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A CONVENIENT SYNTHESIS OF AMIDES FROM CARBOXYLIC ACIDS AND PRIMARY AMINES

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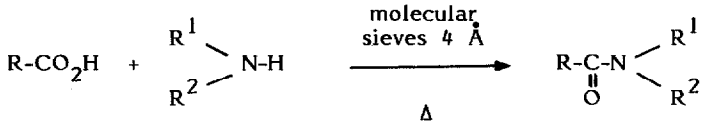
Abstract : *A convenient method for the formation of carboxamides from carboxylic acids and primary amines in the presence of molecular sieves is described. This process is very chemoselective.*

There is considerable interest in the formation of amides from carboxylic acids and amines, as the methods employed may also be utilized in peptide and lactam synthesis. In general, the formation of carboxamides from amines and carboxylic acids implies the activation of the carboxyl.

A frequently used method for the conversion of carboxylic acids into carboxamides involves the transformation of the acid into acyl chloride[1], but in most cases a one-pot procedure has been used[2], utilizing reagents to promote the coupling reaction between acids and amines. Most of the coupling reagents first react with the carboxylic acids to give activated intermediates which undergo subsequently a nucleophilic attack by amines. Carbodiimides, in particular dicyclohexylcarbodiimide (DCC)[1,3], are frequently used as condensing agents. However, the DCC method usually leads to the formation of N-acylureas and carboxylic anhydrides as by-products, rendering the isolation of the desired carboxamides difficult. Similar problems were encountered with the acyl carbamate method[4] which affords the carboxamides only in moderate yield even after long reaction times. N,N'-Carbonyldiimidazole[5] is a reactive acylating agent but the intermediates are very sensitive to moisture. To overcome these problems, many condensing agents have been reported such as N,N'-disuccinimidyl carbonate[6], N-succinimidyl diphenylphosphate[7], and oxalate derivatives[8], which act as activating agents without further coupling reagent such as DCC. Benzotriazole[9], tetrazole[10], benzoxazole derivatives[11] and phosphorus containing reagents[12] are efficient coupling agents but they have to be prepared before use. Triazine[13], 2,2'-dipyridyl disulfide[14], pyridinium salts[15] are commercially available but they do not present any selectivity between primary and secondary amines.

Sultones[16], boranes[17], chlorosulfonyl isocyanate[18], sulfinylamines[19], di-n-butyltin oxide[20] are also used as coupling reagents but either low yields were obtained or no general application has been found.

We report here a facile, mild, general and selective formation of carboxamides from carboxylic acids and primary amines by a one-pot reaction using molecular sieves.



A summary of the results is given in the table. Primary amines react with saturated, ethylenic or alkynic acids (entries 1-6 and entries 17-21) at 140°C to give, after two hours, the formation of the corresponding carboxamides. The obtention of amides from aromatic amines requires a temperature of 170°C (entries 7-8). On the contrary, reaction of secondary amines with carboxylic acids leads to the formation of the ammonium salt rather than carboxamides even at 180°C (entries 9-11). One exception is, however, observed with pyrrolidine (entry 12). This difference of reactivity between pyrrolidine and other secondary amines is due to the higher nucleophilicity of pyrrolidine[21].

When aminoalcohols are reacted with acids in the presence of molecular sieves, the formation of the ester is not detected, but only the amide is obtained in good yield (entries 15-16).

The convenience of handling of molecular sieves, their low price and the high chemoselectivity of the reaction may make this process the method of choice for the large scale preparation of primary carboxamides.

Experimental part

A mixture of carboxylic acid (5.3×10^{-3} moles), amine (5.3×10^{-3} moles) and activated 4 Å molecular sieves (0.2 g) is heated under argon. After 2 h, methylene chloride (10 ml) is added. The reaction mixture is filtered on Celite and washed with methylene chloride. The amide is purified by cristallisation or on a silica gel column with a mixture of methanol-chloroform as eluent.

Table

Entry	Acid 1	Amine 2	T°C	Yield [a] %	m.p. °C (Lit. m.p. °C)
1	phenylacetic acid	benzylamine	140	95	118-119 (119)[23]
2	"	allylamine	140	98	59-61 (60-61)[24]
3	"	N,N'-dimethyl ethylamine	140	98	oil
4	"	methoxyethyl amine	140	99	oil
5	"	isopropylamine	140	95	79-80
6	"	H_2N-$(CH_2)_3$NHTS	140	95	110
7	"	toluidine	180	70	116-117
8	"	aniline	180	50	98
9	"	morpholine	180	0	-
10	"	N-methyl cyclohexylamine	180	0	-
11	"	diallylamine	180	0	-
12	"	pyrrollidine	150	98	oil
15	"	H_2N-$(CH_2)_3$-OH	150	90	oil
16	"	prolinol	150	95	oil
17	propionic acid	H_2N-$(CH_2)_3$-NHTS	140	90	95
18	hydrocinnamic acid	"	140	90	115-116
19	trans-cinnamic acid	"	140	95	93-94
20	4-pentenoic acid	"	140	60	110-112
21	4-pentynoic acid	"	140	97	74-73

[a] Isolated yield. Satisfactory microanalyses were obtained C±0.25, H±0.12, N±0.13.

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