of 3-(2-bromophenylamino)quinolines under microwave irradiation

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Abstract—D-ring substituted 5-methyl-5*H*-indolo[2,3-*c*]quinolines (**4**) have been synthesized in three steps starting from commercially available 3-bromoquinoline (**5**) and 2-bromoanilines (**6**). The methodology consists of two consecutive palladium-catalyzed reactions: a selective Buchwald–Hartwig amination followed by a regioselective intramolecular Heck-type reaction. The latter step has been investigated under microwave irradiation. Heating at 180 °C allows to seriously reduce the catalyst loading and get a full conversion to reaction product in 10 min. In addition, the former simplifies the purification.

1. Introduction

Every year between 300 and 500 million people worldwide are infected by the malaria parasite (*Plasmodium*). One to two million of them die as a direct consequence of this disease.[1] Besides the available synthetic drugs nature also has shown to be an interesting source for antiplasmodial compounds. For instance, in traditional medicine in West and Central Africa a decoction of the root of the plant *Cryptolepis sanguinolenta* is used to treat fevers caused by malaria. Cryptolepine (5-methyl-5*H*-indolo[3,2-*b*]quinoline) (**1**), neocryptolepine (cryptotackieine, 5-methyl-5*H*-indolo[2,3-*b*]quinoline) (**2**) and isocryptolepine (cryptosanguinolentine, 5-methyl-*5H*-indolo[3,2-*c*]quinoline) (**3**) are three of the thirteen characterized alkaloids of the root (Fig. 1).[2] These isomeric indoloquinolines show an interesting antiplasmodial activity. Interestingly, the 'missing' benzo-β-carboline isomer (5-methyl-5*H*-indolo[2,3-*c*]quinoline, for which we have adopted the name isoneocryptolepine (**4a**) (Fig. 1) has hitherto never been found in nature. Recently, we developed an efficient synthetic route for 5-methyl-5*H*-indolo[2,3-*c*]quinoline (**4a**) and its 7*H*-indolo[2,3-*c*]quinoline skeleton.[3] The methodology is based on the combination of a selective Buchwald–Hartwig amination with a regioselective Pd-catalyzed intramolecular arylation reaction starting from commercially available 3-bromoquinoline (**5**) and 2-bromoaniline (**6a**) (Scheme 1).[3,4] Although **4a** is about two times less active (K1 strain of *P. falciparum*, resistant to chloroquine and pyrimethamine) than **1**, the most active compound of the quartet isomeric indoloquinolines, it is four times less cytotoxic (L6 cells).[5] Therefore, **4a** has a much better selectivity index (cytotoxicity/antiplasmodial activity ratio) than **1**, which makes it a better lead compound for further validation of the indoloquinolines as a potential antiplasmodial drugs (Table 1). The mechanism of action of **4a** is similar to that of chloroquine inhibition of the haeme detoxification process.[6] The choice to study first the D-ring substitution of **4a** is based on the fact that the quinoline part in chloroquine and analogues is very important in the haeme complexation and only limited substitutions are tolerated. The commercial availability of several substituted 2-bromoanilines makes the 'selective Buchwald–Hartwig amination—regioselective Pd-catalyzed intramolecular arylation reaction' approach a preferred tool to easily get access to these D-ring functionalized 7*H*-indolo[2,3-*c*]quinolines and isoneocryptolepines.

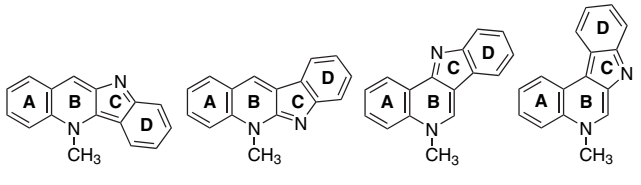

Figure 1. Cryptolepine (**1**), neocryptolepine (**2**), isocryptolepine (**3**) and isoneocryptolepine (**4a**).

Keywords: Palladium; Amination; Heck-type reaction; Microwave; Malaria.
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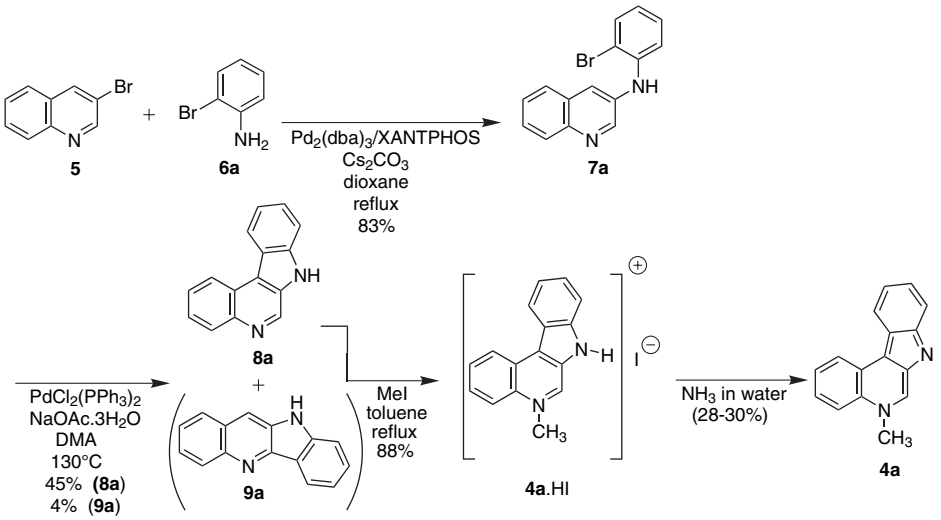


Scheme 1. Synthesis of isoneocryptolepine (**4**) based on a 'selective Buchwald–Hartwig amination—regioselective Pd-catalyzed intramolecular arylation reaction' approach.

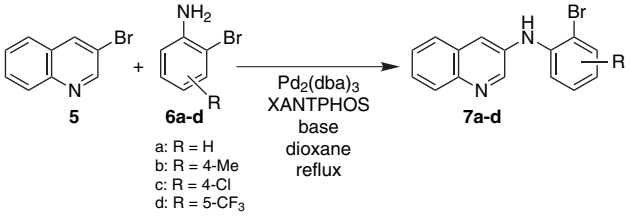
Table 1. Antiplasmodial activity (IC_{50}, μM), cytotoxicity (IC_{50}, μM) and selectivity index of compounds **1**–**4**

Compound	*Plasmodium falciparum* K1 IC_{50} (μM)	Cytotoxicity (L6 cells) IC_{50} (μM)	Selectivity index
1	0.12±0.02	1.12±0.07	9.3
2	2.61±0.67	3.24±0.04	1.2
3	0.78±0.30	1.19±0.26	1.5
4a	0.23±0.04	4.32±0.04	18.8

2. Discussion

First, we focussed on the amination of 3-bromoquinoline (**5**) with 2-bromoanilines (**6**) and decided to restudy the selective coupling of **5** with 2-bromoaniline (**6a**) (Scheme 1), under the same reaction conditions as previously reported by us [standard conditions: 2.5 mol % $Pd_2(dba)_3$/5.5 mol % XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene) catalyst, 1.2 equiv **6a**, 3 equiv Cs_2CO_3, 12 mL dioxane and reflux], in order to determine whether there is a '*base effect*' for this C–N bond forming reaction.[7] Therefore, we carefully followed the reaction of **5** with **6a** by TLC and MS and found that the reaction is already completed after 16 h.[8] An isolated yield of 3-(2-bromophenylamino)-quinoline (**7a**) of 85% was obtained (Table 2, entry 1), which is essentially the same as we reported previously for a 30 h reflux (Scheme 1). When the same experiment was performed using only 2 equiv of caesium carbonate (instead of 3 equiv as used in the standard experiment) an incomplete conversion of starting material was observed in 16 h. Work up of the mixture yielded only 62% of **7a** and a recovery of 26% of substrate **5** (Table 2, entry 2). These data clearly indicate a rate-limiting deprotonation of the Pd(II)-amine complex intermediate formed in the catalytic cycle.[7] Gratifyingly, selective amination of **5** with 2-bromo-4-methylaniline (**6b**) using the optimized reaction conditions gave 85% of 3-(2-bromo-4-methylphenylamino)quinoline (**7b**) (Table 2, entry 3). Unfortunately, amination of **5** with 4-chloro-2-bromoaniline (**6c**) and 2-bromo-5-trifluoromethylaniline (**6d**) gave incomplete conversions and an isolated yield of 3-arylaminoquinoline of 63% (**7c**) and 59% (**7d**) respectively

Table 2. Selective Buchwald–Hartwig amination of 3-bromoquinoline (**5**) with 2-bromoanilines (**6**)



Entry	**6**	$Pd_2(dba)_3$ loading (mol %)	XANTPHOS loading (mol %)	Base	Time (h)	Yield[a] (%)
1	**6a**	2.5	5.5	Cs_2CO_3	16	85
2	**6a**	2.5	5.5	Cs_2CO_3	16	62[b]
3	**6b**	2.5	5.5	Cs_2CO_3	16	85
4	**6c**	2.5	5.5	Cs_2CO_3	16	63
5	**6d**	2.5	5.5	Cs_2CO_3	16	59
6	**6c**	2.5	5.5	Cs_2CO_3	24	55[c]
7	**6c**	2.5	10.0	Cs_2CO_3	24	62
8	**6c**	2.5	5.5	Cs_2CO_3	24	61[d]
9	**6c**	2.5	5.5	K_3PO_4	24	51[e]
10	**6c**	2.5	5.5	Cs_2CO_3	24	37[b]
11	**6c**	5.0	11.0	Cs_2CO_3	24	83

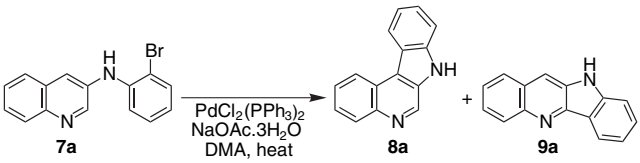
[a] $Pd_2(dba)_3$ (5 mol %), 5.5 mol % XANTPHOS, 3 mmol **5**, 3.6 mmol **6**, 9 mmol Cs_2CO_3, 12 mL dioxane, reflux.
[b] Cs_2CO_3 (6 mmol) was used.
[c] 5.4 mmol **6c** was used.
[d] 6 mL dioxane was used.
[e] 9 mmol K_3PO_4 was used.

(Table 2, entries 4 and 5). We decided to study the coupling of **5** with **6c** in more detail. Altering the excess of **6c** from 1.2 to 1.8 equiv (Table 2, entry 6), changing the palladium/ligand ratio from 1/1.1 to 1/2 (Table 2, entry 7) as well as doubling the concentration of the reaction (Table 2, entry 8) all gave similar isolated yield of **7c** and an incomplete conversion of starting material in a fixed reaction time of 24 h. Also the use of K_3PO_4 as base did not provide us with a better result (Table 2, entry 9). Interestingly, a test experiment with 2 equiv of Cs_2CO_3 gave only 37% **7c** and a recovery of 37% **5** (Table 2, entry 10), which also supports that the deprotonation of the Pd(II)-amine complex intermediate occurs in the

rate-limiting step for the studied type of amination reactions. Interestingly, when we doubled the catalyst loading for the coupling of **5** and **6c** within 24 h under otherwise standard conditions an almost complete conversion was observed with an isolated yield of 83% **7c** (Table 2, entry 11). The selective coupling reactions of **5** with **6a–d** (via chemoselective oxidative addition) can be explained by taking into account that the C–Br bond of **5** is more reactive than the C–Br bond of **6a–d** due to the amino substituent of the latter, which sterically and electronically deactivates the C2–Br bond for oxidative addition. Interestingly, the introduction of a chlorine atom or a trifluoromethyl group (electron withdrawing) on 2-bromoaniline does not seem to influence the selectivity (chemoselective oxidative addition) of the Buchwald–Hartwig amination reaction. Particularly, the successful use of **6c** is interesting since the C4–Cl of **6c** is a potential third position for oxidative addition in the reaction of **5** with **6c**.

Secondly, we turned our attention to the cyclodehydrobromination of **7a–d** via a regioselective intramolecular Heck-type reaction that involves C–H bond activation of an aryl group.[9] The already previously reported cyclization of **7a** required a very high loading of catalyst (23 mol %) and a long reaction time (48 h) to achieve a reasonable result (Scheme 1).[3] Therefore, we decided to study the Pd-catalyzed cyclodehydrobromination of **7a** in more detail with an HPLC–UV system under the same reaction conditions [standard conditions: 23 mol % $PdCl_2(PPh_3)_2$ catalyst, 2.45 equiv $NaOAc\cdot 3H_2O$, 10 mL dimethylacetamide and 130 °C (oil bath temperature)]. Surprisingly, we found that most of the conversion of starting material occurs in the first hour and subsequently an extremely slow further transformation to reaction product **8a** follows (Table 3, A).[10] Also with 5 mol % loading of $PdCl_2(PPh_3)_2$ a similar behaviour could be observed (Table 3, B). For both experiments complete conversion of substrate **7a** can not be achieved and the reaction mixture obtained a dark colour within the first hour of reaction. Importantly, increasing the oil bath temperature to 160 °C for the former experiment gave an almost complete reaction within 1 h (Table 3, C). This observation inspired us to study the cyclodehydrobromination of **7a** under microwave irradiation in a single-mode microwave unit (Discover, CEM).[11] We decided to perform the reactions on a same scale as the oil bath experiments but increased the concentration of the microwave reactions by a factor of ten (use of 1 mL instead of 10 mL DMA) since the standard disposable microwave vials (with crimp cap) have a volume of 10 mL. At 180 °C using a loading of 23 mol % a complete conversion of **7a** was observed within 10 min of irradiation. Astonishingly, a systematic reduction of the catalyst loading revealed that 0.2 mol % still gave a complete transformation of **7a** in 10 min heating under microwave irradiation. This is a reduction in reaction time by a factor of 288 and a 115-fold decrease of the catalyst loading. Working up the reaction mixture gave an isolated yield of 7*H*-indolo[2,3-*c*]quinoline (**8a**) of 66% (Table 4, entry 1). This is 21% higher than the previously reported yield under standard conditions (Scheme 1) and most probably a combination of two main factors.[12] First of all, in an oil bath at 130 °C using 23 mol % of catalyst the reaction can never be brought to complete conversion (even after 48 h of heating) (Table 3, A) and secondly the very high loading of catalyst generates

Table 3. Pd-catalyzed intramolecular arylation of **7a** under conventional heating

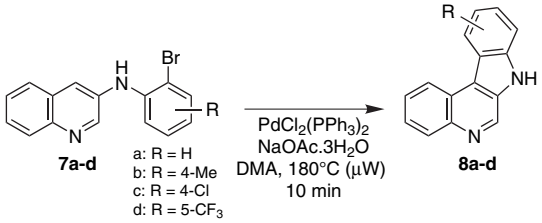


	Time (min)	Conversion (%)[a]	**8a**[b,c] (%)
A[d]			
1	10	48	85
2	20	61	84
3	30	66	81
4	60	71	80
5	120	74	81
6	360	75	79
B[d]			
1	10	26	87
2	20	32	87
3	30	34	85
4	60	36	87
5	120	37	86
6	360	39	86
C[d]			
1	10	71	85
2	20	82	84
3	30	86	85
4	60	90	84
5	120	92	84
6	360	94	83

[a] Conversion based on HPLC–UV: (**8a+9a**)/(**7a+8a+9a**)×100.
[b] X mol % $PdCl_2(PPh_3)_2$, 0.6 mmol **7a**, 1.47 mmol $NaOAc\cdot 3H_2O$, 10 mL DMA.
[c] Percentage of **8a** based on HPLC–UV: **8a**/(**8a+9a**)×100.
[d] A: 23 mol % $PdCl_2(PPh_3)_2$ catalyst at 130 °C, B: 5 mol % $PdCl_2(PPh_3)_2$ catalyst at 130 °C and C: 23 mol % $PdCl_2(PPh_3)_2$ catalyst at 160 °C.

a large amount of triphenylphoshine and triphenylphosphine oxide, which makes the work up very difficult involving a lot of purification steps with reaction product loss as an obvious consequence. An attempt to further reduce the catalyst loading to 0.1 mol % was unsuccessful since starting material **7a** remained and only 30% of **8a** could be obtained in a reaction time of 10 min at 180 °C. We decided to study the Pd-catalyzed cyclodehydrobromination of **7b–d** with a higher catalyst loading (1 mol %) than 0.2 mol % in order to have

Table 4. Pd-catalyzed intramolecular arylation of **7a–d** under microwave irradiation[10]



Entry	**7**	$PdCl_2(PPh_3)_2$ loading (mol %)	Yield[a] (%)
1	**7a**	0.2	66
2	**7b**	1	58
3	**7c**	1	69
4	**7d**	1	76

[a] X mol % $PdCl_2(PPh_3)_2$, 0.6 mmol **7a–d**, 1.47 mmol $NaOAc\cdot 3H_2O$, 1 mL DMA and 180 °C (microwave).

a general applicable protocol for the synthesis of the indoloquinoline skeleton of the substituted 5-methyl-5*H*-indolo[2,3-*c*]quinolines. Upon the use of a 1 mol % catalyst loading, **7b–d** could be smoothly transformed to **8b–d** in only 10 min (Table 4, entries 2, 3 and 4). Complete conversion of the substrates (**7b–d**) as well as the good isolated yields of **8b–d** support the generality of the developed protocol. Interestingly, to the best of our knowledge microwave-assisted Pd-catalyzed intramolecular arylation reactions using dedicated microwave equipment are unprecedented in the literature.[13] The studied intramolecular Heck-type reactions on **7a–d** are regioselective since only a small fraction of quindolines **9a–d** could be isolated during column chromatography.[14] When one accepts the mechanism of the Pd-catalyzed cyclodehydrohalogenation of **7a–d** to occur via the intramolecular electrophilic attack of the oxidative addition complex on a π system,[9,15] the preferential C4–H activation of **7a–d** can be explained by taking into account that in this case three resonance contributors, which do not break the aromatic character of the benzene ring in the carbocationic intermediate, can be drawn versus only one in the case of C2–H activation. In addition, the electron density is larger on C-4 than on C-2.

To investigate a possible existence of non-thermal microwave effects[11b] in the Pd-catalyzed intramolecular arylation reactions, we searched for a method which allows to mimic the heating profile of an oil bath experiment with that of a microwave reaction. This setup choice is inspired by the fact that it should be easier to control microwave heating by altering the power output of the machine (programming of stages with a different set power) than controlling the heating gradient of an oil bath. Comparisons between oil bath and microwave experiments can be best executed with the same vessel and therefore, we constructed a homemade 'attenuator' which allows sealing of the 10 mL microwave vessel, with internal fiber optic temperature measurement, without placing it in the microwave cavity (Figs. 2 and 3). Our system can be easily used to perform on-line pressure and temperature monitoring of the oil bath experiment by programming a hypothetical experiment with a set power of 0 W and a set temperature higher than the desired value. The heating profile we obtained by performing an intramolecular Heck-type reaction on **7a** with 5 mol % of $PdCl_2(PPh_3)_2$ in a preheated oil bath at 155 °C is shown in Figure 4. An oil bath temperature of 155 °C gave an internal temperature of 150 °C. This figure also shows the mimicked profile of exactly the same experiment performed under microwave heating. As can be seen in the figure the two heating profiles are not exactly the same but very similar. Differences are due to the software of the microwave system. A power moderation algorithm is used which automatically

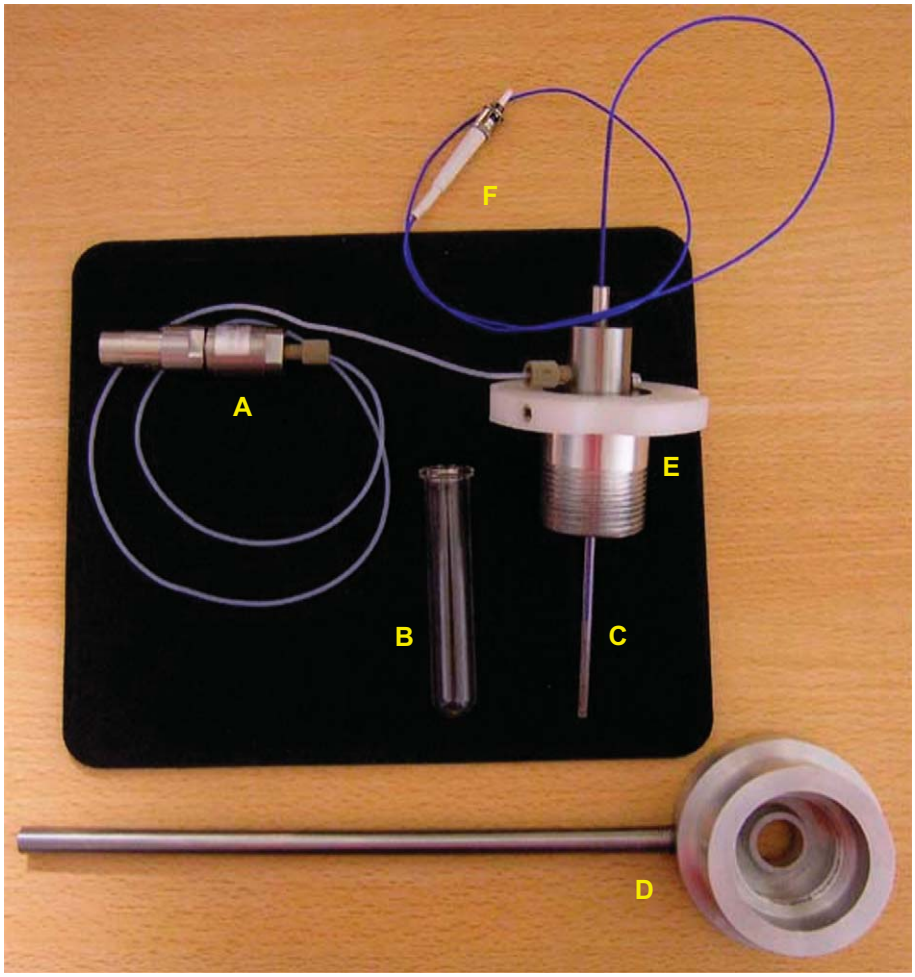
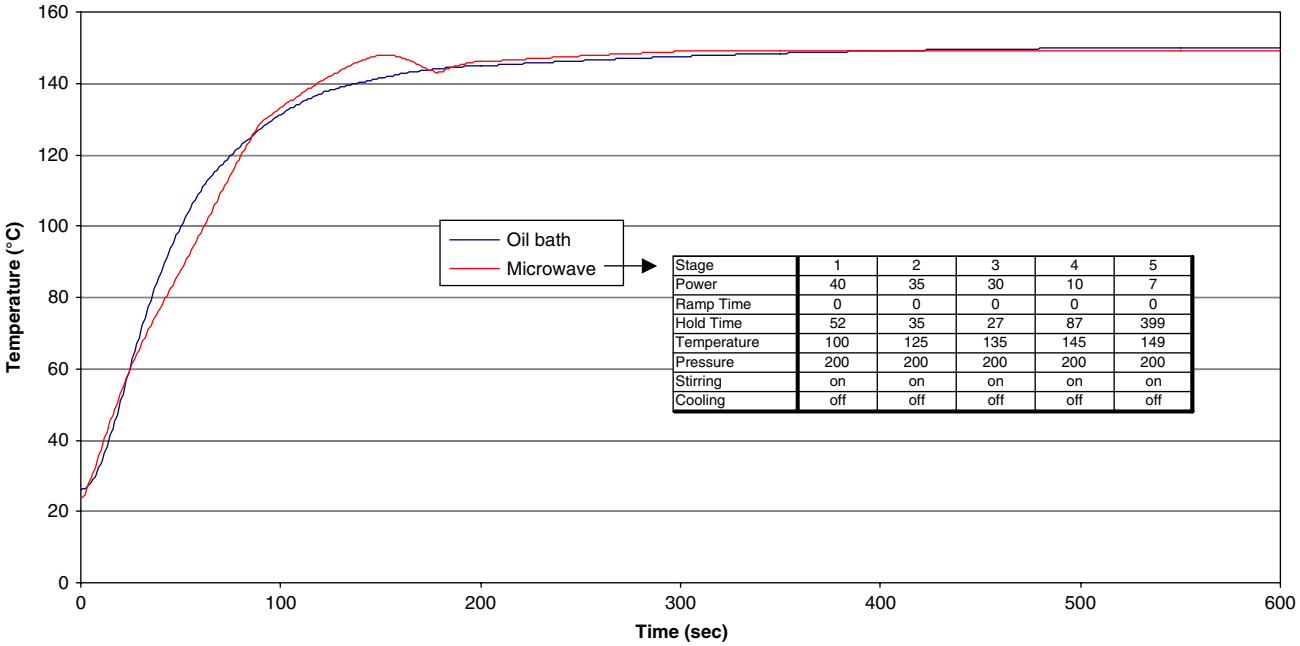


Figure 2. Pressure sensor (A), 10 mL microwave vial (B), thermowell (C), homemade 'attenuator' (D), locking cover assembly (E) and fiber optic temperature sensor (F).

Figure 3. Experimental setup for the determination of a heating profile (via the microwave software) of an experiment executed in an oil bath.

alters the power to a lower value, even though it has not been programmed by the user. This algorithm has been incorporated as a safety feature to prevent explosions due to too rapid heating of a reaction mixture. Although a reasonably good comparison has been obtained between oil bath and microwave heating profile, this algorithm prevented us to exactly mimic the profiles. The two reactions shown in Figure 4 have been analyzed by an HPLC–UV system. Interestingly, both gave exactly the same conversion to reaction products (**8a** and **9a**) in a reaction time of 10 min [microwave: % reaction products = 41.8 (this percentage consists of 85% **8a**), oil bath: % reaction products = 41.4 (this percentage consists of 86% **8a**)] and therefore, non-thermal effects can be excluded. The studied microwave-assisted reactions are governed only by thermal effects (Arrhenius). Nevertheless, from a practical point of view,



Stage	1	2	3	4	5
Power	40	35	30	10	7
Ramp Time	0	0	0	0	0
Hold Time	52	35	27	87	399
Temperature	100	125	135	145	149
Pressure	200	200	200	200	200
Stirring	on	on	on	on	on
Cooling	off	off	off	off	off

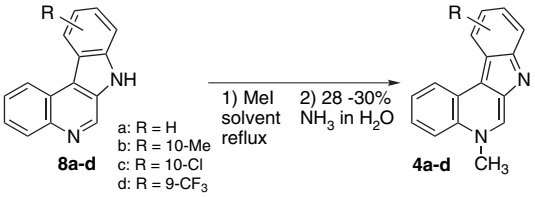
Figure 4. Attempt to mimic the heating profile of an oil bath experiment with that of a microwave experiment.

the microwave-assisted procedure is still more convenient than classical heating since it is easier to reach high temperatures.

For the selective N-5 methylation of the 7*H*-indolo[2,3-*c*]quinolines (**8b–d**) we first tried to use the conditions (CH_3I, toluene, reflux, 2 h; then 28–30% NH_3 in H_2O) we previously reported for the selective methylation of 7*H*-indolo[2,3-*c*]quinoline (**8a**).[3] The use of toluene allowed selective methylation of **8a** since the formed isoneocryptolepinium hydroiodide (**4a**·HI) immediately precipitated and the formation of 7-methylisoneocryptolepinium iodide could therefore be avoided. For 10-methyl-7*H*-indolo[2,3-*c*]quinoline (**8b**) this procedure worked smoothly giving access to the desired 5,10-dimethyl-5*H*-indolo[2,3-*c*]quinoline (**4b**) in 95% yield (Table 5). However, under these reaction conditions methylation of 10-chloro-7*H*-indolo[2,3-*c*]quinoline (**8c**) and 9-trifluoromethyl-7*H*-indolo[2,3-*c*]quinoline (**8d**) yielded the respective 5-methyl-5*H*-indolo[2,3-*c*]quinolines **4c** and **4d** in lower yields (75 and 60%). Interestingly, based on a report for the selective methylation of quindoline, we found that methylation of **8c** and **8d** with MeI in refluxing tetrahydrofuran gave superior results (Table 5).[16] Also in this case a precipitate (**4c**·HI and **4d**·HI) forms during the reaction.

In conclusion, we smoothly synthesized D-ring substituted 5-methyl-5*H*-indolo[2,3-*c*]quinolines (**4b–d**) via our earlier developed three-step approach for the construction of unsubstituted isoneocryptolepine. The procedure consists of the combination of a selective Buchwald–Hartwig amination and a regioselective intramolecular Heck-type reaction. The latter step [Pd-catalyzed intramolecular arylation of 3-(2-bromophenylamino)quinolines] was studied under microwave irradiation. Superior reaction conditions have clearly been identified since the catalyst loading and reaction time can be seriously reduced by performing the ring closure reaction at a higher temperature. In addition the new conditions allow an easier work up. The biological evaluation (antiplasmodial activity and cytotoxicity) of **4b–d** is currently in progress and the screening results will be reported in due course.

Table 5. Methylation of **8a–d**



Entry	8	Solvent	Yield (%)
1	**8a**	Toluene	88[a]
2	**8b**	Toluene	95[a]
3	**8c**	THF	94[b]
4	**8d**	THF	95[b]

[a] 0.5 mmol **8a–b**, 3 mL MeI, 7.5 mL toluene, reflux, 2 h and then 28–30% NH_3 in H_2O.

[b] 0.5 mmol **8c–d**, 0.25 mL MeI, 2.5 mL THF, reflux, overnight and then 28–30% NH_3 in H_2O.

3. Experimental

3.1. General

All melting points were determined on a Büchi apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Brücker spectrometer Avance 400 in the solvent indicated with TMS (**7** and **8**) or CD_3COOD (**4**) as an internal standard. All coupling constants are given in Hertz and chemical shifts are given in parts per million. The assignment of the ^1H NMR signals of **4** is based on 2D NMR techniques (NOESY and COSY). The chemical shifts of the signals in the ^1H NMR spectra of **4** are concentration dependant. For mass spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. Injections (1 μL) were directed to the mass spectrometer at a flow rate of 5 μL/min (CH_3OH and 0.1% formic acid), using a CapLC HPLC system. Accurate mass data were acquired on a Qq-TOF 2 (Micromass) mass spectrometer equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (approx. 35 V) and capillary voltage (approx. 3.3 kV) were optimized on one compound and used for all others. For the determination of the accurate mass of the molecular ion $[M+H]^+$, a solution of polyethylene glycol 300 in CH_3OH/H_2O with 1 mmol ammonium acetate, was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated masses of PEG $[M+H]^+$ and $[M+NH_4]^+$ ions were used as lock mass. For the product ion experiments (MS) the mass of the $[M+H]^+$ was used as lock mass for the fragments. Fragmentation was induced by low energy collisional activation using different collision energies between 20 and 30 eV. All signals with a signal to noise ratio ≥5/1 were reported. 3-Bromoquinoline (Acros), 2-bromanilines (Acros and Aldrich), XANTPHOS (Aldrich), $PdCl_2(PPh_3)_2$ (Aldrich) and $Pd_2(dba)_3$ (Acros) were obtained from commercial sources and used as such. For the Buchwald–Hartwig amination Cs_2CO_3 (99%) (Aldrich) and freshly distilled dioxane (dried over sodium benzophenone) were used. Flash column chromatography was performed on Kieselgel 60 (ROCC, 0.040–0.063 mm).

3.2. Pd-catalyzed amination of 3-bromoquinoline (5) with 2-bromoanilines (6)

3.2.1. 3-(2-Bromo-4-methylphenylamino)quinoline (7b). A round-bottomed flask was charged with $Pd_2(dba)_3$ (0.069 g, 0.075 mmol, 2.5 mol %) and XANTPHOS [9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene] (0.096 g, 0.165 mmol, 5.5 mol %) followed by dry dioxane (12 mL) (freshly distilled). The mixture was flushed with N_2 for 10 min. Meanwhile, in another round-bottomed flask 3-bromoquinoline (**5**) (0.624 g, 3 mmol), 2-bromo-4-methylaniline (**6b**) (0.670 g, 3.6 mmol) and caesium carbonate (2.932 g, 9 mmol) (Aldrich, 99%) were weighed. To this mixture, the Pd-catalyst was added and the flask was flushed with N_2 for 5 min. The resulting mixture was heated at reflux (oil bath temperature: 110 °C) for 16 h under magnetic stirring. After cooling down to room temperature dichloromethane (25 mL) was added and the suspension was filtered over a path of Celite and rinsed with dichloromethane (125 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography on

silica gel using dichloromethane as the eluent yielding the title compound in 85%.

White solid; mp 107 °C; δ_H ($CDCl_3$): 8.74 (d, J=2.7 Hz, 1H, H-2), 8.03 (dd, J=8.4, 0.9 Hz, 1H, H-8), 7.67 (d, J=2.7 Hz, 1H, H-4), 7.63 (dd, J=8.1, 1.4 Hz, 1H, H-5), 7.53 (ddd, J=8.4, 6.9, 1.4 Hz, 1H, H-7), 7.46 (ddd, J=8.1, 6.9, 0.9 Hz, 1H, H-6), 7.42 (d, J=1.5 Hz, 1H, H-3′), 7.26 (d, J=8.3 Hz, 1H, H-6′), 7.05 (dd, J=8.3, 1.5 Hz, 1H, H-5′), 6.15 (br s, 1H, NH), 2.30 (s, 3H, CH_3); MS (ESI): 313, 233, 218, 184; HRMS (ESI) for $C_{16}H_{14}N_2Br$ $[M+H]^+$: calcd 313.0340, found 313.0352.

3.2.2. 3-(2-Bromo-4-chlorophenylamino)quinoline (7c). 2-Bromo-4-choroaniline (0.743 g, 3.6 mmol); eluent: CH_2Cl_2/heptane (9/1); yield: 63%; white solid; mp 139 °C; δ_H ($CDCl_3$): 8.76 (d, J=2.7 Hz, 1H, H-2), 8.06 (dd, J=8.4, 0.9 Hz, 1H, H-8), 7.76 (d, J=2.7 Hz, 1H, H-4), 7.68 (dd, J=8.1, 1.5 Hz, 1H, H-5), 7.60 (ddd, J=8.4, 6.9, 1.5 Hz, 1H, H-7), 7.58 (dd, J=1.8, 0.9 Hz, 1H, H-3′), 7.51 (ddd, J=8.1, 6.9, 0.9 Hz, 1H, H-6), 7.20 (m, 2H, H-5′ and H-6′), 6.25 (br s, 1H, NH); MS (ESI): 333, 253, 218, 204; HRMS (ESI) for $C_{15}H_{11}N_2ClBr$ $[M+H]^+$: calcd 332.9794, found 332.9809.

