An Efficient One-pot Procedure for Preparation of Symmetrical N,N'-Disubstituted Ureas from Aromatic and Aliphatic Amines and Urea under Microwave Irradiation

Khajavi, Mohammad S.*; Dakamin, Mohammad G.; Hazarkhani, Hassan; Hajihadi, Mostafa and Nikpour, Farzad

Department of Chemistry, Faculty of Science, Shahid Beheshti University, Tehran, I. R. Iran

ABSTRACT: *A phosgene-free synthesis of symmetrical N,N'-disubstituted ureas by the reaction of aromatic and aliphatic primary amines and urea promoted by microwave irradiation in the presence of a suitable energy-transfer solvent such as N,N-dimethyl-acetamide is described.*

KEY WORDS: *Microwave irradiation, Amines, N,N'-Disubstituted ureas, N,N-Dimethyl-acetamide, Solvent free reaction, Urea.*

INTRODUCTION

Considerable attention has been focussed on substituted ureas because of the remarkable effect of such substituents on their applications. Many of these compounds are important due to their wide range of biological activities, (enzyme inhibitors [1,2], pseudopeptides [3], antidiabetics, tranquillising drugs and herbicides [4]) or their potential for other applications such as antioxidants in gasoline and corrosion inhibitors [4]. Here we wish to report a safe and an efficient procedure for the synthesis of symmetrical N,N'-disubstituted ureas by the condensation of readily available starting materials under microwave irradiation.

EXPERIMENTAL

^{1}H NMR spectra were obtained on a Brüker AC 80 or JEOL-Ex-90 instrument. IR Spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrometer. Microwave irradiations were carried out in a National Oven, model 5250, at 2450 MHz. Melting points are uncorrected.

For safety reasons all the experiments with microwave ovens should be performed in an efficient hood in order to avoid contact with vapours. If a tall beaker covered with a watch glass or a small stemless funnel

* *To whom correspondence should be addressed*

1021-9986/2000/1/24 5/$/2.50

is used and the microwave irradiation period is interrupted with a 5 min. cooling time, there is a little vaporization while very high conversions can be attained.

Preparation of N,N'-disubstituted ureas under microwave irradiation. The general procedure is illustrated with N,N'-di-p-tolyl urea (2a)

A mixture of *p*-toluidine (2.14 g, 20 mmol) and urea (0.9 g, 15 mmol) in DMAC (5 mL) contained in a tall beaker (100 mL) was placed in the microwave oven and the beaker was covered with a stemless funnel and irradiated at 210 Watts for 3 min. and after 5 min., during this time the reaction mixture cools slowly nearly to room temperature, it was irradiated again at 385 Watts for 4 min.. To control the evolution of ammonia from the reaction mixture and to prevent splashing or frothing these two irradiation sequences was interrupted after every 1 min. of irradiation for some times, i.e., 3 min. The reaction mixture was allowed to cool to room temperature, then 5 mL of water was added and mixed with contents. After further cooling, the precipitate thus obtained was filtered off and the crude product recrystallized from isopropyl alcohol to give 91% of N,N'-di-*p*-tolyl urea. m.p. 264-265°C (lit. [5], 263-264°C); IR(KBr),3290, 3010, 2950, 1641 cm^{-1}; ^1H NMR (DMSO-d_6), δ_H 2.48 (s, 6H, CH_3), 7.15(d, 4H, j=7.8, Ar-H), 7.57(d, 4H, j=7.8, Ar-H), 8.64(s, 2H, NH).

IR and ^1H NMR data of the selected compounds:

2d: IR(KBr), 3310, 1658 cm^{-1}; δ_H(DMSO-d_6), 3.96 (s, 6H, OCH_3), 6.88-7.65(m, 8H, Ar-H), 8.68(s, 2H, NH).

3a: IR(KBr), 3250, 1632 cm^{-1}; δ_H(DMSO-d_6), 7.45-8.52(m, 14H, Ar-H), 9.08(bs, 2H, NH).

