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LETTERS

Solvent-free synthesis of amides from non-enolizable esters and amines using microwave irradiation

Rajender S. Varma [*,†] and Kannan P. Naicker

Department of Chemistry and Texas Research Institute for Environmental Studies (TRIES), Sam Houston State University, Huntsville, Texas 77341-2117, USA

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Abstract

An efficient solid state synthesis of amides is described from non-enolizable esters and amines using potassium *tert*-butoxide under microwave irradiation conditions. © 1999 Elsevier Science Ltd. All rights reserved.

The amide functionality is an important unit among the organic molecules, naturally occurring or synthetic.[1,2] Several protocols have been devised for the amide bond formation, the notable being the solid-phase assembly of peptides.[2b] Although the direct transformation of carboxylic esters to amides is a potentially important synthetic operation, the eco-friendly practical pathways are rather limited for a number of reasons.[1,2] Ester aminolysis, in general, occurs under harsh conditions that require high temperatures and extended reaction periods,[3] or the use of strong alkali metal catalysts under conditions that are not amenable to molecules bearing sensitive functional groups.[4]

The earlier reported direct conversion of esters to amides is normally conducted under stringent conditions employing reagents such as sodium methoxide,[5] lithium aluminum hydride,[6] sodium hydride,[7] sodium metal,[8] butyllithium,[7] potassium amide,[9] Grignard reagents,[10] silicon tetrachloride,[11] boron tribromide[12] and 2-pyridone,[13] although their broader utility has not been established. The void for practical synthetic routes to tertiary amides, however, remains unfulfilled in spite of the use of activated amines such as tin,[14] aluminum[4,15] titanium amides[16] and lithium amides[17] in a specific case for the assembly of amino-*N*-dialkylamides. In continuation of our ongoing research program on solvent-free organic transformations using microwave (MW) or ultrasound irradiation,[18] we decided to explore a convenient, general and efficient solventless route to amides from amines and carboxylic ester that is applicable to tertiary amides. A recently described synthesis of *N*-acylalkylene diamines from the corresponding carboxylic esters and alkylenediamines that requires prolonged reaction time (3–16 h),[19]

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[*] Corresponding author. Fax: (409)-294-1585; e-mail: chm_rsv@shsu.edu

[†] As of August 15, 1999: US Environmental Protection Agency, National Risk Management Research Laboratory, 26 West Martin Luther King Drive, Cincinnati, Ohio 45268, USA.

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prompts us to report our results under solvent-free conditions that proceed to completion in a much shorter time (1–7 min).

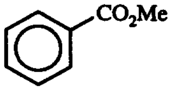
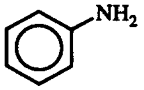
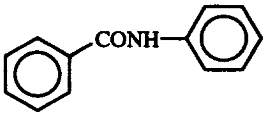
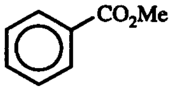
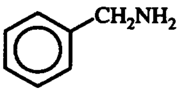
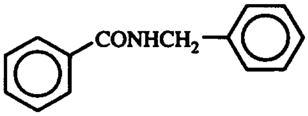
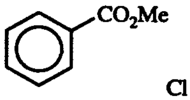
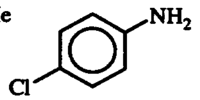
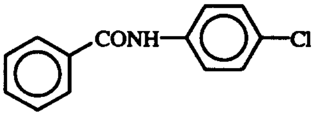
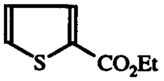
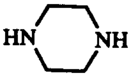
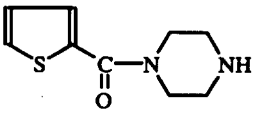
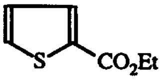
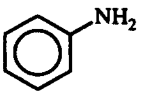
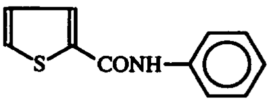
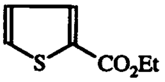
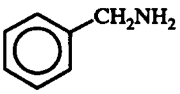
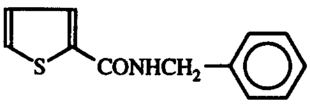
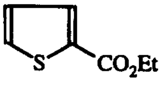
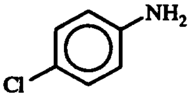
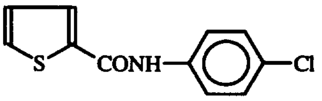
Our simple procedure entails the addition of solid potassium *tert*-butoxide (*t*-BuOK) to a premixed mixture of ester (1 mmol) and amine (1 mmol) and exposing the reaction mixture to microwave irradiation in an unmodified household MW oven.

$$RCO_2X \quad + \quad R'NH_2 \quad \xrightarrow[t\text{-BuOK}]{\text{Microwave}} \quad RCONHR'$$

$$X = Me, Et\ ;\ R = C_6H_5, C_4H_3S;\ R' = C_6H_5, p\text{-}ClC_6H_4, C_7H_7$$

Table 1

Solvent-free synthesis of amides from esters and amines using potassium *tert*-butoxide

Entry	Starting Materials		Products	Time (min)	Yield (%)[a]
	I	II			
1				1	83
2				0.75	91
3				1	85
4				3	55[b]
5				7	75
6				2	75
7				6	80

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[a] The yield refers to isolated products that exhibited physical and spectral properties (NMR and IR spectra) in accord with the assigned structures; [b] Yield obtained by GC-MS analysis.

The results for a variety of substrates are summarized in Table 1. The aryl amines undergo reaction at a relatively slower rate when compared to alkyl amines but the reaction is sluggish with secondary amines (entry 4). Among the esters, the reaction is slower for ethyl-2-thiophenecarboxylate when compared to methylbenzoate. Aliphatic esters (ethyl acetoacetate) do not undergo this conversion to amides as several products are formed in these reactions.

General procedure for the preparation of amides: The synthesis of benzanilide is representative of the typical procedure employed. Potassium *tert*-butoxide (1 mmol) was added to a premixed mixture of aniline (1 mmol) and methylbenzoate (1 mmol) in a glass test tube which was placed in an alumina bath (neutral alumina: 125 g, mesh ~150, Aldrich; bath: 5.7 cm diameter) inside an unmodified household microwave oven and irradiated for the specified time at its full power of 900 watts (see Table 1). On completion of the reaction, as determined by TLC (hexane:EtOAc, 4:1, v/v), the reaction mixture was extracted into ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to afford a residue that upon trituration with hexane gave pure product, benzanilide (83%).

In conclusion, we have developed a solvent-free procedure that utilizes easily accessible reagents, in a simple and efficient approach, to prepare amides in moderate to good yield. The operation simplicity, faster reaction rates, and ease of manipulation renders this a useful and attractive protocol.

Acknowledgements

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