3.2.3. 3-(2-Bromo-5-trifluoromethylphenylamino)quinoline (7d). 2-Bromo-5-trifluoromethylaniline (0.864 g, 3.6 mmol); eluent: CH_2Cl_2/heptane (9/1); yield: 59%; white solid; mp 109 °C; δ_H ($CDCl_3$): 8.83 (d, J=2.6 Hz, 1H, H-2), 8.10 (dd, J=8.5, 1.1 Hz, 1H, H-8), 7.88 (d, J=2.6 Hz, 1H, H-4), 7.75 (dd, J=8.1, 1.5 Hz, 1H, H-5), 7.70 (br dq, J=8.3 Hz, $^5J_{H-F}$=0.8 Hz, 1H, H-3′), 7.66 (ddd, J=8.5, 6.9, 1.5 Hz, 1H, H-7), 7.56 (ddd, J=8.1, 6.9, 1.1 Hz, 1H, H-6), 7.44 (br d, J=1.9 Hz, 1H, H-6′), 7.06 (br ddq, J=8.3, 1.9 Hz, $^4J_{H-F}$=0.6 Hz, 1H, H-4′), 6.44 (br s, 1H, NH); MS (ESI): 367, 287; HRMS (ESI) for $C_{16}H_{11}N_2BrF_3$ $[M+H]^+$: calcd 367.0058, found 367.0069.

3.3. Microwave-assisted intramolecular arylation of 3-(2-bromophenylamino)quinolines (7)

3.3.1. 7*H*-Indolo[2,3-*c*]quinoline (8a). A microwave vial of 10 mL was charged with 3-(2-bromophenylamino)quinoline (**7a**) (0.180 g, 0.6 mmol) and $NaOAc \cdot 3H_2O$ (0.200 g, 1.47 mmol). Subsequently, the vial was flushed with Ar for 1 min. Then, 0.2 mL of a stock solution[†] of the catalyst in DMA (0.2 mol %) and DMA (0.8 mL) was added via a syringe and the resulting mixture was stirred and flushed with Ar for an additional 2 min. Next, the vial was sealed with an Al crimp cap with a septum and heated at 180 °C in a CEM Discover microwave apparatus. The set power was 100 W and the total heating time was 10 min. After the reaction vial was cooled down to room temperature using a propelled air flow, it was opened and poured in a round-bottomed flask. The vial was rinsed with methanol (50 mL) and the combined organic phase was evaporated to dryness. Finally, the crude product was purified via column chromatography on silica gel (the residue was brought on column mixed with silica) using dichloromethane/methanol (98/2) as the eluent yielding the title compound in 66%.[3]

3.3.2. 10-Methyl-7*H*-indolo[2,3-*c*]quinoline (8b). 3-(2-Bromo-4-methylphenylamino)quinoline (**7b**) (0.188 g, 0.6 mmol) and 1 mL of stock solution of catalyst (1 mol %); eluent: dichloromethane/methanol (98/2); yield: 58%; beige solid; mp >270 °C (decomp.); δ_H (DMSO-d_6): 12.06 (br s, 1H, NH), 9.28 (s, 1H, H-6), 8.81 (dd, J=8.2, 1.2 Hz, 1H, H-4), 8.49 (s, 1H, H-11), 8.19 (dd, J=8.3, 1.2 Hz, 1H, H-1), 7.76 (ddd, J=8.2, 6.9, 1.2 Hz, 1H, H-3), 7.66 (ddd, J=8.3, 6.9, 1.2 Hz, 1H, H-2), 7.66 (d, J=8.4 Hz, 1H, H-8), 7.43 (d, J=8.4 Hz, 1H, H-9), 2.59 (s, 3H, CH_3); MS (ESI): 233, 218; HRMS (ESI) for $C_{16}H_{13}N_2$ $[M+H]^+$: calcd 233.1079, found 233.1069.

3.3.3. 10-Chloro-7*H*-indolo[2,3-*c*]quinoline (8c). 3-(2-Bromo-4-chlorophenylamino)quinoline (**7c**) (0.200 g, 0.6 mmol) and 1 mL of stock solution of catalyst (1 mol %); eluent: dichloromethane/methanol (98/2); yield: 69%; light yellow solid; mp >250 °C (decomp.); δ_H (DMSO-d_6): 12.38 (br s, 1H, NH), 9.33 (s, 1H, H-6), 8.82 (dd, J=8.1, 1.1 Hz, 1H, H-4), 8.74 (d, J=1.9 Hz, 1H, H-11), 8.21 (dd, J=8.3, 1.1 Hz, 1H, H-1), 7.81 (d, J=8.8 Hz, 1H, H-8), 7.78 (ddd, J=8.1, 6.9, 1.1 Hz, 1H, H-3), 7.70 (ddd, J=8.3, 6.9, 1.1 Hz, 1H, H-2), 7.62 (dd, J=8.8, 1.9 Hz, 1H, H-9); MS (ESI): 253, 218, 190; HRMS (ESI) for $C_{15}H_{10}N_2Cl$ $[M+H]^+$: calcd 253.0533, found 253.0534.

3.3.4. 9-Trifluoromethyl-7*H*-indolo[2,3-*c*]quinoline (8d). 3-(2-Bromo-5-trifluoromethylphenylamino)quinoline (**7d**) (0.220 g, 0.6 mmol) and 1 mL of stock solution of catalyst (1 mol %); eluent: dichloromethane/methanol (98/2); yield: 76%; light yellow solid; mp 240 °C; δ_H (DMSO-d_6): 12.52 (br s, 1H, NH), 9.41 (s, 1H, H-6), 8.89 (d, J=8.6 Hz, 1H, H-11), 8.82 (dd, J=8.2, 1.2 Hz, 1H, H-4), 8.24 (dd, J=8.3, 1.1 Hz, 1H, H-1), 8.13 (s, 1H, H-8), 7.81 (ddd, J=8.2, 7.0, 1.1 Hz, 1H, H-3), 7.73 (ddd, J=8.3, 7.0, 1.2 Hz, 1H, H-2), 7.67 (d, J=8.6 Hz, 1H, H-10); MS (ESI): 287, 267, 233, 218; HRMS (ESI) for $C_{16}H_{10}N_2F_3$ $[M+H]^+$: calcd 287.0796, found 287.0791.

3.4. Methylation of 7*H*-indolo[2,3-*c*]quinolines (8)

3.4.1. 5,10-Dimethyl-5*H*-indolo[2,3-*c*]quinoline (4b). In a round-bottomed flask 10-methyl-7*H*-indolo[2,3-*c*]quinoline (**8b**) (0.116 g, 0.5 mmol), toluene (7.5 mL) and CH_3I (3 mL) were heated at reflux under N_2 atmosphere (oil bath temperature: 120 °C) for 2 h under magnetic stirring. Then the precipitated material was filtered off and rinsed well with toluene (100 mL). The residue was dissolved in methanol (300 mL) to remove it from the filter and the solution was subsequently evaporated to dryness under reduced pressure. The crude product was purified via column chromatography on silica gel [eluent: dichloromethane/methanol (8/2)]. The residue was brought on column mixed with silica giving 10-methylisoneocryptolepine hydroiodide (**4b**·HI) as a yellow solid. To obtain the free base, **4b**·HI was brought in a mixture of dichloromethane (100 mL) and 28–30% ammonia in water (100 mL). The organic phase was separated and the aqueous phase was subsequently extracted with dichloromethane (2×100 mL). The combined organic phase was

[†] Preparation of the stock solution of catalyst: $PdCl_2(PPh_3)_2$ (0.211 g, 0.03 mmol) was dissolved in 5 mL of DMA. Next, the mixture was flushed with Ar for 5 min and subsequently stirred until the catalyst was completely dissolved.

dried over $MgSO_4$, filtered and evaporated to dryness to quantitatively yield **4b** as a red solid in 75%.

Red solid; mp >180 °C (decomp.); δ_H (CD_3COOD):[17] 9.48 (s, 1H, H-6), 8.62 (d, J=7.2 Hz, 1H, H-1), 8.24 (d, J=8.7 Hz, 1H, H-4), 8.03 (s, 1H, H-11), 7.94 (m, 2H, H-2 and H-3), 7.60 (d, J=8.5 Hz, 1H, H-8), 7.48 (d, J=8.5 Hz, 1H, H-9), 4.60 (s, 3H, NCH_3), 2.50 (s, 3H, CCH_3); δ_C (CD_3COOD): 143.0, 137.7, 134.2, 133.8, 133.4, 130.8, 130.6, 130.3, 127.0, 126.0, 125.0, 123.6, 120.9, 119.6, 114.1, 46.3, 21.6; MS (ESI): 247, 232; HRMS (ESI) for $C_{17}H_{15}N_2$ $[M+H]^+$: calcd 247.1235, found 247.1239.

3.4.2. 10-Chloro-5-methyl-5*H*-indolo[2,3-*c*]quinoline (4c). A round-bottomed flask was charged with 10-chloro-7*H*-indolo[2,3-*c*]quinoline (**8c**) (0.126 g, 0.5 mmol), dry THF (2.5 mL) and MeI (0.25 mL). After overnight heating at reflux (oil bath temperature: 75 °C) under Ar atmosphere and magnetic stirring, the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography on silica gel [eluent: dichloromethane/methanol (9/1)]. The residue was brought on column mixed with silica giving 10-chloroisoneocryptolepine hydroiodide (**4c**·HI) as a yellow solid. To obtain the free base, **4c**·HI was brought in a mixture of dichloromethane (100 mL) and 28–30% ammonia in water (100 mL). The organic phase was separated and the aqueous phase was subsequently extracted with dichloromethane (2×100 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated to dryness to yield **4c** as a red solid in 94%.

Red solid; mp >200 °C (decomp.); δ_H (CD_3COOD):[17] 9.80 (s, 1H, H-6), 8.73 (dd, J=7.2, 2.5 Hz, 1H, H-1), 8.37 (m, 2H, H-4 and H-11), 8.02 (m, 2H, H-2 and H-3), 7.78 (d, J=8.9 Hz, 1H, H-8), 7.62 (dd, J=8.9, 1.7 Hz, 1H, H-9), 4.73 (s, 3H, NCH_3); δ_C (CD_3COOD): 142.4, 138.6, 133.8, 132.0, 131.1, 131.0, 130.7, 128.6, 126.1, 125.6, 124.6, 123.2, 121.0, 119.8, 115.9, 46.5; MS (ESI): 267, 252, 232; HRMS (ESI) for $C_{16}H_{12}N_2Cl$ $[M+H]^+$: calcd 267.0689, found 267.0685.

3.4.3. 9-Trifluoromethyl-5-methyl-5*H*-indolo[2,3-*c*]quinoline (4d). Yield: 95%; orange solid; mp >250 °C (decomp.); δ_H (CD_3COOD):[17] 9.90 (s, 1H, H-6), 8.80 (dd, J=7.3, 2.3 Hz, 1H, H-1), 8.64 (d, J=8.6 Hz, 1H, H-11), 8.40 (dd, J=7.7, 2.2 Hz, 1H, H-4), 8.13 (s, 1H, H-8), 8.03 (m, 2H, H-2 and H-3), 7.67 (dd, J=8.6, 0.8 Hz, 1H, H-10), 4.75 (s, 3H, NCH_3); δ_C (CD_3COOD): 143.4, 139.7, 134.3, 132.8 (q, $^2J_{C-F}$=32.4 Hz), 132.3, 131.3, 131.2, 126.9, 126.0, 125.9 (br d, J_{C-F}=2.8 Hz), 125.4, 125.2 (q, $^1J_{C-F}$=272.2 Hz), 122.9, 120.2, 119.3 (q, J_{C-F}=3.1 Hz), 112.5 (q, J_{C-F}= 4.5 Hz), 46.9; MS (ESI): 301, 286, 281, 233, 183; HRMS (ESI) for $C_{17}H_{12}N_2F_3$ $[M+H]^+$: calcd 301.0953, found 301.0954.

3.5. General procedure for the kinetic experiments

A two-necked round-bottom flask was charged with $PdCl_2(PPh_3)_2$ (0.097 g, 0.138 mmol, 23 mol % or 0.021 g, 0.030 mmol, 5 mol %), 3-(2-bromophenylamino)quinoline (**7a**) (0.180 g, 0.6 mmol), $NaOAc \cdot 3H_2O$ (0.200 g, 1.47 mmol) followed by dimethylacetamide (DMA) (10 mL). The mixture was flushed with Ar for 5 min and then stirred at 130 or 160 °C under Ar atmosphere in a preheated oil bath. At 10, 20, 30, 60, 120 and 360 min 50 μL of fluid was taken from the flask via a septum and diluted with MeOH to a concentration of 1.5×10^{-3} M. The obtained solutions were filtered (0.2 μm; Nylon) and diluted with MeOH to a concentration of 1.5×10^{-4} M. Subsequently, the samples were analyzed with LC–UV–MS. The conversion is determined by dividing the sum of the UV peak areas of 7*H*-indolo[2,3-*c*]quinoline (**8a**) and 10*H*-indolo[3,2-*b*]quinoline (**9a**) by the sum of the peak areas of the starting material (**7a**), 7*H*-indolo[2,3-*c*]quinoline (**8a**) and 10*H*-indolo[3,2-*b*]quinoline (**9a**) after a correction factor on the peak areas, based on the difference in extinction coefficient of the starting material and reaction products at the used wavelength (260 nm), has been taken into account.

3.6. Chromatographic conditions

The analytical column [XBridge C18 (4.6×50) mm, d_p=2.5 μm] was purchased from Waters. The LC analysis was executed with a gradient elution at 1 mL/min starting at 70/30 (v/v) H_2O/MeOH containing 0.1% formic acid. The composition of the mobile phase was altered to 45/55 (v/v) H_2O/MeOH containing 0.1% formic acid in 3 min and subsequently to 20/80 (v/v) H_2O/MeOH containing 0.1% formic acid in 7 min thus giving a total elution time of 10 min. For peak detection a UV-detector (SP8450) from Spectra-physics was used at a fixed wavelength (260 nm). Peak identification was performed with an AQA LC/MS (Quadrupole mass analyzer, $APCI^+$ mode, V_{inj}=25 μL) apparatus from Thermo Finnigan.

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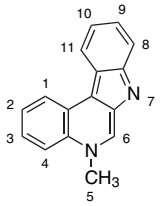
17. Selective N-5 methylation of **8b–d** could be determined by 2D-NMR (NOESY experiment). Observation of a NOE enhancement between the hydrogens of the methyl group and H-4 proved their neighbourhood. Moreover another NOE enhancement, between H-1 and H-11, further supported that in the intramolecular Heck-type reaction 7*H*-indolo[2,3-*c*]quinolines (**8b–d**) were formed as the major isomers.



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The Newman–Kwart rearrangement re-evaluated by microwave synthesis

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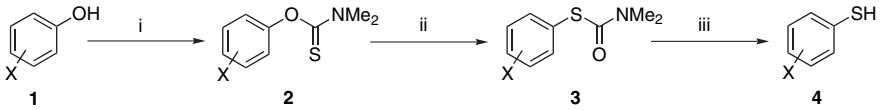
Abstract—The Newman–Kwart rearrangement (NKR) has been re-evaluated by microwave heating. Microwave technology has proven to be ideal for investigating this high temperature rearrangement and facilitated the confirmation of many aspects of this valuable reaction. Comparisons between thermal and microwave results indicate no evidence of a significant microwave effect.

1. Introduction

The Newman–Kwart rearrangement (NKR)[1,2] is a valuable synthetic technique for converting phenols **1** to thiophenols **4** via their *O*- (**2**) and *S*-thiocarbamates (**3**) (Scheme 1). Indeed, such is the utility that other sulfur-containing functional groups have been readily accessed through this methodology, including thioethers, (homo-chiral) sulfoxides, sulfones and sulfonic acids.[3] Alternatively, this approach can be used to access particular aromatic substitution patterns without the phenol/sulfur function, starting from the many widely available phenols, and de-sulfurizing the hydrolysed thiol once the desired transformations are complete. Consequently, the NKR has seen wide application in synthesis,[4] medicinal chemistry,[5] materials and supramolecular chemistry,[6] agrochemicals[7] and dyes.[8]

The NKR proceeds via an *O*- to *S*-aryl migration, which has a high activation energy. Many synthetically useful examples of the NKR require temperatures of 200–300 °C. Electron withdrawing group (EWG) substituents are known to aid the rearrangement, either reducing the reaction time or lowering the required temperature, whilst electron-donating group (EDG) substituents slow the reaction. *Ortho*-substituents can enhance the reaction rate,[9] but doubly *ortho* or very sterically hindered substituents slow the reaction or stop it altogether.[1,9] The rearrangement is proposed to proceed via a four-centre transition state **5** (Fig. 1), which is consistent with these observations. Furthermore, comprehensive kinetic and linear free energy relationships have been conducted,[9,10] which are also in agreement with this model. This should give a first-order reaction, which Newman,[1] Relles[9] and Miyazaki[10a] have shown to be the case. Lastly, this reactive intermediate (**5**) should be stabilised by polar solvents, lowering the activation energy, and thus increasing the reaction rate, but this does not appear to have been studied in detail.[10b]

We were interested in investigating the NKR under microwave irradiation[11] for a number of reasons. It was a reaction with which we had previous experience on scale-up[12] and knew was a sufficiently common motif in the pharmaceutical industry to justify in-depth study.[5] It also held wider synthetic utility.[4,6] Microwave technology provided convenient access to the high temperatures generally required for this reaction. Furthermore, a simple, first-order, unimolecular



Scheme 1. (i) DMTCC (1.1 equiv), DABCO (1.3 equiv), NMP, 50 °C, then water; (ii) solvent, heat or MW; (iii) NaOH or KOH.

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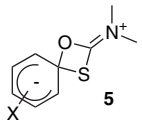


Figure 1. Proposed four-centre transition state intermediate.

model reaction would allow for a thorough and robust investigation of microwave heating. We were also hopeful that the proposed polar transition state intermediate **5** might interact favourably with microwaves,[11d] potentially giving rise to an observable microwave effect, if there was one.

From a practical point, the starting *O*-thiocarbamates **2** could be readily prepared from cheap phenols **1** in a single step. A wide variety of substitution patterns was accessible for **2**, which meant that the reaction parameters could be 'tuned' as desired. All intermediates had good UV chromophores and the NKR is ideal for analytical purposes in that it proceeds cleanly from starting material **2** to product **3** without degradation or impurity formation in most cases. The NKR can thus be readily followed by IR, LC, NMR or TLC as preferred. It was also useful for our purposes that all of substrates **2** and **3** were known; that thorough studies of kinetics with Hammett plots had been conducted;[9,10] and that all these kinetic studies had been conducted with conventional thermal heating;[13] this would provide a secure comparison for our own results.

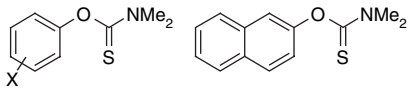
2. Results and discussion

For our initial investigations, we chose phenols **1a–o** covering a range of EWG and EDG substituents from nitro- to methoxyphenyl groups, including the electron neutral unsubstituted phenol (**1j**). To gauge the effect of aromatic substitution, we also included the *ortho* and *meta* nitro- and methoxy-substituted compounds. The starting *O*-thiocarbamates **2a–o** were readily prepared from phenols **1a–o** and dimethylthiocarbamoyl chloride (DMTCC) in fair-to-excellent yields as predominantly crystalline compounds of excellent quality (>98% by LC) (Table 1). We used our previous method[12] adapted from Sebok,[7] which had the advantage of direct isolation of **2** from the quenched aqueous reaction mixtures, thus avoiding tedious chromatography in the majority of cases. With quantities of substrates **2a–o** available, we conducted an initial screening in a focused microwave reactor.

We decided to conduct a coarse survey of reaction conversion after 20 min for all compounds **2a–o**, at 220 °C for EWG substituents and 280 °C for EDG substituents, with the relatively electron neutral compounds (**2g–j**) assayed at both temperatures. The fast reacting nitro substituents had to be reassessed at 180 °C due to over-reaction, so the other EWG compounds were also assayed at this temperature (Table 2).

As can be seen, the trend is as expected when moving from strong EWG to strong EDG substituents, with the latter requiring higher temperatures for equivalent conversions. The substituent effects for the nitro and methoxy compounds were also largely as expected. The *ortho*-substituents

Table 1. Preparation of *O*-thiocarbamates **2a–o**



	X=	Yield (%)	Quality (% LC)[a]	RRF[b] (**2** vs **3**)
2a	2-NO_2	92	100.0	3.20
2b	3-NO_2	93	100.0	1.63
2c	4-NO_2	79	100.0	3.04
2d	4-CN	93	100.0	2.66
2e	4-CO_2Me	92	100.0	2.45
2f	4-CF_3	91	99.9	1.27
2g	2-Naph	72	99.8	1.13
2h	4-Br	84	99.7	1.28
2i	4-Cl	84	99.8	1.39
2j	4-H	56[c]	99.9	3.61
2k	4-Me	66	100.0	2.41
2l	4-F	80	99.7	4.94
2m	4-MeO	49[d]	99.7	1.65
2n	3-MeO	68[c]	98.0	3.78
2o	2-MeO	75[d]	100.0	4.88

[a] Determined at 254 nm.
[b] Relative response factor (RRF) at 254 nm.
[c] Low melting solid purified by chromatography.
[d] Recrystallised from MeOH/water.

appeared to show an additional steric rate acceleration compared to the purely electronic effect of the *para*-substituents, as reported by Relles.[9] The *meta*-substituents **2b** and **2n** also showed the trend expected relative to their *ortho* and *para* regioisomers, given their respective electron withdrawing and donating properties.

From this coarse screen, we were then quickly able to pinpoint the optimum temperature for a convenient 20 min microwave reaction that would give >95% conversion, in the comparable manner reported by Newman.[1] Reaction temperatures and LC conversions for all substrates are collected in Table 3, with Newman's data alongside where available. Generally the results are in good agreement, but some minor differences will be noted, for which we offer the following explanations.

Table 2. Conversion of **2** to **3** after 20 min in microwave at given temperature (20 min in 10 vol NMP)

	X=	Conversion at 180 °C (%)[a]	Conversion at 220 °C (%)[a]	Conversion at 280 °C (%)[a]
2a	2-NO_2	98	>100[b]	—
2b	3-NO_2	4	45	—
2c	4-NO_2	68	>100[b]	—
2d	4-CN	19	99	—
2e	4-CO_2Me	4	75	—
2f	4-CF_3	2	51	—
2g	2-Naph	—	10	97
2h	4-Br	—	7	98
2i	4-Cl	—	7	95
2j	4-H	—	4	78
2k	4-Me	—	—	53
2l	4-F	—	—	51
2m	4-MeO	—	—	27
2n	3-MeO	—	—	92
2o	2-MeO	—	—	76

[a] Determined by LC at 254 nm (RRF corrected).
[b] Indicates all starting material converted and some product degradation had occurred.

Table 3. Temperature required for >95% conversion of **2** to **3** in 20 min by microwave (or conventionally)

	X=	Temp[a] (°C)	Conversion[b] (%)	Temp[c] (°C)	Yield[d] (%)
2a	2-NO_2	180	98	170	90
2b	3-NO_2	240	77[e]	235	>95
2c	4-NO_2	200	98	180	>95
2d	4-CN	220	99 (86)	—	—
2e	4-CO_2Me	240	99 (82)	220	>95
2f	4-CF_3	260	98	—	—
2g	2-Naph	280	97	285	80
2h	4-Br	280	98 (83)	—	—
2i	4-Cl	280	95 (82)	—	—
2j	4-H	290	97 (82)	—	—
2k	4-Me	295[f]	82 (83)	—	—
2l	4-F	295[f]	82	—	—
2m	4-MeO	295[f]	72	290	83
2n	3-MeO	295[f]	85 (86)	—	—
2o	2-MeO	295	95 (80)	280	90

[a] MW, 20 min in 10 vol NMP.
[b] Conversion determined by LC at 254 nm, RRF corrected with isolated yields noted in brackets.
[c] Thermal heating, 20–30 min neat.
[d] Isolated yields except where >95% quoted (from TLC response at 254 nm).
[e] Some decomposition seen above this temperature.
[f] Higher temperatures could not be accessed to achieve >95% conversion in 20 min.

Newman's reactions were conducted neat whereas ours were conducted in 10 vol of NMP (Relles and Kaji used 0.3 M solutions in phenylether). For a first-order, unimolecular reaction, rate should be independent of concentration. However, we know from our other results that there is a subtle effect related to concentration, which we believe accounts for the slight differences in the observed rate. Secondly, the exact end-point of these reactions is difficult to ascertain at 254 nm due to the generally stronger UV responses of *O*-thiocarbamates **2** over their analogous *S*-thiocarbamates **3**. Newman used IR but found this unreliable and reverted to TLC, necessitating an additional 10 min heating time in unspecified cases. We have determined the relative response factors (RRFs) to give accurate LC results (see Table 1 for data and Section 4 for method determination).

Finally, we have briefly surveyed the solvent effect for one substrate (**2a**) at one temperature (140 °C) under both microwave and thermal reaction conditions. The thermal tube reactions were sealed with caps easily removed for sampling purposes, except for the lower boiling solvents formic acid and trifluorotoluene, where crimp caps were used; hence only one time point was taken from these tubes. However, being a rearrangement, no pressure is generated in this reaction below the boiling point of the solvent used, and even at the higher end of the temperature range (250–300 °C), pressures are still relatively modest. Data are shown for both 30 and 60 min time points in Table 4. As can be seen, there is an excellent correlation between microwave and thermal results in all cases (the thermal figures are slightly higher for two low polarity solvents, diphenylether and xylene, the reasons for which are still being investigated). Our studies with other substituted *O*-thiocarbamates (**2**) and various solvents show this agreement between microwave and thermal results to be general. The reaction rate also fits the relative order of solvent polarity, supporting the hypothesis that polar solvents can stabilise polar transition state intermediate **5**. To our knowledge this is the first time such an effect has been confirmed experimentally.

Table 4. Conversion of **2a** at 140 °C in 10 vol of solvent under microwave and thermal heating

Solvent	Time (min)	Conversion (%)[a]	
		Microwave	Thermal
Dichlorobenzene	30	15	15
	60	28	27
Diphenylether	30	12	15
	60	23	27
Formic acid[b]	30	79	78
NMP	30	23	23
	60	39	40
Trifluorotoluene[b]	30	11	11
Xylene	30	8	10
	60	15	19

[a] Conversion determined by LC at 254 nm (RRF corrected).
[b] Conventional heating was conducted above the boiling point of the solvent in a sealed tube in an oil bath.

3. Conclusions

In conclusion, we have shown that the NKR is a well-behaved first-order reaction under microwave heating. We have confirmed several known aspects of the reaction mechanism and provided the first experimental support for a solvent rate effect. Furthermore, we find the reaction rate is essentially unchanged compared to thermal heating under all conditions. In short, we find no evidence for a significant microwave effect in this case, although there may be a subtle effect related to the reaction itself which we are currently investigating.

In addition, microwave technology has proven to be exceptionally convenient in a laboratory setting for accessing the high temperatures required (200–300 °C), both for the personal safety of the chemist and for rapid reactions. Furthermore, we found the IR temperature sensor to be very reliable in our hands, confirmed by comparison to our thermal heating results. Opportunities for further exploitation of the NKR as a probe to investigate microwave heating are ongoing and results will be reported shortly.

4. Experimental

4.1. General

Reaction mixtures and products were analysed by reverse phase HPLC on an Agilent 1100 series instrument according to the following conditions: column, Genesis C18 100×3.0 mm i.d.; eluent A, 95% purified water, 5% acetonitrile, 0.1% v/v formic acid; eluent B, 95% acetonitrile, 5% purified water, 0.1% v/v formic acid; flow rate 0.75 ml/min; wavelength 254 nm; temperature 35 °C; injection volume 10 μl; at t=0 min, 40% eluent B; at t=5 min, 70% eluent B; at t=7 min, 70% eluent B; 3 min post time. Typical retention times (RT) are noted in each case. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H and

^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz, respectively, with chemical shifts given in parts per million relative to TMS at δ=0. Electrospray (ES^+) mass spectra were performed on a Micromass ZQ (*O*-thiocarbamates, **2a–o** and *S*-thiocarbamates, **3d** and **3f**) or a Micromass Platform LC (all other *S*-thiocarbamates) mass spectrometer. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography was carried out by standard procedures using Merck Kieselgel 60 (230–400 mesh). Otherwise wherever not stated, assume standard practices have been applied.

4.2. Typical microwave procedure

Microwave reactions were performed in 10 ml sealed tubes in a regularly calibrated CEM *Discover* focused 300 W microwave reactor with IR temperature monitoring and non-invasive pressure transducer. In a typical procedure, 200 mg of *O*-thiocarbamate (**2**) was dissolved in NMP (2.0 ml) and heated to the required temperature with stirring for a fixed time. The heating time to reach the set temperature was typically 45–90 s, depending on the scale, the maximum wattage supplied (100–300 W) and the temperature required (140–295 °C) (typically 100 W to heat a 2 ml sample to 140 °C in ~45 s, or 300 W to heat to 295 °C in ~90 s). The heating time is not included in the quoted hold time for any given procedure; control studies show that the heating time is negligible for a 20 min reaction time. The *S*-thiocarbamate (**3**) products were isolated either directly by aqueous drown-out from NMP solutions, or by extraction into MTBE followed by flash silica gel chromatography and/or recrystallisation from methanol if required. Data only on *S*-thiocarbamates (**3a–o**) can be found in the Supplementary data. Yields are given only for preparative procedures, typically performed on 1.0 g of substrate **2** in 4.0 ml NMP (all other parameters were kept constant).

4.3. Typical oil bath procedure

For conventional (thermal) heating comparisons, identical scales, temperatures and heating times were used. Procedures were conducted in microwave test-tubes in oil baths pre-heated to the set temperature. Heating times were determined on several control samples, being typically 60–120 s depending on the exact conditions required. The heating time is not included in the quoted hold time for any given procedure; control studies show that the heating time is negligible for a 20 min reaction time. Tubes were generally sealed with CEM's *Intellivent* caps, except when working close to or above the boiling point of a given solvent, when crimp caps were used instead. However, control studies show that for high boiling solvents operating at modest temperatures (e.g., 140 °C), sealing tubes is not necessary to mimic microwave reaction conditions, since no pressure is developed. Work-up and isolation (if required) were performed as for the microwave procedures as above.

4.4. Determination of relative response factors (RRF)

RRFs were determined as follows: an accurately weighed sample of each analytically pure *O*-thiocarbamate **2** was dissolved in $CDCl_3$ with an accurately weighed sample of its respective analytically pure *S*-thiocarbamate analogue **3** in typically ~1:1 ratio. The ^{1}H NMR spectra were obtained using a method with lengthened relaxation delay (for more accurate integration) and the integration of the respective NMe_2 peaks in the ^{1}H NMR spectra compared to the relative responses in the LC spectra at 254 nm. Taking the ^{1}H NMR integration values as the correct ones allowed a correction factor to be determined for the relative response of the *O*-thiocarbamates compared to the *S*-thiocarbamates when using the LC according to the following equation:

$$\text{Relative response factor } (O\text{-thiocarbamate}) = (\text{NMR ratio} \times O\text{-thiocarbamate LC}) / \{S\text{-thiocarbamate LC} \times (1 - \text{NMR ratio})\}$$

So to determine the actual conversion to *S*-thiocarbamate using the LC spectra, the following equation is used:

$$\text{Actual } S\text{-thiocarbamate conversion} = (S\text{-thiocarbamate LC} \times \text{RRF}) / \{(S\text{-thiocarbamate LC} \times \text{RRF}) + O\text{-thiocarbamate LC}\}$$

Several samples had RRFs determined at several ratios (other than 1:1) to validate the consistency of this method.

4.5. Typical laboratory preparations

All the compounds (**2a–o** and **3a–o**) were fully characterised by LC/TLC, ^{1}H and ^{13}C NMR spectroscopy, MS, and mp where applicable. The data are not reproduced here since all compounds are known in the literature (see Supplementary data for full experimental conditions and characterisations in each case). A typical procedure is given below.

4.5.1. Preparation of an *O*-thiocarbamate (2-nitrophenyl-*O*-thiocarbamate, 2a). 2-Nitrophenol (10.43 g, 75 mmol) and DABCO (10.5 g, 93.8 mmol, 1.25 equiv) were heated in NMP (52 ml) to 50 °C with mechanical stirring to give a dark yellow solution. Dimethylthiocarbamoyl chloride (9.73 g, 78.8 mmol, 1.05 equiv) was dissolved in NMP (8 ml) and added dropwise to the previous solution over 3–4 min. (N.B. A 6–8 K exotherm was typically seen on this scale.) Some solid formed in the dark orange solution during this addition. The reaction was monitored by LC and was complete within 2–3 h at 50 °C. Water (120 ml) was added over 10–15 min at 50 °C. The original solid dissolved readily, but then a copious precipitate formed about halfway through the addition, which persisted to the end. The reaction mixture was cooled smoothly to 20 °C and the precipitate isolated by filtration. The product cake was displacement washed twice with water (20 ml each) and dried in vacuo at 50 °C to yield the title compound as an off-white to pale cream coloured crystalline solid (15.6 g, 92%). HPLC (RT 2.1 min, 99.96%); mp 120–121 °C (lit.[1] 112–113 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, d, J=8.4 Hz), 7.67 (1H, t, J=7.8 Hz), 7.41 (1H, t, J=7.8 Hz), 7.26 (1H, d, J=8.0 Hz), 3.46 (3H, s), 3.41 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 185.90, 147.21, 142.01, 134.42, 126.55, 126.49, 125.68, 43.50, 39.09; MS (ZQ) (ES^+) 227 (M+1, 100%).

