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Microwave-enhanced synthesis of cyclic amidines

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Abstract—We present a simple and efficient microwave based protocol for the synthesis of heterocyclic amidines by PPE promoted cyclodehydration of *N*-aryl-*N*′-acylalkylenediamines. The method is general for five- to eight-membered heterocycles and affords high yields of the desired products in remarkably short reaction times.

Cyclic amidines represent an heterocyclic core of wide pharmacological interest. Among them, dihydroimidazoles[1] and tetrahydropyrimidines[2] are found in many biologically active compounds. In addition, some derivatives have been employed as chiral ligands or auxiliaries.[3] In connection to this, we recently reported the synthesis and stereochemical study of some atropisomeric tetrahydropyrimidine derivatives, potentially useful in stereoselective synthesis.[4] Due to their broad spectrum of biological activity, dihydroimidazoles and tetrahydropyrimidines have received a great deal of attention in connection to their synthesis. In contrast, only scattered references on seven and eight-membered cyclic amidines (tetrahydrodiazepines and hexahydrodiazocines, respectively) are available in the literature.

Cyclocondensation is one of the most important methods for the synthesis of heterocycles. These reactions usually require long reaction times, high temperatures and catalyst with Lewis or strong BrØnsted acidity.[5] In particular, ring closure of α,ω-alkanediamine derivatives leading to cyclic amidines usually requires strongly acidic dehydrating reagents or high temperatures.[6] Such conditions may result in partial or total decomposition of sensitive substrates. In previous work we employed polyphosphoric acid esters PPE (ethyl polyphosphate) and PPSE (trimethylsilylpolyphosphate) as mild dehydrating agents for the preparation of tetrahydropyrimidines.[7] The main limitation of this procedure is that long reaction times are often required, resulting in lower yields of the products in some cases. Recently, PPE has been employed in microwave assisted Biginelli reactions,[8] while PPSE was used for dihydroimidazole synthesis by a combination of solid phase and microwave techniques.[9] Reactions performed under microwave irradiation proceed in general faster, more cleanly and with better yields than under conventional heating.[10] Such characteristics, along with the possibility of employing this reaction for high throughput preparation of such compounds, prompted us to investigate the use of microwave irradiation in the synthesis of cyclic amidines by PPE promoted cyclodehydration of *N*-aryl-*N*′-acylalkylenediamines. Among the synthesized derivatives, tetrahydropyrimidines **1a**,**b**,**f** were evaluated as antihelminthic agents.

In this work we have used a domestic microwave oven (Sanyo EM-D2013) adapted for reflux heating.[11] A chloroform solution of PPE was employed as dehydrating agent.[12] Reactions were thus conducted at chloroform reflux temperature under atmospheric pressure. We first examined cyclodehydration of *N*-(4-chlorophenyl)-*N*′-benzoyl-1,3-propanediamine. Under intermittent microwave irradiation,[13] compound **1a** was obtained in less than 2 min with high yield (entry 1), while conventional heating requires 2 h for the reaction to be completed.[14] Similar results were obtained when a fivefold amount of substrate was employed (entry 2). At a lower irradiation power (entry 3), only partial conversion to the product was achieved after 1 h, while employment of a higher potency (320 W) resulted in violent boiling of the reaction mixture even with intermittent heating (Table 1).

Employing the optimum irradiation power, we synthesized tetrahydropyrimidines **1b**–**f** (entries 4–8). No

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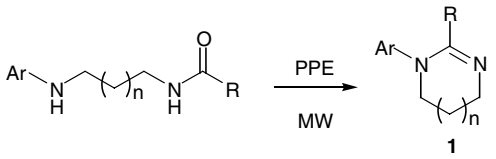
Table 1.



