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HMDS-Promoted *In Situ* Amidation Reactions of Carboxylic Acids and Amines

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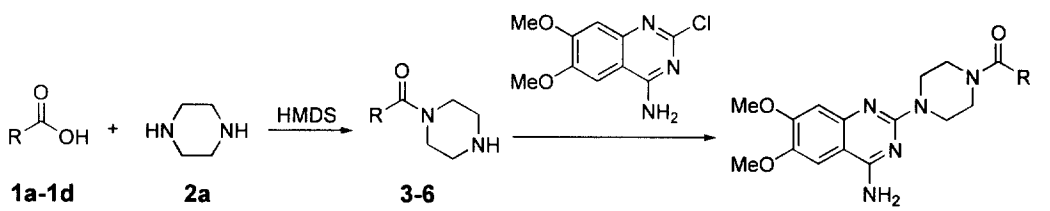
Abstract: A number of *N*-acylalkylenediamines were synthesized in high yields by *in situ* monoamidation of carboxylic acids with diamines. The amidation reactions were carried out simply by heating the substrates at 110 °C for 5–24 h in the presence of HMDS. © 1999 Published by Elsevier Science Ltd. All rights reserved.

As shown in Scheme 1, *N*-acylalkylenediamines[1] are important substrates used to react with 4-amino-2-chloro-6,7-dimethoxyquinazolines to give a variety of antihypertensive agents.[2] There is no precedent synthesis of *N*-acylalkylenediamines by direct monoamidation of acid derivatives with diamines, except for our recent report[3] on the monoamidation of methyl and ethyl esters of carboxylic acids. In this communication, we demonstrate that 1,1,1,3,3,3-hexamethyldisilazane (HMDS)[4,5] is an efficient reagent for amidation reactions of acids with amines. No prior conversion of acids to alkyl esters or other derivatives was required, even for monoamidation of acids with diamines.

Scheme 1



The conventional methods for direct conversion of carboxylic acids to amides[6] require either high reaction temperature (over 190 °C)[7] or special coupling reagents[8] such as carbodiimides, phosphorus reagents and uronium salts. These coupling reagents may require preparation or cause problems in isolation of the desired amidation products. On the other hand, HMDS is a cheap[9] and readily available reagent suitable for activation of carboxylic acids to the corresponding silyl esters,[5c,10] which react *in situ* with amines or diamines (Table 1). Any residual HMDS and its offspring NH_3 can easily be washed off by water upon work-up. Amines are

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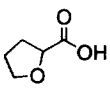
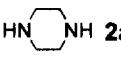
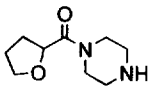
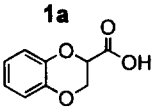
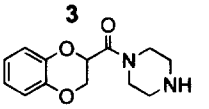
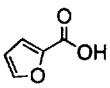
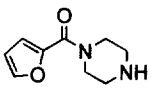
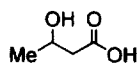
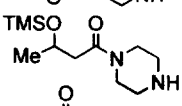
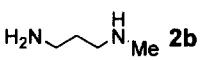
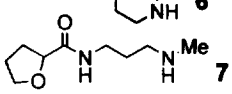
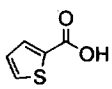
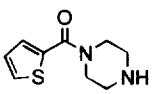
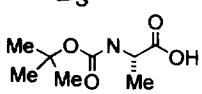
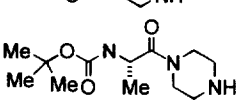
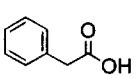
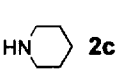
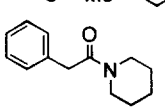
relatively reluctant to silylation by HMDS,[5d] thus amidation reactions occurred selectively in high yields.

Table 1. HMDS-Promoted Amidation Reactions[a]

Entry	Acid	Amine	Additive (eq)	Time (h)	Amide	Yield (%)
1	 **1a**	 **2a**	HMDS (1.0)	8	 **3**	93
2	**1a**	**2a**	TMSCl (1.0)	8	**3**	0[b]
3	**1a**	**2a**	—	8	**3**	0[b]
4	**1a**	**2a**	—	8	**3**	8[c]
5	 **1b**	**2a**	HMDS (2.0)	5	 **4**	91
6	 **1c**	**2a**	HMDS (2.0)	8	 **5**	83[d]
7	 **1d**	**2a**	HMDS (2.0)	20	 **6**	83
8	**1a**	 **2b**	HMDS (2.0)	8	 **7**	85
9	 **1e**	**2a**	HMDS (2.0)	24	 **8**	72[d]
10	 **1f**	**2a**	HMDS (2.0)	12	 **9**	87
11	 **1g**	 **2c**	HMDS (1.0)	12	 **10**	82

[a]The reaction was conducted by heating a mixture of acid, amine and additive at 110 °C for the indicated duration. No solvent is used. [b]Starting material was recovered. [c]The reaction was carried out at 150 °C. [d]A small amount of diamide (5-9%) was also produced.