4.5.2. Preparation of an *S*-thiocarbamate (2-nitrophenyl-*S*-thiocarbamate, 3a). (See Section 4.2, Typical Microwave Procedure, for general method). The concentrated MTBE extract was purified by flash silica gel chromatography eluting with 2:1 *iso*-hexane/ethyl acetate (R_f 0.25) to give the title compound as a bright yellow oil; HPLC (RT 2.46 min, 99.1%); mp oil (lit.[1] 30–32 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, dd, J=7.6, 1.2 Hz), 7.70 (1H, d, J=7.6 Hz), 7.50–7.60 (2H, m), 3.12 (3H, br s), 3.03 (3H, br s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.35, 152.34, 138.16, 132.18, 129.84, 124.76, 124.30, 37.09, 29.65; MS (ES^+) 227 (M+1, 100%).

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The mercury-mediated decarboxylation (Pesci reaction) of naphthoic anhydrides investigated by microwave synthesis

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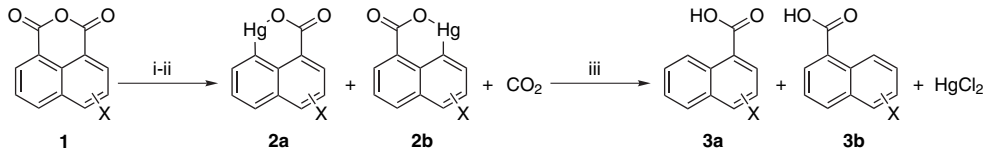
Abstract—The mercury-mediated decarboxylation (Pesci reaction) of several substituted naphthoic anhydrides has been investigated by microwave synthesis. A laboratory microwave reactor was found to be ideal for small-scale preparations of this slow reaction, reducing reaction times from typically four days to less than 1 h for the three-step process. The ionic reaction medium rapidly heated to high temperatures under microwave heating and could be efficiently maintained by low microwave power settings. Generation of stoichiometric CO_2 was safely contained within the reaction tubes. A simplified reaction procedure has been developed. For substituted naphthoic anhydrides, ^{1}H NMR analysis of the naphthoate ester derivatives indicated no change in the regioisomer ratio compared to previously reported thermal values.

1. Introduction

The selective mercury-mediated decarboxylation of an aromatic anhydride to give the mono-acid and carbon dioxide (after acidic hydrolysis) was first reported by Pesci.[1] Whitmore reported on the mechanism and effect of the substitution pattern on the mercury insertion of various phthalic, naphthoic and related anhydrides in a series of reports.[2–5] More recently, Newman has investigated the decarboxylation of phthalic, naphthoic and phenanthroic anhydrides in greater detail,[6] and confirmed many of Whitmore's findings. Mercury-mediated decarboxylations have been reviewed by Deacon et al. in their article on the synthesis of organometallics by decarboxylation reactions.[7]

In the early studies, the arene anhydride (**1**) (Scheme 1, naphthoate series shown for convenience) was hydrolysed to its dicarboxylate anion and treated in situ with HgO in acetic acid and water (effectively $Hg(OAc)_2$). The Hg species possibly adds initially between the carboxyl groups, and then into the arene ring displacing one or other of the carboxylate groups, which is then released as CO_2, giving the anhydro organo-mercury isomers (**2a**,**b**) in typically quantitative yield in all cases. These are very stable compounds that can be isolated and oven dried. They are thought to exist in polymeric chains,[7] which probably account for their low solubility in organic solvents.[8] Acidic hydrolysis (or hydride reduction)[6] releases Hg as its salt to yield the arene mono-acids (**3a**,**b**) (Scheme 1).

These reactions are thermally driven and can take up to 96 h at reflux in water. Newman[6] and others have shown that a radical pathway is unlikely, although it is common in much other organo-mercury synthesis. The exact mechanism is unclear, and this may be because alternative mechanisms are favoured in different cases. Whitmore used an unsymmetrically substituted phthalide to establish that Hg directly displaces one of the carboxylate groups, rather than at either *ortho* position.[2] Further evidence supports both cationic and anionic initiated S_E1 and S_Ei type mechanisms, as well as classical electrophilic aromatic *ipso* substitution pathways. However, the reaction rate appears to be



Scheme 1. (i) NaOH, H_2O; (ii) HgO, $AcOH/H_2O$ (3:1), or $Hg(OAc)_2$ neat; (iii) concentrated HCl.

Keywords: Decarboxylation; Mercury; Microwave; Naphthoic anhydride.
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relatively insensitive to the nature of the substituent, perhaps not surprising given the forcing conditions. The nature and position of any substituent does, however, affect the ratio of the resulting regioisomers, and appears to depend on both polar and steric components; however, release of ring strain may be dominant in sterically crowded cases.[6,7] A more detailed discussion of possible mechanisms can be found in Deacon's review.[7]

Newman has also shown that in higher boiling solvents with powdered glass the reaction can be accelerated to shorter periods, and that $NaBH_4$ can be used to quickly reduce the organo-mercury species (**2a**,**b**) to their respective mono-acids (**3a**,**b**). However, the work-up procedure using these solvents and reagents was both more complicated and more dilute than the original conditions. As we will show, the microwave procedure is very convenient for accelerating the reaction and simplifying the work-up without recourse to high-boiling solvents or reducing agents.

2. Results and discussion

Our interest in this reaction initially resulted from a requirement to synthesise 3-cyano-1-naphthoic acid,[9,10] which has a particularly awkward substitution pattern for electrophilic aromatic substitution chemistry (i.e., two deactivating substituents in the same ring). Application of the Pesci reaction to the decarboxylation of 3-bromonaphthoic anhydride (**4b**) and subsequent derivatisation via its acid (**5b**) and methyl ester (**7b**) actually provides a relatively short sequence to this naphthoic acid (Scheme 2). In our experience, the decarboxylation reaction required from two to four days at reflux in water to complete the decarboxylation step, before a 4 h hydrolysis in refluxing HCl completed the transformation. These conditions are typical of other reported examples.

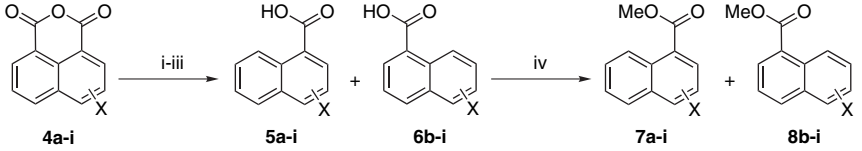
Such a reaction, with its long reaction time at elevated temperature, ionic reaction medium and metal-mediated transformation, seemed an ideal candidate with which to investigate the application of microwave chemistry. We were interested to determine whether microwave synthesis could be used to enhance the rate of reaction, and to see if there was any significant microwave effect. We were also interested to compare the ratio of regioisomeric naphthoic acids derived from various substituted naphthoic anhydrides under microwave conditions with the ratios determined under purely thermal conditions. Lastly, the stoichiometric generation of CO_2 was an additional challenge for use in the sealed microwave tubes typical of modern microwave reactors.[11]

Before commencing any studies in a microwave reactor, a Carius tube test was conducted on a sample of compound **4b** conveniently left over from previous work.[10] Assuming a 20% fill in a 10 mL microwave tube, which conveniently approximated to 1 mmol scale for the limiting naphthoic anhydride, a maximum pressure of ~200 psig was achieved at 180 °C. The tubes are rated for 250 psig in operational use[12] from which a maximum operating limit of 200 °C was extrapolated with an adequate safety margin, assuming no increase in either tube fill or molar equivalents. It must be acknowledged that these pressures, although transient in most cases, would present problems for scale up, although these could be off-set by lower reaction temperatures or slower heat up ramps. In the first instance, however, millimole scale quantities can be prepared to support a medicinal chemistry programme.

For the initial investigations, we started with the conversion of readily available unsubstituted naphthoic anhydride **4a** into naphthoic acid **5a** (Scheme 2). In a standard protocol, the anhydride was dissolved in excess 1 M NaOH at 50 °C for 15 min to achieve hydrolysis to the dicarboxylate salt. Meanwhile, red HgO was dissolved in a warm solution of 3:1 acetic acid/water to give a colourless solution. This was added to the dicarboxylate salt resulting in a dense white precipitate, which was then heated to 100 °C for several days. The intermediate organo-mercury species are highly insoluble and gave very poor chromatography on HPLC. Consequently, the reaction could only usefully be monitored after the acidic hydrolysis step, achieved by adding a large excess of concentrated HCl (~24 equiv) and heating to 100 °C for 4 h. The insoluble product could be filtered from the cooled reaction mixture, washed copiously with water to remove $HgCl_2$ and dried in a vacuum oven to give typically a quantitative yield of naphthoic acid as an off-white solid. LC analysis of the isolated solids was then satisfactory.

To achieve a representative thermal reaction rate profile, a series of tube scale reactions was performed in sealed tubes heated in an aluminium block at 100 °C. At various time points, a reaction was quenched by the addition of HCl and after a further 4 h heating at 100 °C, the resulting solid was isolated as described above. The results are shown in Figure 1, and confirm previous results; namely that whilst ~90% conversion can be achieved after 48 h, more than 96 h (four days) is required to achieve nearly 100% conversion.

We now conducted the reaction under microwave conditions, keeping all the parameters same except the temperature.[13] Rather than lengthening the reaction time excessively, we chose to fix the reaction time to a convenient 15 min, and increased the reaction temperature significantly. We then ran a series of microwave tube scale experiments on



Scheme 2. (i) NaOH, H_2O; (ii) $Hg(OAc)_2$; (iii) concentrated HCl and (iv) $SOCl_2$, MeOH. Substituent X is given in Table 2. NB. Regioisomer notation: **5/7** series, substituent in same ring as carboxylate; **6/8** series, substituent in opposite ring to carboxylate. For X=H, only **5a** and **7a** are used.

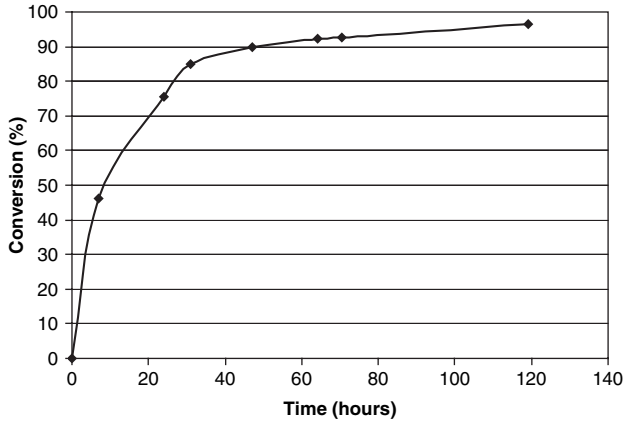


Figure 1. Thermal heating rate (% conversion at time indicated, with HgO).

identical conditions, with a fixed hold time of 15-min microwave irradiation once the set-point temperature had been reached. Temperatures from 100 to 200 °C were studied at 20 °C intervals. The acidic work-up was, however, conducted as before with a 4 h reflux in excess HCl at only 100 °C under conventional heating. The results are shown in Figure 2 and the comparison with Figure 1 shows that 15 min in the microwave at ~180–200 °C is approximately equivalent to the thermal heating rate at 100 °C after ~48 h.[14] This comparison of the thermal and microwave heating data strongly suggests that there is no inherent difference in reaction rate when allowing for the increased reaction temperature under microwave conditions, i.e., the thermal rate at these elevated temperatures would give comparable reaction rates.

Making up a solution of HgO in a specific ratio of pre-heated acetic acid/water was rather tedious and we determined to simplify the procedure by swapping this with neat $Hg(OAc)_2$. Initially we added acetic acid and water to the NaOH solution to keep the overall solution volume constant, but found that both could be eliminated and the reaction and work-up still performed reliably. Adding $Hg(OAc)_2$ (initially 1.25 equiv) in place of HgO gave comparable results with >90% conversions in similar times, as long as the $Hg(OAc)_2$ was thoroughly mixed by shaking with the hydrolysed dicarboxylate before microwave irradiation began.

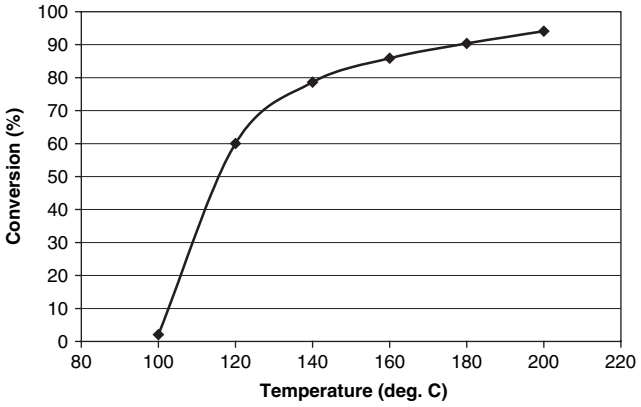


Figure 2. Microwave heating rate (% conversion after 15 min. MW heating at set temperature, with HgO).

We also tested microwave heating for the NaOH hydrolysis step and found that 1 min at 100 °C was adequate to form the dicarboxylate anion.

We had deliberately separated the acidic hydrolysis from the decarboxylation reaction so far, but clearly a 4 h hydrolysis for a 15-min microwave reaction was highly inefficient. Therefore, a series of tubes was run under what were now our standard microwave conditions (i.e., 180 °C for 15 min with $Hg(OAc)_2$), and then hydrolysed with concentrated HCl at several elevated temperatures from 120 to 150 °C. The results at 120 °C proved most reliable, with no significant difference being seen between heating for 15, 30, 60 or 120 min (conversions varied from 90–93%, i.e., within experimental error). Heating for 15 min at higher temperatures proved less robust; the product was often isolated in poor form under these conditions being typically a hard brown solid rather than the usual off-white powder, and LC analysis was variable. Therefore, hydrolysis at 120 °C for 15 min under microwave heating was chosen for future reactions, since this was both convenient and robust, and 15 min appeared to be adequate under most conditions.

Confident that we could now run the whole reaction sequence under microwave conditions in less than 1 h, we now decided to investigate other parameters systematically in the microwave. Initial studies had been conducted with a slight excess of HgO (or $Hg(OAc)_2$), from 1.05 to 1.15 equiv. Using the same conditions as before, but now with microwave assisted HCl hydrolysis at 120 °C for 15 min, we assessed the impact of Hg stoichiometry on the reaction conversion. The results are shown graphically in Figure 3 where it can be seen that no benefit is achieved by adding more than ~1.2 equiv of Hg (given its toxicity, clearly the less used the better). This graph also shows a duplicate point for a repeat reaction, which was performed to assess the overall reproducibility of the microwave procedure now that it was well-defined; as can be seen, the reproducibility was excellent.

The reaction did not quite reach completion even with a significant excess of Hg available, however. We speculated that if the release of CO_2 was a reversible process, then the increased partial pressure of CO_2 in a sealed tube might inhibit complete conversion (Le Chatelier's principle). Although

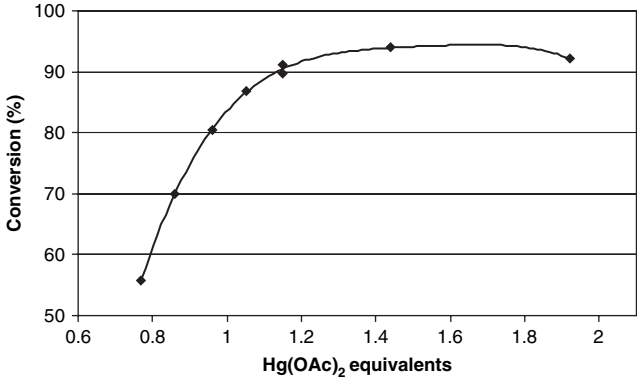


Figure 3. % Conversion with increasing $Hg(OAc)_2$ stoichiometry.

Table 1. % Conversion under microwave heating (isolated yields)

Temperature (°C)	Standard protocol (1×15 min)	With gas venting (2×7 min)	With pulsed heating (3×4 min)
160	85.9	84.9	88.2
180	90.4	93.4	94.0
200	94.1	96.4	95.4

we did not think this very likely, it was worth investigating briefly. Several reactions were conducted under the previously described conditions, but in two 7 min cycles of microwave heating, with the cool down in the middle used to vent CO_2 from the reaction tubes. Total heating for 14 min with two heat up cycles was taken to be approximately equal to one period of 15 min with a single heat up period. Reactions were performed at 160, 180 and 200 °C, with the cooled tubes vented to atmosphere at the halfway point. An analysis of the gas generation from the initial hazard study, and the gas pressure profile from the microwave reactions themselves, showed that most of the CO_2 release occurred in the first 7 min; the additional pressure generated in the second 7 min was relatively low. Therefore, although the conversions were already high after 7-min heating, this also maximised the removal of CO_2, which we felt would afford the best conditions for detecting any further progress in conversion. The results are presented in Table 1 along with the equivalent results from Figure 2 for comparison. This shows that there was in fact no benefit in releasing CO_2; higher conversions were achieved simply due to higher temperatures, which matched previous results.

Some anecdotal reports attribute microwave enhancements to rapid heating effects rather than the absolute temperature reached. We attempted to test this hypothesis by subjecting a number of standard reactions to pulsed heating protocols of three cycles of 4-min heating at 160, 180 and 200 °C and compared them to the control values for a single 15 min reaction. However, there was no discernable difference between these protocols within the experimental error of reproducibility for these reactions (~2–3%) (Table 1). As with the gas-venting experiments, the product was a pale cream solid of good form and yield.

Finally, to check for robustness in our procedure, we ran a further set of six reaction tubes, varying NaOH equivalents at two levels (2.0 and 2.5 mmol) and $Hg(OAc)_2$ equivalents at three levels (1.05, 1.15 and 1.25 equiv), but with all other parameters using the standard conditions (i.e., 180 °C for minutes). The form of the product was good in all cases, with conversions typically 93–96%, indicating that the process was robust for minor charging errors within the tested range. With these final results, an optimised tube reaction was performed as described in Section 4. This used a microwave NaOH hydrolysis step (1 min at 100 °C), 1.05 equiv of $Hg(OAc)_2$ with microwave heating (15 min at 200 °C), and completed with a microwave HCl hydrolysis step (15 min at 120 °C), to give an isolated yield of 99% of naphthoic acid with 98.9% quality by LC as a pale cream powder of good form. Significantly, all stages were performed in the same reaction tube in a 'one pot' process by sequential addition of the required reagents, thus simplifying the overall procedure. This process was then used as the basis for decarboxylation of the substituted naphthoic anhydrides.

Substituted naphthoic anhydrides **4b–i** were subjected to the Pesci reaction under microwave heating using the conditions optmised for the unsubstituted compound **4a** (Scheme 2). Further limited optimisation was required for each substituent, with temperature varying from 180 to 200 °C, time from 15 to 30 min and $Hg(OAc)_2$ charge from 1.05 to 1.15 equiv. The specific conditions and results are presented in Table 2. In nearly all cases a high conversion with a quantitative yield could be obtained. The electron-withdrawing substituents (Br, Cl and NO_2) tended to give better conversions with longer heating at 200 °C, compared to the electron-donating ones (**4a**,**e**–**f**). The exact equivalents of $Hg(OAc)_2$ appeared to be less critical. In as much as these conditions appear to favour electron-donating groups over electron-withdrawing ones, this suggests that a classical electrophilic aromatic substitution may be operating. But as Deacon warns in cases that are extremely forcing (such as these), one should be cautious in deducing too much about the preferred mechanism.[7]

Product quality was good in all cases, with the colour generally derived from the quality of the input anhydride **4a–i**. Only the 4-chloro acids (**5d/6d**) gave less than full recovery, which appeared to be due to higher water solubility. The 3-OH acids (**5e/6e**), available from commercially available **4e**, gave a product of moderate form and quality. The strong mustard yellow colour was certainly carried through from the starting material. Attempts to force consumption of **4e**

Table 2. Optimised conditions for conversion of substituted naphthoic anhydrides (**4**) to naphthoic acids (**5** and **6**) under microwave heating

Entry	Anhydride (**4**) X=	Temperature (°C)	Time (min)	Equivalents of $Hg(OAc)_2$	Conversion[a] (%)	Product quality	Product colour	Total yield (%)
a	H	200	15	1.05	98.9	Good	Cream	100
b	3-Br	200	30	1.05	94.6	Fair	White	100
c	4-Br	200	30	1.15	84.7	Good	White	100
d	4-Cl	200	30	1.05	82.2	Good	White	70[b]
e	3-OH	180	15	1.15	66.9[c]	Poor	Mustard	181[d]
f	3-OMe	180	15	1.15	98.4	Good	Yellow	100
g	2-NO_2	180	15	1.05	93.0	Good	Light brown	89
h	3-NO_2	200	30	1.15	94.1	Good	Cream	100
i	4-NO_2	200	30	1.05	89.1	Good	Brown	100

[a] Determined by LC on isolated dried product.
[b] This product retained high water solubility and much was lost on washing.
[c] The product was contaminated with 25% residual starting material.
[d] Visible mercury was present, which probably accounts for the high yields.

could be achieved, but gave a black product of poor form and significant impurities. The yield was also suspiciously high, which may be explained by naphthol salt formation, although metallic mercury was also visibly present. Unsurprisingly, derivatisation to the esters was unsuccessful. Given the relative ease of alternative synthesis of naphthoic acids with hydroxyl substituents, we did not pursue this example further. However, the 3-OMe series (**4/5/6f**), derived from methylation of **4e**[15] gave excellent results throughout.

The regioisomer ratio of the naphthoic acids could not be easily determined by HPLC, as there were known to be significant differences in the UV responses at a given wavelength for each pair of alternately substituted naphthoic acids.[16] Furthermore, although direct analysis of the acids (**5/6**) by ^{1}H NMR is in principle possible, their solubility even in d_6-DMSO was too low to give reliable results. We therefore decided to derivatise samples of the mixed acids to their respective methyl esters (**7/8**), which could then be analysed by ^{1}H NMR in $CDCl_3$. The methyl ester signal also provided a further peak to check the integration against, although in most cases, at least one distinctive aromatic signal could be found to determine the regioisomer ratio. Assignments of the major and minor regioisomers were also made on esters **7/8**.

The methyl esters were prepared by treatment with excess thionyl chloride in methanol (or concentrated H_2SO_4 in methanol for **4a**),[10] concentrated to dryness and purified by flash silica gel chromatography. No attempt was made to separate the methyl ester isomers, and ^{1}H NMR analysis was conducted on the clean product mixtures as planned. The results are shown in Table 3, alongside the reported ratios where available for the naphthoic acids (**5/6**). These figures are mainly derived from Whitmore's work,[2,4] and Newman is wise to point out that the number of fractional crystallisations involved in some cases makes the comparison uncertain. However, using the most reliable figures from Whitmore, with which Newman also agrees, our microwave mediated regioisomer ratios are in good-to-excellent agreement with all previously reported values. Furthermore, for those compounds with no previous data, the regioisomer ratios matched the observed trend, i.e., generally ~3:1 for 3-/6-substituents, and ~6:4 for 4-/5-substituents. Only the 4-chloro (**4/7/8d**) and 2-nitro series (**4/7/8g**) gave an alternative ratio in favour of substitution in the opposite ring to that of the remaining carboxyl functionality. The effect was slight for the 4-chloro series (35:65 **7d**:**8d**); consequently the ^{1}H and ^{13}C NMR assignments were re-examined at some length and the original assignments confirmed. The effect on the ratio was complete and unambiguous in the case of the 2-nitro series (0:100 **7g**:**8g**), thus showing that steric constraints are dominant for 2-substituted naphthalenes, as is generally the case. In summary, microwave heating has not altered the regioisomer ratio resulting from mercury-mediated decarboxylation. Our results are in full agreement with those of Whitmore[4] and Dewar[9] and refute again the disputed results discussed by Deacon.[7,17]

3. Conclusions

We have investigated the mercury-mediated decarboxylation (Pesci reaction) of eight substituted naphthoic anhydrides and shown that microwave heating is especially convenient for this type of slow, metal-mediated reaction. Reaction times have been reduced from four days to less than 1 h for the three-step sequence with a simplified reaction procedure, which can be conducted as a 'one pot' process. Stoichiometric generation of CO_2 was safely contained within the microwave reaction tubes. For substituted naphthoic anhydrides, the regioisomer ratio of the resulting acids was identical to those previously reported by thermal methods. Accounting for the temperature increase under microwave conditions, no significant increase in the reaction rate was detected beyond what would be expected under identical thermal conditions. In this case, microwave chemistry has therefore been proven to be a reliable and predictable substitute for thermal reaction conditions, with the additional benefit of convenient access to very high reaction temperatures.

4. Experimental

4.1. General

All microwave reactions were performed exclusively in a regularly calibrated CEM *Discover* 300 W focused microwave reactor with IR temperature monitor and non-invasive pressure transducer in 10 mL sealed tubes. The heating time

Table 3. Regioisomer ratios and data on substituted methyl naphthoate esters **7b–i** and **8b–i**

Entry	Anhydride (**4**) X=	Ratio **7**:**8** (MW)[a]	Ratio **5**:**6** (lit.)[b]	Lit. ref.		Total yield[c]
				7	**8**	**7**+**8** (%)
b	3-Br	72:28	75:25 (9, 10)	18, 19	9, 10	65
c	4-Br	60:40	n/d	20	20	50
d	4-Cl	35:65	n/d	19, 20	19, 20	76
e	3-OH	n/d	n/d	n/a	n/a	n/a
f	3-OMe	72:28	n/d	21	20	78
g	2-NO_2	0:100	n/d	22	9, 23	47
h	3-NO_2	76:24	65:35 (4); 83:17 (6)[d]	19, 20	20	100
i	4-NO_2	96:4	96:4 (4)	20	20	73

n/a=Not applicable.
n/d=Not determined.
[a] Determined from ^{1}H NMR integration of esters **7** and **8**.
[b] Literature values reported for acids **5** and **6** (references given in parentheses).
[c] Total yield of combined esters from **4**; low yields may reflect incomplete decarboxylation reactions to acids **5** and **6**.
[d] The data are difficult to interpret; the minor isomer is almost certainly over-estimated in Ref. 4 and a ratio of ~3:1 would be more likely.

to reach the set temperature was typically 45–90 s, depending on the maximum wattage supplied (30–90 W) and the temperature required (100–200 °C) (typically 90 W to heat a 2 mL sample to 200 °C in ~90 s). The heating time is not included in the specified hold time for any given procedure; control studies show that the heating time has negligible effect on a 15 min reaction. The maximum wattage supplied was capped well below the maximum 300 W available to avoid the reaction mixture significantly over-shooting the set-point temperature; the ionic reaction medium absorbs microwaves very readily in this case. Reaction tubes were rapidly cooled once irradiation was complete by a stream of compressed air, and generally removed from the instrument when at 70 °C.

Isolated products were fully characterised by LC/TLC, ^{1}H and ^{13}C NMR spectroscopy, MS and mp where applicable. Except where relevant to the discussion in the main text, the data are not reproduced since all compounds are known in the literature (see Table 3 for references). The regioisomer ratios of the methyl naphthoate esters (**7** and **8**) were determined by ^{1}H NMR spectroscopy ($CDCl_3$) on any cleanly resolved and identifiable peaks between any pair of regioisomers, ideally using the methyl ester signal and a resolved aromatic signal. The ^{13}C NMR integration was usually in very good agreement with the ^{1}H NMR integration results. The regioisomers were also determined where possible by LC but the NMR results have been used in preference, since the LC results are subject to variations in the UV chromophores between the regioisomers, which are known to be significant in many cases.[16]

Reverse phase HPLC was performed on an Agilent 1100 series instrument as follows: column, Zorbax SB-C8, 750 mm×4.6 mm i.d., 3.5 μm packing; flow rate 1.00 mL/min; temperature 45 °C; injection volume 5 μL; wavelength 240 nm; eluent A, 100% purified water with 0.02% v/v formic acid; eluent B, 100% methanol; timetable; 0 min, 60% eluent A; 6 min, 30% eluent A; 7.5 min, 5% eluent A; 10 min, 5% eluent A; post-time, 2.5 min. HPLC purities are area % normalised, unless noted otherwise. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz, respectively, with chemical shifts given in parts per million relative to TMS at δ=0. Electrospray (ES^+) mass spectra were performed on a Micromass ZQ LCMS using ESCi mode with both positive and negative ionisation; a water/acetonitrile gradient with either formic acid or ammonium carbonate was used for the LC component. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography (for lab work) was carried out by standard procedures using Merck Kieselgel 60 (230–400 mesh). Where not stated otherwise, assume that standard practices have been applied.

4.2. Specific thermal and microwave procedures

4.2.1. Thermal rate reactions (with HgO). Ten reactions were conducted in sealed boiling tubes in an aluminium heating block as follows. In each tube naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) and heated in an aluminium hot block with magnetic stirring at 50–60 °C for 15–20 min. In a separate flask, a stock solution was prepared of HgO dissolved in water and glacial acetic acid (1:3 ratio) with magnetic stirring at 50–60 °C for 15–20 min to give a clear, colourless solution of $Hg(OAc)_2$. A 1.0 mL aliquot of this Hg salt solution (~1.20–1.25 mol equiv) was added to each tube of hydrolysed naphthoic anhydride to give a dense white precipitate, which was shaken up thoroughly to achieve intimate mixing of the Hg salts. Each tube was simultaneously heated to 100 °C in the heating block with magnetic stirring. At convenient intervals, concentrated HCl (2.0 mL) was added to a given tube, shaken up and re-heated in the hot block at 100 °C with stirring for a further 4 h. Some foaming was observed at this point. Once complete, the tube was allowed to cool to rt, the solid filtered off and the product slurry washed twice on a small sinter with water (5 mL each; later increased to 10 mL). The crude product cake was pulled dry on the sinter and dried in a vacuum oven at 45 °C to yield naphthoic acid as a pale cream solid in typically quantitative yield (0.16–0.18 g). Each sample was analysed in duplicate by LC and the mean result is used in Figure 1. Tubes allowed to run for long time points (>48 h) tended to lose solvent and had to be topped up with purified water to keep the volume constant.

4.2.2. Microwave rate reactions (with HgO). Six reactions were conducted in microwave tubes at temperatures from 100 to 200 °C at 20 °C intervals. In each tube naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M (2.50 mmol) NaOH in a microwave tube and heated in aluminium hot block with magnetic stirring at 50–60 °C for 15–20 min. In six separate vials, HgO (241 mg, 1.10 mmol) was dissolved in water (241 μL) and glacial acetic acid (721 μL) with magnetic stirring at 50–60 °C for 15–20 min to give a clear, colourless solution of $Hg(OAc)_2$. This was added in one portion to the hydrolysed naphthoic anhydride to give a dense white precipitate, which was shaken up thoroughly to achieve intimate mixing of the Hg salts. Each tube was then heated in the microwave with stirring at 30–90 W maximum power, depending on the final temperature required. After 15 min of heating at the desired temperature, compressed air cooled the tube and concentrated HCl was added (2.0 mL). This was shaken up and re-heated in the hot block at 100 °C with stirring for 4 h. The crude product was isolated, washed and dried as above, to yield naphthoic acid in typically quantitative yield (0.16–0.18 g). Each sample was analysed in duplicate by LC and the mean result is used in Figure 2.

4.2.3. Microwave rate reactions with $Hg(OAc)_2$. The same procedure was used throughout as reported in Section 4.2.2 above, with the exception that instead of HgO in an acetic acid/water mixture, solid $Hg(OAc)_2$ (411 mg, 1.25 mmol) was added to the NaOH solution after the hydrolysis period, and shaken well before commencing microwave heating. An additional charge of water (0.96 mL) had been added to the NaOH solution to maintain the overall solvent volume in these cases (not used in later experiments). The rest of the procedure and work-up was identical to that reported above and the naphthoic acid products were isolated as pale cream solids in typically 95–105% yield (0.16–0.18 g). Each

sample was analysed in duplicate by LC and gave results comparable to those in Figure 2.

4.2.4. Microwave HCl hydrolysis reactions. Seven reactions were conducted in microwave tubes varying the HCl hydrolysis time and temperature under microwave heating as follows: 15, 30, 60 and 120 min at 120 °C, and 15 min at 130, 140 and 150 °C. In each tube naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) in a microwave tube and heated in aluminium hot block with magnetic stirring at 50–60 °C for 15–20 min. After this time $Hg(OAc)_2$ (374 mg, 1.15 mmol) was added in one portion to the hydrolysed naphthoic anhydride to give a dense white precipitate, which was shaken up thoroughly to achieve intimate mixing of the Hg salts. Each tube was then heated in the microwave with stirring at 80 W maximum power, to achieve after ~90 s a set-point temperature of 180 °C, which was maintained for 15 min. After compressed air cooling, concentrated HCl (2.0 mL) was added to each tube and shaken up, and further microwave heating was applied at the set-point temperature for 15 min or longer as appropriate with stirring. The crude product was isolated, washed and dried as in previous examples, except for using 10 mL wash volumes, to yield the naphthoic acid in typically quantitative yield (0.17–0.18 g). Each sample was analysed in duplicate by LC and the mean result was used. Samples hydrolysed at 120 °C gave a typically good form of pale cream naphthoic acid, whilst those hydrolysed at higher temperatures gave darker coloured solids with fair to poor form, including hard brown lumps. Yields remained consistently high for all.

4.2.5. Microwave Hg stoichiometry reactions. Eight reactions were conducted in microwave tubes varying the $Hg(OAc)_2$ equivalents as follows: 0.77 equiv (250 mg); 0.86 (281 mg); 0.96 (312 mg); 1.05 (343 mg); 1.15 (375 mg); 1.44 (468 mg); 1.92 (624 mg). In each tube naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) in a microwave tube and heated in aluminium hot block with magnetic stirring at 50–60 °C for 15–20 min. After this time $Hg(OAc)_2$ was added in one portion to the hydrolysed naphthoic anhydride to give a dense white precipitate, which was shaken up thoroughly to achieve intimate mixing of the Hg salts. Each tube was then heated in the microwave with stirring at 80 W maximum power, to achieve after ~90 s a set-point temperature of 180 °C, which was maintained for 15 min. After compressed air cooling, concentrated HCl (2.0 mL) was added to each tube and shaken up, and further microwave heating was applied at 120 °C for 15 min with stirring. The crude product was isolated, washed and dried as in previous examples, except for using 10 mL wash volumes, to yield the naphthoic acid in typically quantitative yield (0.17–0.18 g). Each sample was analysed in duplicate by LC and the mean result is used in Figure 3. The 1.15 equiv reaction was repeated as above but with a 16 h NaOH hydrolysis time at rt.

