Catalyst-free aqueous multicomponent domino reactions from formaldehyde and 1,3-dicarbonyl derivatives†

Yanlong Gu,[b] Rodolphe De Sousa,[a] Gilles Frapper,[a] Christian Bachmann,[a] Joël Barrault[a] and François Jérôme*[a]

Received 13th July 2009, Accepted 18th August 2009
First published as an Advance Article on the web 18th September 2009
DOI: 10.1039/b913846c

Here we report a catalyst-free aqueous multicomponent domino reaction (MCR) capable of affording a wide range of valuable dihydropyran derivatives from simple, cheap and readily available reactants such as formaldehyde, 1,3-dicarbonyl derivatives, styrene, indole and aniline derivatives. Within the framework of green chemistry, these MCRs gather many advantages such as (i) utilization of water as a solvent, (ii) creation of up to six bonds in one sequence, (iii) 100% of carbon economy and (iv) water as a sole waste. These MCRs exhibit a broad substrate scope and open access to valuable chemicals traditionally produced through multistep processes involving catalysts or organic solvents. More generally, this work opens a new way for creating molecular complexity with maximum simplicity.

Introduction

Within the framework of green chemistry, the search of innovative solutions for the reduction of chemical steps, wastes and energy in organic processes has become a challenging task. In this context, multicomponent domino reactions (MCRs) represent a fascinating tool to achieve this goal.[1] Indeed, efficient MCRs lead to the creation of several bonds in one sequence without changing the reaction conditions, isolating the intermediates or adding reagents, thus allowing a minimization of waste, cost and labor. To be efficient, MCRs have to be highly selective in order to avoid an important production of waste which makes complex and costly the purification work-up. Toxicity of produced waste has also to be considered. On the other hand, MCRs have to be capable of affording highly valuable substrates with good yields from cheap and readily available derivatives.

Generally, in MCRs, control of the selectivity is achieved by addition of a catalyst combined with the dilution of reactants in an organic solvent.[2] With respect to green chemistry, the possibility of designing catalyst-free MCRs using water as a sole solvent is ideally the best choice owing to an easier work-up procedure and the inherent environmental and economical advantages of such process. To the best of our knowledge, most of the successful aqueous and catalyst free MCRs involve the Ugi or Passerini reactions (or derived reactions) and new reaction pathways are now strongly needed in order to increase the portfolio of environmentally benign organic reactions.[3] Development of new MCRs using water as a solvent is strongly limited by (i) the low solubility of organic substrates in water and (ii) the sensitivity of chemical groups towards hydrolytic degradations. One of the solution to circumvent this issue consists in the addition of a phase transfer agent.[4] However, even if spectacular results have been reported in micellar conditions, this strategy still suffers from a complex purification work-up.

Here, we wish to report an efficient aqueous and catalyst-free MCR capable of affording, in water and without assistance of any catalyst or phase transfer agent, a wide range of substituted and valuable dihydropyran derivatives with good yields. These MCRs involve cheap and readily available reactants such as formaldehyde, 1,3-dicarbonyl compounds, styrene or indole derivatives which represent a prerequisite for the viability of a new MCR. On the other hand, from an environmental point of view, these MCRs gather numerous advantages such as (i) utilization of water as a solvent, (ii) creation of up to six bonds in one sequence, (iii) 100% of carbon economy and (iv) water as a sole waste.

More generally, all these reported examples show that the development of aqueous MCRs is not only attractive from the viewpoint of environmentally benign reactions or atom efficiency but also open a novel and straightforward way for the creation of molecular complexity and diversity from simple, cheap and readily accessible organic building blocks.

Results and discussion

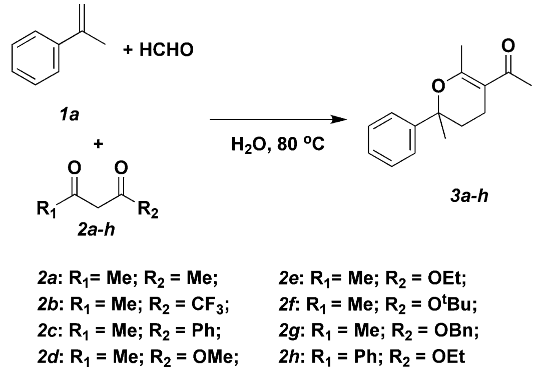
In a first set of experiments, α-methylstyrene (**1a**) and 2,4-pentanedione (**2a**) were heated at 80 °C with aqueous formalin (HCHO, 37 wt% in water). Under these conditions, we were pleased to see that an "ABC" three-component reaction selectively took place. Indeed, after 3h of reaction, a highly pure