3b: IR(KBr), 3340, 2945, 1622 cm^{-1}; δ_H(DMSO-d_6), 4.16(d, 4H, j=5.8, CH_2), 6.54(t, 2H, j=5.8, NH), 7.05-7.45(m, 10H, Ar-H).

3c: IR(KBr), 3310, 2950, 2830, 1616 cm^{-1}; δ_H (DMSO-d_6); 1.23-2.07(m, 20H, CH_2), 3.52(m, 2H, CH), 7.05(d, 2H, NH).

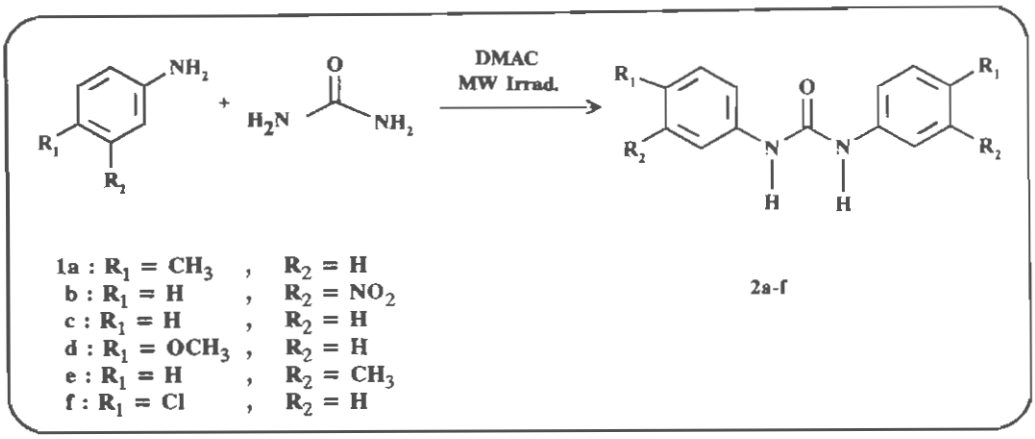
RESULTS AND DISCUSSION

A number of general procedures for the preparation of N,N'-disubstituted ureas have been described. The most widely used routes to the synthesis of these compounds are essentially based on the chemistry of isocyanates [6a] and phosgene [6b]. However, the potential hazards associated of handling of phosgene and isocyanates render these methods inappropriate. Alternatively a variety of reagents based on carbonic acid derivatives [7], carbamates [8] and carboxylic acid derivatives [9], such as bis(trichloromethyl) carbonate (triphosgene) [10], 2,4,5-trichlorophenyl chloroformate [11], (phenoxycarbonyl)tetrazole [12] and *p*-nitrophenyl chloroformate [13] have been developed.

Among other publications that have described the preparation of N,N'-disubstituted ureas one can mention: (i) oxidative carbonylation of amines in the presence of a transition metal complex [14]; (ii) from carbon dioxide and aromatic amines in the presence of a strong amidine base and trimethylamine-sulfur trioxide complex [15]; (iii) decomposition of aryl azides by iron pentacarbonyl under acidic conditions [5].

In this context, our earlier studies of the rapid synthesis of different derivatives of benzimidazolin-2-ones under microwave irradiation from the condensation of *o*-arylene diamines and urea (as a carbonyl source) without resorting to high pressures or high tempratures [16], led us to develop a convenient procedure for the preparation of symmetrical N,N'-disubstituted ureas by the reaction of aromatic or aliphatic primary amines and urea promoted by microwave irradiations. Thus in a typical experiment, treatment of *p*-toluidine (**1a**) with urea in N,N-dimethylacetamide (DMAC) under microwave irradiation for 7 min was found to give N,N'-di-*p*-tolyl urea (**2a**) in 91% yield (Scheme 1 and Table 1). Under similar conditions N,N'-bis(*m*-nitrophenyl) urea (**2b**) was prepared in high yield from *m*-nitroaniline. Cram, in his synthesis of the hosts containing cyclic urea binding sites have used this compound as the building block for the introduction of cyclic urea unit [17]. A number of symmetrical N,N'-disubstituted ureas with various substituents were prepared by this procedure (Table 1).

