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CAN PROMOTED SYNTHESIS OF AMIDE DERIVATIVES:A GREEN TECHNOLOGY FOR PHARMACEUTICALS

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ABSTRACT

Green technologies are required essentially to protect our environment from pollution. These techniques are potentially valuable as they reduce the need for organic solvents and also increase 'atom economy' by improving product selectivity and chemical yield. This method displays both economic and environmental advantages. High yields are achieved even on a gram scale, while reaction times are considerably shortened. Ceric Ammonium Nitrate (CAN) has been found to be an efficient catalyst for the solid phase green synthesis of amide derivatives of substituted carboxylic acid with urea in excellent yields under microwave irradiation conditions.
Present paper reveals the method of synthesis of some amide derivatives using CAN as catalyst and their pharmaceutical applications have been reviewed.

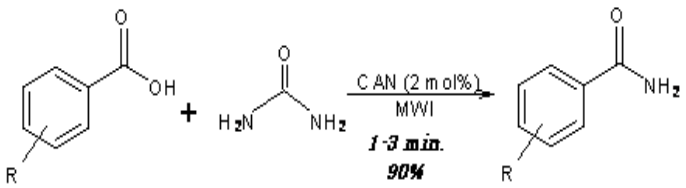
KEYWORDS

Atom economy, CAN, Microwave irradiation, Amide derivatives.

INTRODUCTION

Microwave-assisted rapid organic reactions constitute an emerging green technology that could make industrially important organic synthesis more eco-friendly than conventional reactions[1]. CAN provides both an inexpensive and nontoxic green solution to the synthesis of many amide derivatives of pharmaceutical uses.[2] Microwave may be considered as more efficient source of heating than conventional systems[3,4] .The reactions in solid phase occur more efficiently and more selectivity compared to reactions carried out in conventional solvents. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and are especially important in pharmaceutical industry. Attempts have been made to design synthesis for manufacturing processes in such a way that the waste products are minimum, they have no effects on the environment and their disposal is convenient.[5]

Among the lanthanide reagents cerium (IV) ammonium nitrate (CAN) is one of the most important catalyst in organic synthesis.[6] 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 short reaction



Scheme 1

time(Scheme1).

The reaction of benzoic acid with urea in the presence of CAN (2mol%) under microwave irradiation gave the corresponding product in 90% yield. 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.

MATERIAL AND METHOD

Fisher Johns apparatus was used for determining melting point of the amide derivatives. NMR spectra of the products were taken with a Varian Gemini (200MHz) 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 microwave oven (LG Electronics, India Ltd.) has been used.

GENERAL PROCEDURE

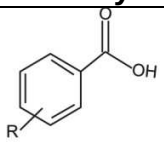
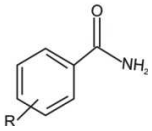
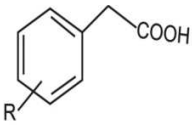
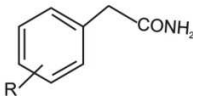
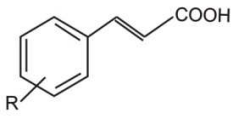
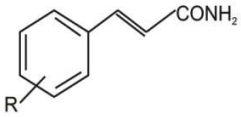
CAN (2 mol %) has been mixed with carboxylic acid(1mmol) and urea (2mmol) .The mixture was subjected under microwave irradiation at 160W for 1 minute. On completion of the reaction, the reaction mixture was cooled to room temperature and extracted with ethyl acetate.Washing of the extract was done with solution of 2 M HCl, 5% $NaHCO_3$ and with water. The organic layer was dried over anhydrous $MgSO_4$. The substituted amide derivatives obtained were purified by simple washing with hexane.

RESULTS AND DISCUSSION

A solvent free/ solid phase procedure with easily accessible reagents, in a simple and efficient approach, has been developed to prepare amides in excellent yields (Table 1).

Table1.

CAN Promoted MORE Synthesis of Amide Derivatives

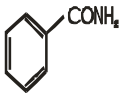
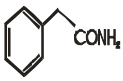
S.No.	Carboxylic acid	Time (sec.)	Product	Yield (%)
				
1.	R=H	60	R=H	90
2.	R=2-Cl	120	R=2-Cl	82
3.	R=4-Cl	120	R=4-Cl	86
4.	R=4-CH_3	150	R=4-CH_3	77
				
5.	R=H	180	R=H	88
6.	R=2-Cl	220	R=2-Cl	90
				
7.	R=H	90	R=H	86
8.	R=2-Cl	180	R=2-Cl	80
9.	R=4-Cl	180	R=4-Cl	84
10.	R=4-CH_3	210	R=4-CH_3	90

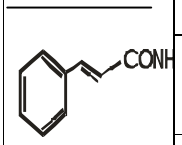
The microwave irradiation reactions were usually completed within 3-5 minute, in comparison to normal heating that requires 12 hours for completion of reaction.

The N-substituted benzamide derivatives have been reviewed as given in (Table-2) for antibacterial, anti-inflammatory, analgesic and antiulcer actions.[7] Pharmaceutical compositions of amide derivatives are used as, therapeutic agents for hypertension, angina, pectoris, asthma, renal and peripheral circulatory disturbances and inhibitors of vasospasm. The compounds are useful where cell death is due to trauma, viral infection, neurodegenerative disorder, cardiovascular disease, immune deficiency disorder, autoimmune disorder, renal disease, syndromes or pancreatitis. Substituted benzamides are acting as inhibitors of HIV protease[8]

Table 2.

Pharmaceutical Applications of Amide Derivatives

S.N.	Amides	Derivatives	Pharmaceutical Applications	R.N.
1.		(a) 4-[(methyl sulfonyl) amino] benzamides	Antiarrhythmic	9
		(b) N-(2-hydroxy-4 substituted phenyl) benzamides	Antimicrobial	10
		(c) (2- oxochromen-3-yl) benzamides	Antiinflammatory	11
		(d) N- (β diethylaminoethyl) benazamide	Tuberculostatic	12
		(e) 2,2' Dithio (2-hydroxy phenyl) Benzamide (DNBH)	Antibacterial	13, 14
		(f) 3-[(2,4-dioxothia zolidin-5-yl) methyl] benzamide	Antidiabetic	15
		(g) Acylaminosalicylic acid amide	Pesticide	16
2.		(a) (1,3-oxazolidin-3-yl) phenyl acetamide	Antitumor	17
		(b) Gem-difluoro derivative of phenylacetamide	Antiinflammatory & antirheumatic	18
		(c) N-substituted phenylacetamide	Antineuropathic Antirheumatoid arthritis & Antiinflammatory	19
		(d) N,N-Diethyl Phenyl acetamide	Insect repellent on foetus and	20

			reproduction in rats	
		(e) N-Substituted Phenylacetamide	Antimicrobial	10
3.		(a) p-Arylthio cinnamide	Antagonist & antiinflammatory	21, 22, 23
		(b) N-(Phenylalkyl) cinnamide	Antagonist	24,25
		(c) Piperidinylindoline cinnamide		
		(d) Aminocycloalkyl Cinnamide	Arrhythmia, Analgesic & Anesthetic	26

This method is no time one pot synthesis and is a boon for developing pharmaceutical industry in India, as for its operational simplicity, faster reaction rates, high conversions and cleaner reaction profile, non-toxic, inexpensive and environmentally friendly, that makes it a useful and attractive strategy for the preparation of various amide derivatives.

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