---

[a] *Laboratoire de Catalyse en Chimie Organique, Université de Poitiers-CNRS, 40 Avenue du recteur Pineau, Poitiers Cedex, 86022, France. E-mail: francois.jerome@univ-poitiers.fr; Fax: +33 5 49 45 33 49; Tel: +33 5 49 45 40 52*
[b] *Institute of Physical Chemistry and Industrial Catalysis, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037, Luoyu road, Hongshan District, Wuhan, 430074, Hubei, China*

† Electronic supplementary information (ESI) available: Product characterisation and ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b913846c

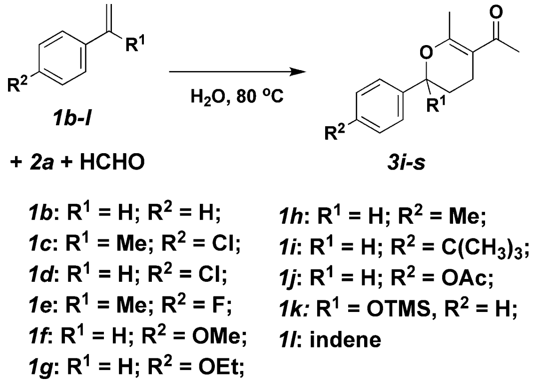
Table 1 MCR between **1a**, formaldehyde and 1,3-dicarbonyl compounds in/on water[a]



Entry	1,3-Dicarbonyl	Product	Time (h)	Isolated yield (%)
1[b]	**2a**	**3a**	3	78
2[c]	**2a**	**3a**	3	41
3[d]	**2a**	**3a**	3	22
4[e]	**2a**	**3a**	3	31
5	**2b**	**3b**	3	82
6	**2c**	**3c**	5	80
7	**2d**	**3d**	3	78
8	**2e**	**3e**	4	77
9	**2f**	**3f**	5	70
10	**2g**	**3g**	4	81
11	**2h**	**3h**	5	64

[a] Formalin was used, **1a**/1,3-dicarbonyl/formaldehyde: 1/1.5/2.5; [b] **1a**/**2a**/formaldehyde: 1/2/2.5; [c] **1a**/**2a**/formaldehyde: 1/1/2.5; [d] **1a**/**2a**/formaldehyde: 1/2/1; [e] **1a**/**2a**/formaldehyde: 1/2/4.

Table 2 MCR between styrene derivatives, **2a** and formaldehyde in/on water[a]



Entry	Olefin	Product	Time (h)	Isolated yield (%)
1	**1b**	**3i**	6	54
2	**1c**	**3j**	3	84
3	**1d**	**3k**	6	28
4	**1e**	**3l**	4	81
5	**1f**	**3m**	3	93
6	**1g**	**3n**	3	91
7	**1h**	**3o**	3	71
8	**1i**	**3p**	6	67
9	**1j**	**3p**	4	72
10[b]	**1k**	**3r**	0.5	40
11	**1l**	**3s**	4	79

[a] Formalin was used, olefin/**2a**/formaldehyde: 1/2/2.5; [b] 60 °C.

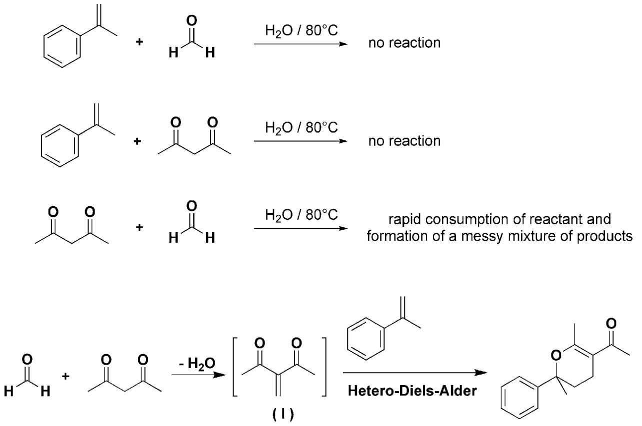
colorless liquid, identified as a 3-acyl-2,6-dimethyl-6-phenyl-5,6-dihydropyran (**3a**), was obtained. After optimization of the reaction conditions (molar ratio **1a**/**2a**/formaldehyde = 1/2/2.5), **3a** was isolated with 78% yield (Table 1, entries 1-4).

