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Fast Solvent-free Alkylation of Amides and Lactams under Microwave Irradiation

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Abstract: *N*-Substituted amides and lactams are rapidly *N*-alkylated under solvent-free phase-transfer catalytic conditions using microwaves.

Keywords: amides, lactams, *N*-alkylation, solvent-free, microwave.

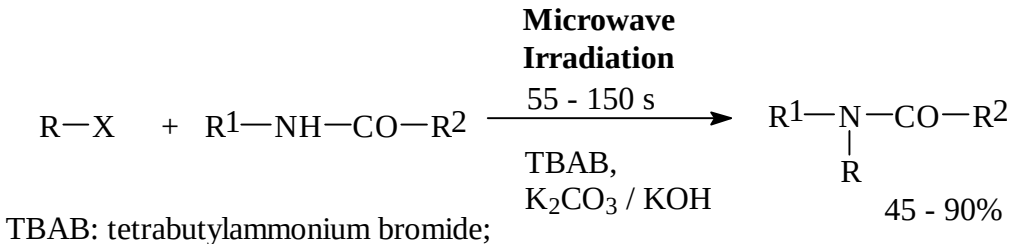
Introduction

The *N*-alkylation of amides to *N,N*-disubstituted amides is an important transformation in organic synthesis because disubstituted amides are valuable material for the synthesis of tertiary amines [1]. On the other hand, amides are very weak bases so they must first be converted to their conjugate bases in order to be alkylated [2]. For instance, the preparation of *N*-substituted and *N,N*-disubstituted amides can be performed with their sodium salts and alkyl bromides or iodides [3]. In the past, three methods were applied to convert amides into their alkali salts and further preparation of substituted amides. In the first method, an amide and sodium were dispersed in an inert solvent followed by addition of an alkyl halide [4]. In the second, a mixture of amide, potassium hydroxide, and alkyl halide was reacted in an ethanolic solution [5], whereas third method utilised sodium hydride to form the sodium salt of an amide followed by addition of an alkyl halide [6]. All of them suffered from prolonged reaction time under rather drastic conditions. Later, it have been found that amides could be turned into their salts and directly alkylated without the preliminary step of salt formation under phase-transfer catalytic (PTC) conditions [7].

Results and Discussion

The use of inorganic solid materials for the supports of organic reactants and catalysts have been broadly exemplified and well established as environmental benign technology [8]. In recent years, it has been shown that microwave irradiation was of particular benefit for such reactions, particularly for the reactions carried out in the absence of solvents [9]. The solventless reactions offer a number of advantages: solvents are often expensive, toxic, and difficult to remove in the case of aprotic solvents with high boiling point. Moreover, the absence of solvent reduces the risk of explosions when reaction takes place in a microwave oven, and the liquid-liquid extraction can be avoided for the isolation of reaction products. At present, the reactions under solid-liquid phase-transfer catalytic (PTC) conditions which are specially useful for anionic activation processes are numbered among the 'dry' reactions [10].

Since we have shown that many different compounds could be alkylated under solvent-free PTC [11] conditions, in particular phthalimide [11f], we decided to explore the use of microwave heating under such conditions for *N*-alkylation of other amides. In continuation of our ongoing program on microwave chemistry, we report a facile protocol for *N*-alkylation of *N*-substituted amides and lactams (Scheme 1).



TBAB: tetrabutylammonium bromide;

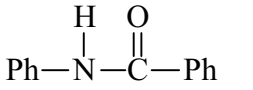
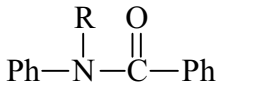
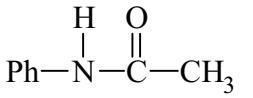
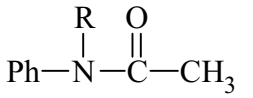
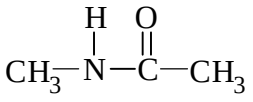
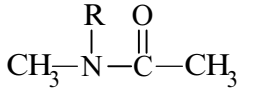
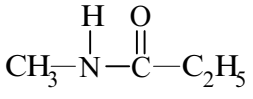
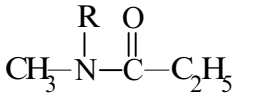
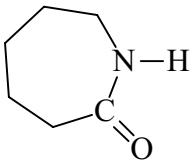
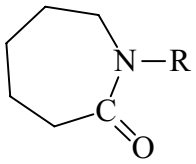
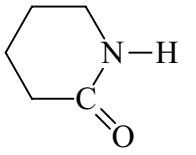
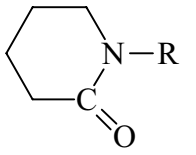
$R^1—NH—CO—R^2$: acetanilide, benzanilide, caprolactam, valerolactam, N-methylacetamide, N-methylpropionamide.