4.2.6. Microwave reactions with gas venting. The standard procedure described in Section 4.2.5 above was used, but with 1.15 equiv of $Hg(OAc)_2$ (374 mg, 1.15 mmol) in every case. Tubes were heated at 160, 180 and 200 °C under microwave heating at 70–90 W for 7 min before cooling to 70 °C. The residual gas pressure was released by opening the caps (care). The tubes were then re-sealed and re-heated to the set temperature for a further 7 min, then hydrolysed and isolated as described above. All samples gave a pale cream solid of good form. Each sample was analysed in duplicate by LC and the mean result is used in Table 1. Typical maximum pressures recorded were initially ~200–240 psig, reducing to ~50–60 psig residual pressure after the first 7-min heating. Residual pressure after the second period of heating was typically only 6–18 psig.

4.2.7. Optimised microwave process for naphthoic anhydride. (This optimised procedure is conducted in a single tube as a 'one pot' process by sequential additions of reagents.) Naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) in a microwave tube and heated in a microwave with magnetic stirring at 100 °C for 1 min. After cooling to 70 °C, $Hg(OAc)_2$ (341 mg, 1.05 mmol) was added in one portion, mixed thoroughly and heated in a microwave with stirring at 200 °C (with 90 W maximum power) for 15 min. After cooling to 70 °C, concentrated HCl (2.0 mL) was added, mixed thoroughly and heated in a microwave with stirring at 120 °C for 15 min. After cooling to rt, the crude product was isolated on a sinter, slurry was washed twice with water (10 mL each) and dried in a vacuum oven at 45 °C to yield the naphthoic acid product as a pale cream solid (0.17 g, 99%). LC quality 98.9%.

4.2.8. Microwave reactions with substituted naphthoic anhydrides. (This procedure is conducted in a single tube as a 'one pot' process by sequential additions of reagents.) The appropriate naphthoic anhydride **4** (1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) in a microwave tube and heated in a microwave with magnetic stirring at 100 °C for 1 min. After cooling to 70 °C, $Hg(OAc)_2$ (341 mg, 1.05 mmol or 374 mg, 1.15 mmol) was added in one portion, mixed thoroughly and heated in a microwave with stirring at 180 or 200 °C (80–90 W maximum power) for 15 or 30 min. After cooling to 70 °C, concentrated HCl (2.0 mL) was added, mixed thoroughly and heated in a microwave with stirring at 120 °C for 15 min. After cooling to rt, the crude product was isolated on a sinter, slurry washed twice with water (10 mL each) and dried in a vacuum oven at 45 °C to yield the substituted naphthoic acids (**5** and **6**) as an unresolved mixture. Exact conditions, yield and quality for each anhydride are shown in Table 2.

4.3. Preparation of methyl naphthoate esters (7/8)

4.3.1. Methyl naphthoate (7a). Six combined naphthoic acid samples (0.95 g in total with a mean quality of 90% w/w, 4.97 mmol) were slurried in methanol (9.5 mL) and concentrated H_2SO_4 was added (150 μL, 2.48 mmol). The resulting mixture was heated to reflux (65 °C) for 20 h, after which time LC analysis showed that the reaction was 90% complete. A further three drops of H_2SO_4 were added and heating continued for a further 10 h, after which a slight improvement was detected. The reaction mixture was cooled to rt and water (20 mL) was added, which gave a milky white suspension. This was extracted with MTBE (4×15 mL), the combined organic extracts washed with saturated brine (1×15 mL), dried over $MgSO_4$ and

concentrated to dryness to give a brown oil (921 mg). The crude oil was purified by flash silica chromatography in 7:1 to 1:1 *iso*-hexane/ethyl acetate to yield the title compound as a light oil (819 mg, 88%), comparable to a commercially available sample (Aldrich) (LC R_t=7.29 min; TLC R_f=0.60 in 4:1); and recovered naphthoic anhydride as a light brown solid (37 mg, 4%), comparable to a commercially available sample (Aldrich) (LC R_t=4.48 min; TLC R_f=0.16 in 4:1).

4.3.2. Preparation of methyl naphthoate esters (7/8). The following is a typical procedure for the formation, isolation and characterisation of methyl naphthoate esters **7/8**. An unresolved mixture of the 3- and 6-methoxynaphthoic acids (**5f/6f**) (150 mg, 0.74 mmol) was slurried in methanol (2.0 mL) and thionyl chloride was (108 μL, 1.48 mmol) added dropwise over 1 min. The resulting yellow solution was heated thermally in a sealed tube to 75 °C for 3 h, and then cooled to rt and the methanol allowed to evaporate. The crude oil was purified by flash silica chromatography in 9:1 *iso*-hexane/MTBE to yield an unresolved mixture of the methyl 3- and 6-methoxynaphthoate esters (**7f/8f**) as a light brown gum (115 mg, 79% from starting naphthoic anhydride **4f**). TLC R_f=0.42, strong blue spot; MS (ES^+) 217 (M+1, 100%), 185 (M–OMe, 19%). The regioisomer ratio was determined by ^1H NMR spectroscopy ($CDCl_3$) integration of the aromatic H-7 signal to be 74:26 in favour of the 3-methoxy-substituted naphthoate ester (**7f**) over the 6-methoxy-substituted naphthoate ester (**8f**) (the OMe and Me-ester signals were not resolved in this case).

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12. A CEM *Discover* was used throughout this work. Due to the high pressures these reactions can generate in a sealed tube, the maximum safe pressure limits for both tubes and instruments should be checked if using alternative microwave reactors.
13. The Hg stoichiometry was also reduced from 1.2 to 1.1 equiv in the later microwave case, but as subsequent studies showed (Fig. 3), this was inconsequential.
14. We also repeated the identical procedure using 1.25 equiv of $Hg(OAc)_2$. This gave very similar results but with the experimental advantage of being operationally much simpler, as discussed in the main text.
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Convenient preparation of substituted 5-aminooxazoles via a microwave-assisted Cornforth rearrangement

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Abstract—The preparation of oxazole-4-carboxamides and their subsequent thermal rearrangement to 5-aminooxazole-4-carboxylates is optimized in a high-speed microwave-assisted procedure. The reaction sequence is effective with a variety of substituted oxazoles, and produces products in good yield and high purity.

1. Introduction

The biological activity and therapeutic potential of 5-aminooxazole containing structures is demonstrated in the pseudomonic acid derived antibiotic **1**,[1a] oxazolo-[5,4-*d*]pyrimidine **2** an inhibitor of ricin and shiga toxins,[1b] and peptidomimetics with oxazole-incorporated amino acids **3**.[1c] Additionally, 5-(*p*-tolyl)urea-oxazole **4** is shown to have in vitro activity as a Raf kinase inhibitor with the possibility of use as a treatment for cancers (Fig. 1).[1d]

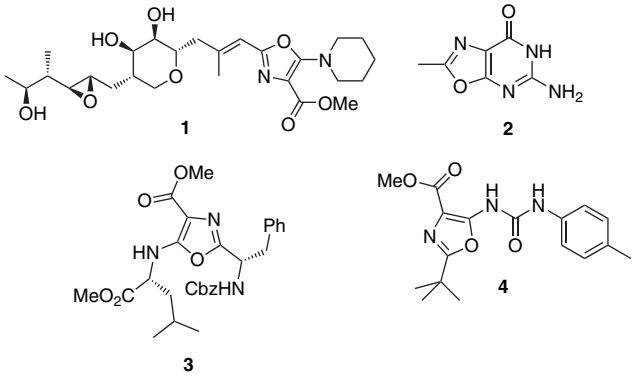
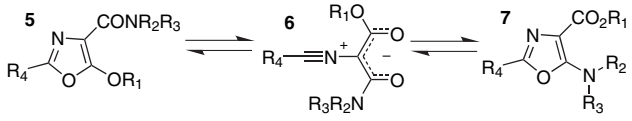


Figure 1. Biologically active 5-aminooxazoles.

A number of synthetic routes have been described for the preparation of 5-aminooxazoles.[1–3] While they are adequate for the generation of individual compounds, the typical procedures do not lend themselves to the rapid generation of a large number of diverse products. Although novel, efficient methodology has been developed, these reactions do not make use of readily available starting materials and hence, are not easily applied in a parallel format. A particularly attractive alternative presents itself in the Cornforth rearrangement (Scheme 1). This formal rearrangement occurs upon heating 5-alkoxyoxazole-4-carboxamides at $\geq$100 °C for 17 h and is believed to proceed via an intermediate nitrile ylide such as **6**. Originally discovered by Cornforth during studies related to penicillin, the reaction was studied in detail by Dewar[3] whose mechanistic and computational work defined the intermediate as a delocalized zwitterion.[4] Intermediate **6** exhibits a psuedo-symmetrical dicarbonyl structure, which can cyclize either to reform **5** or proceed to **7**. Because the formation of **6** is reversible, the final product distribution (**5**:**7**) is wholly determined by the relative thermodynamic stabilities of the 5-alkoxy-oxazole-4-carboxamide and 5-amino-oxazole-4-carboxylate. Despite its intriguing mechanism and synthetic potential, the reaction has received relatively little attention since these pioneering studies.



Scheme 1. Cornforth rearrangement.

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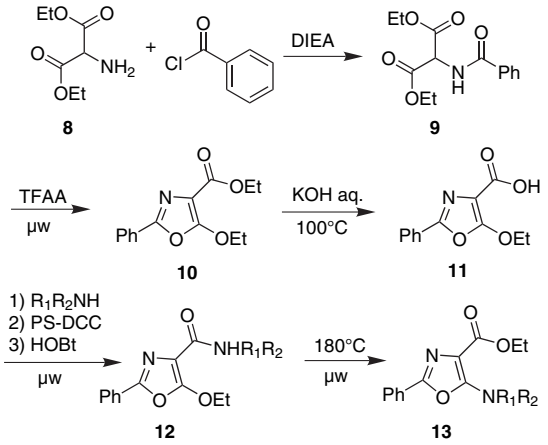
Based on this precedent, we envisioned a synthesis such as that shown in Scheme 2.[2f] Acylation of 2-amino diethylmalonate followed by cyclodehydration would afford oxazole **10**, which after saponification and amide coupling would generate the Cornforth substrate **12**. Thermal rearrangement then produces the 5-amino-oxazole-4-carboxylate **13**.



Scheme 2. General synthesis of 5-amino-oxazole-4-carboxylates.

This route enables the incorporation of diverse substituents at all positions of the oxazole and importantly does so via the use of readily available carboxylic acid chloride and amine building blocks. This affords the opportunity to generate fully substituted oxazoles with a diverse array of functionality.

A secondary goal was to generate these structures rapidly and therefore microwave-assisted conditions were investigated. Microwave-assisted organic synthesis (MAOS) has been widely utilized recently as it is typically associated with dramatic reductions in reaction times, a diminution in side product formation, and increased yields.[5]

In this paper we describe the microwave-assisted formation of several 5-aminooxazole compounds and apply this methodology to the formal synthesis of a biologically active target (Fig. 1), 4-(methoxycarbonyl)-2-(1-normon-2-yl)-5-piperidin-1-yloxazole (**1**).[1a]

2. Results and discussion

Preparation of rearrangement substrate **12** proceeded with straightforward acylation of 2-amino diethylmalonate (DIEA, benzoyl chloride, 94%). Cyclodehydration to form oxazoles has been performed using a number of dehydrating reagents under thermal conditions. For example, the generation of 5-amino-oxazole-4-carboxylates from 2-amidomalonates has been reported, in only moderate yield, using 1 equiv PCl_5 in toluene and heating for 30 min to 14 h at reflux.[2f,6] Other reagents such as triphenylphosphine/iodine or trichloroacetyl chloride, in conjunction with conventional heating, have been used as well.[1a,7]

In an effort to accelerate the cyclodehydration step a range of solvents, dehydrating reagents, microwave irradiation times, and temperatures were surveyed. Optimal conditions for the transformation of **9** to **10** were identified as a 2:1 mixture of trifluorotoluene/trifluoroacetic anhydride (TFAA) and heating at 160 °C for 10 min. A dramatic reduction in reaction time was observed (5 min vs 0.5–14 h) and good yields of the oxazole **10** were obtained (79%). This reaction was successfully scaled up from 0.03 g to 3.00 g without reoptimization of the microwave conditions. The solvent/substrate ratio, the duration, and temperature of the microwave heating was maintained and afforded 2-aryloxazoles in multigram quantities.

Basic hydrolysis of the cyclization product with 15% aq potassium hydroxide, heated at 100 °C, cleanly gives the carboxylic acid **11**.[3] Amide bond formation under a variety of conditions (PS-DCC, HOBt; EDCI, HOBt) was sluggish, and therefore the recently disclosed microwave procedure using polymer bound carbodiimide was employed.[8] PS-carbodiimide amide coupling was accelerated by microwave heating (100 °C, 10 min) and after filtration of the solid-phase reagent(s), the 5-ethoxy-2-phenyloxazolamides **12** were obtained in excellent yields. Although formed at 100 °C, these amides had clearly not undergone a Cornforth rearrangement (^{1}H NMR, see below). Excess HOBt can be removed from the products prior to the rearrangement step by treatment with MP-carbonate. However, we observed that the presence of HOBt does not alter the success of the rearrangement step and it is likely that the reagent is thermally decomposed to volatile and gaseous byproducts when targeted rearrangement temperatures are reached.[9]

Cornforth rearrangement products were produced by heating 5-alkoxy-oxazole-4-carboxamides **12** using microwave irradiation (Table 1). The reaction requires temperatures >170 °C for complete conversion to the thermodynamically more stable products **13**. As can be seen in Table 1, small changes in temperature have a large impact on conversion at these short reaction times. While excellent conversions (by LC–MS) were realized in acetonitrile and trifluorotoluene, isolated yields were much higher in trifluorotoluene. Optimized microwave heating at 180 °C for 5 min in trifluorotoluene gave compounds in 23–99% yield and of purity greater than 93% by ^{1}H NMR (Table 2); entry 11 required chromatographic purification to obtain product **13k**. A range of functional groups are tolerated in the reaction including acetals, thioethers, sulfonamides, and Boc-protected amines. Primary and secondary amines perform equally well in the amide formation rearrangement sequence.

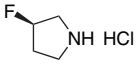
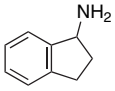
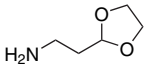
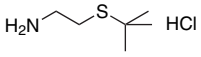
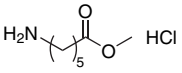
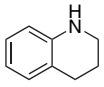
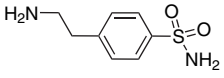
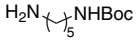
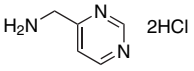
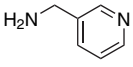
Three characteristic observations allowed us to distinguish the starting materials from products in the final step of the synthesis. First, HPLC retention times differed for

Table 1. Cornforth rearrangement temperature optimization study

Entry	Solvent	Rearrangement conditions	Product/starting material[a]
1	Acetonitrile	150 °C, 10 min	1:99
2	Acetonitrile	160 °C, 10 min	31:69
3	Acetonitrile	170 °C, 10 min	42:58
4	Acetonitrile	180 °C, 10 min	99:1
5	$PhCF_3$	180 °C, 5 min	99:1

[a] Determined by UV HPLC.

Table 2. Microwave-assisted amide formation and Cornforth rearrangement

Entry	Amine	Coupling conditions	Product	Rearrangement conditions	Yield (%)
1		100 °C, 5 min	**13a**	180 °C, 5 min.	76
2		100 °C, 5 min	**13b**	180 °C, 5 min	98
3		100 °C, 5 min, PS-DIEA (1 equiv)	**13c**	180 °C, 5 min	47
4		100 °C, 5 min	(±)-**13d**	180 °C, 5 min	99
5		100 °C, 5 min	**13e**	180 °C, 5 min	99
6		100 °C, 5 min	**13f**	180 °C, 5 min	23
7		100 °C, 5 min, PS-DIEA (1 equiv)	**13g**	180 °C, 5 min	51
8		100 °C, 5 min, PS-DIEA (1 equiv)	**132h**	180 °C, 5 min	76
9		100 °C, 5 min	**13i**	180 °C, 5 min	85
10		100 °C, 5 min	**13j**	180 °C, 5 min	19
11		100 °C, 5 min	**13k**	180 °C, 5 min	99
12		100 °C, 5 min, PS-DIEA (2 equiv)	**13l**	180 °C, 5 min	23[a]
13		100 °C, 5 min	**13m**	180 °C, 5 min	82
14		100 °C, 5 min	**13n**	180 °C, 5 min	97

[a] After flash chromatography.

compounds **12** and **13**. Second, HMBC NMR studies of compound **12b** and its Cornforth product **13b** showed a partial carbonyl shielding effect on the 2- and 5-position methylene protons of the pyrrolidine amide. This with a change in carbon shifts for the ethyl group in both molecules suggested that the rearrangement had successfully occurred. And third, the diisobutyl aluminohydride reduction of **13e** to the corresponding alcohol **14** unequivocally confirmed the rearrangement of **12e** (Fig. 2).

The formal synthesis of **1** began with N-acylation of 2-amino-dimethylmalonate to form the amide **15** (Scheme 3).

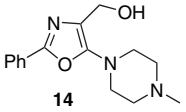
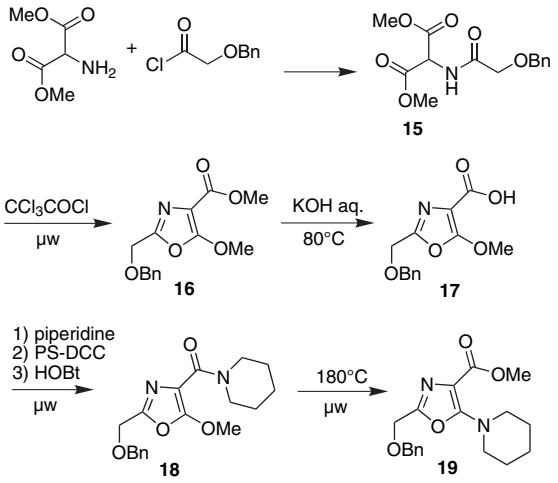


Figure 2. (5-(4-Methylpiperazin-1-yl)-2-phenyloxazol-4-yl)methanol.



Scheme 3. Formal synthesis of 4-(methoxycarbonyl)-2-(1-normon-2-yl)-5-piperidin-1-yloxazole (**1**).

The established cyclodehydration procedure was then applied, however microwave heating at 160 °C for 10 min with TFAA resulted only in 50% conversion (^{1}H NMR) of the starting material to oxazole **16**. Increased temperatures (≥160 °C) caused noticeable decomposition and did little to facilitate the conversion to the oxazole. Longer heating times were also unsuccessful. After trying several dehydrating reagents, it was discovered that trichloroacetyl chloride provided an improved product ratio and virtually no degredation was observed. While increased heating times and temperatures did not give the desired product, five successive heat cycles at 160 °C for 20 min resulted in 97% conversion (^{1}H NMR) to the cyclodehydration product.[10]

Hydrolysis of the oxzaole-4-carboxylate **17** was accomplished by heating at 80 °C for 15 min in KOH (15% aq). Amide formation, and the thermal rearrangement were then conducted under the usual conditions to give the benzyl protected compound **19**. Hydrogenation to deprotect the 2-hydroxymethyl oxazole, followed by halogenation and phosphorylation would prepare the right-hand piece for connection with the ozonolyzed psuedomonic acid substrate.[11]

3. Conclusion

The incorporation of microwave heating dramatically decreases the time required for the polymer-assisted formation of 5-alkoxyoxazole-4-carboxamides and their subsequent rearrangement to 5-aminooxazoles. A range of 5-aminooxazoles can be obtained using the methodology we describe. To further illustrate the utility of our synthetic procedure, we have successfully carried out a formal synthesis of 4-(methoxycarbonyl)-2-(1-normon-2-yl)-5-piperidin-1-yloxazole (**1**).

4. Experimental

4.1. Ethyl-5-ethoxy-2-phenyloxazole-4-carboxylate (10)

In a 10–20 mL microwave vial (Biotage) with stir bar was placed diethyl-2-(benzamido)malonate (3.0 g, 10.7 mmol) and trifluoroacetic anhydride (5.0 mL, 40.7 mmol) in trifluorotoluene (10 mL). The vial was sealed and heated at 160 °C for 10 min in the microwave (Biotage Emrys Optimizer). The desired temperature was reached in approximately 1 min at 300 W power. The crude material was concentrated and purified by flash chromatography (0–25% EtOAc/*n*-hexanes) to give 2.2 g (79%) of **10**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–8.00 (m, 2H), 7.43–7.46 (m, 3H), 4.60 (q, J=6.9 Hz, 2H), 4.41 (q, J=7.2 Hz, 2H), 1.54 (t, J=7.2 Hz, 3H), 1.40 (t, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 161.6, 151.3, 130.6, 128.9, 126.8, 126.2, 108.9, 70.3, 61.0, 15.2, 14.7. HRMS calcd for $C_{14}H_{16}NO_4$ (M+H) 262.1074, found 262.1079.

4.2. 5-Ethoxy-2-phenyloxazole-4-carboxylic acid (11)

To ethyl 5-ethoxy-2-phenyloxazole-4-carboxylate (1.0 g, 3.83 mmol) was added a solution of 15% aq KOH (2.15 mL, 5.75 mmol). The reaction was heated at 100 °C in an oil bath for 30 min then cooled to 0 °C and acidified with 10% aq H_2SO_4 until a pH of around three was obtained. The resulting suspension was filtered and the solid was collected and dried in vacuo to give 0.424 g (48%) of pure product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.954–7.97 (m, 2H), 7.45–7.47 (m, 3H), 4.68 (q, J=7.2 Hz, 2H), 1.56 (t, J=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 161.9, 151.1, 130.6, 128.8, 126.2, 126.0, 107.4, 70.4, 15.0. HRMS calcd for $C_{12}H_{12}NO_4$ (M+H) 234.0761, found 234.0774.

4.3. General procedure for the preparation of compounds 12a–m

In a 2–5 mL microwave vial with stir bar was placed 5-ethoxy-2-phenyloxazole-4-carboxylic acid (**11**) 0.028 g, (0.12 mmol), PS-DCC (0.093 g, 0.12 mmol), HOBt (0.016 g, 0.12 mmol), and amine (0.12 mmol) in trifluorotoluene (3 mL). The vial was sealed and heated at 100 °C for 5 min using the microwave. The desired temperature was reached in approximately 30 s at 300 W power. The reaction mixture was filtered to remove the solid-phase reagents and the resin was rinsed with an additional milliliter of trifluorotoluene. The filtered solution was then transferred to a clean 2–5 mL microwave vial and used directly in the next step of the synthesis.

4.4. General procedure for the preparation of compounds 13a–m

The crude products **12** were heated at 180 °C in the microwave for 5 min. The desired temperature was reached in approximately 2 min at 300 W power. Removal of the trifluorotoluene solvent under reduced pressure left products that were ≥93% pure by ^{1}H NMR analysis.

4.4.1. Ethyl 2-phenyl-5-(piperidin-1-yl)oxazole-4-carboxylate (13a). Purified by silica gel flash chromatography (*n*-hexanes/EtOAc, 3–10% gradient over 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.95 (m, 2H), 7.36–7.42 (m, 3H), 4.38 (q, J=14, 7.2 Hz, 2H), 3.63–3.64 (m, 4H), 1.70–1.74 (m, 6H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 160.0, 150.7, 129.9, 128.7, 127.1, 126.0, 108.1, 60.6, 49.8, 25.8, 24.3, 14.8. HRMS calcd for $C_{17}H_{21}N_2O_3$ (M+H) 301.1547, found 301.1550.

4.4.2. Ethyl 2-phenyl-5-(pyrrolidin-1-yl)oxazole-4-carboxylate (13b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.94 (m, 2H), 7.34–7.43 (m, 3H), 4.35 (q, J=14, 6.8 Hz, 2H), 3.75–3.79 (m, 2H), 1.98–2.04 (m, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 158.1, 149.9, 129.6, 128.7, 127.2, 125.8, 60.3, 50.2, 25.7, 14.8. HRMS calcd for $C_{16}H_{19}N_2O_3$ (M+H) 287.1390, found 287.1377.

4.4.3. Ethyl 5-(3-fluoropyrrolidin-1-yl)-2-phenyloxazole-4-carboxylate (13c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H), 7.39–7.45 (m, 3H), 5.36 (d, J=52.8 Hz, 1H), 4.37 (q, J=6.9 Hz, 2H), 3.88–4.20 (m, 5H), 2.34–2.46 (m, 1H), 2.01–2.28 (m, 1H), 1.42 (t, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 157.5, 150.2, 129.7, 128.6, 126.8, 125.7, 106.3, 92.3 (d, J=176.6 Hz), 60.3, 56.7 (d, J=23.0), 47.4, 32.1 (d, J=21.2), 14.6. HRMS calcd for $C_{16}H_{18}FN_2O_3$ (M+H) 305.1296, found 305.1285.

4.4.4. (±)-Ethyl 5-(2,3-dihydro-1*H*-inden-1-ylamino)-2-phenyloxazole-4-carboxylate (13d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.97 (m, 2H), 7.22–7.44 (m, 7H), 6.55 (d, J=8.4 Hz, 1H), 5.38 (q, J=15.6, 7.6 Hz, 1H), 4.37 (q, J=14.4, 7.2 Hz, 2H), 3.07–3.14 (m, 1H), 2.91–2.99 (m, 1H), 2.68–2.77 (m, 1H), 2.02–2.11 (m, 1H), 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.3, 150.4, 143.3, 142.4, 129.9, 128.9, 128.7, 127.2, 127.1, 125.9, 125.2, 124.2, 60.4, 59.0, 34.8, 30.4, 14.9. HRMS calcd for $C_{21}H_{21}N_2O_3$ (M+H) 349.1547, found 349.1539.

4.4.5. Ethyl 5-(4-methylpiperazin-1-yl)-2-phenyloxazole-4-carboxylate (13e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H), 7.40–7.43 (m, 3H), 4.38 (q, J=14.4, 7.2 Hz, 2H), 3.77 (t, J=4.8 Hz, 4H), 2.65 (t, J=4.8 Hz, 4H), 2.40 (s, 3H), 1.41 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 159.4, 151.2, 130.1, 128.8, 126.9, 126.1, 108.9, 60.8, 54.6, 48.1, 46.1, 14.8. HRMS calcd for $C_{17}H_{22}N_3O_3$ (M+H) 316.1656, found 316.1647.

4.4.6. Ethyl 5-(2-(1,3-dioxolan-2-yl)ethylamino)-2-phenyloxazole-4-carboxylate (13f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H), 7.36–7.44 (m, 3H), 6.75–6.79 (m, 1H), 5.05 (t, J=4.2 Hz, 1H), 4.38 (q, J=7.2 Hz, 2H), 3.99–4.07 (m, 2H), 3.88–3.96 (m, 2H), 3.67 (q, J=6.3 Hz, 2H), 2.07–2.13 (m, 2H), 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 160.4, 150.2, 129.7, 128.8, 127.1, 125.8, 103.2, 65.3, 60.3, 38.5, 33.2, 14.8. HRMS calcd for $C_{17}H_{21}N_2O_5$ (M+H) 333.1445, found 333.1439.

4.4.7. Ethyl 5-(2-(*tert*-butylthio)ethylamino)-2-phenyloxazole-4-carboxylate (13g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H), 7.36–7.44 (m, 3H), 6.60 (t, J=5.6 Hz, 1H), 4.39 (q, J=14.4, 7.2 Hz, 2H), 3.68 (q, J=13.6, 6.8 Hz, 2H), 2.84 (t, J=7.2 Hz, 2H), 1.41 (t, J=7.2, 3H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 160.1, 150.2, 129.7, 128.6, 126.8, 125.6, 104.8, 76.8, 60.3, 43.4, 42.73, 42.72, 31.1, 28.3, 14.7. HRMS calcd for $C_{18}H_{25}N_2O_3S$ (M+H) 349.1581, found 349.1577.

4.4.8. Ethyl 5-(5-(methoxycarbonyl)pentylamino)-2-phenyloxazole-4-carboxylate (13h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.95 (m, 2H), 7.36–7.44 (m, 3), 6.34 (s, 1H), 4.38 (q, J=14.4, 7.2 Hz, 2H), 3.67 (s, 3H), 3.50 (q, J=6.4 Hz, 2H), 2.35 (t, J=7.6 Hz, 2H), 1.67–1.76 (m, 4H), 1.44–1.50 (m, 2H), 1.41 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 160.9, 150.2, 129.8, 128.8, 127.1, 125.8, 104.6, 76.9, 60.4, 51.7, 43.2, 34.0, 30.0, 26.4, 24.7, 14.9. HRMS calcd for $C_{19}H_{25}N_2O_5$ (M+H) 361.1758, found 361.1750.

4.4.9. Ethyl 5-(3,4-dihydroquinolin-1(2*H*)-yl)-2-phenyloxazole-4-carboxylate (13i). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.97 (m, 2H), 7.22–7.44 (m, 7H), 6.55 (d, J=8.4 Hz, 1H), 5.38 (q, J=15.6, 7.6 Hz, 1H), 4.37 (q, J=14.4, 7.2 Hz, 2H), 3.07–3.14 (m, 1H), 2.91–2.99 (m, 1H), 2.68–2.77 (m, 1H), 2.02–2.11 (m, 1H), 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.3, 150.4, 143.3, 142.4, 129.9, 128.9, 128.7, 127.2, 127.1, 125.9, 125.2, 124.2, 60.4, 59.0, 34.8, 30.4, 14.9. HRMS calcd for $C_{21}H_{21}N_2O_3$ (M+H) 349.1547, found 349.1544.

4.4.10. Ethyl 5-({2-[4-(aminosulfonyl)phenyl]ethyl}-amino)-2-phenyl-1,3-oxazole-4-carboxylate (13j). ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 7.72–7.73 (m, 4H), 7.43–7.50 (m, 5H), 7.26 (s, 2H), 4.20 (q, J=6.9 Hz, 2H), 3.67 (br s, 2H), 3.01 (t, J=6.6 Hz, 2H), 1.25 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 163.1, 160.5, 149.2, 143.8, 142.9, 130.2, 129.9, 129.7, 127.2, 126.4, 125.6, 103.8, 59.7, 44.4, 36.1, 15.3. HRMS calcd for $C_{20}H_{22}N_3O_5S$ (M+H) 416.1275, found 416.1271.

4.4.11. *tert*-Butyl 3-(4-(ethoxycarbonyl)-2-phenyloxazol-5-ylamino)propylcarbamate (13k). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.99 (m, 2H), 7.36–7.43 (m, 3H), 6.60 (s, 1H), 4.66 (s, 1H), 4.39 (q, J=6.8 Hz, 2H), 3.55 (q, J=6.8, 2H), 3.27 (q, J=6.4 Hz, 2H), 1.86 (apparent quintet, J=6.6, 2H), 1.46 (s, 9H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 160.4, 156.3, 150.0, 129.6, 128.6, 126.9, 125.6, 104.5, 60.2, 40.5, 37.6, 30.9, 28.4, 14.7. HRMS calcd for $C_{20}H_{28}N_3O_5$ (M+H) 390.2024, found 390.2023.

4.4.12. Ethyl 5-((pyrimidin-4-yl)methylamino)-2-phenyloxazole-4-carboxylate (13l). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23–9.24 (m, 1H), 8.74 (d, J=5.4 Hz, 1H), 7.88–7.91 (m, 2H), 7.38–7.44 (m, 4H), 7.23–7.27 (m, 1H), 4.81 (d, J=5.7 Hz, 2H), 4.43 (q, J=7.2 Hz, 2H), 1.44 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.1, 159.9, 159.0, 157.7, 150.8, 130.0, 128.9, 126.8, 125.9, 118.6, 105.7, 60.7, 47.4, 14.8. HRMS calcd for $C_{17}H_{17}N_4O_3$ (M+H) 325.1222, found 325.1294.

4.4.13. Ethyl 5-((pyridin-3-yl)methylamino)-2-phenyloxazole-4-carboxylate (13m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.58–8.59 (m, 1H), 7.89–7.92 (m, 2H), 7.71–7.74 (m, 1H), 7.39–7.41 (m, 3H), 7.31–7.34 (m, 1H), 6.72–6.75 (m, 1H), 4.69 (d, J=6.4 Hz, 2H), 4.39 (q, J=7.2 Hz, 2H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.2, 150.7, 149.7, 149.3, 135.3, 133.3, 130.0, 128.9, 126.8, 128.9, 124.0, 105.4, 76.9, 60.6, 45.0, 14.8. HRMS calcd for $C_{18}H_{18}N_3O_3$ (M+H) 324.1343, found 324.1332.

4.4.14. Ethyl 5-(cyclopropylamino)-2-phenyloxazole-4-carboxylate (13n). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.99 (m, 2H), 7.37–7.45 (m, 3H), 6.50 (s, 1H), 4.37 (q, J=7.2 Hz, 2H), 2.81–2.87 (m, 1H), 1.41 (t, J=3.6 Hz, 3H), 0.87–0.91 (m, 2H), 0.73–0.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.5, 150.8, 129.8, 128.9, 128.8, 127.1, 125.9, 60.5, 24.6, 14.9, 7.4. HRMS calcd for $C_{15}H_{17}N_2O_3$ (M+H) 295.1053, found 295.1052.

