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Note

Ceric ammonium nitrate (CAN) promoted efficient solid phase synthesis of amide derivatives: A green approach

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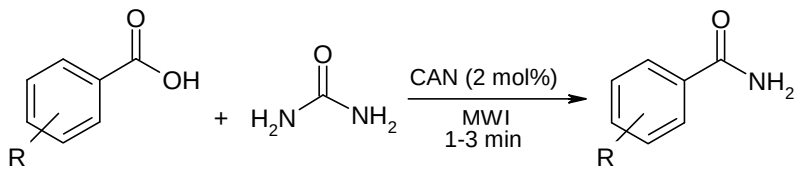
Ceric ammonium nitrate (CAN) has been found to be an efficient catalyst for the solid phase synthesis of amide derivatives of a wide range of substituted carboxylic acids and urea in excellent yields under microwave irradiation conditions. High yields are achieved even on a gram scale, while reaction times are considerably shortened. This method displays both economic and environmental advantages.

Keywords*:* Ceric ammonium nitrate (CAN), solid phase, amides, microwave irradiation

The amide functionality is an important unit among the naturally occurring and synthetic organic molecules[1,2]. Several protocols have been devised for the amide bond formation, the notable being the solid-phase assembly of peptides[2b]. The formation of carboxamides from carboxylic acids implies the activation of the carboxyl group[3]. The most common methods involve either conversion of carboxylic acid to a more reactive functional group such as an acyl chloride, mixed anhydride, acylazide or ester, or *via* an *in situ* activation of carboxylic group by some coupling reagents such as carbodiimides[4,5]. Other systems such as titanium or divalent tin reagents of the type $Sn(N(TMS)_2)_2$ (Ref. 6), treatment with equivalent amounts of triphenylphosphine and NBS[7] or with trichloroacetonitrile[8] were also recommended. However, many of these procedures involve extended reaction times, use of expensive reagents, high temperature reaction condition, *etc*. Therefore, there is a scope to find potential alternate procedures, especially those that are in high demand and having advantages such as low cost, non-toxic, and environmentally benign.

In this regard and in continuation of the interest in developing novel synthetic methodologies, particularly, carbon-carbon, carbon-heteroatom bond formation[9], and being interested in the use of lanthanide salts as environmentally friendly reagents for organic synthesis, a study of the utility of lanthanide salts as catalyst for the synthesis of amide derivatives was undertaken. Among the lanthanide reagents, cerium(IV) ammonium nitrate (CAN) is one of the most important catalyst in organic synthesis. It is useful for introducing and removing protecting groups *via* single electron transfer or Lewis acid catalyst[10]. Recently CAN has been utilized for many synthetic organic transformations[11]. This reagent has been reviewed[12] for reactions involving C-N, C-S, C-Se, C-X bond formations, which prompted the exploration of the utility of cerium(IV) catalyst for the synthesis of amides from urea, a source of ammonia, and carboxylic acids. Accordingly, herein is reported the carboxylic acid-urea reaction in the presence of catalytic amount of CAN (2 mol%) under microwave irradiation with high yields and with a short reaction time (**Scheme I**).

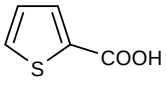
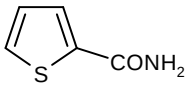
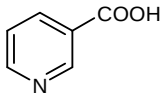
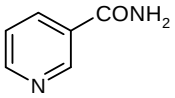
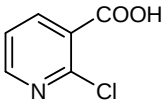
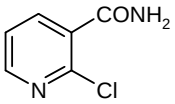
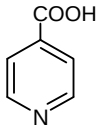
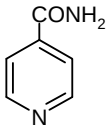
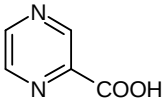
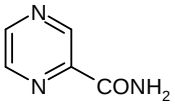
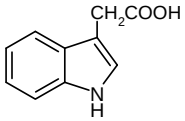
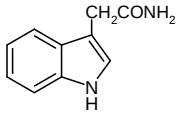
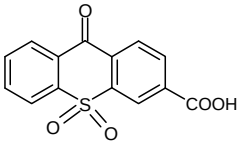
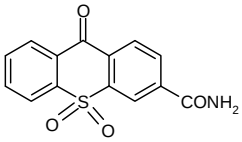
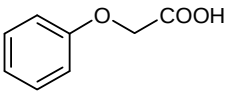
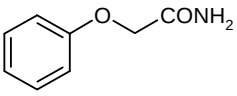
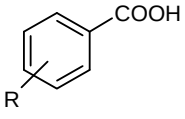
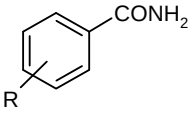
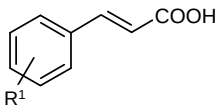
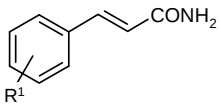
The reaction of benzoic acid with urea in the presence of CAN (2 mol%) under microwave irradiation gave the corresponding product in 90% yield (**Table I**). There was no reaction in the absence of catalyst even after irradiating for a longer time, indicating that this is indeed a CAN catalyzed reaction and the use of a smaller amount of CAN (1 mol% or 1.5 mol%) took longer time for completion of the reaction. To demonstrate the generality and scope of this method, the reaction was carried out with various structurally diverse carboxylic acids such as aromatic carboxylic acids, hetero aromatic acids,



1 **2** **3**

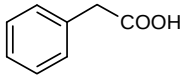
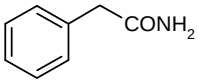
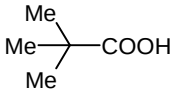
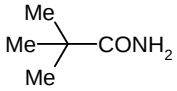
Scheme I