Having these first results in hand, various 1,3-dicarbonyl compounds and styrene derivatives were subject to the optimized conditions in order to determine the scope of this aqueous MCR. The results are summarized in Table 1 and Table 2. All examined 1,3-dicarbonyl compounds including 1,3-diketones and β-carbonyl esters reacted smoothly with α-methylstyrene and formaldehyde affording the corresponding 5,6-dihydropyran derivatives in good to high yields (64-82%, Table 1).

Styrenes with a methyl group in the α-position afforded better yields than those without substituent (Table 2, entries 1-3). The presence of an electrondonating group on the aromatic ring of the styrenes led to an increase of the reaction rate (Table 2, entries 2-9). A styrene type silyl enol ether, 1-phenyl-1-trimethylsiloxyethylene **1k**, also reacted successfully with formaldehyde and 2,4-pentanedione affording, after only 30 minutes of reaction at 60 °C, the corresponding dihydropyran in 40% yield (Table 2, entry 10). It is noteworthy that the present MCR was also proved to be tolerant to cyclic styrene since, starting from indene, a 79% yield was obtained (Table 2, entry 11). Remarkably, in all experiments, dihydropyran derivatives were always obtained as a single regioisomer.

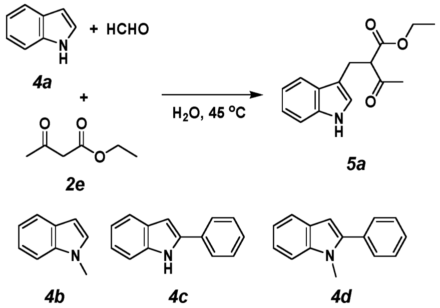
Among heterocyles, substituted dihydropyran derivatives represent an important family of compounds and a lot of studies are devoted to their synthesis. Dihydropyran derivatives are not only used as odorous substances and intermediates for the preparation of plant-protective agents and antiarrhythmic drugs,[5] but are also key intermediates for the synthesis of many natural products.[6] Synthetic methods previously reported for the synthesis of analogous dihydropyran derivatives require multistep processes with assistance of acid or transition metal catalysts and organic solvents.[7] In 2009, Botta *et al.* reported an efficient MCR for the synthesis of 2,3-dihydropyran derivatives. However, in this work, the MCR was carried out in toluene, catalyzed by a Grubbs catalyst and with assistance of microwaves.[8] The most efficient synthetic method was recently reported by Tietze and co-workers.[9] However, utilization of dichloromethane as a solvent, the low yield obtained (23-37%) and the poor substrate scope represent the main limitation of this work. Reactions summarized in Table 1 and Table 2 open a direct and catalyst free access to a diverse array of substituted dihydropyran derivatives (up to 93% yield) from simple and easily available molecules, showing the economical effectiveness of this methodology. On the other hand, within the framework of green chemistry, this process gathers many advantages such as (i) 100% of carbon economy (ii) creation of three bonds in one sequence and (iii) water as a sole waste.

With the aim of proposing a plausible reaction mechanism, three counter experiments were undertaken. First, α-methylstyrene was heated at 80 °C either with 2,4-pentanedione and water or with aqueous formaldehyde. In these cases, no reaction occurs and the reactants remained unaltered (Scheme 1). These results are consistent with the literature. Indeed, successful reactions between (i) styrene derivatives and aqueous formaldehyde[10] or (ii) styrene derivatives and 1,3-dicarbonyl compounds[11] normally require assistance of an acid



Scheme 1 Plausible mechanism for the formation of **3a**.