4.4.15. (5-(4-Methylpiperazin-1-yl)-2-phenyloxazol-4-yl)methanol (14). In a clean, dry 40 mL sample vial was placed ethyl 5-(4-methylpiperazin-1-yl)-2-phenyloxazole-4-carboxylate (0.089 g, 0.28 mmol) in dry dichloromethane under N_2. The stirred solution was cooled to −78 °C and Dibal-H (0.84 mL, 0.84 mmol) was added via syringe. After 10 min, the reaction was complete by LC–MS and quenched with H_2O. After warming to rt the crude reaction mixture was filtered through packed Celite and extracted with EtOAc

(3×10 mL). Purification by flash chromatography (5–10% MeOH/DCM) gave 0.070 g (91%) of **14**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.92 (m, 2H), 7.37–7.44 (m, 3H), 4.62 (s, 2H), 3.31 (t, J=4.8 Hz, 2H), 2.55 (t, J=4.8 Hz), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 129.8, 128.9, 127.8, 127.3, 125.7, 122.4, 57.1, 54.9, 50.1, 46.5. HRMS calcd for $C_{15}H_{20}N_3O_2$ (M+H) 274.1550, found 274.1541.

4.4.16. Dimethyl 2-(2-(benzyloxy)acetamido)malonate (15). To a stirred suspension of 2-amino-dimethylmalonate hydrochloride (1.0 g, 5.45 mmol) in dichloromethane (20 mL) was added diisopropylethylamine (1.8 mL, 10.9 mmol) and the reaction was stirred at rt for 10 min. To the resulting clear slightly yellow solution was added benzoylacetoxychloride (0.87 mL, 5.45 mmol) and the reaction was stirred at rt for 15 min. The mixture was diluted with dichloromethane, washed with 1 N HCl then satd aq $NaHCO_3$. The aqueous layer was extracted with dichloromethane (2×10 mL), the organic extracts were washed with brine and dried over Na_2SO_4. Filtration and removal of solvent under reduced pressure gave 1.56 g (97%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.64 (m, 1H), 7.30–7.41 (m, 4H), 5.27 (d, J=7.2 Hz, 1H), 4.63 (s, 2H), 4.04 (s, 2H), 3.83 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 166.7, 136.8, 128.8, 128.5, 128.2, 73.9, 69.3, 55.6, 53.7. HRMS calcd for $C_{14}H_{18}NO_6$ (M+H) 296.1129, found 296.1126.

4.4.17. Methyl 2-((benzyloxy)methyl)-5-methoxyoxazole-4-carboxylate (16). In a 2–5 mL microwave vial with stir bar were placed dimethyl 2-(2-(benzyloxy)acetamido)malonate (**15**) (0.020 g, 0.07 mmol), trichloroacetyl chloride (1 mL), and trifluorotoluene (3 mL). The vial was heated at 160 °C for 20 min then cooled to rt, and this heating cycle was repeated five times. The desired temperature was reached in approximately 1 min at 300 W power. Flash chromatography of the concentrated crude product (30–60% EtOAc/*n*-hexanes) yielded 0.170 g (31%) of **16**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.38 (m, 5H), 4.60 (s, 2H), 4.52 (s, 2H), 4.18 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 161.9, 150.0, 137.2, 128.72, 128.71, 128.3, 128.2, 73.1, 64.2, 60.0, 52.0. HRMS calcd for $C_{14}H_{16}NO_5$ (M+H) 278.1017, found 278.1023.

4.4.18. 2-((Benzyloxy)methyl)-5-methoxyoxazole-4-carboxylic acid (17). In a 40 mL sample vial with stir bar was placed **16** (0.120 g, 0.43 mmol) and KOH (3 mL of a 15% aq solution). The vial was heated at 80 °C for 15 min in an oil bath, then cooled to 0 °C and neutralized with H_2SO_4 (10% aq solution). The mixture was diluted and extracted with EtOAc (2×10 mL), and the organic extracts washed with brine, and dried over Na_2SO_4. The solution was filtered, concentrated, and dried under reduced pressure to give 0.118 g (99%) of analytically pure **17** as an off-white solid. HRMS calcd for $C_{13}H_{14}NO_5$ (M+H) 264.0867, found 264.0867.

4.4.19. (5-Ethoxy-2-phenyloxazol-4-yl)(piperidin-1-yl)-methanone (18). In a 0.5–2 mL microwave vial with spin van were placed **17** (0.038 g, 0.14 mmol), piperidine (0.014 mL, 0.14 mmol), PS-DCC (0.107 g, 0.14 mmol), and HOBt (0.019 g, 0.14 mmol) in $PhCF_3$ (2 mL). The vial was sealed and heated at 100 °C for 5 min in the microwave. The desired temperature was reached in approximately 30 s at 300 W power. Filtration and removal of the solid-phase reagent gave the crude product **18**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.36 (m, 5H), 4.60 (s, 2H), 4.47 (s, 2H), 4.07 (s, 3H), 3.59–3.75 (m, 4H), 1.55–1.69 (m, 5H); ^{13}C NMR δ 161.5, 149.2, 137.3, 128.7, 128.23, 128.21, 73.0, 64.1, 60.0, 24.9. HRMS calcd for $C_{18}H_{23}N_2O_4$ (M+H) 331.1658, found 331.1658.

4.4.20. Methyl 2-((benzyloxy)methyl)-5-(piperidin-1-yl)oxazole-4-carboxylate (19). In a 0.5–2 mL microwave vial with spin vane was placed **18** (0.030 g, 0.09 mmol) in $PhCF_3$ (2 mL). The vial was sealed and heated at 180 °C for 5 min. The desired temperature was reached in approximately 2 min at 300 W power. The contents were concentrated and dried under reduced pressure to give 0.030 g (99%) of analytically pure **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.34 (m, 5H), 4.58 (s, 2H), 4.48 (s, 2H), 3.85 (s, 3H), 3.57–3.61 (m, 4H), 1.66–1.71 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 160.5, 149.3, 137.5, 128.6, 128.13, 128.12, 73.0, 64.2, 51.7, 49.5, 25.8, 24.2. HRMS calcd for $C_{18}H_{23}N_2O_4$ (M+H) 331.1653, found 331.1656.

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Optimisation and scale-up of microwave assisted cyanation

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Abstract—A microwave enhanced palladium catalysed cyanation procedure was optimised for the final step of a production method for citalopram **2**. The method was demonstrated on multigram batch scale for the synthesis of escitalopram (*S*)-**2** and then in a stop-flow continuous process for citalopram.

1. Introduction

Microwave-assisted organic synthesis is a rapidly expanding area of research, aided, in recent years, because of the availability of commercial systems that offer safe and reproducible heating. The last decade has seen a growing number of papers and reviews appearing in the literature on the subject.[1] Microwave heating seems to be particularly compatible with transition metal catalysed processes normally associated with long reaction times (>4 h), bringing these times down to minutes and reducing the levels of by-products from (thermal) side-reactions.[2]

The substituted benzonitrile motif is present in a significant proportion of pharmaceuticals, agrochemicals and natural products.[3] The nitrile group also offers a useful functionality for subsequent manipulations to important functional groups such as acids, ketones, oximes, amines and also various heterocycles. The nitrile group can be used as a convenient starting point for short-lived radiocarbon-labelled functional groups.[4]

Although simple benzonitriles can be easily prepared by ammoxidation,[5] the most common, and direct method for the introduction of the cyano group is via cyanation of the parent aryl halide. Industrially this tends to be achieved by the Rosemund–von Braun reaction, requiring stoichiometric amounts of copper(I) cyanide.[6] The alternative Sandmeyer reaction also uses copper(I) cyanide. The selectivity and waste considerations involved in these reactions led to the use of transition metal (usually palladium) catalysed cyanations being examined by various industrial groups.[7] The relatively high catalyst loading requirements have prompted various innovative methods for stabilising the catalyst. Cyanide ions poison homogeneous palladium catalysts and thus the cyanide concentration in solution needs to be kept low. The levels of cyanide can vary significantly with even small amounts of other additives.[8] Most solutions to this problem involve slow addition of soluble cyanide sources such as TMSCN[9] or acetone cyanohydrin,[10] or the use of an insoluble cyanide source with an additive to transmetallate the cyanide. Examples of the latter utilised potassium cyanide in solvents in which it is virtually insoluble are: in toluene with TMEDA,[11] in THF with copper(I) iodide,[12] or in acetonitrile with catalytic tributyltin chloride, generate low levels of Bu_3SnCN.[13] Recently potassium hexaferricyanide has been employed as a non-toxic source of cyanide.[14] The slow release of cyanide from the complex maintains low levels in solution.[†] This procedure was further refined to obviate the needs for palladium by employing a copper catalyst.[15]

Our interest in cyanation was for the improvement of the last step in the synthesis of citalopram **2** from the parent bromide **1** (Scheme 1). The cyanation via Rosemund–von Braun conditions took 24 h, and was low yielding after exhaustive, time consuming wash cycles used to purify the material. It was our belief that a transition metal catalysed method could be employed, and enhanced with microwave-assisted heating, to provide a highly selective transformation with a good impurity profile. The work by Hallberg and Alterman[16] had shown a precedent for using microwave heating to increase the rate of cyanation of various bromides with the previously utilised palladium–tetrakistriphenylphosphine.[17] However, Maligres and co-workers at Merck Process Research had screened a range of phosphine ligands and found 1,1′-diphenylphosphinoferrocene (dppf) to be superior and

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[†] During the course of this work we had tested $K_4[Fe(CN)_6]$ (see Table 2, entry 4) as a cyanide source—it seems the slow breakdown of the complex is unsuitable for the rapid microwave timescale, giving only trace amounts of product.

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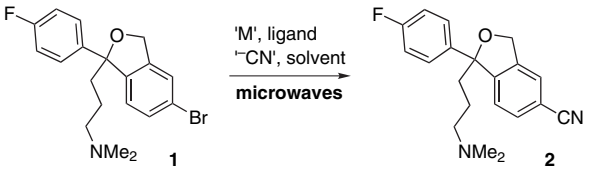
more consistent and had demonstrated the cyanation on kilo-scale.[18] A room temperature palladium catalysed cyanation has recently been reported employing *tert*-butylphosphine as the ligand.[19]



Scheme 1.

All these methods utilised zinc cyanide in DMF. Zinc cyanide is very sparingly soluble in DMF, a factor that keeps the concentration of cyanide ions at the required low level.[20] The Merck process provided the cleanest reaction with DMF and 2–5% water. Other additives used to improve the zinc cyanide/DMF/palladium system include zinc,[21] zinc with bromine[22] and zinc acetate.[23] These observations formed the starting point for our investigations.

2. Results and discussion

Initially we tested $Pd_2(dba)_3$ and dppf (1:1) at 5 mol % in DMF in the cyanation of 4-bromoacetophenone. The reaction (1.0 mmol starting material, 2 mL solvent) was heated with microwave irradiation to 120 °C and after 5 min it showed complete conversion. It was determined to keep the reaction time at a maximum of 5 min to assist eventual transfer to a continuous flow system for scale-up. With no catalyst present starting material was recovered quantitatively. Reduction of the level of palladium to 1 mol % was not detrimental to the yield. Further reduction to 0.1 mol % gave incomplete conversion at 120 °C, but was quantitative at 180 °C. Repeating the reactions with a range of nickel catalysts under similar conditions resulted in little or no conversion.[24]

Surprisingly, subjecting the bromo-precursor **1** to cyanation at 180 °C with 0.1 or 1 mol % of palladium–dppf gave no reaction. A range of additives were then investigated with the results shown in Table 1.

Although water as an additive allowed good conversion, detectable quantities of the amide, from hydrolysis of the nitrile, and debrominated material were formed. Since these impurities needed to be kept below 0.2%, exclusion of protic solvents became important. Levels of the amide, bromo-reduced material and unreacted **1** were measured by HPLC. Full conversion was critical in achieving low impurity levels.

Table 1

Entry	Additives	Conversion (%)
1	None	0
2	1% H_2O	97
3	5% Zn	90
4	5% CuI	15
5	20% TMEDA	100

All reactions with 1 mol % Pd–dppf, 1 equiv $Zn(CN)_2$, DMF, MW at 180 °C for 300 s.

Table 2

Entry	Cyanide source	Conversion (%)
1	Acetone cyanohydrin	0
2	KCN	1
3	CuCN	60
4	$KFe(CN)_6$	1
5	TMSCN	0

All reactions with 1 mol % Pd–dppf, 1 equiv cyanide source, 0.2 equiv TMEDA, DMF, MW at 180 °C for 300 s.

TMEDA as an additive provided a quantitative yield with high purity. Changes in the solvent were briefly examined; acetonitrile and THF both gave lower yields than in DMF. Addition of TMEDA also allowed the temperature to be dropped to 140 °C with no loss in conversion or purity of the crude material. At this lower temperature, discolouring of the reaction mixture was eliminated.

Further optimisation showed zinc cyanide could also be used at 0.6 equiv, consistent with previous work suggesting both cyano groups are transferred.[18] Alternative cyanide sources were tried, all giving lower yields than zinc cyanide, as shown in Table 2. Interestingly the addition of only 10 mol % of acetone cyanohydrin to the zinc cyanide reaction increased cyanide ions in solution sufficiently to poison of the catalyst and reduce the yield to 10%.

Altering the ligand had a significant effect on the yield. Triphenylphosphine or tri-2-furylphosphine in place of dppf gave no reaction. Bidentate ligands dppe and dpppe gave trace amounts of product whereas DPE-phos gave complete reaction. This prompted the test of Xantphos, which in contrast to dppf, allowed the use of 0.5 mol % Pd (1 mol % ligand) at 140 °C. These conditions are the lowest reported catalyst levels for microwave-enhanced cyanation to date (Fig. 1).[25]

Lastly, examination of reaction time revealed the cyanation to be complete after 120 s at the target temperature. The reaction takes around 100 s to achieve the target temperature (max. power 300 W) and around 1 min to cool to below 40 °C giving an overall time for the process of under 5 min.

Scale-up was achieved in the CEM Voyager SF microwave reactor.[26] The Voyager is based on the same microwave cavity as the Discover, but uses a larger (80 mL) glass vessel, with a sealed head that has inlets for a temperature probe and a tube for addition/removal of reaction mixtures. Valves seal the vessel during operation through a loop containing a pressure sensor. The addition/removal of solutions/slurries requires calibration, but can then be automated to give a stop-flow continuous process capability.

The optimised conditions were exactly reproduced at 50 mL (14 g of **1**) batch scale. The same program could be used, only by changing the increase in target temperature (160 °C), which was required for complete conversion (isolated yield 99%, >98.5% purity). The target temperature difference is presumably due to the reported discrepancy in temperature measurement between the Discover and Voyager systems (infra-red vs fibre optic).[27] With the larger vessel, but same maximum power input (300 W), the overall

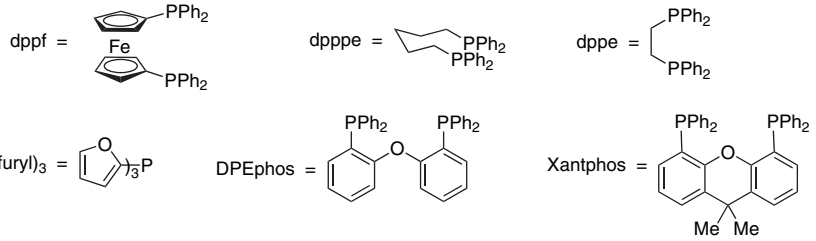


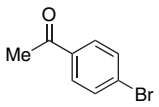
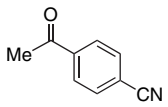
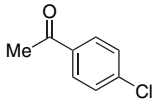
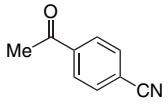
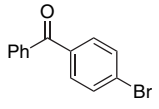
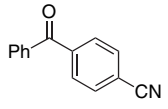
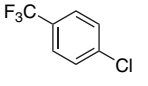
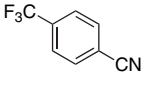
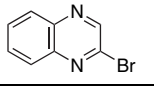
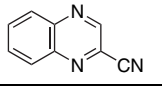
Figure 1.

heating step takes lightly longer. Target temperature is still reached in less than 2 min, but cooling takes around 3 min rather than one to reach a safe temperature. This equates to around a 7 min heating step. When the addition/removal automation time is added for stop-flow use, this gives a cycle time of around 10 min per batch, with approximately 12 g of starting material processed per batch.

Two batches of (*S*)-**1** were subjected to the procedure yielding over 20 g of escitalopram with no loss of enantiomeric purity. Racemic **1** (56 g) was run under a continuous (stop-flow) process in four cycles yielding 47 g of citalopram **2** (>98% purity) in a total run time of 40 min. A sample from each cycle was analysed by HPLC, showing a very high degree of consistency between batches. A longer run provided 150 g in 11 cycles (under 2 h). Extrapolation of this shows multikilogram quantities could be produced in a useful timeframe (days).

The system developed for citalopram was tested on a series of simple aryl halide substrates. Xantphos as ligand was demonstrated to give more active catalysts for aryl chlorides than dppf. Cyanation conditions were rapidly optimised in the microwave for a small selection of aryl halides; all giving very high yields in clean reactions (see Table 3).

Table 3

Entry	Starting material	Product	Catalyst (mol %)	Conversion (%)
1			0.1	100
2			0.5	100
3			0.2	100
4			1.0	93
5			0.5	100

All reactions with Pd–Xantphos, 0.6 equiv $Zn(CN)_2$, 0.2 equiv TMEDA, DMF, MW at 180 °C for 300 s.

3. Conclusions

We have developed a robust cyanation procedure for **1**, using the lowest catalyst loadings yet reported for microwave-enhanced cyanation. The process cuts the reaction time from 24 h to 2 min with an excellent impurity profile. These conditions have been demonstrated to be generally applicable to cyanation for a range of substrates. The cyanation was successfully run in a continuous stop-flow reactor.

4. Experimental

Microwave reactions were carried out in a commercially available monomode system (CEM Discover or Voyager). The reactor has a variable power output from 0 to 300 W. Small scale (<2 g) test reactions were carried out in the Discover with the accompanying 10 mL (5 mL working volume) tubes with septum tops. The Voyager batch reactions were performed in a thick-walled glass vessel (capacity 80 mL, maximum working volume 50 mL). The vessel is isolated from the computer controlled system for charging the reaction contents by a valve. The pressure is controlled and monitored by a load cell connected through this valve with a 300 psi release valve for safety. The temperature of the reaction mixture was monitored using a fibre-optic probe inserted into the reaction vessel in a sapphire immersion well. The contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure and power profiles are recorded by the accompanying software.

4.1. Preparation of escitalopram (*S*)-2, batch method

To a solution of bromo compound (*S*)-**1** (>98% ee, 13.88 g, 36.7 mmol) in DMF (35 mL) in an 80 mL CEM Voyager microwave tube *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.1 mL, 7.3 mmol, 0.2 equiv), zinc cyanide (2.58 g, 22.0 mmol, 0.6 equiv), tris(dibenzylideneacetaone)dipalladium(0) (84 mg, 92 μmol, 0.5 mol %) and Xantphos (213 mg, 0.37 mmol, 1.0 mol %) were added successively. The reaction tube was sealed and heated to 160 °C under microwave irradiation with a 200 s hold time, and 300 W maximum power input. After cooling under a stream of compressed air, the reaction mixture was washed out (with dichloromethane) through a pad a Celite with a thin layer of silica in the middle.

The combined filtrates were concentrated, and then dried extensively under high vacuum to give escitalopram as a yellow

gum (~22 g). Structure confirmed by GC–MS and ^{1}H NMR; chiral purity measured by cHPLC (OD-H column, 95:5 hexane with 0.4% diethylamine to isopropanol, 0.5 mL min^{-1}, 220 nm detection) shows >98% ee.

4.2. Preparation of citalopram 2, continuous stop-flow method

The cyanation was also carried out in a continuous process for racemic citalopram.

The CEM Voyager stop-flow reactor was fed from two stirred vessels: (1) tris(dibenzylideneacetaone)dipalladium(0) (400 mg, 0.87 mmol, 0.6 mol %) and Xantphos (920 mg, 1.59 mmol, 1.1 mol %) slurried in DMF (40 mL), and (2) the bromo starting material **1** (56.0 g, 148 mmol), zinc cyanide (ground to 600 micron powder, 10.8 g, 92 mmol, 0.62 equiv) and TMEDA (4.8 mL, 32 mmol, 0.22 equiv) slurried in DMF to a total volume of 160 mL. A program cycle was calibrated to add 10 mL from vessel 1 and 40 mL from vessel 2, then heat with microwave irradiation to 160 °C (300 W max. power) for a 200 s hold time, cool to 50 °C then remove to a clean vessel. The program was repeated continuously over four cycles with a total run time of 40 min. The slurry generated was filtered through Celite and analysed by GC–MS to show >98% conversion. Chemical purity was further determined by HPLC as >98% (Zorbax SB C_{18} column, 25 cm×4.6 mm, MeCN/[NaH_2PO_4/$OctSO_3H$ aqueous buffer pH 2.8] 32:68, 1.5 mL min^{-1}, 210 nm detection).

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Microwave-assisted polymer chemistry: Heck-reaction, transesterification, Baeyer–Villiger oxidation, oxazoline polymerization, acrylamides, and porous materials

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Abstract—Several questions are still open concerning the different effects of microwave (MW) irradiation in organic and macromolecular chemistry. Analyzing experimental results on a relatively broad investigation area, we came to elucidate three main effects of microwave irradiation: efficient non-contact heating, an accelerating effect, and what we term a special effect. In this paper, we report the first MW-assisted synthesis of poly(2,5-dibutoxy-1,4-phenylenevinylene) via Heck-polycondensation as an example for efficient heating. The facile synthesis of the higher lactones 1-oxa-2-oxocyclooctanone and 1-oxa-2-oxocyclononanone via Baeyer–Villiger reaction offers indeed an example for the MW-accelerating effect. A survey of our recent work is also given to explain the effects more in detail and to provide examples of the special MW effect.

1. Introduction

Besides the fact that commercially available microwave (MW) reactors provide a comfortable, safe, and clean way of working, MW irradiation shows remarkable advantages in chemical reactions. It accelerates many syntheses providing selective activation with short start-up phase and allows fast optimization of reactions. In macromolecular chemistry as well, the application of microwaves opens up many opportunities[1,2] to improve monomer and polymer preparation and enhances polymer analogue reactions.

In this work we want to report some examples of chemical reactions that allow us to define three main aspects of MW effect. We found that the Heck-polycondensation or the synthesis of ε-caprolactone based macromonomers[3] are reactions that can be performed with comparable results under MW irradiation and under normal conditions (thermal heating in oil bath). In this case the MW effect can be defined just as a convenient non-contact heating.

Investigating the lactone synthesis via Baeyer–Villiger reaction or the polymerization of 2-phenyl-2-oxazoline,[4] we could recognize an improvement, under MW irradiation, in terms of higher yield or shorter reaction time. Accordingly, we like to delineate the MW effect as a way to accelerate the monomer and polymer synthesis. Finally, we provide examples of synthetic pathways not accessible under normal conditions. It is the case of the acrylamide formation[5] or the preparation of channel-containing materials that can be described invoking a special MW effect.[6]

2. Results and discussion

2.1. Convenient non-contact heating

Heating in oil bath and in microwave shows different temperature gradients.[7] In the case of heating with external heat sources as hot oil, for example, the heat comes from the outer environment and becomes less in the inner reaction solution. Otherwise, microwaves directly heat up the reactive centers of the reagents and the solvent, if a dipole moment exists. The reaction vessels used are, in general, transparent to microwaves. In this way the most effective energy transfer can be provided.

2.2. Heck-polycondensation

Although many reactions show different behavior under microwave irradiation, there also exist reactions, which

Keywords: Microwave; Heck-reaction; Macromonomer; Poly-oxazoline; Baeyer–Villiger oxidation; Acrylamide; Coating.
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show the same progression in oil bath and in microwave without differences in yield or reaction time. Homogeneous transition metal catalyzed reactions provide an abundance of possibilities for carbon–carbon or carbon–heteroatom bond formation with high yields and stereo- and/or regioselectivity. One example for this kind of reactions is the investigated synthesis of poly(phenylene vinylene) via Heck-polycondensation. According to literature, the employment of MW reactors in organic metal catalysis may reduce the reaction time up to tenfold.[8] MW-assisted Stille and Suzuki cross-coupling reactions have been used to prepare semiconducting polymers within 10 min without affecting the yield, molecular weight or the quality of the material.[9] Low molecular weight Heck-reactions were also reported to be accelerated via MW-assisted synthesis.[8,10]

Up to now, the synthesis of poly(2,5-dibutoxy-1,4-phenylenevinylene) via Heck-reaction by using MW irradiation has not been studied. Thus, the following section deals with the kinetics of Heck-reactions focusing on the preparation of poly(phenylene vinylene) (Scheme 1).

In this type of metal catalyzed reaction the polymer is formed stepwise. Thus, the kinetics can be correlated to the molecular weight M_n. To compare the kinetics, the reactions must be performed at exactly defined temperatures. To avoid inaccuracies in determination of temperatures, the reactions were carried out in boiling solvent. It turned out that refluxed solutions of 1,4-dioxane were suitable for the Heck-reaction and therefore, should offer a constant bulk temperature of 102 °C both for MW and oil bath assisted synthesis, respectively. Thus, a direct comparison between the kinetics of both is possible. As 1,4-dioxane is a poor MW absorber (low dipole moment), a simple and instantaneous heating effect of the solvent was excluded. MW irradiation is normally highly effective in the case of polar structures.[4,5,11] It was predicted that the MW field interacts with the dipolar metal complex at the chain end (Fig. 1).

Surprisingly, the results obtained in boiling 1,4-dioxane showed almost equal yields (Fig. 2) and that there was only a minor acceleration effect for MW-assisted Heck-polycondensations (Fig. 3). Within 1 h reaction time, MW-promoted reactions always yielded polymers with M_n values

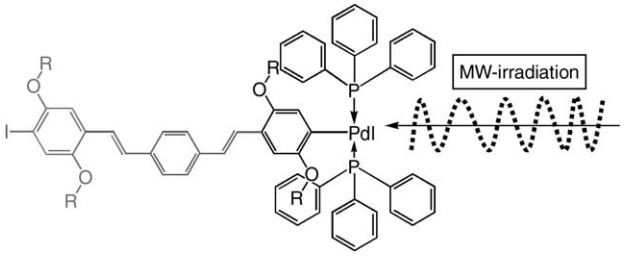


Figure 1. Schematic illustration of the postulated interaction of MW with the chain end.

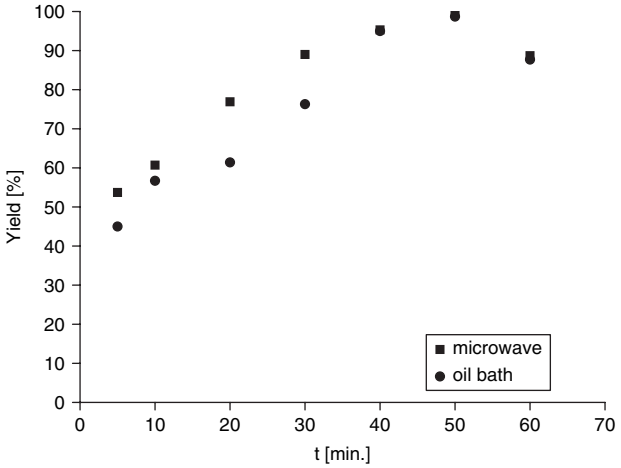
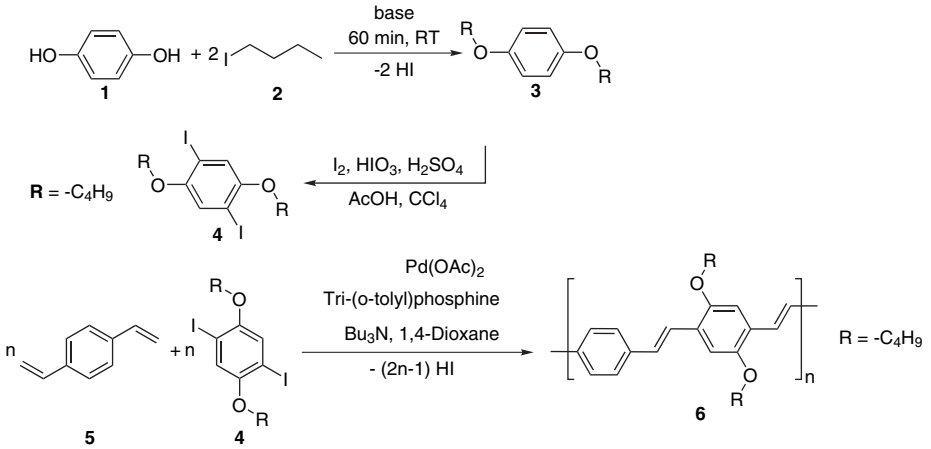


Figure 2. Dependence of yield (%) on reaction time in boiling 1,4-dioxane.

of about 1000 g/mol higher molecular weight on an average than the corresponding polymer samples obtained from classical oil bath heating. This low effect is clearly in contrast to some earlier published papers, dealing with MW-accelerated low molecular weight Heck-reactions.[8,10]

In conclusion, our results show that reactions in boiling solvents are a good method to compare precisely the kinetics of the Heck-reaction in MW and oil bath. Only a small effect of MW irradiation on the kinetics of the Heck-polycondensation of PPV (**6**) could be detected.



Scheme 1. Synthesis of poly(2,5-dibutoxy-1,4-phenylenevinylene) (PPV) (**6**).

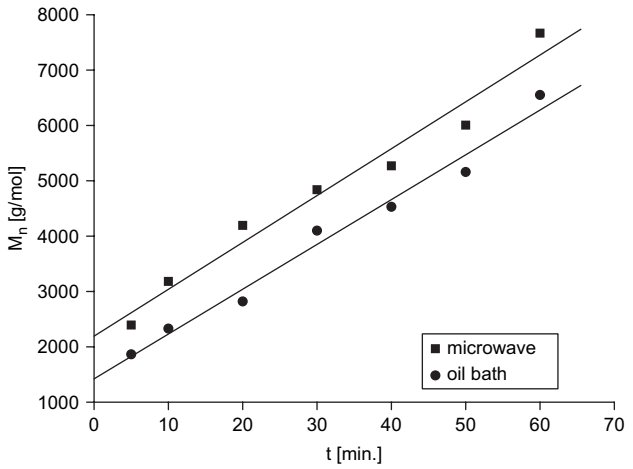
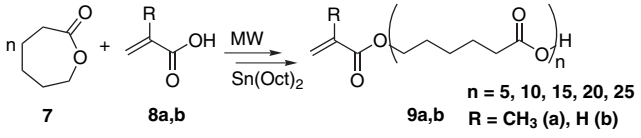


Figure 3. Dependence of molecular weight (M_n) on reaction time in boiling 1,4-dioxane.

2.3. Synthesis of macromonomers

The synthesis of macromonomers is another interesting field in polymer chemistry. In the investigated system of ε-caprolactone (**7**) in presence of (meth)acrylic acid (**8a** and **8b**) and tin octoate as catalyst we used microwave irradiation as a powerful energy source for the ring-opening polymerization and functionalization of the polyester in a single step (Scheme 2).[3] Due to the rapid non-contact heating under microwave conditions, fast optimization of the synthesis applying short reaction times was possible. However, comparison with classical thermal activation showed no significant acceleration effect under microwave conditions.



Scheme 2. Preparation of macromonomers (**9a**,**b**).

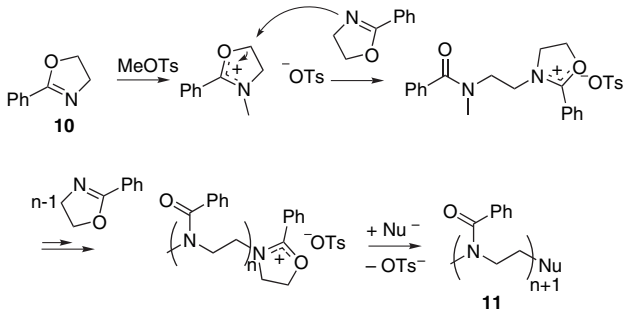
Polyester macromonomers can principally be prepared by two procedures: end-capping of polylactones with vinylic derivatives[12,13] or by initiation of the lactone polymerization by a vinylic derivative with a suitable initiation group.[14] Both methods require mostly two steps and often the addition of activation reagents. In contrast to common syntheses, we found a fast access to polyester macromonomers with high degree of functionalization and defined chain length using microwave irradiation. All reactions were carried out in a mono-mode microwave apparatus under temperature control at 180 °C (measured using a fiber optic device inserted directly into the reaction mixture) with a reaction time of 90 min starting from unpurified reagents and working in air. It is interesting to note that even at such high temperatures the spontaneous free radical polymerization of the (meth)acrylic derivates can be prevented. We polymerized different molar ratios of ε-caprolactone (**7**) and (meth)acrylic acid (**8a** and **8b**) to yield the macromonomers **9a** and **9b** with accordant chain length as shown in Scheme 2.

2.4. Accelerated monomer and polymer synthesis

In many cases using the microwave can accelerate the reaction procedure. This phenomenon of course can be connected to the fast and uniform heating profile. But it is obvious, that especially in case of existing dipolar moments in the reacting molecules the reaction occurs in an unexpected way. The presence of the alternating electric field seems to play an important role in microwave chemistry. The following examples should confirm this fact.

2.5. Polymerization of 2-phenyl-2-oxazoline

Kinetics of the cationic ring-opening polymerization of 2-phenyl-2-oxazoline (**10**) under microwave irradiation shows enhancement of reaction rate in comparison to normal heating.[4] The cationic ring-opening polymerization of 2-substituted 2-oxazolines has been intensively studied since the mid 1960s by several groups.[15–18] It is known that the polymerization of 2-phenyl-2-oxazoline takes place by treating the monomer with strong electrophiles (e.g., methyl tosylate) yielding poly(*N*-benzoylethylenimine) (**11**) (Scheme 3).



Scheme 3. Mechanism of the cationic ring-opening polymerization of 2-phenyl-2-oxazoline (**10**) via methyl tosylate.

2-Phenyl-2-oxazoline (**10**) has been polymerized under microwave conditions both in closed and open reaction vessels. It is interesting to note that, synthesis in open and closed systems show nearly the same enhancement of reaction rate if the reaction is performed using microwave irradiation (Table 1).