In these reactions to optimize the yield, two irradiation sequences with different power were used



Scheme 1

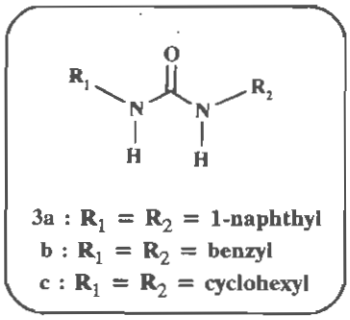
Table 1: Symmetrical N,N'-disubstituted ureas from aromatic and aliphatic primary amines and urea

Entry	Product	R_1	R_2	Irradiation conditions[a]				Yield(%)[b]	m.p.	Lit. m.p.
				(1)P_1/W	t_1/min.	(2)P_2/W	t_2 /min.		(°C)	(°C)
1	2a	CH_3	H	210	3	385	4	91	264-265	263-265[5]
2	2b	H	NO_2	210	4	490	3	96	224-225	225[17]
3	2c	H	H	210	3	385	3	88	234-236	235-236[14b]
4	2d	OCH_3	H	210	4	385	2	91	237-238	236-238[5]
5	2e	H	CH_3	210	4	385	4	88	219-220	219-220[5]
6	2f	Cl	H	210	4	385	3	95	304-306	303-305[14b]
7	3a	1-naphthyl	1-naphthyl	210	3	385	5	86	285-287	284[14c]
8	3b	benzyl	benzyl	210	2.5	385	3	78	163-165	162-164[9c]
9	3c	cyclohexyl	cyclohexyl	210	3	385	4	86	232-234	232-233[18]

a) To control the reaction the irradiation was carried out in two stages, with a cooling period between each irradiation.

b) Yields of pure, isolated products based on amines.

(t_1 at P_1 and t_2 at P_2) and in all experiments, the reaction was performed in a tall beaker covered with a stemless funnel. Furthermore to control the evolution of ammonia from the reaction mixture, the irradiation was interrupted after every 1 min irradiation.



Scheme 2

In a similar manner the reaction of aliphatic amines, benzylamine and cyclohexylamine with urea gave the products **3b-c** in good yields(Scheme 1 and Table 1).

It is noteworthy that we have investigated the use of other solvents or solvent free condition for this reaction. The results of this study are summarized in Table 2. From these results the following points deserve attention; (i) the yields of reaction were dependent on the nature of the solvent. DMAC (b.p. 165°C, miscible with water), an excellent energy transfer solvent, which has a high dielectric constant is the solvent of choice for this reaction giving the optimum result (Entry 1).

Presumably, the exellent behaviour of DMAC is the result of its ability to transfer the microwave energy to reactants faster than other solvents(Entry 2-4) with lower dielectric constant. Alternatively, it could be argued that the greater solubility of the reactants and products at the reaction temperature in DMAC provide a uniform heating; (ii) under solvent free conditions uneven heating of the reactants due to their different interactions with microwave radiation (dielectrically mismatched) and low interaction with the radiation (except for *m*- nitroaniline which has a high dielectric constant), lower dielectric constant of the reactants in comparison with DMAC, are the major problems.

Table 2: The effect of solvent on the reaction of amines with urea under microwave irradiation[a]

Entry	Product	Solvent	Yield(%)[b]
1	2a	DMAC	91
2	2a	Chlorobenzene	56
3	2a	Dioxane	37
4	2a	Butyl acetate	58
5	2a	Neat[c]	43
6	2b	Neat	74
7	3a	Neat	32
8	3b	Neat	46

a) All reactions were run under the same power and duration of radiation ca. 210 Watts for 3 min. and 385 Watts for 4 min. Using 20 mmol of amines and 15 mmol of urea in 5 mL of the appropriate solvent.

b) Isolated yields, based on amines .

c) Solvent free reaction.

The structure of compounds **2a-f** and **3a-c** were confirmed by IR, ^{1}H NMR spectral analyses and their physical properties were identical with those of authentic samples.