Table 3 MCR between indoles, formaldehyde and 1,3-dicarbonyl compounds in/on water[a]



Entry	Indole	1,3-Dicarbonyl	Product	Time (h)	Yield (%)
1	**4a**	**2e**	**5a**	6	70
2	**4a**	**2d**	**5b**	6	64
3[b]	**4a**	**2e**	**5c**	20	54
4	**4b**	**2e**	**5d**	9	71
5	**4b**	**2d**	**5e**	15	70
6[c]	**4b**	**2f**	**5f**	15	51
7[d]	**4c**	**2e**	**5g**	17	50
8[d]	**4d**	**2e**	**5h**	17	52

[a] Formalin was used as source of formaldehyde, **4a**/1,3-dicarbonyl/formaldehyde: 1/1.5/2; [b] 3,3′-diindolylmethane was also isolated in 11% yield, 60 °C; [c] 3,3′-di(N-methylindolyl)methane was also isolated in 17% yield; [d] 50 °C.

catalyst. Interestingly, when 2,4-pentanedione was now heated with aqueous formaldehyde at 80 °C, a messy mixture of products was rapidly formed. This result indicates that the MCR is initiated by a reaction involving 2,4-pentanedione and formaldehyde. On the basis of these counter experiments, we propose in Scheme 1 a plausible reaction mechanism. First, we postulate for a Knoevenagel-type reaction between 2,4-pentanedione and formaldehyde to produce a 2-methylene-1,3-dicarbonyl compound (I). This species, known to be highly unstable,[9,12] would be rapidly trapped with α-methylstyrene by means of a hetero Diels–Alder reaction yielding **3a**.

Encouraged by these results, we then explored a novel three-component reaction involving, this time, aqueous formaldehyde, indole and ethyl acetoacetate. The targeted C3-substituted indole derivatives are potent tryptophan precursors. In the literature, three methods were developed to synthesize such derivatives: i) coupling of ethyl acetoacetate to gramine derivatives in the presence of bases; ii) oxidative Michael reaction of Baylis–Hillman adducts with indole derivatives promoted by iodoxybenzoic acid (IBA); iii) condensation between 2-(2-nitrophenyl)propenal and ethyl acetoacetate.[13] Unfortunately, these methods suffer either from a lack of commercially available starting materials or environmental problems due to the use of toxic chemicals and the important generation of waste.

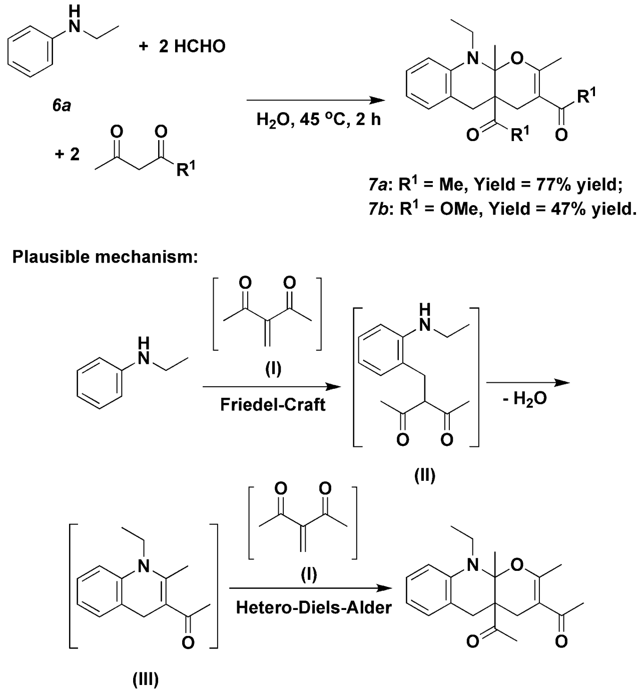
As observed above for the synthesis of **3a-u**, we found that indole derivative **5a** can be directly prepared from aqueous formaldehyde, indole and ethyl acetoacetate without assistance of any catalyst. Indeed, after 6 hours of reaction at 45 °C, indole and ethyl acetoacetate were selectively assembled with aqueous formaldehyde to generate the desired C3-substituted indole with 70% yield. Here again, water was the sole by-product (Table 3, entry 1). Note that the 30% remaining are unaltered starting materials, further indicating the high selectivity of this process.

Investigation of the substrate scope revealed that many indoles and *β*-ketone esters can be successfully used and all the desired C3-substituted indole derivatives were obtained with good yields (Table 3). On the basis of the above-described mechanism, we assume that the reaction proceeds here according to a tandem procedure involving a Knoevenagel-type reaction between formaldehyde and **2e** followed by a Michael addition of indole to the generated 2-methylene-*β*-ketone ester (ESI, Scheme S1).†[14] From indole derivatives, Knoevenagel/Michael tandem reactions are usually difficult to achieve mainly because it normally requires the concomitant presence of acid and base catalysts in the same reaction pot, thus showing the convenience of the presented MCRs.[15]