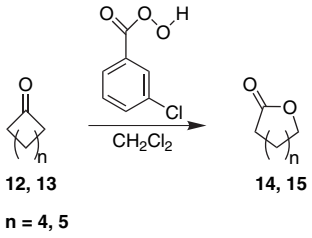
Table 1. Reaction rate coefficient of the polymerization of (**10**) in closed vessel (CV) and open vessel (OV) under different conditions

	Rate coefficient (10^{-2}/min)	
	CV	OV
Microwave	4.17	3.55
Oil bath	1.08	1.11

2.6. Synthesis of lactones via Baeyer–Villiger oxidation

Ionic species are found as intermediates in all redox processes. Since microwaves strongly interact with polar species, especially with ions, redox reactions may be expected to proceed much faster under MW irradiation. As an example the Baeyer–Villiger rearrangement was investigated. Starting from ketones, reaction with peroxide species such as peroxybenzoic acid or *m*-chloroperoxy benzoic acid yields esters. Using cyclic ketones this method represents

a convenient pathway to lactones (Scheme 4), which are common monomers for ring-opening polymerization.



Scheme 4. Synthesis of lactones (**14**, **15**) via Baeyer–Villiger oxidation.

Higher cyclic ketones with $n>3$ and their derivatives usually require reaction times up to several days or even weeks for high conversion.[19] We investigated the lactone formation with cycloheptanone (**12**) and cyclooctanone (**13**) as substrates for microwave-promoted Baeyer–Villiger oxidation. The experiments were performed under reflux in CH_2Cl_2 in open vessels using microwave irradiation as well as comparison studies in an oil bath. Calculating the ketone conversion by ^{1}H NMR from the ratio of the OCH_2– and the $COCH_2$– signals of the lactone and the $COCH_2$– signal of the ketone the kinetics displayed in Figure 4a and b were obtained. We could observe acceleration of the reaction rate for both cycloheptanone (**12**) and cyclooctanone (**13**). Especially in case of the latter, the formation of the lactone **15** proceeded significantly faster.

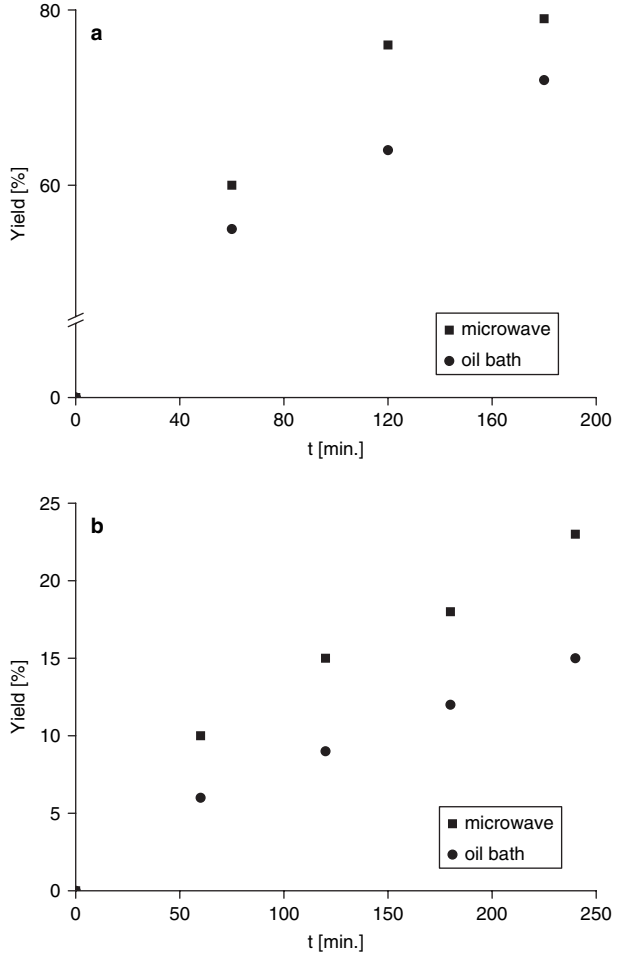


Figure 4. Kinetics of the Baeyer–Villiger oxidation of (a) cycloheptanone (**12**) and (b) cyclooctanone (**13**) in boiling CH_2Cl_2.

2.7. Special microwave effects and application

A special focus should be directed on the synthetic pathways that are not achievable under conventional heating conditions but can easily be realized using MW irradiation.

2.8. Direct synthesis and one-pot polymerization of acrylamide

Efficient synthetic routes towards acrylamides are through the conversion of acid chlorides, essentially in the presence of bases like triethylamine or pyridine, or directly, from acid and amine using activating agents like *N*,*N*′-dicyclohexylcarbodiimide. We previously investigated the MW-assisted reaction between (meth)acrylic acid and a chiral amine in the presence and in the absence of a radical initiator.[11] Focusing on the behavior of acrylic acid and (*R*)-1-phenylethylamine, we found that MW irradiation accelerates considerably the process of acrylamide formation with high selectivity.[5] After irradiation for only 15 min with a microwave power of 50 W, the amide **18** was synthesized in 93% yield (GC/MS). The reaction was performed in bulk without any activation reagents (Scheme 5).

Numerous attempts to perform the same synthesis by conventional thermal heating in an oil bath led to almost complete polymerization of the acrylic acid–amine salt (**17a**) after only 2 min of reaction time.

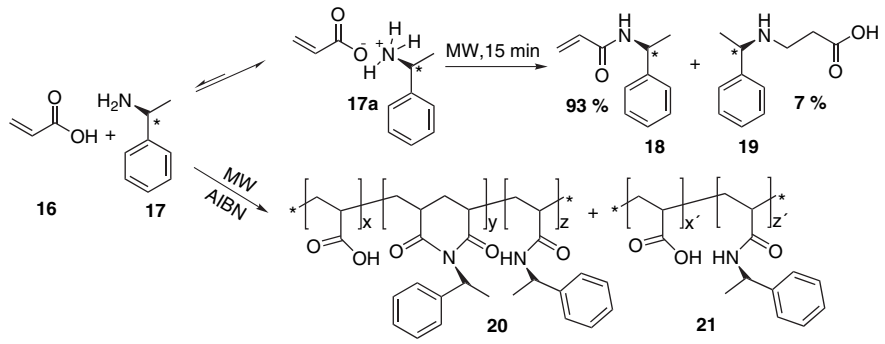
The MW-assisted reaction, carried out in the presence of AIBN, afforded optically active polymers in a single step. The ^{1}H NMR and DSC analyses suggest the presence of blends containing two different polymeric structures: a terpolymer containing imide moieties (**20**) and a copolymer containing acrylic acid and acrylamide units (**21**) (Scheme 5). The applied irradiation power and the average molecular weight of the polymers were inversely related. On the other side, the yield was observed to increase with power.

In conclusion, MW irradiation accelerates considerably the acrylamide formation with exceptional selectivity. The same results are not achievable by conventional thermal heating in an oil bath. The MW-assisted one-pot polymerization offers a good method for the synthesis of optically active polymers. These materials are possible candidates as chiral stationary phases for applications in chiral resolutions.

2.9. Coatings

Coatings, channel containing polymeric materials and the way to produce them play an important role, for example, in industry as protection against corrosion or in medical research for bone replacement.[6] Often the question rises, how to prepare materials, which contain ordered and defined structures.

It is well known that metals show fast heat development under MW irradiation.[20,21] This property, based on electrical resistance, was used to develop a new technique for the



Scheme 5. MW-assisted bulk amidation and one-pot polymerization.

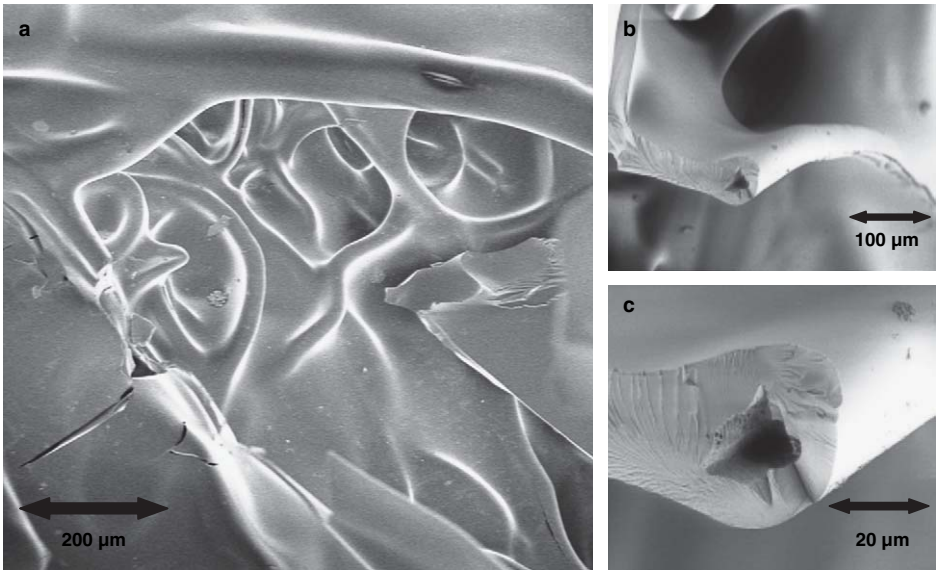


Figure 5. (a) SEM picture of channels in the polymer network synthesized by MW irradiation. (b) A tube opening of a channel after dissolving the iron component in HCl. The surface of the polymer cover is smooth. (c) Close up view of the tube opening in Figure 5b. The angular outlines of the metal fibers due to the production process can be recognized.

coating of metal fibers and the preparation of polymeric materials with defined channel structures.

MW irradiation of iron fibers, which are located in a monomer solution consisting of methyl methacrylate (MMA), ethylene glycol dimethacrylate as cross-linker, *N*,*N*′-azoisobutyronitrile (AIBN) as free radical initiator and toluene as solvent and weak MW absorber led to the formation of polymeric material on the iron surface. The thermal decomposition of the initiator predominantly took place close to the heated metal surface whereas the solution temperature outside the iron fibers was too low.[6] In contrast to MW irradiation, classical thermal heating leads to a temperature gradient in the opposite direction. As expected the polymerization reaction started first at the wall of the flask and then in the solution. Thus, it was not possible to adjust the reaction conditions in the way that polymer is formed only at the iron surface.

By dissolving the covered iron component in hydrochloric acid after polymerization it was possible to obtain polymeric materials with defined structures in the form of iron fibers. Scanning electron microscopy (SEM) elucidated the structure and distribution of the channels in the polymer matrix. The exterior surface of these tubes was smooth in contrast to the interior structures, which showed a rough surface. This fact can be attributed to the roughness of the metal fiber surface (Fig. 5).

This method represents a cheap, fast, and convenient pathway to defined porous materials and coatings, which was not possible to reproduce in an oil bath.

3. Conclusion

It can be concluded from the above described results that MW activation is in general a convenient method to carry out chemical reactions on a laboratory scale. However, in some cases it may not only accelerate certain chemical conversions but also influence the course of reactions. MW irradiation provides fast and convenient access to chiral (meth)acrylamides and their polymers in a one-pot synthesis. We could also show that it is possible to obtain well defined channel-like structures in a polymer matrix by focused heating of metals under MW irradiation in a monomer solution. Moreover, this method allows fast and effective excess to a multitude of other interesting monomers and macromonomers. Also the generation of selected polymers as

polyoxazoline and poly(phenylene vinylene) under usage of metal catalysts can be provided.

4. Experimental

4.1. Materials and methods

p-Divinylbenzene was synthesized and purified according to literature procedures.[22,23]

All reagents used in our experiments were of analytical grade and were used without further purification.

The identity of the synthesized compounds was confirmed by mass spectrometry, NMR, and IR measurements. ^{1}H NMR and ^{13}C NMR were performed using a Bruker Advance DRX 500 spectrometer at 500.13 and 200.13 MHz for proton and 125.77 MHz for carbon in $CDCl_3$ as solvent. The δ-scale relative to TMS was calibrated to the deuterium signal of the solvent as internal standard. Infrared spectra were recorded on a Nicolet 5SXB FTIR spectrometer. Size exclusion chromatography (SEC) was performed on a SEC-system consisting of a Waters 486 tunable absorbance detector at 275 nm and a Waters 410 differential refractometer, using THF as eluent. The system was calibrated with polystyrene standards with a molecular weight range from 580 to 1,186,000 D. The flow rate was 1 mL/min. Polymer solution [100 μL of a 0.125% (w/w)] was injected to a HEMA-column-combination consisting of a pre-column of 40 Å and main columns of 40, 100, and 300 Å porosities. For MW-assisted synthesis a monomodal microwave (CEM-Discover) equipped with an infrared pyrometer with maximum operation power of 300 W was used.

4.2. Synthesis

4.2.1. 1,4-Diiodo-2,5-dibutoxybenzene (4). 1,4-Diiodo-2,5-dibutoxybenzene was synthesized according to literature procedures shown in Scheme 1.[24]

4.2.2. Poly(2,5-dibutoxy-1,4-phenylenevinylene) (6). Tributylamine (0.53 mL, 2.2 mmol) was added to a solution of 1,4-diiodo-2,5-dibutoxybenzene (**4**) (474 mg, 1 mmol), *p*-divinylbenzene (144 μL, 1 mmol), Palladium-(II)-acetate (9 mg, 0.04 mmol), and tri-(*o*-tolyl)phosphine (61 mg, 0.2 mmol) in 5 mL 1,4-dioxane. For a series of kinetics 5 mL samples were taken from a 70 mL stock solution. MW-assisted reactions were irradiated to reflux at 300 W in a mono-mode microwave reactor under nitrogen atmosphere. Reaction mixture in oil bath was heated up to reflux under nitrogen atmosphere. The reaction mixture (5 mL each) was poured into 20 mL of methanol. The precipitated orange polymer was collected by filtration, washed several times with 20 mL of methanol, and dried for 12 h under vacuum.

FTIR (diamond): 2955 (ν_{C-H}), 2929 (ν_{-CH_3}), 2867 (ν_{-CH_2-}), 1594 (ν_{Ar}), 1495 (ν_{Ar}), 1466 ($\delta_{CH_2-CH_3}$), 1420, 1200 (ν_{-C-O-C}), 1027, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.47 (Ar), 7.10 (vinyl), 4.03 (–OCH_2), 0.93–1.81 ppm (polymer backbone); ^{13}C NMR ($CDCl_3$): δ=151.57 (O–C–Ar), 138.74 (vinyl), 124.22–129.37 (Ar), 111.23 (vinyl), 69.69 (O–CH_2), 32.02 (CH_2–CH_2–CH_2), 19.91 (CH_2–CH_3), 14.42 ppm (CH_3).

4.2.3. 1-Oxa-2-oxocyclooctanone (14) and 1-oxa-2-oxocyclononanone (15). *m*-Chloroperoxy benzoic acid with 30% water content (5.2 g, 20 mmol) was added to a solution of the cyclic ketone (**12** or **13**) (20 mmol) in 20 mL methylene chloride. The mixtures were refluxed for 3 and 4 h, respectively. For kinetic measurements samples were taken every hour. MW-assisted reactions were performed under 100 W irradiation and else same conditions.

Compounds **14**: ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=4.45–4.32 (t, 2H, OCH_2), 2.65–2.55 (t, 2H, $COCH_2$), 1.95–1.54 ppm (m, 8H); **15**: ^{1}H NMR (200.13 MHz, $CDCl_3$): δ=4.38–4.29 (t, 2H, OCH_2), 2.38–2.28 (t, 2H, $COCH_2$), 2.00–1.32 ppm (m, 6H).

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Efficient synthesis of small molecule macroarrays: optimization of the macroarray synthesis platform and examination of microwave and conventional heating methods

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Abstract—We report a method for the efficient construction of small molecule macroarrays using microwave-assisted SPOT-synthesis. Macroarrays of 1,3-diphenylpropenones (chalcones) were synthesized rapidly and in high purity starting from robust, Wang-linker-derivatized planar supports. We have optimized the entire chalcone macroarray construction process and evaluated the efficiency and utility of microwave-assisted reactions in array synthesis. Microwave heating was found to be most beneficial for reactions that require temperatures greater than the boiling points of the solvents. These microwave-assisted conditions permitted straightforward access to macroarrays of 2,4,6-triarylpyridines derived from the original chalcone scaffold.

1. Introduction

Combinatorial chemistry is now an established tool for the discovery of small molecules and materials with new properties. This approach has seen wide use in the fields of drug development,[1] chemical biology,[2] supramolecular chemistry,[3] material science,[4] and chemical sensor development.[5] With the advent of high-throughput screening and ultra-sensitive analytical techniques,[6,7] the amount of material required for evaluation has been reduced to the nanomolar and sub-nanomolar range. As a result, combinatorial synthesis techniques have been developed that provide maximum structural diversity at an exceedingly small scale.[8] These techniques have relied typically on solid-phase synthesis methods using polymeric supports;[9] however, the conventional beaded supports are frequently expensive, mechanically fragile, and incompatible with many on-bead assays. Further, the reaction rates for solid-phase reactions are often considerably slower than their homogeneous counterparts (e.g., 10–100 times).[10] These drawbacks have motivated the development of improved synthesis and screening platforms for combinatorial chemistry.

SPOT-synthesis represents an attractive alternative to the use of conventional polymeric resins for combinatorial synthesis.[11] Originally developed for peptide synthesis, this method involves spatially addressed synthesis on derivatized cellulose sheets (readily prepared from inexpensive laboratory filter or chromatography paper) to generate arrays of unique molecules (1–10,000 spots per array, Fig. 1).[12,13] In contrast to conventional polystyrene resins, the hydrophilic membrane sheets are easy to manipulate during synthesis and

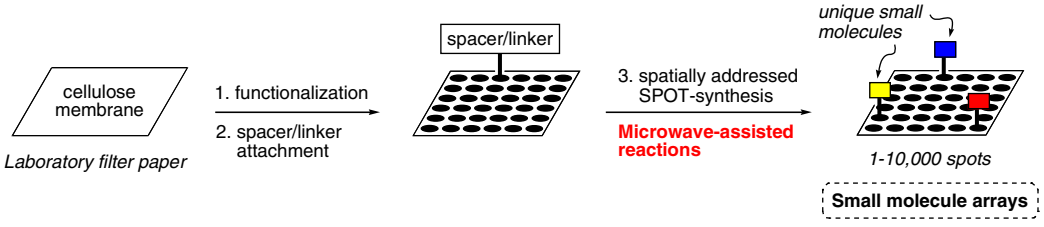

Figure 1. Schematic of the SPOT-synthesis process used to generate small molecule macroarrays.

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washing steps and are mechanically robust. Furthermore, planar cellulose supports are compatible with various on support biological screening methods, including protein-binding assays, enzyme-linked immunosorbent assays (ELISA), and agar overlays.[14] Assays also can be performed after compound cleavage—each spot of the macroarray commonly yields 50–200 nmol of compound, which is sufficient for evaluation in miniaturized solution-based bioassays.[15]

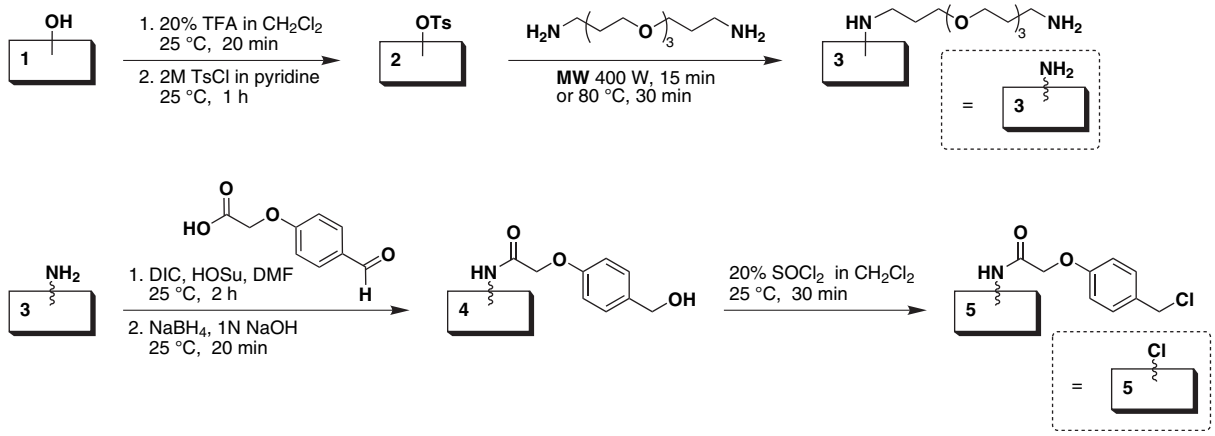
Examples of non-peptidic libraries generated via SPOT-synthesis are limited, and most have relied on simple acylation chemistry.[16] More demanding chemistry has not been pursued, in part, because (1) SPOT-synthesis suffers from slow reaction rates similar to conventional solid-phase synthesis, and (2) general, reproducible methods for heating spatially addressed reactions are not available. We reasoned that the application of microwave (MW) heating during SPOT-synthesis could address these two limitations and broaden the reaction scope of the method.[17] The use of MW irradiation as an unconventional heating method for organic synthesis has increased dramatically over the past decade, primarily due to the observed reductions in reaction times and concomitant enhancements in conversion and purity.[18] The wider availability of commercial MW synthesis reactors has also played a role in the expansion of this nascent field.

Recently, we demonstrated the successful union of these two technologies through the efficient MW-assisted synthesis of high purity 1,3-diphenylpropenone (chalcone),[19] dihydropyrimidine, and α-acylamino amide macroarrays.[20] These macroarrays represent some of the most complex small molecule libraries generated via SPOT-synthesis to date. In this preliminary work, we developed two robust cellulose support systems functionalized with orthogonal linker systems (Fig. 1): one acid-cleavable,[19] and the other photocleavable.[20] The application of MW irradiation to selected reactions in macroarray synthesis allowed for small molecule libraries (ca. 100-member) to be constructed at unprecedented rates (on the order of hours). This work sets the stage for the full integration of MW-assisted reactions in SPOT-synthesis to examine the scope and limitations of small molecule macroarrays as a new combinatorial chemistry platform.

Toward this goal, we have performed a systematic optimization of the MW-assisted SPOT-synthesis process using our chalcone macroarrays[19] as a lead example. Here, we report full details of this optimization study, including (1) the synthesis of the linker-derivatized support, (2) the loading of initial building blocks, and (3) the Claisen–Schmidt condensation to produce the chalcones. We also critically evaluated the efficiency and utility of MW-assisted reactions in array synthesis in comparison to conventional heating methods. Our optimization study ultimately revealed new modes of reactivity for certain library building blocks used in chalcone macroarray synthesis—this discovery permitted straightforward access to a set of 2,4,6-triarylpyridine macroarrays.

2. Results and discussion

Optimization of linker derivatization procedure. Our first goal was to reduce the total time required to generate the acid-cleavable (Wang-type)[21] linker-derivatized support used in macroarray synthesis. Our originally reported reaction sequence took over 21 h and was a considerable bottleneck in macroarray construction.[19] The overall procedure for preparation of linker-derivatized support **4** is outlined in Scheme 1. The first step was a pre-swelling of the cellulose support (**1**, 20 cm×20 cm sheet) using trifluoroacetic acid (TFA) to increase the surface area and thus the number of reactive sites for derivatization. We found that by doubling the concentration of TFA in the initial swelling step from 10% to 20% we could achieve better reproducibility in linker loading levels. Removing the residual TFA from the support prior to subsequent steps, however, required lengthy drying times in a vacuum oven (over 16 h). We were pleased to find that replacing the vacuum drying with two 5-min washes of anhydrous CH_2Cl_2 and a 20 min drying time using a stream of N_2 gave a support of equal quality. Notably, this simple procedural adjustment significantly reduced the synthesis time (by 15 h). Next, the pre-swelled paper (**1**) was reacted with tosyl chloride (TsCl) in pyridine (2.0 M) at room temperature following our original procedure to generate tosylated cellulose support **2**.[19] We found that subjecting the support to the TsCl solution for variable amounts of time gave different and reproducible tosylation



Scheme 1. Preparation of Wang-linker-derivatized support **4** and chloride-derivatized, 'activated linker', support **5**. Supports were washed with various solvents and dried routinely between each synthetic step.

levels (1 h ~3.8 μmol/cm^2, 10 h ~10.0 μmol/cm^2, as determined via subsequent amination reactions).[22] A flexible diamino 'spacer' unit, 4,7,10-trioxa-1,13-tridecanediamine, was then introduced to support **2** through standard nucleophilic substitution chemistry (Fig. 1). This 'spacer' unit has been shown to improve the accessibility of array-bound molecules for subsequent reactions and on support assays.[23] We found that the spacer could be coupled to tosylated support **2** by either MW-assisted conditions (400 W, 15 min in a Milestone MicroSYNTH Labstation multimode MW reactor)[24,25] or by conventional heating in an oven (80 °C, 30 min; see below) to achieve equivalent amine loadings (ca. 4–10 μmol/cm^2). Thus, use of the MW reactor in this displacement step provided only a minor reduction in synthesis time.

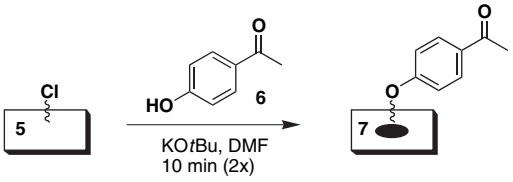
We found that the Wang-linker-derivatized membrane **4** could be prepared from amino support **3** using two different, yet complimentary, methods. Both methods involve two stages: first, the 'pro-linker', 4-formylphenoxyacetic acid, was coupled to support **3** via a standard carbodiimide (DIC) coupling at room temperature. Next, the resulting aldehyde support was reduced using sodium borohydride ($NaBH_4$) at room temperature to yield benzylalcohol-derived support **4**. The two methods only differed in *how* the pro-linker was physically applied to the planar support in the first step. In the first method, the entire membrane was immersed in the pro-linker coupling solution for 2 h in a 'blanket-type' functionalization. This method gave the highest linker loading overall (2.6 μmol/cm^2).[26] However, this bulk procedure required a large quantity of pro-linker reagent, and does not represent a general linker loading strategy if the linker reagent is either expensive or difficult to synthesize. In the second method, the pro-linker was applied in a spatially addressed, or 'spotted', manner, delivering 6.0 μL aliquots of the activated solution to individual spots on amino support **3** (applied twice over 2 h). Spatially addressed delivery only required 20% of the quantity of linker relative to the blanket-type method; however, linker loadings were diminished (1.8 μmol/cm^2). Since 4-formylphenoxyacetic acid is readily available either synthetically[19,27] or from commercial sources, we chose to use the blanket-type functionalization technique to generate support **4** throughout the present study. Using this optimized method, we routinely prepared four 20 cm×20 cm sheets of linker-derived support **4**, each with 120 spot-capacity, in less than 8 h. This represents a significant improvement in synthesis efficiency, as our original method required over 21 h to generate a single sheet of support **4**. The sheets were found to be stable at room temperature for at least one month (stored in a desiccator) and could be used in an 'off-the-shelf' manner for small molecule macroarray construction.

Benzylic alcohol-derived support **4** requires activation prior to the attachment of macroarray building blocks; we found conversion of support **4** to the benzylic chloride **5** to be an effective activation approach (Scheme 1). In our initial work, we examined chlorination of support **4** with TsCl in anhydrous DMF.[19] This method was extremely sensitive to the level of moisture in the DMF solvent. Careful optimization of the chlorination procedure revealed that chlorination with $SOCl_2$ in anhydrous CH_2Cl_2 gave comparable chlorination levels to our original method (based on the loading of 4′-hydroxyacetophenone (**6**), see below), yet was far more reproducible. We ascribe this to the relative ease of maintaining an anhydrous environment with CH_2Cl_2. After chlorination, activated membranes **5** were stored under N_2 and had to be submitted promptly to macroarray construction (within 15 min of preparation) in order to minimize hydrolysis.

Optimization of initial building block loading. We next examined the loading of hydroxyacetophenone building blocks onto activated support **5** under a variety of conventional and MW heating conditions to determine if MW-assisted reactions provided an advantage for this step in macroarray construction (Table 1). We selected 4′-hydroxyacetophenone (**6**) as a model substrate, and identical conditions were used for all reactions to facilitate direct comparison between the two heating methods (3.0 μL aliquot of 2.0 M **6** and 2.0 M KO*t*Bu in anhydrous DMF, 10 min). Application of this volume of reagent to support **5** provided a spot with a 0.3 cm^2 area. Conventional heating conditions were examined in a standard laboratory drying oven (VWR model #13OOU, for ≥80 °C) or a laboratory incubator (Lab-Line Imperial II, for 40 °C reactions). MW heating conditions for this step were examined in the Milestone MicroSYNTH multimode MW reactor. We discovered that the temperature of the planar support surface could be measured easily during these reactions using a non-contact IR thermometer (Craftsman model # 82327) positioned in apertures at the top of either the oven or MW reactor.

The first challenge that needed to be overcome in this study was the inconsistency of heating in a drying oven. We found that, depending on the position in the oven, the temperature could vary easily by up to ±10 °C. This made the uniform heating of 20 cm×20 cm planar support sections in the oven difficult, especially over short times (e.g., 5–10 min).

Table 1. Optimization of loading of model acetophenone substrate **6** onto planar support **5**



Entry	Conditions (final membrane temperature)	Substrate loading (nmol/cm^2)[a]
1	Room temperature (22 °C)	60
2	Oven (40 °C)[b]	80
3	Oven (80 °C)	260
4	MW 500 W (40 °C)[c]	120
5	MW 500 W, on Pyrex dish (80 °C)[d]	120
6[e]	Oven (80 °C)	190

[a] Determined by integration of the HPLC trace with UV detection at 254 nm. Integration values were compared to a UV calibration curve generated for **6**. Error ±10 nmol/cm^2.
[b] Performed in a laboratory incubator.
[c] Support suspended in the middle of the MW reactor cavity using tape to minimize heating due to conduction from a surface.
[d] Support placed in flat 2.6 L Pyrex dish and then on rotor in MW cavity. Pyrex dish thickness=0.5 cm.
[e] Prepared using support **4** on which the linker was applied in a spatially addressed manner.

We solved this homogeneity problem by placing a large sand bath in the oven that was allowed to equilibrate to the target temperature overnight prior to a conventional heating experiment. The sand bath was found to give stable and reproducible temperatures that varied only by ±1 °C. The planar membranes were heated by simply placing the membrane on top of the sand. The sand bath provided an added benefit to conventional heating in the oven, as we found its presence minimized dramatic temperature changes that accompanied the opening and closing of the oven door.

Not surprisingly, the loading of model acetophenone **6** increased steadily with increasing temperature using conventional heating methods, with the highest achievable loading obtained at 80 °C (Table 1, entries 1–3). Our original heating method using the MW oven (entries 4 and 5), however, resulted in an intermediate loading level relative to conventional heating, even when the final temperature of the membrane also reached 80 °C (entry 5).[25] The rapid heat transfer observed from the pre-heated sand bath in the oven to the support could explain this difference, in part. After 30 s of heating on the sand bath, the temperature of the support was measured to be 80 °C. In contrast, the temperature of the Pyrex dish used in the MW-assisted reaction only reached 80 °C (from room temperature) after 20 min of constant irradiation in the MW reactor (500 W).

Interestingly, the loading values achieved when the support was heated either in or outside of a Pyrex dish in the MW reactor were equivalent (entries 4 and 5). This suggests that a different heating mechanism than simple conduction could be operative for these MW-assisted reactions. Quantifying such a heating mechanism is difficult using bulk temperature measurements such as IR, as often these measurements do not reflect microenvironments of higher temperatures in a material (or 'hotspots').[28] The presence of such hotspots could explain the higher loading achieved using the MW reactor (without the Pyrex dish, entry 4) versus heating in the oven at 40 °C (entry 2), even though the bulk temperatures of the membranes were measured to be identical. Finally, comparison of entries 3 and 6 illustrates the lower hydroxyacetophenone loadings obtained when the pro-linker is applied in a spatially addressed manner as opposed to in a blanket-type functionalization (see above).

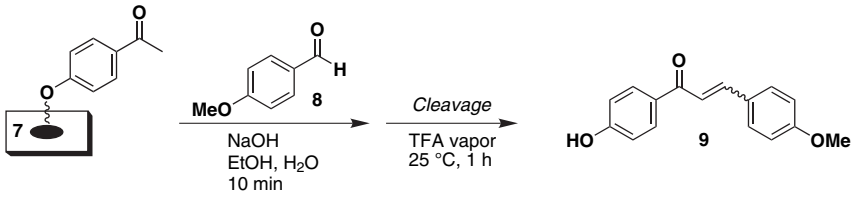
This study revealed that heating in an 80 °C oven was the highest yielding method for initial hydroxyacetophenone substrate attachment. We note, however, that this procedure only gave hydroxyacetophenone loading values equal to 10% of the available reactive linker sites (260 nmol/cm^2 vs 2.6 μmol/cm^2).[22] Repetitive applications of reagents and heating failed to show a significant improvement in loading for this reaction. We believe that there are two possible causes for this outcome. First, the benzylic chlorides of activated support **5** could simply react with residual water in the membrane or with free hydroxyls on the cellulose surface as opposed to substrate **6**. The use of non-anhydrous DMF or older bottles of KO*t*Bu has been observed to reduce loading. Second, native hydroxyl groups on the cellulose paper also could be activated during the chlorination protocol and compete with the activated linker for substrate. Evidence for this latter theory was obtained when fluorescent hydroxyacetophenones were coupled to **5** and repeated exposure to cleavage and elution conditions failed to remove the substrates completely from the surface (i.e., fluorescence was observed when the membranes were irradiated with UV light). Ongoing efforts are focused on developing alternate activation protocols for linker-derivatized support **4** to surmount these two obstacles and increase loadings.