Entry	Compd **1**	Ar	R	*n*	Microwave irradiation			Conventional heating	
					Reaction time (min)	Pot. (W)	Yield (%)	Reaction time (h)	Yield (%)
1	**a**	4-ClC_6H_4	C_6H_5	1	1.30	240	98	2	96[a]
2[b]	**a**	4-ClC_6H_4	C_6H_5	1	1.30	240	97	2	96[a]
3	**a**	4-ClC_6H_4	C_6H_5	1	60	160	46	2	96[a]
4	**b**	4-ClC_6H_5	C_2H_5	1	1.30	240	92	5	79
5	**c**	4-$NO_2C_6H_4$	C_2H_5	1	1.30	240	97	5	83
6	**d**	4-$NO_2C_6H_4$	$C(CH_3)_3$	1	2.00	240	97	5	86
7	**e**	2,4,6-Tri$CH_3C_6H_2$	C_2H_5	1	2.00	240	91	5	82
8	**f**	C_6H_5	$C_2H_4C_6H_5$	1	1.30	240	79	5	73
9	**g**[c]	2-$NO_2C_6H_4$	C_6H_5	0	1.30	240	97	5	95
10	**h**	2-$NO_2C_6H_4$	$C(CH_3)_3$	0	2.00	240	93	5	89
11	**i**[c]	1-$C_{10}H_7$	C_6H_5	0	2.00	240	97	5	85
12	**j**	2-$NO_2C_6H_4$	C_2H_5	2	2.30	240	93	12	79
13	**k**	4-BrC_6H_4	C_6H_5	2	2.30	240	89	12	84
14	**l**	1-$C_{10}H_7$	$C(CH_3)_3$	2	6.50	320	84	12	77
15	**m**	C_6H_5	C_6H_5	3	6.00	320	83	2[d]	39
16	**n**	4-$CH_3C_6H_4$	C_6H_5	3	6.00	320	79	—	—

[a] Ref. 14.
[b] 5 mmol of the precursor and 30 mL of PPE were employed.
[c] Ref. 6c.
[d] Ref. 6b.

difference regarding reaction times was observed for derivatives with electron withdrawing groups in the *N*-aryl moiety. Instead, higher reaction times were required for compounds with steric hindrance either in the aryl or the R substituents (entries 6 and 7). Analogous results were obtained for dihydroimidazoles **1g–i** (entries 9–11). In all cases, reaction times were significantly shortened and yields improved if compared to conventional heating. Tetrahydropyrimidines **1a**,**b**,**f** were investigated as antihelminthic agents, showing moderate activity.[15]

To widen the scope of the method, we applied it to the preparation of seven- and eight-membered cyclic amidines, which usually require prolonged reaction times or more drastic conditions under conventional heating.[6b,16] Such compounds were specially interesting because only very few papers report on the microwave-assisted synthesis of seven-membered heterocyclic rings,[5] and none on their higher homologues. Tetrahydrodiazepines **1j–l** were obtained employing the same irradiation power but longer reaction times than the lower homologues, and showed an analogous dependence on steric hindrance (entries 12–14). Under the conditions described in the literature for *N*-nitroaryl derivatives (neat PPE, conventional heating at 120 °C, 2 h),[6b] hexahydrodiazocine **1m** was obtained in 39% yield. Employing microwave heating, compounds **1m**,**n** were obtained in 6 min with satisfactory yields (entries 15 and 16). Interestingly, no intermolecular condensation products were obtained for compounds **1j–n**.

In conclusion, we have developed a simple and efficient microwave based protocol for the synthesis of cyclic amidines, which does not require specialized equipment. The method is general for five- to eight-membered heterocycles with different substitution patterns and affords high yields of the desired products in remarkably short reaction times. The reaction conditions are sufficiently mild to be employed for the construction of the heterocyclic amidine system in more complex molecules, and suitable for high throughput synthesis of the compounds.

In a typical experiment, a mixture of the corresponding *N*-aryl-*N*′-acylalkylenediamine (1 mmol) and a chloroform solution of PPE (6 ml) was reacted in the microwave oven at the indicated potencies, alternating 10 s of irradiation and 10 s without irradiation.[13] After reaching room temperature, the resulting solution was extracted with water (5 × 6 ml). The aqueous phases were pooled, filtered and made alkaline in an ice bath and the mixture extracted with chloroform (2 × 30 ml). The organic layer was washed with water (5 ml), dried over sodium sulfate and filtered. The solvent was removed in vacuo. The crude products were purified by flash chromatography. The structure of all compounds was confirmed by ^{1}H NMR and ^{13}C NMR analyses. Spectral data of new compounds are given as Supplementary data.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.042.

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