Remarkably, when indole derivatives were now replaced by N-ethylaniline (**6a**), we observed that a novel "ABBCC"-type five-component reaction selectively took place. Indeed, when a mixture of N-ethylaniline and acetylacetone (molar ratio is 1/2.5/2.5) was heated with aqueous formaldehyde at 45 °C for only 2 hours, a complex tricyclic skeleton, identified as a 3,4a-diacetyl-2,10a-dimethyl-10-ethyl-4,4a,5,10,10a-pentahydropyrano[2,3-b]quinoline **7a**, was obtained (Scheme 2). To our great delight, **7a** was isolated with 77% yield, which is a very impressive yield considering the fact that five molecules are involved in its construction.

From the viewpoint of green chemistry, this water-based MCR is nearly perfect, since only three molecules of water are released during the reaction and 100% of carbon economy is still achieved. On the other hand, during the synthesis of **7a**, six bonds were created in one sequence. Note that the use of aniline derivatives in MCRs normally requires not only the assistance of Brønsted acid, transition metals or bromoalkylsulfonium bromide salt as catalyst but also the use of organic solvents, showing here again the versatility of this procedure.[16]

Inspired by the observations made above, we assume that the tricyclic **7a** derivative might be formed through a cascade of elementary reactions involving i) Friedel-Craft addition of *N*-ethylaniline to (I);[17] ii) dehydrative cyclization of the adduct (II)[18] and iii) a hetero Diels Alder reaction between the cyclized product (III) and (I) (Scheme 2). Interestingly, as observed above for the "ABC" three-component reaction, the hetero Diels–Alder step was also regioselective and **7a** was obtained as a single



Scheme 2 "ABBCC"-type five component reaction in/on water.

regioisomer. Note that this "ABBCC"-type five-component reaction is not diastereoselective and diastereoisomers of **7a** were equally produced. An analogous five-component reaction involving methyl acetoacetate, *N*-ethylaniline and formaldehyde also proceeded well and **7b** was obtained in a 47% yield.

Conclusions

We showed here that the combination of formaldehyde and 1,3 dicarbonyl derivatives was a powerful tool to create molecular complexity while perfectly fitting with the concept of green chemistry. In this context, two new aqueous "ABC"-type three component reactions involving formaldehyde, 1,3-dicarbonyl compounds and styrenes or indoles derivatives were successfully developed yielding dihydropyran and C3-substituted indole derivatives in fair to good yields. The presented MCRs exhibit a broad substrate scope and afford a direct access to a wide range of complex organic skeletons, usually synthesized through multistep processes. Note that this MCR is also tolerant to the use of aniline derivatives which normally require assistance of a catalyst further demonstrating the usefulness of this aqueous MCR.

Experimental

Typical procedure for three component reaction of *α*-methylstyrene, formaldehyde and 2,4-pentanedione

All reactions were conducted in a 10 mL V-type flask equipped with triangle magnetic stirring. In a typical procedure, aqueous formaldehyde (203 mg, 2.5 mmol, 37 wt% in H_2O) was mixed with α-methylstyrene (118 mg, 1.0 mmol) and 2,4-pentanedione (200 mg, 2.0 mmol) under air. The mixture was then stirred for 3 hours at 80 °C. After completion of the reaction, the products were extracted from water with a solution of ethyl acetate and heptane (1:4 v/v, 6 mL × 2). After concentration of the organic phases, the crude compounds were purified by flash chromatography over silica gel.

Selected product: 3-Acyl-2,6-dimethyl-6-phenyl-5,6-dihydropyran (**3a**): Colorless liquid, 78% yield (Heptane/ethyl acetate: 2/1), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3H), 1.85-2.08 (m, 2H), 2.11 (s, 3H), 2.15-2.33 (m, 2H), 2.37 (s, 3H), 7.19-7.27 (m, 3H), 7.32-7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 21.3, 29.4, 29.5, 32.6, 79.3, 109.6, 124.2, 127.0, 128.5, 144.7, 163.2, 198.8. IR (cm^{-1}): 2980, 2929, 2966, 1668, 1567, 1446, 1375, 1284, 1095, 1073, 945, 766, 699. HRMS (ESI): calcd for $C_{15}H_{18}O_2$, [M] 230.3022; found: 230.3109.