Optimization of the Claisen–Schmidt condensation. We have shown previously that the Claisen–Schmidt condensation proceeds smoothly under MW-assisted conditions on planar support-bound acetophenones (400 W, 20 min).[19] For the present study, we were interested in systematically comparing the MW-assisted reaction to that performed under conventional heating, using the analogous drying oven conditions and non-contact temperature measurements described above for acetophenone loading. Support-bound acetophenone **7** was selected as the substrate for optimization studies (Table 2). We found that a wide variety of substituted benzaldehydes were reactive with **7** under the following spatially addressed, Claisen–Schmidt condensation conditions: 6.0 μL aliquot of 1.0 M benzaldehyde and 1.5 N NaOH in 50% aq EtOH, 10 min. We chose *p*-anisaldehyde (**8**) as a condensation partner for further optimization studies, as this substrate was found to react to give chalcone product **9** at a rate that was convenient for repeated analyses (e.g., entry 1, 22% conversion to **9** after 10 min at room temperature). Again, macroarray spots of 0.3 cm^2 area were examined. Conversion and yield of chalcone **9** were determined after TFA vapor compound cleavage from the support (see Section 4 for full details of the cleavage protocol).

Similar to our observations for acetophenone **6** loading, conversion to chalcone product **9** increased steadily with increasing temperature using conventional heating and one application of anisaldehyde (**8**) (entries 1–4). Application of a second aliquot of anisaldehyde (**8**) and heating again at either 80 °C or 120 °C were observed to increase conversion (entries 5 and 6); however, substantial byproducts appeared and the yield of chalcone **9** was diminished at the higher temperature. MW-assisted conditions (500 W) with one application of anisaldehyde (**8**) (entry 7) gave similar conversions to chalcone product **9** as conventional heating in the oven at 40 °C (entry 2).[25] Here, as expected, heating to 40 °C using either the MW reactor or oven gave similar results. Again, the use of the Pyrex dish did not significantly impact conversion for the MW-assisted reaction (entry 8). Analogous to conventional heating, a double application of anisaldehyde (**8**) in the MW-assisted reaction gave a marked increase in the product conversion (entry 9) that was comparable to double coupling and conventional heating at 80 °C (entry 5). However, the yield of chalcone **9** was slightly reduced. Finally, careful optimization of both heating methods revealed that spotting the anisaldehyde (**8**) solution and heating at 80 °C in the oven three times gave the highest yield and purity of chalcone product **9** (entry 10). Conventional heating methods for the Claisen–Schmidt condensation therefore appear slightly superior for this step in macroarray synthesis.

We next investigated the potential use of hydroxybenzaldehydes, as opposed to hydroxyacetophenones, as the planar support-bound substrate in the Claisen–Schmidt condensation. This approach was attractive because a substantially

Table 2. Optimization of Claisen–Schmidt condensation of support-bound acetophenone **7**



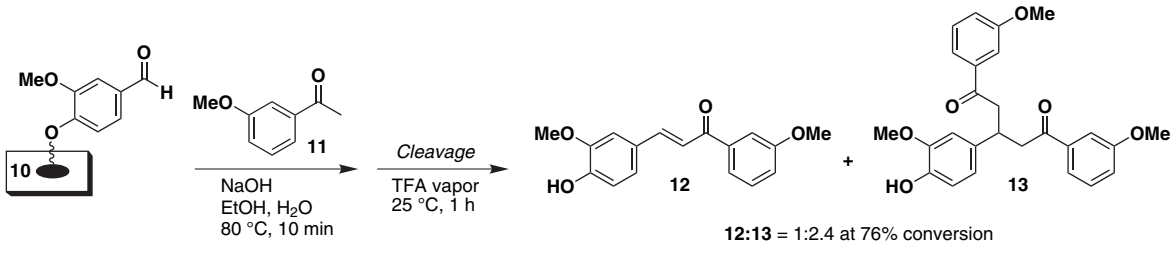
Entry	Conditions (final temperature)	Conversion (%)[a]	Purity of **9** (%)[b]	Yield of **9** (%)[c]
1	Room temperature (22 °C)	22	13	16
2	Oven (40 °C)[d]	46	29	30
3	Oven (80 °C)	81	62	48
4	Oven (120 °C)	90	76	59
5[e]	Oven (80 °C)	95	83	72
6[e]	Oven (120 °C)	97	69	49
7	MW 500 W (40 °C)[f]	45	26	26
8	MW 500 W Pyrex dish (70 °C)	47	24	23
9[g]	MW 500 W Pyrex dish (80 °C)	92	81	62
10[g]	Oven (80 °C)	>99	97	87

[a] Based on residual **6** observed in HPLC spectra and quantified using a UV calibration curve at 254 nm. Error ±3%.
[b] Determined by integration of HPLC spectra with UV detection at 254 nm. Error ±3%.
[c] Quantified using a UV calibration curve at 254 nm. Error ±5%.
[d] Performed in a laboratory incubator.
[e] Anisaldehyde (**8**)/base solution was applied a second time and the support was heated for an additional 10 min.
[f] Support suspended in the middle of the MW reactor cavity using tape to minimize heating due to conduction from a surface.
[g] Anisaldehyde (**8**)/base solution was applied a third time and the support was heated for an additional 10 min.

larger number of substituted hydroxybenzaldehyde building blocks are commercially available relative to substituted hydroxyacetophenones, and could permit the construction of chalcone macroarrays with increased structural complexity. We were pleased to observe that our optimized loading conditions for hydroxyacetophenones described above were directly translatable to hydroxybenzaldehydes, achieving analogous compound loadings (ca. 290 nmol/cm^2). However, problems arose during the subsequent Claisen–Schmidt condensation step between support-bound hydroxybenzaldehydes and solution-phase acetophenones, due to two competing reaction pathways. A representative reaction of support-bound vanillin (**10**) with 3′-methoxyacetophenone (**11**) is shown in Scheme 2. We discovered that the desired Claisen–Schmidt condensation reaction between **10** and **11** was in competition with Michael addition of **11** to the newly formed chalcone. Even after one application of the acetophenone (**11**) solution, three distinct species could be observed after 10 min at 80 °C (in the oven): (1) the starting material vanillin, (2) the target chalcone **12**, and (3) a byproduct **13** (as determined post-cleavage). The latter compound was the major product (2.4:1 **13**:**12** at 76% conversion). Its identity as 1,5-diketone **13** was confirmed by comparison to an authentic sample of **13** that was synthesized and characterized separately (see Section 4). Further optimization of this reaction to give chalcone **12** selectively is ongoing in our laboratory.

The side reaction to generate diketone **13**, while initially unwanted, proved fortuitous. By spotting vanillin-derived support **10** with acetophenone **11** and heating four times in succession (80 °C in the oven, 10 min each), we were able to drive the reaction predominantly to the 1,5-diketone product **13** (88% conversion). In our previous work, we had already demonstrated the versatility of the chalcone scaffold for the generation of second-generation heterocyclic macroarrays.[19] We sought to use this new reaction pathway to our advantage for the construction of small molecule macroarrays with increased structural complexity. Thus, we submitted support-bound 1,5-diketones to a variety of reaction conditions to explore their reactivity in macroarray synthesis.

Synthesis of triarylpyridine macroarrays. Diketones such as **13** have been used previously as precursors to 2,4,6-triarylpyridines.[29,30] Triarylpyridines have found wide use as building blocks for supramolecular chemistry[31] and as chemosensors,[32] and the development of efficient methods to generate this class of compounds has attracted considerable interest. Traditional syntheses of triarylpyridines involving acetophenones and benzaldehydes are low yielding, due to



Scheme 2. Reaction of support-bound vanillin **10** gives two products (**12** and **13**).

the intermediate dihydropyridine reducing the intermediate chalcone.[33] To alleviate this unwanted side reaction, Kröhnke developed an elegant alternative utilizing pyridinium salts.[29] Recent reports of MW-assisted and solid-phase synthetic routes to triarylpyridines from chalcone precursors[34,35] inspired us to attempt their synthesis from support-bound diketones (e.g., compound **14** in Scheme 3). We chose to examine MW-assisted reaction conditions with **14** first to establish if the chemistry was feasible. Ammonium acetate (NH_4OAc) has been used frequently in conjunction with acetic acid in this reaction; however, we believed that the acid-cleavable linker on the macroarray could be unstable under these conditions, especially at elevated temperatures. Instead, we chose to use a neutral, concentrated solution (3 M) of NH_4OAc in water for this condensation reaction.

Our initial screen of MW-assisted reaction conditions to generate 2,4,6-triarylpyridine **15** from support-bound diketone **14** revealed that the reaction proceeded best when the entire membrane was submerged in the aq NH_4OAc solution, that is, under blanket-type reaction conditions. To examine reactions on small sections of support **14** (e.g., several punched-out spots), we found that performing the reaction in sealed 10 mL glass reaction vessels in a CEM Explorer monomodal MW system was most convenient.[36] These sealed-tube MW reaction conditions had two positive attributes: they permitted (1) automated temperature control during the MW reaction and (2) heating over the boiling point of the solvent (i.e., 100 °C for water). The latter feature was important, as high temperatures were required for this reaction to proceed. Different temperatures were evaluated (120–180 °C) over 20 min reaction times. We found that 160 °C afforded the highest purity of the triarylpyridine product **16r** product (82%), as compared to the 70% purity achieved at either 120 °C or 180 °C (as determined post-cleavage).[37] We were pleased to observe that the cellulose support was physically stable under these more forcing reaction conditions.

For the synthesis of full triarylpyridine macroarrays (40 spots), we found that the standard, 10 mL glass MW reaction tubes were not large enough to accommodate the planar support (6 cm×15 cm, rolled into a tube). Instead, using a 70 mL Teflon/polyetheretherketone (PEEK) reaction vessel (shown in Fig. 2) in the Milestone MW multimode reactor proved more suitable for full macroarray synthesis. The temperature of the MW-assisted reaction could be controlled using a fiber-optic probe threaded into the vessel. In general, MW-assisted conditions directly translated from the monomodal to multimodal MW systems, if the reactions were performed under temperature control.[38] The only minor change we incorporated was a slower 10 min ramp time to 160 °C in the Milestone MW reactor relative to the CEM MW reactor, in order to protect the integrity of the reusable Teflon inserts. The total reaction time was 1 h, consisting of a 10 min ramp, a 20 min hold time, and a 30 min cool down period (no MW) to 70 °C, after which the vessel could be safely opened to retrieve the membrane.

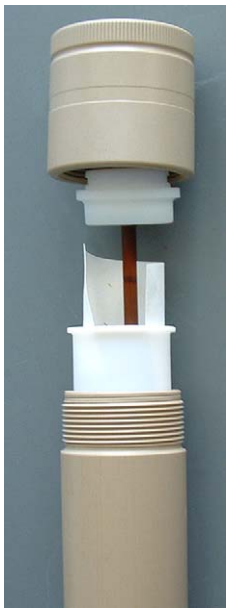
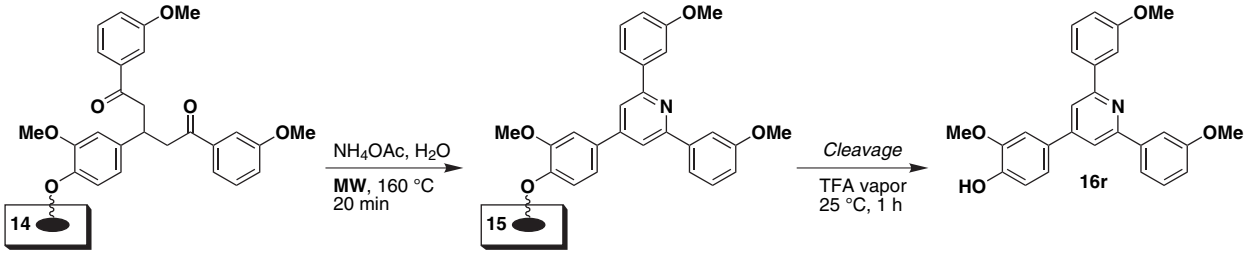


Figure 2. Reaction format for MW-assisted macroarray reactions. Shown is a macroarray that was rolled and placed into a 70 mL Milestone Teflon/PEEK reaction vessel. Reactions are performed in reusable Teflon inserts (white) that fit inside the PEEK outer casing (beige). A ceramic sheath in the center (brown) houses a fiber-optic probe for direct temperature measurement during the reaction. Vessel dimensions: 12 cm tall with an internal diameter of 3 cm.

In analogy to the optimization studies above, we also examined this reaction under conventional heating conditions. Heating the sealed polymeric vessel to 160 °C, however, was problematic for two reasons. First, the outer PEEK vessel acts as a highly efficient insulator; for example, in the MW-assisted triarylpyridine condensation reaction, the temperature of this outer vessel was measured to be only 120 °C (using a non-contact IR thermometer) even after the contents had been heated at 160 °C for 20 min (as determined by using a fiber-optic probe). This insulation made it extremely difficult to mimic the MW temperature gradient inside the vessel using an external, conventional heating source (e.g., an oil bath). Matching heating gradients is a frequent challenge when performing comparisons of conventionally heated processes with MW-assisted variants.[18a] Second, we

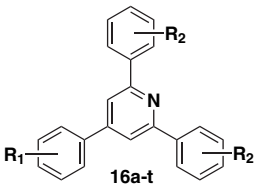


Scheme 3. Representative MW-assisted synthesis of 2,4,6-triarylpyridines (**16**) from support-bound diketones (**14**).

had safety concerns about the prolonged conventional heating of closed vessels for macroarray synthesis. Thus, we examined this reaction at 80 °C under atmospheric conditions in the drying oven. These conditions gave lower conversion: for example, triarylpyridine **16r** was generated in only 55% conversion when membrane **14** was heated in aq NH_4OAc in the oven at 80 °C for 1 h. However, complete conversion (>99%) and high purity product (89%) were obtained after 12 h at 80 °C in the oven. Therefore, application of MW heating to this condensation reaction provides a clear advantage over conventional heating in terms of reaction time. These benefits are achievable, in part, because the MW reactor and specialized MW vessels allow the safe and reproducible heating of solvents over their boiling points.[18] Indeed, we believe that this is one area of chemistry where MW-assisted reactions are poised to make a large impact.

We used the optimized MW-assisted method developed above to construct a 40-member macroarray of symmetrical 2,4,6-triarylpyridines (**16**) using four hydroxybenzaldehyde and 10 acetophenone building blocks. Starting from linker-derived support **4**, the macroarray was synthesized and the array compounds were cleaved in only 12 h (Table 3). Analysis of 20 randomly selected macroarray members (50% of the library) by LC–MS indicated good to excellent product purities (63%–91%). Purities were largely substrate dependent, with the lowest purities occurring when a fluoro- or methoxy-substituent was in the *para* position of the incoming acetophenone. We speculate that this reduction in purity could be due to positive mesomeric effects deactivating the chalcone for subsequent Michael addition. Two triarylpyridines (**16l** and **16r**) were selected for synthesis in solution as controls in order to determine representative overall reaction yields on the triarylpyridine macroarray. Examination of calibration curves generated for **16l** and **16r** showed product yields of 78% and 88%, respectively, after cleavage of these compounds from the macroarray. These results demonstrate that macroarray synthesis represents a rapid and high yielding approach for the generation of symmetrical 2,4,6-triarylpyridines (**16**).

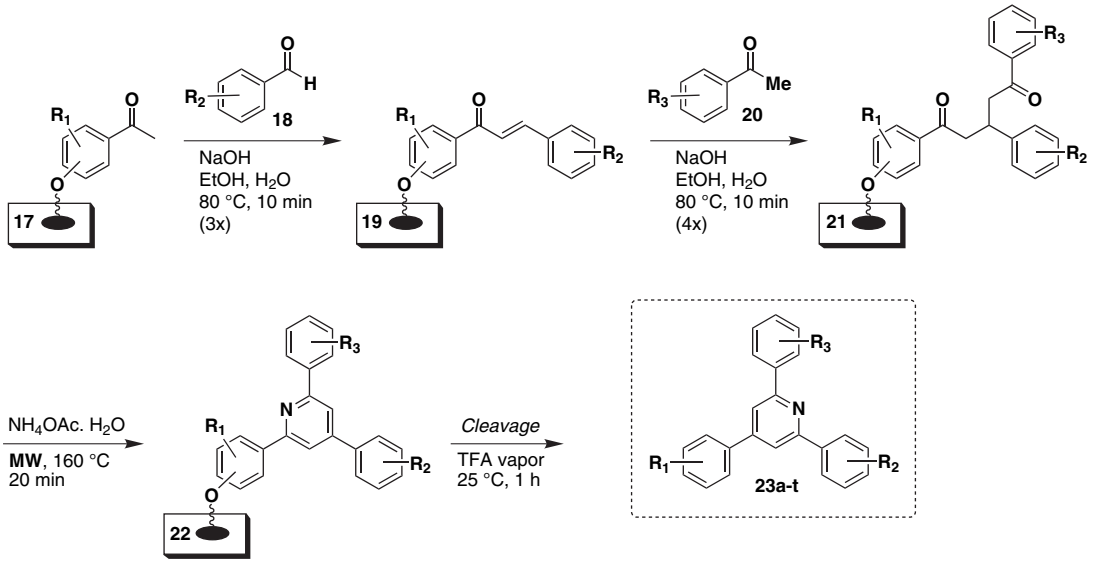
Table 3. Purity data for selected members of symmetrical 2,4,6-triarylpyridine macroarray **16**



Entry	Compound	R_1	R_2	Purity (%)[a]
1	**16a**	3-OH	3-F	85
2	**16b**	3-OH	4-F	75
3	**16c**	3-OH	3-Br	84
4	**16d**	3-OH	3-CF_3	85
5	**16e**	3-OH	4-CF_3	83
6	**16f**	4-OH	H	91
7	**16g**	4-OH	4-Br	83
8	**16h**	4-OH	3-MeO	86
9	**16i**	4-OH	3,4-MeO	63
10	**16j**	4-OH	3-CF_3	85
11	**16k**	4-OH, 3-OMe	3-F	76
12	**16l**	4-OH, 3-OMe	3-Br	78
13	**16m**	4-OH, 3-OMe	4-Br	84
14	**16n**	4-OH, 3-OMe	3-OMe	90
15	**16o**	4-OH, 3-OMe	4-OMe	63
16	**16p**	3-OH, 4-OMe	3-F	75
17	**16q**	3-OH, 4-OMe	4-F	67
18	**16r**	3-OH, 4-OMe	3-OMe	88
19	**16s**	3-OH, 4-OMe	3-CF_3	73
20	**16t**	3-OH, 4-OMe	4-CF_3	74

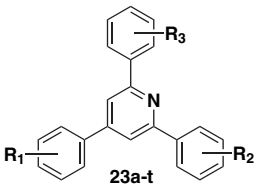
[a] Crude purity determined by integration of the HPLC trace with UV detection at 254 nm. Error ±3%.

Further examination of triarylpyridine synthesis on our planar support platform revealed that unsymmetrical triarylpyridines were also accessible. Starting with support-bound acetophenones, rather than benzaldehydes, we found that a far greater diversity of triarylpyridine products (**23**) could be achieved, as the products could be constructed in a step-wise manner (Scheme 4). In an initial step, bound acetophenone building blocks (**17**) could be reacted with a series of benzaldehydes (**18**) to form chalcone macroarrays (**19**),



Scheme 4. Synthesis of unsymmetrical 2,4,6-triarylpyridine macroarray **23**.

Table 4. Purity data for selected members of unsymmetrical 2,4,6-triarylpyridine macroarray **23**



23a-t

Entry	Compound	R_1	R_2	R_3	Purity (%)[a]
1	**23a**	4-OH	H	4-Br	81
2	**23b**	4-OH	H	4-CF_3	79
3	**23c**	4-OH	3-Br	3-CF_3	80
4	**23d**	4-OH	3-Br	3-OMe	75
5	**23e**	4-OH	4-OMe	4-Br	70
6	**23f**	4-OH	4-Cl	3-OMe	67
7	**23g**	3-OH	H	3-OMe	72
8	**23h**	3-OH	H	3-CF_3	81
9	**23i**	3-OH	3-Br	4-Br	78
10	**23j**	3-OH	3-Br	4-CF_3	76
11	**23k**	3-OH	4-OMe	H	76
12	**23l**	3-OH	4-Cl	4-Br	76
13	**23m**	3-OH	4-Cl	3-CF_3	80
14	**23n**	3-OH	4-OMe	3-OMe	74
15	**23o**	4-OH, 3-OMe	H	3-OMe	70
16	**23p**	4-OH, 3-OMe	3-Br	4-Br	79
17	**23q**	4-OH, 3-OMe	3-Br	4-CF_3	82
18	**23r**	4-OH, 3-OMe	4-OMe	H	70
19	**23s**	4-OH, 3-OMe	4-OMe	3-CF_3	77
20	**23t**	4-OH, 3-OMe	4-Cl	3-CF_3	84

[a] Crude purity determined by integration of the HPLC trace with UV detection at 254 nm. Error ±3%.

using the optimized reaction conditions described above. In a subsequent step, the chalcones were treated with a second set of acetophenones to generate diketones (**21**). Here, we utilized conventional heating conditions to achieve full conversion to the diketones (see above). Finally, diketones (**21**) could be condensed with NH_4OAc using our optimized MW-assisted conditions in the Milestone MW reactor to give triarylpyridine arrays (**22**). This step-wise synthesis is noteworthy, as it allows for control of the substituents on each phenyl ring of the triarylpyridine (**23**), and thus is amenable to the construction of triarylpyridine macroarrays (**23**) of high structural complexity.

To evaluate the feasibility of this reaction strategy in macroarray synthesis, we constructed a 60-member macroarray of unsymmetrical 2,4,6-triarylpyridines (**22**) using three hydroxyacetophenone, four benzaldehyde, and five acetophenone building blocks (Table 4). Macroarrays of this size were readily constructed and cleaved in less than one day. Analysis of a random sampling of a third of the library members by LC–MS showed moderate to good purities (67%–84%). Overall, the ease of macroarray synthesis, along with the wide availability of numerous acetophenones and benzaldehydes, renders this method a powerful new technique for the rapid synthesis of 2,4,6-triarylpyridines (**23**).

3. Conclusions and outlook

We have performed a systematic optimization of the MW-assisted SPOT-synthesis process using chalcone macroarrays as our primary focus. Each step in the small molecule macroarray synthesis was critically examined and streamlined, including: (1) the synthesis of the linker-derivatized support, (2) the loading of initial building blocks, and (3) the Claisen–Schmidt condensation to give the chalcones. This work allowed for a dramatic reduction in synthesis time required to generate the linker-derivatized support **4** (by over 15 h); improved accessibility of this support will advance the examination of additional library pathways on the macroarray platform. Our optimization study also revealed new modes of reactivity for support-bound benzaldehydes and acetophenones used in chalcone macroarray synthesis—this discovery permitted straightforward production of a set of novel 2,4,6-triarylpyridine macroarrays, **15** and **22**, respectively.

This study also inspired a detailed comparison of MW heating versus conventional heating in macroarray synthesis. For both of the steps in chalcone synthesis, conventional heating methods gave equal, if not slightly improved, results relative to MW-assisted conditions. However, we found that for reactions that require temperatures higher than the boiling points of the solvents, i.e., in triarylpyridine synthesis, the use of the MW reactor provided more convenient and safe access to these temperatures and pressures relative to conventional heating. These results indicate that, while small molecule macroarray synthesis benefits from MW-assisted reactions, the technique is not fully reliant on them. This discovery is important, as it broadens the availability of our synthesis platform to researchers who may not have access to a commercial MW reactor.

Overall, this study has extended the scope of the small molecule macroarray synthesis technique and streamlined the construction process. The stage is now set for the systematic exploration of the chemical reactions and screening formats that are compatible with the small molecule macroarray platform. These studies are underway in our laboratory. In the future, the synthetic route to 2,4,6-triarylpyridines (**16** and **23**) described herein could be developed further to generate arrays of different, and potentially useful, molecules. For example, terpyridines and bipyridines, which have found widespread application in chemical sensors[39] and organic light emitting diodes,[40] could be synthesized readily using this method through the incorporation of acetyl pyridine building blocks. The planar array format could facilitate a rapid screening of their sensing or photophysical properties while bound to the support.[41] Current efforts in our laboratory are focused broadly in this area and will be reported in due course.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer in deuterated solvents at 300 MHz and 75 Hz, respectively. Chemical shifts are reported in parts per million (ppm, δ) using tetramethyl silane (TMS) as a reference (0.0 ppm). Coupling constants are reported in Hertz. LC–MS (ESI) was obtained using a Shimadzu LCMS-2010 (Columbia, MD) equipped with two pumps (LC-10ADvp), controller (SCL-10Avp), autoinjector (SIL-10ADvp), UV diode array detector (SPD-M10Avp), and single quadrupole

analyzer (by electrospray ionization, ESI). The LC–MS is interfaced with a PC running the Shimadzu LC–MS solution software package (Version 2.04 Su2-H2). A Supelco (Bellefonte, PA) 15 cm×2.1 mm C-18 wide-pore reverse phase column was used for all LC–MS work. Standard reverse phase HPLC conditions for LC–MS analyses were as follows: flow rate=200 μL/min; mobile phase A=0.4% formic acid; mobile phase B=0.2% formic acid in acetonitrile. HPLC analyses were performed using a Shimadzu HPLC equipped with a single pump (LC-10ATvp), solvent mixer (FCV-10ALvp), controller (SCL-10Avp), autoinjector (SIL-10AF), and UV diode array detector (SPD-M10Avp). A Shimadzu Premier 25 cm×4.6 mm C-18 reverse phase column was used for all HPLC work. Standard reverse phase HPLC conditions were as follows: flow rate=1.0 mL/min; mobile phase A=0.1% trifluoroacetic acid (TFA); mobile phase B=0.1% TFA in acetonitrile. UV detection at 254 nm was used for all HPLC analyses. Compound purities were determined by integration of the peaks in HPLC traces measured at this wavelength.

Attenuated total reflectance (ATR)-IR spectra were recorded with a Bruker Tensor 27 spectrometer, outfitted with a single reflection MIRacle Horizontal ATR by Pike Technologies. A ZnSe crystal with spectral range 20,000–650 cm^{-1} was used. UV spectra were recorded using a Cary 50 Scan UV–Vis spectrometer running Cary WinUV 3.00 software. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (E-5715-7, Merck). All reported melting points are uncorrected. Reactions subjected to oven heating were performed on a pre-heated bed of sand in a VWR 13OOU drying oven. Temperature measurements of planar surfaces were acquired using a Craftsman (model # 82327) non-contact IR thermometer with an error of ±2.5%. An Eppendorf pipette with a calibrated range between 0.5 μL and 10.0 μL outfitted with disposable plastic tips was used to 'spot' or apply reagents onto the membrane in a spatially addressed manner.

4.2. Microwave synthesis instrumentation

MW reactions involving macroarrays of greater than five spots were performed in a Milestone MicroSYNTH Labstation multimode MW synthesis reactor.[24] This instrument is equipped with a continuous power source (1000 W max) and interfaced with an Ethos MicroSYNTH Lab Terminal PC running EasyWave reaction monitoring software. Using this reactor system, MW irradiation can be applied to reactions using either power (wattage) control or temperature control. The MW reactor is equipped with a fiber-optic temperature sensor that allows direct monitoring of the internal temperature of reaction vessels, and an infrared sensor (installed in the side wall of the reactor cavity) that can monitor the surface temperature of reaction vessels inside the cavity. Solvent depths of ca. 1 cm in the reaction vessel are required for accurate temperature monitoring using the submerged fiber-optic temperature probe.

MW reactions involving macroarrays of less than five spots were performed in a CEM Discover MW reactor.[36] This monomode MW reactor is interfaced with a laptop PC running CEM ChemDriver software (v. 3.5.4) and is equipped with an autosampler (CEM Explorer) capable of holding 24×10 mL thick-walled Pyrex tubes. An external IR sensor is used to monitor the temperature. For each MW-assisted reaction, the ramp time to reach the target temperature was set to 40 min. However, in all of the reactions studied herein, the Discover MW reactor required no more than 2 min to reach the target temperature. Once the target temperature is reached, the MW system automatically starts to count down the hold time at this temperature. A non-invasive pressure sensor is used to monitor the pressure. The upper pressure limit was set to 280 psi: note, this pressure limit was never reached during the reactions outlined herein.

MW-assisted solution-phase reactions were performed in the Milestone MicroSYNTH MW reactor using specialized 70 mL Teflon/PEEK vessels (shown in Fig. 2). Reactions are performed in Teflon inserts that fit inside the PEEK outer casing that is designed to withstand temperatures of up to 200 °C and pressures of up to 280 psi. The internal temperature of the vessel can be monitored using a fiber-optic temperature sensor in a protective ceramic sheath. At pressures above the 280-psi limit, the vessels are designed to release excess pressure by venting and then reseal themselves. No evidence for the venting was observed during the course of the reactions described herein.

4.3. Materials

All reagents were purchased from commercial sources (Alfa-Aesar, Aldrich, and Acros) and used without further purification. Solvents were purchased from commercial sources (Aldrich and J. T. Baker) and used as obtained, with the exception of dichloromethane (CH_2Cl_2), which was distilled over calcium hydride immediately prior to use. Planar cellulose membranes (Whatman 1Chr chromatography paper, 20×20 cm^2) were purchased from Fisher Scientific and stored in a desiccator at room temperature until ready for use.

4.4. Methods

4.4.1. Preparation of cellulose supports.

4.4.1.1. Representative synthesis of amino cellulose support (3). The cellulose amination procedure was adapted from a literature protocol.[16c] Spots were marked on a 15 cm×18 cm sheet of Whatman 1Chr paper (**1**) at distances 1.4 cm apart using a #2 lead pencil. In this format, 120 spots (0.3 cm^2) can be accommodated on a single sheet without any detectable cross contamination. The sheet was immersed in 100 mL of 20% TFA in CH_2Cl_2 for 10 min in a covered 2.6 L Pyrex dish. The acid solution was decanted carefully away from the sheet. The sheet was washed by adding 60 mL of CH_2Cl_2, allowing the sheet to soak for 5 min, and then decanting the CH_2Cl_2. This washing procedure was repeated an additional time, then the membrane was dried under a stream of air for 20 min. TsCl (19.0 g, 50 mmol) was dissolved in 50 mL pyridine in a covered 2.6 L Pyrex dish. The solution was swirled for 5 min, after which the acid-swelled sheet was added. The sheet was swirled for 1 h, after which the TsCl solution was decanted. The support was washed by immersion in two consecutive baths of EtOH (100 mL, 5 min each), followed by immersion in CH_2Cl_2 for 5 min. Tosylated support **2** was dried under a stream of N_2 for 20 min.

A 60 mL aliquot of 4,7,10-trioxa-1,13-tridecanediamine was added to a covered 2.6 L Pyrex dish and heated in an oven to 80 °C. Tosylated support **2** was immersed in the pre-heated amine solution and heated for 30 min at 80 °C. The amine solution was carefully decanted from the paper. The support then was washed by adding and then decanting 70 mL portions of DMF, EtOH, 1.0 N NaOH, H_2O, EtOH (2×), and CH_2Cl_2 (5 min in each wash). Amino support **3** was dried under a stream of N_2 for 10 min.

4.4.1.2. Representative Fmoc quantitation protocol on cellulose supports. The amine loading of support **3** was quantified according to standard UV Fmoc analysis procedures.[22] A spot (6 mm diameter) was punched from amino support **3** using a desktop hole punch and immersed in 200 μL of 0.60 M *N*-(9-fluorenylmethoxycarbonyloxy) succinimide (Fmoc–OSu) in DMF for 2 h. The spot was washed with 10 mL of EtOH, 10 mL of acetone, and 10 mL of CH_2Cl_2. The spot was allowed to air dry for 20 min in a glass vial, after which 960 μL of DMF and 40 μL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were added. The spot was swirled in this mixture for 30 s and then allowed to stand for 15 min. The mixture was swirled again for 30 s, then 100 μL of this solution was removed and diluted with 2.0 mL of DMF. The solution was swirled again for 30 s. The absorbance was read at 296 nm (ε_{296}=9500 M^{-1} cm^{-1}) in a quartz cuvette. The value was multiplied by 21 to account for the dilution. Loadings of 1.0–10 μmol/cm^2 were obtained using this method. Longer tosylation reaction times gave higher levels of functionalization (e.g., 1 h= 3.8 μmol/cm^2, 12 h=10 μmol/cm^2).

4.4.1.3. Representative synthesis of Wang-type linker functionalized cellulose support (4). 4-Formylphenoxyacetic acid[19] (5.40 g, 30.0 mmol), diisopropylcarbodiimide (DIC, 4.7 mL, 30.0 mmol), *N*-hydroxysuccinimide (HOSu, 3.45 g, 30.0 mmol), NEt_3 (4.2 mL, 30.0 mmol), and DMF (50 mL) were combined in a 2.6 L Pyrex dish. The dish was covered and swirled for 30 min at room temperature. A 15 cm×18 cm sheet of amino cellulose support (**3**) was added. The dish was covered again and the mixture was swirled at room temperature for 2 h on a rotary shaker. The coupling solution was decanted. The support was then washed by adding and then decanting 70 mL portions of DMF (2×), EtOH (2×), and CH_2Cl_2 (5 min in each wash). The aldehyde-derivatized support was dried under a stream of N_2.

A 100 mL aliquot of 1.0 M $NaBH_4$ in 1.0 M aq NaOH was added to the aldehyde-derivatized support. The mixture was swirled for 20 min, after which the $NaBH_4$ solution was decanted. The support was washed by adding and then decanting 70 mL portions of H_2O (2×), EtOH (2×), and CH_2Cl_2 (5 min in each bath). The benzyl alcohol-derivatized support (**4**) was dried under a stream of N_2. To approximate the linker loading, the amount of residual amine on support **4** was measured by Fmoc quantitation as described above, except an 11-fold dilution was used instead. Residual amine loadings on support **4** were found to be ca. 600–800 nmol/cm^2.

4.4.2. Preparation of small molecule macroarrays.

4.4.2.1. Preparation of chloride-derivatized support (5). A 15 cm×18 cm sheet of benzyl alcohol-derivatized support **4** was immersed in a solution of $SOCl_2$ (10 mL, 137 mmol) in CH_2Cl_2 (40 mL) in a 2.6 L Pyrex dish. The dish was covered and swirled for 30 min at room temperature. The $SOCl_2$ solution was carefully decanted, and the support was washed by immersing and decanting 100 mL portions of CH_2Cl_2 (3×, 2 min in each wash). The chloride-derivatized, or 'activated linker', support (**5**) was placed under a stream of N_2 to dry for 10 min and then used immediately in the next step.