Table I — CAN-promoted efficient solid phase synthesis of amides

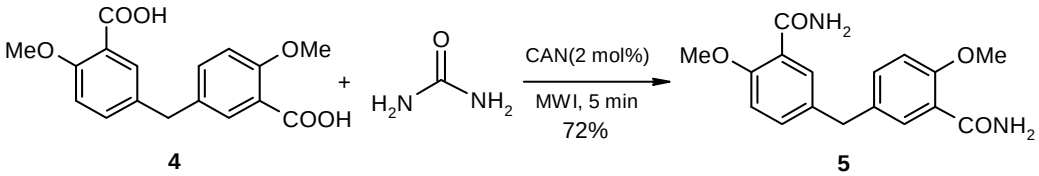
Entry	Carboxylic acid	Time (sec)	Product	Yield (%)[a]
1		90		85
2		90		88
3		120		87
4		120		91
5		60		90
6		90		89
7		180		82
8		60		86
9	 R=H	60	 R=H	90
10	R = 2-Cl	120	R = 2-Cl	82
11	R = 4-Cl	120	R = 4-Cl	86
12	R = 4-CH_3	150	R = 4-CH_3	77
13	R = 4-OCH_3	180	R = 4-OCH_3	78
14	R = 4-NO_2	60	R = 4-NO_2	92
15	 R^1=H	90	 R^1=H	86
16	R^1 = 4-Cl	180	R^1 = 4-Cl	84
17	R^1 = 2-NO_2	90	R^1 = 2-NO_2	92

— Contd

Table I — CAN-promoted efficient solid phase synthesis of amides — *Contd*

Entry	Carboxylic acid	Time (sec)	Product	Yield (%)[a]
18	R^1 = 4-NO_2	60	R^1 = 4-NO_2	92
19		180		88
20		180		89

[a]The yields refer to isolated products that exhibited physical and spectral properties (^{1}H NMR, MS and IR spectra) in accord with the assigned structure.



4 **5**

Scheme II

α,β-unsaturated carboxylic acids, phenylacetic acids, bearing electron-withdrawing and electron-releasing groups, and urea and it was found that in all the cases high yields of product are formed. The results with a variety of substrates are summarized in **Table I**. The carboxylic acids with electron-releasing groups undergo reaction at a relatively slower rate (entries 12, 13) when compared to aromatic acids with electron-withdrawing groups (entries 4, 5, 14, 17). Among the cinnamic acids, the reaction is slower for 4-chlorocinnamic acid (entry 16) when compared to other cinnamic acids. The isolated products were characterized by IR, ^{1}H NMR and mass spectroscopy.

This reaction is further explored for the synthesis of 5-[3-(aminocarbonyl)-4-methoxy benzyl]-2-methoxybenzamide **5** by the reaction of 5-(3-carboxy-4-methoxybenzyl)-2-methoxy benzoic acid **4** and three equivalents of urea under similar conditions. Compound **5** is obtained in excellent yield (**Scheme II**).

In conclusion, a solvent-free/solid phase procedure that utilizes easily accessible reagents, in a simple and efficient approach, has been developed to prepare amides in good to excellent yields. The attractive features of this method are operational simplicity, faster reaction rates, high conversions, and cleaner reaction profile, non-toxic, inexpensive and environmentally friendly catalyst, all of which make it a useful and attractive strategy for the preparation of various amide derivatives, simply by changing the substrates (carboxylic acids).

Experimental Section

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. NMR spectra were taken with a Varian Gemini (200 MHz) spectrometer. IR spectra were obtained using Perkin-Elmer spectrum BX series FT-IR 5000 spectrometer. Mass spectra were performed on a VG-micromass 7070H spectrometer. For microwave irradiation the unmodified house hold microwave oven (LG Electronics, India Ltd.) was used.

General procedure for the synthesis of amides 3. A mixture of carboxylic acid (1 mmol) and urea (2 mmol) was ground well and mixed with CAN (2 mol %). The mixture was taken in a glass tube and was irradiated at 160 W for the specified time (**Table I**). On completion of the reaction, (monitored by TLC hexane: EtOAc, 4:1 v/v), the reaction mixture was cooled to RT and extracted with ethyl acetate. The extract was washed successively with a solution of 2 M HCl, 5% $NaHCO_3$ and with water. The organic layer was dried over anhyd. $MgSO_4$ and the solvent removed under reduced pressure to afford a residue that upon triturating with hexane gave the product. The obtained product was purified by simple washing with hexane.

Pivalamide (entry 20). White solid, m.p. 181-82°C; IR (KBr): 3250, 2935, 1663, 1425 cm^{-1} ; ^{1}H NMR (DMSO-d_6): δ 4.89 (s, 2H), 1.33 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 172.6, 35.6, 23.2; MS: *m/z* 102 $(M+1)^+$. Anal. Calcd. for $C_5H_{11}NO$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.02; H, 10.89; N, 13.77%.

5-[3-(aminocarbonyl)-4-methoxybenzyl]-2-methoxybenzamide, 5. Pink solid, m.p. 260-62°C; IR (KBr): 3352, 3190, 2960, 1663, 1620, 1425, 1270 cm^{-1}; ^1H NMR (DMSO-d_6) : δ 8.02 (bs, 4H), 7.44 (d, *J* =8.7, 2H), 7.30 (s, 2H), 7.0 (d, *J* =8.7, 2H), 4.95 (s, 2H), 3.7 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 176.6, 160.2, 135.7, 132.8, 127.6, 117.8, 56.3, 42.7; MS: *m/z* 315 $(M+1)^+$. Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.92; H, 5.73; N, 8.90%.

Acknowledgements

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