Characterizations of all other products (**3b-u**) as well as copies of NMR spectra are provided in the ESI.†

Typical procedure for three component reaction of indole, formaldehyde and ethyl acetoacetate

All reactions were conducted in a 10 mL V-type flask equipped with triangle magnetic stirring. In a typical procedure, aqueous formaldehyde (160 mg, 2.0 mmol, 37 wt% in H_2O) was mixed with indole (117 mg, 1.0 mmol), ethyl acetoacetate (195 mg, 1.5 mmol) and water (850 mg) under air. The mixture was then stirred for 6 hours at 45 °C. After completion of reaction, the products were extracted from water with a solution of ethyl acetate and heptane (1:1 v/v, 6 mL × 2). After concentration of the organic phases, the crude compounds were purified by flash chromatography over silica gel.

Selected product: Ethyl α-benzoyl-1H-indole-3-propanoate (**5c**): Red liquid, yield: 54% (Heptane/ethyl acetate: 4/1), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.1 Hz, 3H), 3.42 (dd, J_a = 7.8 Hz, J_b = 2.2 Hz, 2H), 4.02 (ddd, J_a = 14.3 Hz, J_b = 7.2 Hz, J_c = 1.8 Hz, 2H), 4.68 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 2.2 Hz, 1H), 7.07 (quint/double, J_a =7.0 Hz, J_b = 1.2 Hz, 2H), 7.24 (dd, J_a = 7.4 Hz, J_b = 1.2 Hz, 1H), 7.33 (t, J = 7.7 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.56 (d, J = 0.5 Hz, 1H), 7.87 (dd, J_a = 7.5 Hz, J_b = 1.4 Hz, 2H), 8.0 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 23.6, 54.0, 60.4, 110.2, 111.4, 117.4, 118.4, 121.0, 121.9, 126.1, 127.6, 132.4, 135.1, 135.2, 168.7, 194.2. IR (cm^{-1}): 3403, 3056, 2948, 2871, 1730, 1688, 1671, 1458, 1448, 1393, 1368, 1323, 1303, 1227, 1182, 1148, 1096, 1044, 967, 928, 911, 781, 740. HRMS (ESI): calcd for $C_{20}H_{19}NO_3$, [M + H$^+$] = 322.3777; found: 322.3794.

Characterizations of all other products (**5a-h**) as well as copies of NMR spectra are provided in the ESI.†

Typical procedure for the "ABBCC"-type five component reaction of N-ethylaniline, formaldehyde and acetylacetone

All reactions were conducted in a 10 mL V-type flask equipped with triangle magnetic stirring. In a typical procedure, aqueous formaldehyde (203 mg, 2.5 mmol, 37 wt% in H_2O) was mixed with N-ethylaniline (123 mg, 1.0 mmol), acetylacetone (250 mg, 2.5 mmol) and water (850 mg) under air. The mixture was then stirred for 2 hours at 45 °C. After completion of the reaction, the products were extracted from water with a solution of ethyl acetate and heptane (1:1 v/v, 6 mL × 2). After concentration of the organic phases, the crude compounds were purified by flash chromatography over silica gel.

Selected product: 3,4a-diacetyl-2,10a-dimethyl-10-ethyl-4,4a,5,10,10a-pentahydropyrano[2, 3-b]quinoline (**7a**): Yellow pale liquid, yield: 77% (Heptane/ethyl acetate: 4/1), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.15$ (t, $J = 7.4$ Hz, 3H), 1.89 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.44 (dd, $J_a = 15.1$ Hz, $J_b = 7.5$ Hz, 2H), 2.81 (d, $J = 15.8$ Hz, 1H), 3.20 (d, $J = 15.8$ Hz, 1H), 3.54 (d, $J = 12.5$ Hz, 1H), 3.87 (dd, $J_a = 12.5$ Hz, $J_b = 2.3$ Hz, 1H), 7.01 (d, $J = 7.3$ Hz, 1H), 7.12-7.29 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 13.3$, 18.3, 22.1, 25.0, 25.5, 28.5, 29.3, 53.0, 64.4, 101.4, 126.4, 127.3, 128.3, 140.6, 141.9, 153.8, 194.6, 202.6, 202.7. IR (cm^{-1}): 2977, 2876, 1698, 1636, 1516, 1489, 1357, 1233, 1146, 1119, 1046, 968, 943, 911, 775, 728, 683. HRMS (ESI): calcd for $C_{20}H_{25}NO_3$, $[M + H^+] = 328.4253$; found: 328.4255.

