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Microwave-Assisted Solid-Phase Synthesis of Phthalimides

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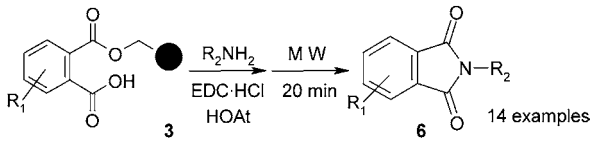
ABSTRACT



A traceless solid-phase synthesis of substituted phthalimides is proposed. The target compounds are obtained within minutes by a microwave-assisted cyclative cleavage in good yields and excellent purities.

Among the strategies developed for the traceless solid-phase synthesis of compound libraries,[1] cyclative cleavage is one of the most broadly used. The traceless approach advantageously combines the cleavage with a synthetic step and also allows a selective release of the target compounds from the support, while potential byproducts are retained. This method is particularly suited for the preparation of heterocycle libraries, and its synthetic value has been largely illustrated by the syntheses of urazoles,[2] hydantoins,[3] (di)ketopiperazines,[4] pyrimidine-diones,[5] and cyclic imides.[6,7] Among these scaffolds, phthalimides are of particular biological interest and have been reported as antipsychotics,[8] antiinflammatory agents,[9] herbicides,[10] and insecticides.[11]

As we became interested in an optimization program based on the phthalimide scaffold, we focused our attention on high-throughput solid-phase approaches. However, we experienced that the cleavage times of several hours required by the existing protocols[6,7] strongly impaired their applicability to large library production. Recently, the solution-phase synthesis of phthalimides has been substantially improved by the use of microwave irradiation for the imide ring formation.[12,13] We have now adapted this chemistry to the solid phase and propose herein an expeditious traceless synthesis of phthalimides via a microwave-assisted cyclative cleavage under neutral conditions.

The first part of our study was focused on the determination of the optimal cyclative cleavage conditions on a model compound. For this purpose, phthalic acid (R_1 = H) was loaded on Wang resin **1** (PS 2% DVB cross-linked). Upon comparison of various esterification methods, we found that the Mitsunobu protocol leads to the highest loadings and purities. The resulting acid resin **3a** was then further reacted with 3-phenylpropylamine under standard amide coupling conditions.[14] The isolated resin **5a** was finally suspended in various solvents for irradiation in a single-mode microwave oven[15] (see Scheme 1 and Table 1).

The conversion of resins **5** into compounds **6** was monitored on-bead by FT-IR and in solution by weighing

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(15) Emrys Creator microwave oven from Personal Chemistry was used for our study.

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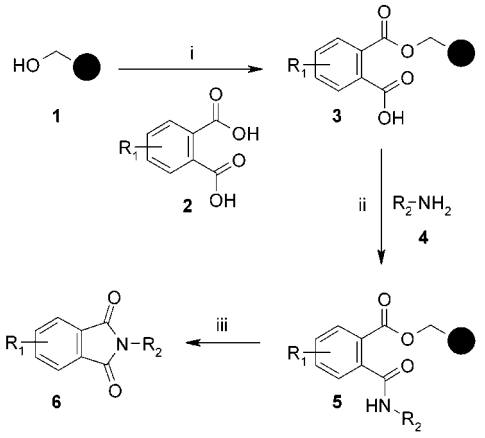
Scheme 1. Synthetic Route to Substituted Phthalimides **6**[a]



[a] Conditions: (i) Diacid **2** (5.5 equiv), DIAD (3 equiv), triphenylphosphine (5.5 equiv), THF, rt, 24 h; (ii) amine **4** (11 equiv), EDC·HCl (11 equiv), HOAt (11 equiv), DCM, rt, 18 h; (iii) M W, DMF, 170 °C, 20 min.

the isolated product. As shown in entries 1−4, the reactions performed at 150 °C afforded the desired product, although in moderate yields. Upon comparing the use of DMF (entries 3 and 4) and of a mixture of 90% dioxane and 10% acetic acid (entries 1 and 2), we found that aprotic reaction conditions were more adapted to the cyclative cleavage than protic media. An increase in the reaction time resulted in an improved yield when DMF was used as the solvent (entries 3 and 4), whereas no effect was observed in the case of dioxane/AcOH (entries 1 and 2). Raising the temperature to 170 °C was achieved in DMF and dramatically improved the cyclization rate (entries 4 and 5). Finally, complete release of the desired phthalimide **6a** was achieved by exposing a suspension of the resin **5a** in DMF to the microwaves for 20 min at 170 °C (entry 6). In this case, the expected product was obtained with excellent purity (95%) and in good yield (80%). Under the reaction conditions used for the cleavage, no macroscopic change of the resin was observed. Interestingly, attempts performed with amide-ester resins of type **5** loaded on hydroxymethyl-polystyrene resin resulted in a maximum yield of 55%, probably due to the lower flexibility of the linker.

Table 1. Optimization of the Cyclative Cleavage Conditions

entries	solvents	reaction time (min)	temp (°C)	yield[a] (%)
1	dioxane−10% AcOH	10	150	25
2	dioxane−10% AcOH	20	150	26
3	DMF	10	150	45
4	DMF	20	150	65
5	DMF	10	170	69
6	DMF	20	170	80

[a] Based on the loading determined by TFA cleavage. All compounds were >90% pure as determined by HPLC−UV at 210 nm.