In conclusion, the particular suitability of DMAC in the reaction of primary amines and urea promoted by microwave irradiation, allowed us to develop a procedure for the synthesis of N,N'-disubstituted ureas in a very effective way. This method which is operationally simple and fast provides products of high purity in high yields and is more convenient and safer than the traditional procedures using phosgene, phosgene substitutes or isocyanates. Further exploration of this methodology to the synthesis of heterocyclic systems will be reported in due course.

Received, 12th April 1999 ; Accepted, 26th December 1999

REFERENCES

[1] Getman, D. P., DeCrescenzo, G. A., Heintz, R. M., Reed, K. L., Talley, J. J., Bryant, M. L., Clare, M., Houseman K. A., Marr, R. R., Mueller, R. A., Vazquez, M. L., Shien, H. S., Sallings, W. C. and Stegeman, R. A., *J. Med. Chem.*, **36,** 288(1993).

[2] Kempf, D. J., Marsh, K. C., Paul,D. A., Knigge, M. F., Norbeck, D. W., Kohlbrenner, W. E., Codacovi, L., Vasavanonda, S., Bryant, P., Wang, X. C., Wideburg, N. E., Clement, J. J., Plattner, J, J. and Erickson, J. W., *Antimicrob. Agents Chemother.*, **35,** 2209(1991).

[3] Gante, J., *Synthesis,* 405(1989).

[4] Vishnyakova, T. P., Glebova, I. A. and Glebova, E. V., *Russ. Chem. Rev.(Engl. Transl.),* **54,** 249(1985).

[5] Iqbal, A. F. M., *Helv. Chim. Acta,* **59,** 655(1976).

[6] (a) Ozaki, S., *Chem. Rev.*, **72,** 457(1972); (b) Knölker, H. J., Braxmeier, T. and Schlechtingen, G., *Angew. Chem., Int. Ed. Engl.*, **34,** 2497(1995).

[7] Majer, P. and Randad, R. S., *J. Org. Chem.*, **59,** 1937(1994).

[8] (a) Flyes, T. M., James, T. D., Pryhitka, A. and Zojsji, M., *J. Org. Chem.*, **58,** 7456(1993); (b) Wolman, Y. and Gallop, P. M., *J. Org. Chem.*, **27,** 1902(1962).

[9] (a) Overman, L. E., Taylor, G. F., Petty, C. B. and Jessup, P. J., *J. Org. Chem.*, **43,** 2164(1978); (b) Bigi, F., Maggi, R., Sartori, G., and Zambonin, E., *Chem. Commun.*, 513(1998); (c) Pihuleac, J. and Bauer, L., *Synthesis,* 61(1989).

[10] Eckert, H. and Foster, B., *Angew. Chem., Int. Ed. Engl.*, **26,** 894(1987).

[11] Lipkowski, A. W., Tam, S. W. and Portoghese, P. S., *J. Med. Chem.*, **29,** 1222(1986).

[12] Adamiak, R. W. and Stawinsk, J., *Tetrahedron*

Lett., 1935(1977).

[13] Gante, J., *Chem. Ber.,* **98,** 3334(1965).

[14] (a) Giannoccaro, P., *J. Organomet. Chem.,* **336,** 271(1987); (b) Dieck, H. A., Laine, R. M. and Heck, R. F., *J. Org. Chem.* **40,** 2819(1975); (c) Arena, F., Floriani, C., Chiesi-Villa, A. and Guastini, C., *Inorg. Chem.,* **25,** 4589(1986).

[15] Cooper, C. F. and Falcone, S. J, *Synth. Commun.,* **25,** 2467(1995).

[16] (a) Khajavi, M. S., Hajihadi, M. and Naderi, R., *J. Chem. Res. (S),* 92(1996); (b) Khajavi, M. S., Hajihadi, M. and Nikpour, F., *J. Chem. Res. (S),* 94,(1996).

[17] Nolte, R. M. and Cram, D. J., *J. Am. Chem. Soc.,* **106,** 1416(1984).

[18] "Aldrich Catalogue / Handbook of Fine Chemicals", p. 516 (1996-1997).