Characterization of **7b** as well as copies of its NMR spectra is provided in the ESI.†

Acknowledgements

Authors are grateful to the CNRS and the French Ministry of research for their financial supports. YG also thanks the CNRS for the funding of his temporary research associate position. DDS is grateful to the Agence Nationale de la Recherche (action CP2D) for his PhD grant.

Notes and references

1 (*a*) W. Bannwarth, E. Felder, *Combinatorial Chemistry*, Wiley-VCH, Weinheim, 2000; (*b*) J. Zhu, H. Bienaymé, *Multicomponent reactions*, Wiley-VCH, Weinheim, 2005; (*c*) A. Döling, *Chem. Rev.*, 2006, **106**, 17–89; (*d*) G. Balme, E. Bossharth and N. Monteiro, *Eur. J. Org. Chem.*, 2003, 4101–4111; (*e*) R. V. A. Orru and M. De Greef, *Synthesis*, 2003, 1471–1499; (*f*) H. Bienaymé, C. Hulme, G. Oddon and P. Schmitt, *Chem.–Eur. J.*, 2000, **6**, 3321–3329.

2 (*a*) J. D. Sunderhaus and S. F. Martin, *Chem.–Eur. J.*, 2009, **15**, 1300, DOI: 10.1002/chem.200802140; (*b*) D. Tejedor and F. Garcia-Tellado, *Chem. Soc. Rev.*, 2007, **36**, 484–491; (*c*) A. Döling, *Chem. Rev.*, 2006, **106**, 17–89; (*d*) R. V. A. Orru and M. De Greef, *Synthesis*, 2003, 1471–1499; (*e*) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Methen and L. Balagopal, *Acc. Chem. Res.*, 2003, **36**, 899–907; (*f*) A. Döling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168–3210; (*g*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136.

3 As selected works see: (*a*) M. C. Pirrung and K. C. Sarla, *J. Am. Chem. Soc.*, 2004, **126**, 444–445; (*b*) S. J. Tu, Y. Zhang, H. Jiang, H. Jiang, B. Jiang, J. Y. Zhang, R. H. Jia and F. Shi, *Eur. J. Org. Chem.*, 2007, (9), 1522–1528; (*c*) I. Kanizsai, Z. Szakonyi, R. Sillanpää and F. Fülöp, *Tetrahedron Lett.*, 2006, **47**(51), 9113–9116; (*d*) M. Abbas, J. Bethke and L. A. Wessjohann, *Chem. Commun.*, 2006, (5), 541–543.

4 As selected works see: (*a*) Y. Ye, Q. Ding and J. Wu, *Tetrahedron*, 2008, **64**(7), 1378–1382; (*b*) Y.-L. Liu, L. Liu, Y.-L. Wang, Y.-C Han, D. Wang and Y.-J. Chen, *Green Chem.*, 2008, **10**, 635–640; (*c*) S. Luo, H. Xu, J. Li, L. Zhang, X. Mi, X. Zheng and J.-P. Cheng, *Tetrahedron*, 2007, **63**(46), 11307–11314; (*d*) L. Zhong, Q. Gao, J. Gao, J. Xiao and C. Li, *J. Catal.*, 2007, **250**, 360–364; (*e*) S. Shirakawa and S. Kobayashi, *Org. Lett.*, 2007, **9**, 311–314; (*f*) L. Zhang and J. Wu, *Adv. Synth. Catal.*, 2007, **349**, 1047–1051; (*g*) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 5527–5529; (*h*) K. Manabe, S. Limura, X.-M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 11971–11978; (*i*) K. Manabe, X.-M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, 2001, **123**, 10101–10102; (*j*) K. Manabe, Y. Mori and S. Kobayashi, *Tetrahedron*, 2001, **57**(13), 2537–2544; (*k*) K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 7202–7207.

5 (*a*) W. Hoffmann, *Ger. Offen*, 1971DE 1960811 19710609.; (*b*) E. T. Angelakos and A. H. Hegnauer, *J. Pharm. Exp. Therap*, 1959, **127**, 137–145; (*c*) M. M. Winbury, M. L. Hemmer, D. H. Papierski, D. G. Wright, B. J. Runyon and R. G. Bianchi, *J. Pharm,. Exp. Therap.*, 1955, **113**, 402–413; (*d*) M. M. Winbury and M. L. Hemmer, *Circ. Res.*, 1955, **3**, 474–477.