In a second group of attempts, the influence of the substitution of the amino part of the template on the ring closure was studied. The optimized conditions defined previously were applied to a range of resins **5** derived from phthalic acid and from a diverse set of amines (see Table 2).

Table 2. Influence of the Amine on Ring Closure (R_1 = H)

5, **6**	R_2	yield[a] (%)	purity[b] (%)	yield[c] (%)
a	C_3H_6Ph	80	95	68
b	$CH(CH_3)C_2H_4Ph$	83	97	83[d]
c	C_8H_{17}	90	70	56
d	4-CH_3OBn	56[e]	82	24[e]
e	4-ClBn	62[f]	54	12[f]
f	C_5H_9	84	95	35

[a] Crude yield. [b] HPLC−UV purity at 210 nm. [c] Yield of purified compound after precipitation, >95% HPLC−UV purity at 210 nm. [d] Compound obtained as an oil. [e] Based on a 70% loading determined by TFA cleavage. [f] Based on a 50% loading.

The resins **5b**−**f** were prepared as previously described for resin **5a** and analyzed by on-bead FT-IR spectroscopy followed by HPLC−MS and ^{1}H NMR spectroscopy of the cleaved products. As shown by columns 1 and 2, the desired phthalimides **6a**−**f** were obtained in satisfactory yields and purities. Introduction of an alkyl substituent on the α-position of the amine did not affect the course of the cyclization. Thus, 1-methyl-3-phenylpropyl and cyclopentyl derivatives **6b** and **6f** were isolated in similar yields as *n*-alkyl-substituted compounds **6a** and **6c**. However, in the case of benzyl derivatives, the reduced reactivity of the amines resulted in lower yields. The desired phthalimides **6d** and **6e** were then obtained in 56 and 62% yields, respectively, according to the loading of the starting resins determined on the starting resins **5d** and **5e**. Aromatic amines could not be included in our study, as an autoinduced ring closure unexpectedly occurred during the conversion of resin **3** into the corresponding resins **5**. Interestingly, most of the compounds could be easily isolated in pure form by precipitation from acetonitrile−water mixtures. In a final set of reactions, the influence of the ring substitution was studied.

To this end, phthalimides characterized by different substitution patterns on the aromatic ring and various amines were synthesized (see Table 3). As already observed for modification of the amino part of the template, the introduction of substituents on the aromatic ring was well tolerated. The desired phthalimides **6** were generally obtained in good yields and satisfactory purities. Upon monitoring the cleavage of the supported materials from the support by FT-IR spectroscopy, we found that iteration of the cleavage sequence was sometimes required to reach a complete release of the products. Thus, phthalimides **6l** and **6n** derived from α,α-disubstituted amines and bearing electron-donating groups on the aromatic ring showed very low reactivity. After two irradiation cycles, full release of these compounds was, however, achieved, and satisfactory yields were obtained.

Table 3. Synthesis of Substituted Phthalimides **6a**,**g**−**n**

5, **6**	R_1[a]	R_2	yield[b] (%)	purity (%)	yield[c] (%)
a	H	C_3H_6Ph	80	95	68
g	4-F	C_3H_6Ph	58	86	/
h	4-F	C_5H_9	55	55	13
i	5-Br	C_3H_6Ph	87	81	/
j	4,5,6,7-F	C_3H_6Ph	66[d]	81[d]	/
k	5-CH_3	C_3H_6Ph	88	75	/
l	5-CH_3	C_5H_9	74[e] 77[f]	49[e] 99[f]	61
m	5,6-C_4H_4	C_3H_6Ph	81	95	73
n	5,6-C_4H_4	C_5H_9	102[e] 51[f]	61[e] 99[f]	78

[a] Numbering of groups R_1 determined on compounds **6**. [b] Crude yield. [c] Nonoptimized yield after precipitation or flash column chromatography, >95% HPLC−UV purity at 210 nm. [d] Referring to the 4,7-difluoro-5,6-dihydroxy derivative. [e] First irradiation. [f] Second irradiation.

These examples illustrate the advantage of a short cleavage that can eventually be repeated for the reaction of unreactive species in acceptable reaction times. We were also particularly interested in fluoro-substituted phthalimides. Previous attempts to synthesize these compounds in solution were indeed unsuccessful, due to the occurrence of aromatic nucleophilic substitution of the fluor by the amines as a side reaction. We were pleased to find that irradiations of fluoro-substituted resins **5g** and **5h** afforded the expected phthalimides **6g** and **6h**. In the case of the activated perfluoro derivative **6j**, hydrolysis on positions 5 and 6 due to the presence of water in DMF during the cleavage led to the isolation of the 4,7-difluoro-5,6-dihydroxy-derived phthalimide.

In conclusion, a rapid and efficient method for the traceless solid-phase synthesis of substituted phthalimides was developed. The reactions proceed under neutral conditions, and the desired compounds are obtained within minutes in good yields and purities. An extension of the method to solvent free conditions is actually being optimized and already allowed the synthesis of compound **6a** in a 25% isolated yield. We will report on these results in due course.

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Supporting Information Available: General procedures for the synthesis and characterization of resins **3** and **5**, and cyclative cleavage conditions and full characterization of the final compounds **6a**−**n**.

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