A typical procedure for the amidation reactions (Table 1) is described. HMDS (1–2 mmol) was added to a mixture of appropriate carboxylic acid **1a–g** (1 mmol) and amine **2a–c** (1–2 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 110 °C for 5–24 h to complete the amidation reaction by monitoring TLC analysis. After cooling, the mixture was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The organic phase was washed with water, dried (Na_2SO_4) and chromatographed to give the desired amides **3–10** in 72–93% yields. All products are fully characterized by comparison with the authentic samples previously prepared in our laboratory.

Though monoamidation of alkylenediamines with an acid chloride has been reported for the preparation of *N*-acylalkylenediamines, however, the reaction requires appropriately masked diamines such as monoacetates or hydrogen halides.[1,2] Otherwise, undesired diamidation can also occur. For example, a previous preparation of **3** (60% yield) requires a tedious procedure: (i) treatment of furan-2-carboxylic acid (**1c**) with $SOCl_2$ to give the acid chloride, (ii) amidation with piperazine hydrobromide in MeOH, and (iii) catalytic hydrogenation of the furan moiety to tetrahydrofuran. The alternative procedure by heating tetrahydrofuran-2-carboxylic acid (**1a**) and 2 equivalents of piperazine (**2a**) in the presence of HMDS (1 equiv.) gave a 93% yield of **3**, a useful precursor of the popular antihypertensive drug Terazosin. The HMDS appeared to promote monoamidations selectively. For example, no diamide was found by treating the amide **4** with the acid **1b** (1:1) in the presence of HMDS at 110 °C for 5 h. Only the silyl ester of **1b** was formed. Our present method is obviously superior in terms of selectivity, high yield and simple operation.

An excess of HMDS can be used as the solvent and silylating agent when the starting materials of high melting points involved. In the absence of HMDS (entries 3 and 4), no desired amidation occurred at 110 °C, and only a small amount (8%) of **3** could be obtained after a prolonged heating of the substrates at 150 °C in a sealed tube. We also evaluated the possibility of using chlorotrimethylsilane (TMSCl)[11] as a promoter in the amidation reactions. When TMSCl was added to the mixture of **1a** and **2a** (entry 2), a solid mass formed immediately. No desired amidation product was found after heating for 8 h.

The HMDS-promoted *in situ* amidation reactions are generally applicable to the synthesis of *N*-acylalkylenediamines **4**–**7** for using in generic antihypertensive drugs, Doxazosin, Prazosin, Metazosin and Alfuzosin. The reactions proceeded smoothly with aliphatic or aromatic acids including the substrates bearing oxy or amino substituents at the α- or β- positions. The β-hydroxyl group gave the silyl ether along with the amidation (entry 7). A small amount of diamide (5–9 %) could be formed in case a more reactive aromatic acids was used as the starting material (entries 6 and 9). Fortunately, the side product could be removed by simple extraction. All of the examined acyclic and cyclic diamines were suitable to the monoamidation reactions. The primary amine appeared to have higher reactivity than the secondary amine in the amidation (entry 8). Though secondary amines are reluctant to amidation in the absence of activation reagents, we could still carry out the amidation reaction with piperidine (a secondary monoamine) by the promotion of HMDS (entry11).

Amidation of *N*-Boc-L-alanine was also carried out at 110 °C (entry 10) . The *t*-Boc group did not interfere with this reaction, but a considerable racemization occurred, giving amide **9** with 25% ee. This reaction was improved by amidation at 75 °C to afford **9** in 91% ee[12] (40%). On the other hand, the methyl ester of *N*-Boc-L-alanine could not react with piperazine at 75 °C. Under the similar conditions (HMDS, piperazine, 75 °C, 12 h), tetrahydrofuran-2-carboxylic acid was successfully converted to the amide **3** (38%), but the corresponding ester was inert. These experiments show that amidation from acids using the present method may have advantage over the procedure from esters.[3]

In summary, we have demonstrated a general and efficient method of amidation by using HMDS as the promoter. The operation is simple, and the desired secondary and tertiary amides are prepared in high yields for further elaboration to antihypertensive agents.

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8. All references cited on page 279-281 in reference 6(a).
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10. The silyl ester of **1b** was prepared by treating **1b** with HMDS at 110 °C for 2 h, and its subsequent reaction with piperazine at 110 °C for 5 h yielded the desired amide **4**.
11. TMSCl has been used to catalyze the estification of carboxylic acids. Nakao, R.; Oka, K.; Fukumoto, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1267.
12. The enantiomeric excess of **9** (mp 142.0-142.5 °C, $[\alpha]_D^{23}$ -18.5° (c 0.2, MeOH)) was determined to be 91% by HPLC analysis with chiral stationary phase (Chiralcel OJ column (Daicel) using 2-propanol:n-hexane, 1:10 as the eluent) and also compared with the sample (prepared at 0 °C by using BOP-Cl as the coupling reagent).