6 (*a*) T. Oishi, Y. Ohtsuka, In *Studies in Natural Products Synthesis*, Atta-ur-Rahman, Ed., Elsevier, Amsterdam, 1989, Vol. 3, p73; (*b*) L. Yet, *Chem. Rev.*, 2000, **100**, 2963–3007.

7 (*a*) R. Ballini, S. Gabrielli and A. Palmieri, *Synlett*, 2007, 2430–2432; (*b*) S. Ma, L. Lu and J. Zhang, *J. Am. Chem. Soc.*, 2004, **126**, 9645–9660; (*c*) H. M. C. Ferraz, M. K. Sano, M. R. S. Nunes and G. G. Bianco, *J. Org. Chem.*, 2002, **67**, 4122–4126; (*d*) S. Cacchi, G. Fabrizi, R. C. Larock, P. Pace and V. Reddy, *Synlett*, 1998, 888–890; (*e*) R. Verhé, N. De Kimpe, D. Courtheyn, L. De Buyck and N. Schamp, *Tetrahedron*, 1982, **38**, 3649–3660; (*f*) W. Hoffmann, *Ger. Offen.*, 1972DE 2056196 19720518.; (*g*) M. Maier and R. R. Schmid, *Liebigs Ann. Chem.*, 1985, 2261–2284.

8 D. Castagnolo, L. Botta and M. Botta, *Tetrahedron Lett.*, 2009, **50**, 1526–1528.

9 L. F. Tietze, N. Bohnke and S. Dietz, *Org. Lett.*, 2009, **11**(13), 2948.

10 Y. Gu, A. Karam, F. Jérôe and J. Barrault, *Org. Lett.*, 2007, **9**, 3145–3148.

11 (*a*) J. Kischel, D. Machalik, A. Zapf and M. Beller, *Chem.–Asian J.*, 2007, **2**(7), 909–914; (*b*) K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *Angew. Chem., Int. Ed.*, 2006, **45**, 2605–2609.

12 (*a*) B. D. Wilson, *J. Org. Chem.*, 1963, **28**, 314–320; (*b*) V. G. Nenajdenko, A. V. Statsuk and E. S. Balenkova, *Tetrahedron*, 2000, **56**, 6549–6556.

13 (*a*) D. T. G. Jones, D. Artman and R. M. Williams, *Tetrahedron Lett.*, 2007, **48**, 1291–1294; (*b*) J. S. Yadav, B. V. S. Reddy, A. P. Singh and A. K. Basak, *Tetrahedron Lett.*, 2007, **48**, 4169–4172; (*c*) A. V. Novikov, A. Sabahi, A. M. Nyong and J. D. Rainier, *Tetrahedron: Asymmetry*, 2003, **14**, 911–915; (*d*) M. Iwao and O. Motoi, *Tetrahedron Lett*, 1995, **36**, 5929–5932; (*e*) H. Tanaka, Y. Murakami and S. Torri, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 4061–4062; (*f*) H. R. Synder, C. W. Smith and J. M. Stewart, *J. Am. Chem. Soc.*, 1944, **66**, 200–204.

14 Y. Gu, J. Barrault and F. Jéôe, *Adv. Synth. Catal.*, 2008, **350**, 2007–2012.

15 Y. Oikawa, H. Hirasawa and O. Yonemitsu, *Tetrahedron Lett.*, 1978, **19**, 1759–1762.

16 (*a*) S. Chen, Z. Hou, Y. Zhu, J. Wang, L. Lin, X. Liu and X. Fenh, *Chem. Eur. J.*, 2009, DOI: 10.1002/chem..200900392; (*b*) H. Cao, X. Wang, H. Jiang, Q. Zhu, M. Zhang and H. Liu, *Chem.–Eur. J.*, 2008, **14**(36), 11623–11633; (*c*) A. T. Khan, T. Parvin and L. H. Choudhury, *J. Org. Chem.*, 2008, **73**(21), 8398–8402.

17 (*a*) A. Kumar and R. A. Maurya, *Tetrahedron Lett.*, 2008, **49**, 5471–5474; (*b*) H. Takahashi, N. Kashiwa, Y. Hashimoto and K. Nagasawa, *Tetrahedron Lett.*, 2002, **43**, 2935–2938.

18 R. K. Vohra, J.-L. Renaud and C. Bruneau, *Synthesis*, 2007, 731–738.