R: butyl, hexyl octyl, benzyl

Scheme 1.

The reactions were carried out by simply mixing of an amide with 50% excess of an alkyl halide and a catalytic amount of tetrabutylammonium bromide (TBAB). The mixtures were adsorbed on the mixture of potassium carbonate and potassium hydroxide and then irradiated in an open vessel in a domestic microwave oven for 55-150 s. The results of the reactions are summarized in **Table.** Since the shape and size of the reaction vessel are important factors for microwave heating, the preferred reaction vessel was a conical flask of much larger capacity than the volume of the reaction mixture, and bearing a loose cotton cover. Superheating of liquids is common under microwave irradiation; thus the strategy of the reactions is to keep the reaction temperature substantially below the boiling point of each compound used for the reaction. Because of difficulties with adjusting temperature in a domestic microwave oven, one of the best solutions is to repeat an experiment several times increasing the power slowly so that vapors do not escape the flask.

Table. Results of *N*-alkylation of amides and lactams under microwave irradiation in dry media[a,b].

Compound	R-X	Product	Time [s]	Temp.[c] [°C]	m.p. [°C]; b.p. [°C/Torr]	Yield [%]
	C_6H_5-CH_2-Cl		115	150	106-8	91
	CH_3-$(CH_2)_7$-Br		120	155	oil	72
	CH_3-$(CH_2)_3$-Br		90	115	51-4	47
	C_6H_5-CH_2-Cl		95	175	54-57	89
	CH_3-$(CH_2)_7$-Br		105	160	oil	87
	CH_3-$(CH_2)_3$-Br		95	150	116-119/4	51
	C_6H_5-CH_2-Cl		95	160	40-42	90
	CH_3-$(CH_2)_7$-Br		105	170	130-2/2	86
	CH_3-$(CH_2)_5$-Br		55	135	114-8/2	84
	C_6H_5-CH_2-Cl		55	175	120-123/2	92
	CH_3-$(CH_2)_7$-Br		70	165	136-8/2	89
	CH_3-$(CH_2)_5$-Br		55	155	126-9/2	75
	C_6H_5-CH_2-Cl		95	175	55-57	91
	CH_3-$(CH_2)_7$-Br		110	145	155-61/5	89
	CH_3-$(CH_2)_3$-Br		80	130	139-43/17	53
	C_6H_5-CH_2-Cl		120	175	193-5/8	94
	CH_3-$(CH_2)_7$-Br		150	180	oil	90
	CH_3-$(CH_2)_3$-Br		80	120	116-20/12	45

[a] *reagents ratio*: an amide or lactam (5 mmol), alkyl halide (7.5 mmol), tetrabutylammonium bromide (0.5 mmol), K_2CO_3 (20 mmol), KOH (20 mmol);[b] the reaction were carried out in a Philips household microwave oven with maximum power 900 W which was reduced to 300W; [c] the final temperature of the reaction mixture measured with a thermocouple after the completion.

The alkylation of benzanilide by benzyl chloride is representative of the general procedure employed. Potassium hydroxide (1,12g, 20mmol) was ground in a mortar, thoroughly mixed with potassium carbonate (2.70g, 20mmol), TBAB (0.16g, 0.50mmol), and benzanilide (0.98g, 5.0mmol) and placed in an open conical flask. Then benzyl chloride (0.94g, 7.5mmol) was added dropwise, the mixture was stirred with a spatula for a few seconds, placed in a domestic microwave oven, and irradiated for 115 seconds. Upon completion of the reaction, monitored by GC/MS, the product is extracted into methylene chloride, solvent removed and the residue recrystalized from ethanol to afford 1.3 g (91%) of *N*-benzyl-*N*-phenylbenzamide. In that case, the final temperature of the reaction mixture was 150°C.

All the liquid products were purified by means of Kugelrohr distillation, while solid products were re-crystalized from ethanol.

Conclusion

In conclusion, we have developed a simple method for the *N*-alkylation of various amides and lactams that occurs remarkable fast under mild conditions using inexpensive reagents and a household microwave oven as the irradiation source. Moreover, the procedure is alternative to those which rely on the use of dry solvents, and several procedure that rely on "standard" PTC methods.

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Samples Availability: available from the author and MDPI.