4.4.2.2. Synthesis of hydroxybenzaldehyde/hydroxyacetophenone macroarrays (10 and 17). Solutions of various hydroxyacetophenones or hydroxybenzaldehydes (2.0 M) and KO*t*Bu (2.0 M) were prepared in anhydrous DMF in 4 mL vials and quickly sealed with Teflon caps. Aliquots (3.0 μL) of these solutions were applied to the appropriate spots on a 15 cm×18 cm sheet of activated linker support **5**. The spotted support then was placed on a bed of pre-heated sand in a drying oven set to 80 °C for 10 min. The spotting and heating steps were repeated (1×). The support was removed and washed by adding and decanting 100 mL portions of 1.0 N aq NaOH, H_2O, EtOH (2×), and CH_2Cl_2 (5 min in each wash). The resulting hydroxybenzaldehyde (**10**) or hydroxyacetophenone macroarrays (**17**) were dried under a stream of air for 20 min.

4.4.2.3. Representative synthesis of chalcone macroarray (19). A ca. 300–500 μL solution of substituted benzaldehyde (**18**, 1.0 M) and NaOH (1.5 N) was prepared in 50% aq EtOH in a 4 mL vial and sealed with a Teflon cap. (A 0.5 M solution of substituted benzaldehyde (**18**) in 1.5 N NaOH in 50% aq EtOH can also be substituted in cases where preparing a 1.0 M solution of benzaldehyde substrates is impossible due to solubility reasons. For example, 4-chlorobenzaldehyde and *m*-anisaldehyde require these alternate conditions). A 6.0 μL aliquot of this solution was applied to the appropriate spots on a 15 cm×18 cm sheet of hydroxyacetophenone macroarray **17**. The support then was placed on a bed of pre-heated sand in a drying oven set to 80 °C for 10 min. The spotting and heating steps were repeated (2×). The support was removed and washed by adding and decanting 100 mL portions of 1% aq AcOH, DMSO, EtOH (2×), and CH_2Cl_2 (5 min in each wash). The resulting chalcone macroarray (**19**) was dried under a stream of air for 20 min.

4.4.2.4. Representative synthesis of diketone macroarrays (15 and 22). A ca. 300–500 μL solution of substituted acetophenone (1.0 M) and NaOH (1.5 N) was prepared in 66% aq EtOH in a 4 mL vial and sealed with a Teflon cap. (A 0.5 M solution of acetophenone in 1.5 N NaOH in 66% aq EtOH can be substituted in cases where preparing a 1.0 M solution of acetophenone substrate is impossible due to solubility reasons. For example, 4′-bromoacetophenone and 3′-bromoacetophenone require these alternate conditions). A 6.0 μL aliquot of this solution was applied to the appropriate spots on hydroxybenzaldehyde macroarray **10** to generate symmetrical diketones or chalcone macroarray **19** to generate unsymmetrical diketones. The support was placed on a bed of pre-heated sand in the oven set to 80 °C for 10 min. The spotting and heating steps were repeated (3×). The membrane was removed and washed by adding and decanting 100 mL portions of 1% aq

AcOH, DMSO, EtOH (2×), and CH_2Cl_2 (5 min in each wash). The resulting symmetrical diketone (**15**) and unsymmetrical diketone macroarrays (**22**) were dried under a stream of air for 20 min.

4.4.2.5. Representative synthesis of triarylpyridine macroarrays (16 and 23). A 3.1 M stock solution of aq NH_4OAc was prepared by dissolving NH_4OAc (77.08 g, 1.0 mol) in 250 mL of water. A dried diketone macroarray (**15** or **22**) measuring 15 cm×6 cm (40 spots) was gently rolled into a tube and placed inside a 70 mL Teflon/PEEK MW reaction vessel. A 50 mL portion of the aq NH_4OAc solution was added to the vessel, and the vessel was sealed. Using this method, multiple macroarrays could be prepared simultaneously using multiple Teflon/PEEK reaction vessels. The vessels were placed on a rotating base inside the Milestone MW reactor, and the fiber-optic probe was introduced into one of the vessels. Using a maximum wattage of 800 W, the reaction mixtures were heated from room temperature to 160 °C over 10 min, held at 160 °C for 20 min, and allowed to cool for 30 min. The supports were removed, unrolled, and washed by adding and decanting 100 mL portions of H_2O, EtOH (2×), and CH_2Cl_2 (5 min in each wash). The resulting triarylpyridine macroarrays (**16** and **23**) were dried under a stream of N_2 for 20 min.

4.4.2.6. TFA vapor compound cleavage procedure. Compound spots were punched out using a standard desktop hole punch (0.6 cm diameter) and placed in individual 4 mL vials. A 10.0 mL portion of TFA was added to the bottom of a glass vacuum desiccator. The vials containing the spots were placed on a perforated ceramic platform in the desiccator that was situated 7 cm above the TFA. The desiccator was evacuated to 60 mm Hg over a 10 min period. The desiccator was disconnected from the vacuum, sealed, and allowed to stand for an additional 50 min at room temperature. The vials were removed from the desiccator and 1.0 mL of CH_3CN was added to each vial. The vials were sealed and shaken for 15 min, after which the spots were removed and the CH_3CN was concentrated under reduced pressure. The resulting residue was dissolved in 150 μL 50% aq CH_3CN and analyzed by HPLC.

4.4.3. Preparation of solution-phase standard compounds.

4.4.3.1. 4′-Hydroxy-4-methoxychalcone (9). 4′-Hydroxyacetophenone (**6**, 1.63 g, 12 mmol) and *p*-anisaldehyde (**8**, 1.45 mL, 12 mmol) were dissolved in MeOH (30 mL) in a 70 mL Teflon Milestone MW reaction vessel. A 2 mL aliquot of 50% (w/v) aq NaOH was added, and the solution was stirred until the reactants had dissolved fully. The reaction vessel was closed tightly and heated with stirring in a Milestone MW reactor from room temperature to 150 °C over 15 min, held at 150 °C for 20 min, and allowed to cool to room temperature over 20 min. The reaction mixture was poured over ca. 30 g of ice and acidified to pH 1.0 with 1.0 N HCl, forming a yellow precipitate. This solid was isolated by filtration and recrystallized from MeOH to afford 900 mg of golden crystals of **9** (30% yield). TLC: R_f=0.25 (hexane/EtOAc 3:2); melting point: 185–188 °C; ^{1}H NMR: (300 MHz, DMSO-d_6) δ 10.35 (br s, 1H), 8.05, 6.89 (AA′XX′, $J_{AA'}=J_{XX'}=2.4$, $J_{AX}=8.6$, $J_{AX'}=0.2$ Hz, 4H), 7.92, 7.00 (AA′XX′, $J_{AA'}=J_{XX'}=2.4$, $J_{AX}=8.6$, $J_{AX'}=0.2$ Hz, 4H), 7.80, 7.60 (AB peak, J=15.5 Hz, 2H); ^{13}C NMR: (75 MHz, DMSO-d_6) δ 187.7, 162.7, 161.8, 143.3, 131.7, 131.2m, 130.0, 128.207, 120.3, 116.0, 115.0, 56.0; IR (ATR): 3200, 2990, 1643, 1602, 1562, 1512, 1430, 1352, 1286, 1223, 1165, 1046 cm^{-1}; ESI-MS: expected, 254.1; observed, *m*/*z* 254.8 [M+H$^+$].

4.4.3.2. 3,3′-Dimethoxy-4-hydroxychalcone (12). 3-Methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)-oxy]-benzaldehyde (hereafter called THP-vanillin,[42] 500 mg, 2.1 mmol), 3′-methoxyacetophenone (315 mg, 2.1 mmol), NaOH (84 mg, 2.1 mmol), and 5.0 mL of MeOH were combined in a 20 mL round-bottom flask equipped with a magnetic stirring bar and stirred for 12 h at room temperature. Acetyl chloride (0.5 mL, 7.0 mmol) was then added quickly to the flask. After stirring for 10 min, the mixture was poured into 20 mL of 1.0 N HCl and 20 mL of CH_2Cl_2. The solution was extracted twice with CH_2Cl_2. The organic phases were combined and extracted with 40 mL of 1.0 N NaOH. The aq phase was washed twice with CH_2Cl_2, acidified to pH 1.0 with 1.0 N HCl, and then extracted with 20 mL of CH_2Cl_2 (2×). The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to a brown oil. The oil was purified by flash silica gel chromatography (CH_2Cl_2/EtOAc 4:1) to give 120 mg of **12** as a yellow oil (20% yield). TLC: R_f=0.69 (CH_2Cl_2/EtOAc 4:1); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.78 (d, J=15.6 Hz, 1H), 7.57 (dt, J=7.7, 1.3 Hz, 1H), 7.52 (dd, J=4, 1.3 Hz), 7.37 (t, J=7.9 Hz, 1H), 7.34 (d, J=15.6 Hz, 1H), 7.18 (dd, J=8.2, 2.0 Hz, 1H), 7.10 (br s, 1H), 7.09 (ddd, J=8.2, 2.6, 1.0 Hz, 1H), 6.94 (d, J=8.2 Hz, 1H), 6.30 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 190.6, 160.1, 148.7, 147.2, 145.6, 140.1, 129.7, 127.6, 123.7, 121.2, 119.9, 119.1, 115.2, 113.2, 110.4, 56.2, 55.7; IR (ATR): 3394, 3055, 2940, 2836, 1657, 1577, 1513, 1487, 1465, 1452, 1431, 1376, 1321, 1200, 1174, 1158, 1123 cm^{-1}; ESI-MS: expected, 284.1; observed, *m*/*z* 285.0 [M+H$^+$].

4.4.3.3. 1,5-Di-(3-methoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)-1,5-pentanedione (13). THP-vanillin[42] (500 mg, 2.1 mmol), 3′-methoxyacetophenone (630 mg, 4.2 mmol), and NaOH (168 mg, 4.2 mmol) were ground together in a mortar and pestle for 30 min. The resulting yellow paste was allowed to stand at room temperature for 12 h. The paste then was dissolved in 20 mL of 1.0 N HCl and 20 mL of CH_2Cl_2. The mixture was stirred for 1 h, after which the organic phase was separated. The aq phase was extracted two times with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated to give a brown oil. The oil was purified using flash silica gel chromatography (CH_2Cl_2/EtOAc 4:1) to give 30 mg of **13** as a colorless oil (0.5% yield). TLC: R_f=0.72 (CH_2Cl_2/EtOAc 4:1); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.54 (dt, J=8.0, 1.2 Hz, 2H), 7.46 (dd, J=2.5, 1.2 Hz, 2H), 7.35 (t, J=8.0 Hz), 7.09 (ddd, J=8.0, 2.5, 1.2 Hz, 2H), 6.78 (m, 3H), 5.50 (s, 1H), 3.99 (p, J=7.0 Hz, 1H), 3.42, 3.38 (AB component of ABX system, J_{AB}=16.5, $J_{AX}=J_{BX}$=7.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 198.6, 159.8, 146.4, 144.3, 138.4, 135.7, 129.6, 120.8, 119.6, 119.5, 114.5, 112.3, 110.7, 55.9, 55.4, 45.3, 37.2; IR (ATR): 3727, 3703, 3629, 3595, 3054, 1684, 1597, 1583, 1517, 1486, 1465, 1452, 1430, 1361, 1288, 1210, 1160, 1125 cm^{-1}; ESI-MS: expected, 434.2; observed, *m*/*z* 435.1 [M+H$^+$].

4.4.3.4. 2,6-Di-(3-bromophenyl)-4-(4-hydroxy-3-methoxyphenyl)-pyridine (16l). THP-vanillin[42] (500 mg, 2.1 mmol), 3′-bromoacetophenone (836 mg, 4.2 mmol), and NaOH (168 mg, 4.2 mmol) were ground together in a mortar and pestle for 30 min. The resulting orange paste was allowed to stand at room temperature for 1 h. The paste was then transferred to a 70 mL Teflon MW reaction vessel along with a magnetic stirring bar. A 0.5 mL aliquot of acetic acid was added to the reaction vessel, followed by butanol (5.0 mL) and hydroxylamine hydrogen chloride (510 mg, 7.3 mmol). The reaction vessel was closed tightly and heated with stirring in the Milestone MW reactor from room temperature to 170 °C over 10 min, held at 170 °C for 10 min, and allowed to cool to room temperature over ca. 30 min. A 20 mL portion of water was added to the vessel, and the reaction mixture was stirred for 8 h at room temperature. A white solid gradually formed. This solid was filtered to give 86 mg of triarylpyridine **16l** (8% yield). TLC: R_f=0.55 (1% AcOH in CH_2Cl_2). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.31 (t, J=1.8 Hz, 2H), 8.11 (ddd, J=7.8, 1.5, 1.2 Hz, 2H), 7.81, (s, 2H), 7.59 (ddd, J=8.0, 2.2, 1.1 Hz, 2H), 7.40 (t, J=8.0 Hz, 2H), 7.29 (dd, J=8.3, 1.9 Hz, 1H), 7.20 (d, J=1.9 Hz, 1H), 7.08 (d, J=8.3 Hz, 1H), 5.81 (s, 1H), 4.04 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 156.3, 150.8, 147.3, 147.2, 141.7, 132.3, 130.5, 130.3, 125.9, 123.2, 120.9, 117.6, 115.3, 109.6, 56.5; IR (ATR): 3509, 3061, 1601, 1567, 1548, 1518, 1478, 1469, 1442, 1422, 1387, 1369, 1350, 1271, 1241, 1212, 1177, 1120 cm^{-1}; ESI-MS: expected, 509.0; observed, *m/z* 509.9 [M+H$^+$].

4.4.3.5. 2,6-Di-(3-methoxyphenyl)-4-(4-hydroxy-3-methoxyphenyl)-pyridine (16r). Vanillin (1.00 g, 6.57 mmol), 3′-methoxyacetophenone (1.97 g, 6.57 mmol), NH_4OAc (2.00 g, 25.9 mmol), and 30 mL of acetic acid were combined in a 70 mL Teflon MW reaction vessel. A magnetic stirring bar was added to the vessel. The vessel was closed tightly and heated with stirring in the Milestone MW reactor from room temperature to 180 °C over 10 min, held at 180 °C for 20 min, and allowed to cool to room temperature over ca. 30 min. The MW heating sequence was repeated (1×). The reaction mixture was concentrated to an oil under reduced pressure. The oil was dissolved in 50 mL of EtOAc and washed with satd aq $NaHCO_3$ (2×), brine, and H_2O. The organic phase was concentrated under reduced pressure to give a brown oil. The oil was purified by flash silica gel column chromatography (1% AcOH in CH_2Cl_2) to give 65 mg of triarylpyridine **16r** as a colorless oil (2% yield). TLC: R_f=0.26 (1% AcOH in CH_2Cl_2); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.79 (dd, J=2.6, 1.4 Hz, 2H), 7.74 (dt, J=8.0, 1.4 Hz, 2H), 7.42 (t, J=8.0 Hz, 2H), 7.29 (dd, J=8.2, 2.0 Hz, 1H), 7.21 (d, J=2.0 Hz, 1H), 7.07 (d, J=8.2 Hz, 1H), 7.00 (dd, J=8.0, 2.6 Hz, 2H), 5.79 (s, 1H), 4.01 (s, 3H), 3.92 (s, 6H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 160.2, 157.4, 150.3, 147.2, 147.0, 141.4, 131.5, 129.9, 120.8, 119.8, 117.3, 115.2, 114.8, 113.0, 109.7, 56.4, 55.6; IR (ATR): 3727, 3600, 3052, 1599, 1583, 1547, 1515, 1492, 1401, 1288, 1169, 1125 cm^{-1}; ESI-MS: expected, 413.2; observed, *m/z* 414.1 [M+H$^+$].

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Direct conversion of aryl halides to phenols using high-temperature or near-critical water and microwave heating

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Abstract—The direct conversion of aryl halides to the corresponding phenols has been achieved using microwave heating. High-temperature or near-critical water is used as the solvent in conjunction with a copper catalyst and a mineral base.

1. Introduction

The concept of efficient and selective synthesis in water has been exemplified as the rates, yields, and selectivities observed for many reactions in water have begun to match, or in many cases, surpass those in organic solvents.[1] In contrast to many other solvents, water not only provides a medium for solution chemistry but also often participates in elementary chemical events on a molecular scale. Water also offers practical advantages over organic solvents. It is cheap, readily available, non-toxic, and non-flammable. Another area of current growing research interest is the use of microwave energy as a heating source. This is evidenced by the number of papers and recent reviews appearing in the literature.[2–4] As well as being energy efficient, microwave heating can also enhance the rate of reactions and in many cases improve product yields. With the advent of scientific focused microwave systems, it is possible to control the temperature, pressure, microwave power, and reaction times very easily and with a high degree of reproducibility. Bringing these two areas (chemistry in water and microwave heating) together offers a clean, easy, and efficient method for organic synthesis. An example of this is in the Suzuki coupling reaction where it is possible to use parts per million levels of palladium catalysts when using water as a solvent in conjunction with microwave heating.[5]

In addition to using water for chemistry at ambient pressure in open vessels there has been a growth of interest in the use of high-temperature, near-critical, and supercritical water.[6–8] High-temperature water is broadly defined as liquid water above 200 °C, near-critical water as that between 200 and 300 °C, and supercritical water as that above 374 °C and 218 atm. At these temperatures the water approaches properties more like polar organic solvents. Using conventional heating, a range of chemistries can be performed in superheated water and it has been found that acid or base-catalyzed reactions require less catalyst than normal, if any. Strauss and co-workers showed in 1997 that by using microwave heating, it is possible to open up new avenues for synthesis by working with water above 200 °C.[9] For example, they have performed etherifications and multi-component reactions that were not otherwise possible.[10] This work was performed in a specially designed microwave apparatus. The majority of chemistry undertaken using water as a solvent using commercially available single-mode apparatus has been undertaken at temperatures at or below 200 °C. This is because they have a pressure limit of 20–30 bar thereby limiting the temperature to which the water can be heated. However, using a dedicated multi-mode reactor it is possible to perform reactions in heavy-walled quartz reaction vessels with operating limits of 80 bar thus allowing water to be heated to temperatures close to 300 °C.[11] The use of this apparatus for some organic transformations in near-critical water has recently appeared in the literature.[12] We too have become interested in developing microwave methodologies for performing synthetic transformations using high-temperature (~200 °C) and near-critical (~300 °C) water. One particular transformation of interest to us was the direct conversion of aryl halides to the corresponding phenols. We present the results of our initial studies here.

2. Results and discussion

The conversion of aryl halides to the corresponding phenols in one step generally involves long reaction times and often harsh conditions are required. In addition, most of the work has been focused on chloro-, bromo- or iodo-benzene or on

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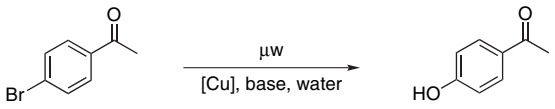
electron-deficient aryl fluorides. Examples include performing the reaction in a steel bomb for 1½ days using CuI as a catalyst,[13] radical[14–16] and photochemical[17] reactions, and fluoride displacement from electron-deficient substrates.[18–20] To circumvent these methods, there have been numerous multi-step approaches reported.[21] A theme running through most of the direct methods is the use of water as a solvent, copper salt as catalysts, elevated temperatures, and lengthy reaction times. We were keen to see if, using microwave heating, it was possible to perform the reaction efficiently and rapidly using high-temperature or near-critical water as a solvent. We started our investigations working at the lower temperature of 200 °C using a monomode microwave apparatus and working on a 1 mmol scale. We screened a range of copper sources as catalysts in conjunction with mineral bases (3.1 M in water) for the direct conversion of 4-bromoacetophenone to 4-hydroxyacetophenone. The reaction mixtures were heated to 200 °C and then held at this temperature for 20 min before being allowed to cool. Our results are summarized in Table 1. Of those screened, copper dust was found to be the best catalyst for the reaction, the use of Cu (I) and Cu (II) sources leads to lower product yields (Table 1, entries 2, 4, and 5) and a catalyst loading of 10 mol % was found to be optimal (Table 1, entries 1–3). Using 3.1 equiv sodium hydroxide gave the best results, with less leading to lower yields because of incomplete conversion and more leading to product decomposition (Table 1, entries 6 and 7). Sodium carbonate and sodium acetate proved less successful as potassium hydroxide (Table 1, entries 8–10). Running the reaction for a shorter time led to lower conversion (Table 1, entry 11). We next decided to screen a range of aryl halide substrates using our conditions of 10 mol % copper powder, 3.1 equiv NaOH for a reaction time of 20 min at 200 °C. The results are shown in Table 2. Using activated aryl bromides and iodides, good yields of the corresponding phenols were obtained but with de-activated substrates product yields were significantly lower. In the case of 4-chloroacetophenone, no product was formed.

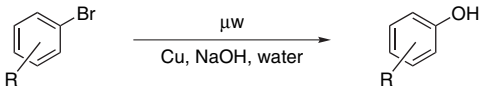
Table 1. Catalyst and base screening for the direct conversion of 4-bromoacetophenone to 4-hydroxyacetophenone[a]

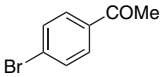
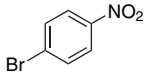
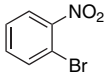
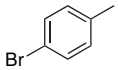
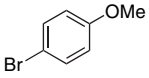
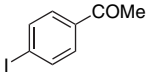
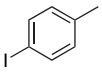
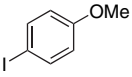
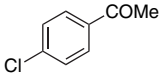


Entry	Copper source	Base	Yield (%)
1	Cu dust (5 mol %)	NaOH (3.1 equiv)	60
2	Cu dust (10 mol %)	NaOH (3.1 equiv)	65
3	Cu dust (20 mol %)	NaOH (3.1 equiv)	58
4	CuI (10 mol %)	NaOH (3.1 equiv)	40
5	$Cu(OAc)_2$ (10 mol %)	NaOH (3.1 equiv)	52
6	Cu dust (10 mol %)	NaOH (2.0 equiv)	32
7	Cu dust (10 mol %)	NaOH (5.0 equiv)	53
8	Cu dust (10 mol %)	KOH (3.1 equiv)	19
9	Cu dust (10 mol %)	Na_2CO_3 (3.1 equiv)	25
10	Cu dust (10 mol %)	NaOAc (3.1 equiv)	11
11[b]	Cu dust (10 mol %)	NaOH (3.1 equiv)	37

[a] Reactions were run in a sealed tube using 1 mmol 4-bromoacetophenone and base dissolved in water to give a 1 M solution. An initial microwave irradiation power of 75 W was used and the temperature being ramped from rt to 200 °C where it was then held for 20 min.
[b] Reaction mixture held at 200 °C for 10 min.

Table 2. Direct transformation of aryl halides to phenols in water using copper powder as a catalyst and sodium hydroxide as base[a]

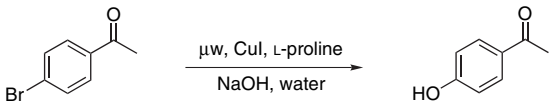


Entry	Aryl halide	Yield (%)
1		65
2		70
3		30
4		0
5[b]		17
6		74
7		12
8		31
9		0

[a] Reactions were run in a sealed tube using 1 mmol aryl halide, 10 mol % Cu powder and 1.0 mL of a 3.1 M NaOH solution. An initial microwave irradiation power of 75 W was used and the temperature being ramped from rt to 200 °C where it was then held for 20 min.
[b] Reaction mixture held at 200 °C for 30 min.

Ma and co-workers have recently reported the use of L-proline as a promoter for the CuI-catalyzed coupling reaction of aryl halides with amines.[22,23] We were interested to see if this catalytic system could also be applicable for our direct synthesis of phenols. Again working with 4-bromoacetophenone as a test substrate, we set out to probe this. Our results are summarized in Table 3. We found that using a 1:2 ratio of CuI (10 mol %) to L-proline as reported for the amination reactions led to a 60% yield of the desired phenol after heating at 200 °C for 20 min with NaOH as base (Table 3, entry 1). Reduction of this ratio to 1:0.5 led to an increase in product yield to 70% after heating at 200 °C for 20 min and to 82% if the reaction time at 200 °C was extended to 30 min (Table 3, entries 2 and 3). With these conditions in hand we screened representative substrates and the results being shown in Table 4. In the case of aryl iodides, yields of product were generally higher than those obtained using copper powder as the catalyst (Table 4, entries 1–3). Aryl bromides other than 4-bromoacetophenone proved less successful (Table 4, entries 4–7) and, in the case of 4-chloroacetophenone, some product was formed (Table 4, entry 8).

Table 3. Screening for the direct conversion of 4-bromoacetophenone to 4-hydroxyacetophenone using CuI as a catalyst and L-proline as an additive[a]

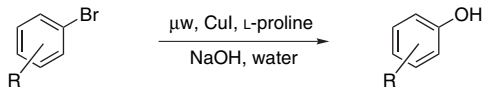


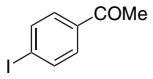
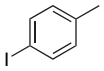
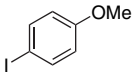
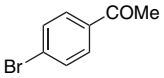
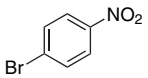
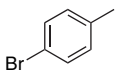
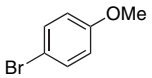
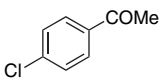
Entry	Catalyst mixture	Reaction time	Yield (%)
1	CuI/L-proline (1:1)	20 min at 200 °C	60
2	CuI/L-proline (1:0.5)	20 min at 200 °C	70
3	CuI/L-proline (1:0.5)	30 min at 200 °C	82

[a] Reactions were run in a sealed tube using 1 mmol aryl halide, 10 mol % CuI, and 3.1 mL of a 1 M NaOH solution. An initial microwave irradiation power of 35 W was used and the temperature being ramped from rt to 200 °C where it was then held for the allotted time.

In a further probe of the chemistry, we decided to use the same catalytic system (10 mol % CuI, 5 mol % L-proline, and NaOH as base) but work at 300 °C in the dedicated multi-mode reactor to see if the higher reaction temperature had a beneficial effect on product yield, especially in the case of aryl bromides. As shown in Table 5, we find that, with aryl iodides, product yields can be further improved by working at

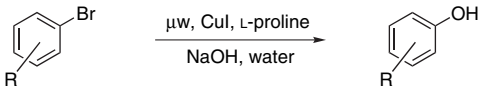
Table 4. Direct transformation of aryl halides to phenols in water at 200 °C using CuI as a catalyst, L-proline as an additive, and sodium hydroxide as base[a]

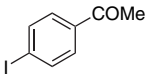
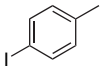
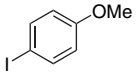
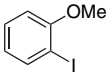
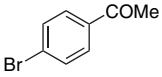
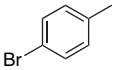
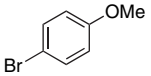
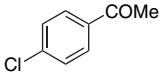


Entry	Aryl halide	Yield (%)
1		99
2		42
3		53
4		82
5		10
6		0
7		0
8		14

[a] Reactions were run in a sealed tube, using 1 mmol aryl halide, 10 mol % CuI, 5 mol % L-proline, and 1.0 mL of a 3.1 M NaOH solution. An initial microwave irradiation power of 35 W was used and the temperature being ramped from rt to 200 °C where it was then held for 30 min.

Table 5. Direct transformation of aryl halides to phenols in water at 300 °C using CuI as a catalyst, L-proline as an additive, and sodium hydroxide as base[a]



Entry	Aryl halide	Reaction time	Yield (%)
1		Heat to 300 °C and stop	100
2		Heat to 300 °C and stop	39
3		Heat to 300 °C and stop	65
4		Heat to 300 °C and stop	37
5		Heat to 300 °C and hold for 30 min	94
6		Heat to 300 °C and hold for 30 min	30
7		Heat to 300 °C and hold for 30 min	43
8		Heat to 300 °C and hold for 30 min	44

[a] Reactions were run in a sealed tube using 5 mmol aryl halide, 10 mol % CuI, 5 mol % L-proline, and 10 mL of a 1.5 M NaOH solution. An initial microwave irradiation power of 1400 W was used and the temperature being ramped from rt to 300 °C then cooled to 50 °C.

the higher temperature (Table 5, entries 1–4). The reaction mixtures are heated to 300 °C and then allowed to cool. Holding the reaction at 300 °C for 30 min is necessary when working with aryl bromides (Table 5, entries 5–7); shorter times lead to lower product yield. Using the same conditions, with 4-chloroacetophenone as a substrate a 44% yield of product was obtained (Table 5, entry 8).

3. Conclusion

In conclusion, we have shown that it is possible to convert the aryl halides directly to the corresponding phenols using high-temperature or near-critical water as a solvent. The best base for the reaction is sodium hydroxide. Whilst simple copper powder is found to be a good catalyst (10 mol %) for the reaction, the optimum catalyst system is 10 mol % CuI together with 5 mol % L-proline as an additive. For aryl bromide substrates, best results are obtained by heating the reaction mixture to 300 °C and holding at this temperature for 30 min. The same was found to be true for an aryl chloride example. For aryl iodides, best results are obtained by heating the reaction mixture to 300 °C and then allowing the reaction mixture to cool. It is also possible to perform the

reaction at a lower temperature of 200 °C but to the slight detriment of product yield.

4. Experimental

4.1. General

All materials were obtained from commercial suppliers and used without further purification. Standard distilled water was used throughout the study. All reactions were carried out in air. NMR spectra were recorded at 293 K on a 300 or 400 MHz spectrometer. All products are known and were characterized by comparison of NMR data with that in the literature.

4.2. Description of the microwave apparatus

For reactions performed at 200 °C, a commercially available monomode microwave unit (CEM Discover) was used. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0–300 W. Reactions were performed in 10 mL capacity vessels sealed with a septum. The pressure was controlled by a load cell connected directly to the vessel and the temperature of the contents of the vessel was monitored using a calibrated IR sensor located outside the reaction vessel. The contents of the vessel were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure, and power profiles were monitored using commercially available software provided by the microwave manufacturer. For reactions performed at 300 °C, a commercially available multimode microwave unit (Anton Paar Synthos 3000) was used. The instrument is equipped with two magnetrons, with combined continuous microwave output power from 0 to 1400 W. Heavy-walled quartz reaction vessels (80 mL capacity, up to 60 mL working volume) were used. These vessels are dedicated for reactions at high pressure (up to 80 bar) and temperatures. The quartz vessels were capped with special seals with a protective PEEK cap and then were placed inside protecting air cooling jackets made of PEEK. The seals comprise of a release valve that could be manually operated. The individual vessels were placed in an eight-position rotor and fixed in place by screwing down the upper rotor plate, and the rotor was finally closed with a protective hood. The temperature was monitored using an internal gas balloon thermometer placed in one reference vessel and additionally by exterior IR thermography. Pressure was monitored by a simultaneous hydraulic pressure-sensing device for all vessels, with recording of the highest pressure level and pressure increase. Reaction vessels were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

4.3. General procedure for conversion of aryl halides to phenols using copper dust as a catalyst

In a 10 mL glass tube 4-bromoacetophenone (199 mg, 1.0 mmol), copper powder (6 mg, 0.1 mmol), and 1.0 mL of a 3.1 M NaOH solution was placed. The vessel was then sealed with a septum and placed into the microwave cavity. Initial microwave irradiation of 75 W was used and the temperature being ramped from rt to the desired temperature of 200 °C. Once this was reached, the reaction mixture was held at this temperature for 20 min. The reaction mixture was stirred continuously during the reaction. After allowing the mixture to cool to rt, the reaction vessel was opened and the contents were acidified with 2 M hydrochloric acid to pH 5–7. The aqueous layer was extracted with ethyl acetate (3×15 mL). The organic washings were combined, dried over $MgSO_4$, and then ethyl acetate was removed in vacuo. This left the crude product, which was isolated and characterized by comparison of NMR data with that in the literature.

4.4. General procedure for conversion of aryl halides to phenols at 200 °C using copper iodide as a catalyst and L-proline as an additive

In a 10 mL glass tube 4-bromoacetophenone (199 mg, 1.0 mmol), copper iodide (19 mg, 0.1 mmol), L-proline (5 mg, 0.05 mmol), and 1.0 mL of a 3.1 M NaOH solution was placed. The vessel was then sealed with a septum and placed into the microwave cavity. Initial microwave irradiation of 35 W was used and the temperature being ramped from rt to the desired temperature of 200 °C. Once this was reached, the reaction mixture was held at this temperature for 30 min. The reaction mixture was stirred continuously during the reaction. After allowing the mixture to cool to rt, the reaction vessel was opened and the contents were acidified with 2 M hydrochloric acid to pH 5–7. The aqueous layer was extracted with ethyl acetate (3×15 mL). The organic washings were combined, dried over $MgSO_4$, and then ethyl acetate was removed in vacuo. This left the crude product, which was isolated and characterized by comparison of NMR data with that in the literature.

4.5. General procedure for conversion of aryl halides to phenols at 300 °C using copper iodide as a catalyst and L-proline as an additive

In an 80 mL quartz tube 4-bromoacetophenone (996 mg, 5.0 mmol), copper iodide (95 mg, 0.5 mmol), L-proline (25 mg, 0.25 mmol), and 10 mL of a 1.55 M NaOH solution was placed. The vessel was sealed and loaded onto the rotor. Three other vessels were prepared similarly. The loaded rotor was subjected to a maximum of 1400 W microwave power in a ramp to 300 °C (limited by a maximum pressure of 80.0 bar) over a period of 10 min and then held at this temperature for 30 min before being allowed to cool to 50 °C, this takes around 30 min. The reaction mixture was stirred continuously during the reaction. The vessel was vented, removed from the rotor, and the contents were acidified with 2 M hydrochloric acid to pH 5–7. The aqueous layer was extracted with ethyl acetate (3×15 mL). The organic washings were combined, dried over $MgSO_4$, and then ethyl acetate was removed in vacuo. This left the crude product, which was isolated and characterized by comparison of NMR data with that in the literature.

Acknowledgments

The University of Connecticut is thanked for funding. Anton Paar GmbH and CEM Microwave Technology are thanked for equipment support.

References and notes

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