



Synthesis of N, N'-Disubstituted Ureas from Biuret And Anilines

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ABSTRACT

Symmetrical N, N'- disubstituted ureas have been synthesized from biuret and anilines. The urea products were obtained in good to excellent yields under solvent-free conditions. A variety of anilines were reacted with biuret in 1:2 molar ratio to give the corresponding ureas. These included aniline, p-toluidine, anisidine, o-phenylenediamine, phenylhydrazine etc.

Keywords: N, N'- disubstituted ureas, biuret, anilines, Dry media, MW.

INTRODUCTION

Ureas are very significant compounds in organic synthesis. Urea based organic compounds have fascinative pharmacotherapeutic profiles[1]. They are used in treatment of various inflammatory diseases such as asthma, multiple sclerosis etc., in cytostatic activities against colon carcinoma, murine leukemia[2-5], rheumatoid arthritis etc. The urea functionality is a key structural element of many biologically active compounds such as enzyme inhibitors[6], protein kinase and peptidomimetics[2]. Some compounds containing urea functionality possess neuroprotective activity[6-10] and have many other applications such as plant growth regulators and rafkinase inhibitors[11-21]. In particular, dissymmetric ureas[22,23] have attracted attention due to their range of applications as agricultural pesticides[13], dyeing material for hair and cellulose fibers, antioxidants in gasoline and additives in detergents to prevent carbon deposits and corrosion inhibitors[14]. They can also serve as tranquilizers and anticonvulsants[14,15], pseudo peptides[16].

MATERIALS AND METHODS

Melting points were determined in open capillaries. IR spectra were recorded on a FT-IR spectrometer. ¹H NMR spectra were measured on a 400MHz spectrometer at SAIF.

General procedure for the synthesis of N,N'-disubstituted ureas: Biuret (1mmol) and an aniline (2mmol) were taken in a beaker and the reaction mixture mixed intimately with the help of a glass rod (5s) and irradiated at 45^oC. This temperature was found to be the optimum. The reaction was monitored by TLC. The product was isolated by extraction with water (50 mL) and was further purified by crystallization from ethanol for carrying out spectral analysis. Structural confirmation of the all the

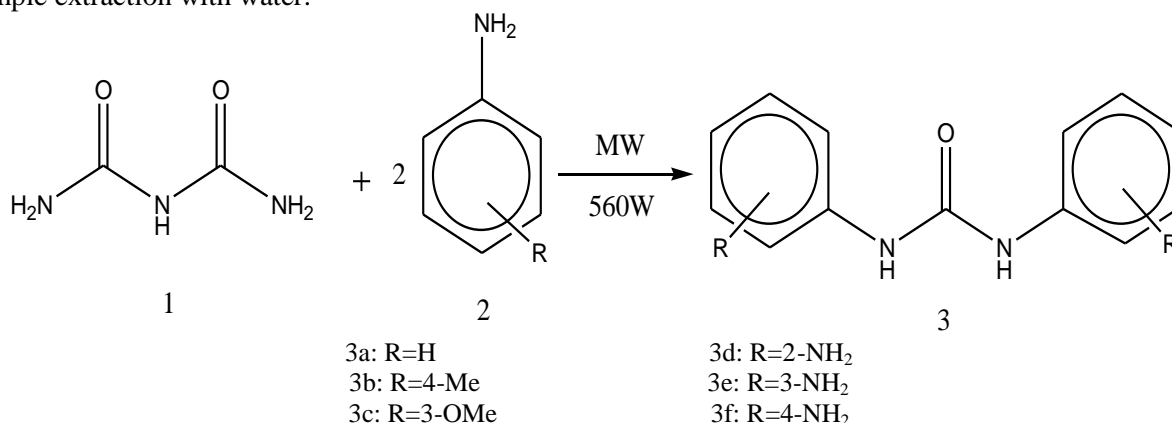
products was done on the basis of spectroscopic analyses- NMR, IR, Mass spectroscopy and by comparison of their m.p. with those of authentic samples available commercially or prepared according to literature methods[17].

RESULTS AND DISCUSSION

We have earlier reported the rapid synthesis of N, N'-disubstituted ureas by the reaction between urea and substituted anilines[17]. In order to unravel the mechanism of the formation of the urea products via that reaction, we envisaged the intermediacy of biuret, which was likely to result from the heating of urea itself under the reaction conditions. Urea is known to get converted into biuret upon heating. In case, the reaction did occur via the intermediacy of the envisaged biuret intermediate, we thought that the reaction of biuret with anilines would give the corresponding products under identical reaction conditions. We now report herein our results for the synthesis of N, N'-disubstituted ureas, by the reaction between biuret and anilines in 1:2 molar ratio. The synthesis of the ureas through this method is unknown hitherto to the best of our knowledge.

To initiate the reaction, biuret was reacted with aniline in 1:2 molar ratio at a temperature of 45°C in an open vessel. The progress of the reaction was monitored by TLC which showed the reaction to be complete after about 8 minutes of irradiation. The product, N,N'-diphenyl urea was formed in 85% yield. Encouraged by these anticipated results, we now attempted to extend the scope and versatility of the method developed for the synthesis of the other N, N'-disubstituted ureas by reacting biuret with variously (electron-donating and electron withdrawing) substituted anilines (scheme 1).

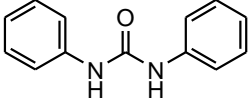
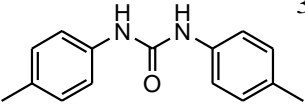
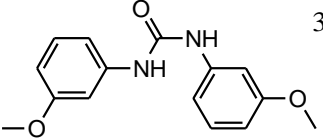
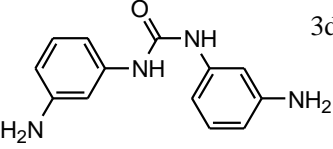
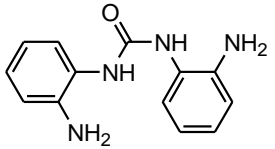
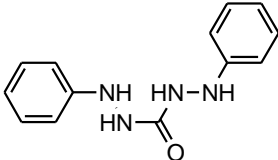
When biuret (1), and variously substituted anilines (2) were irradiated in 1:2 ratio in dry media, the desired N, N'-disubstituted ureas (3) were indeed obtained in good yields. The results obtained are collected in table 1. Further, the disubstituted ureas (3) were isolated in a practically pure form after simple extraction with water.



Scheme 1

The method developed involves the irradiation of a mixture of biuret with an aniline in the absence of a solvent followed by addition of water to the crude reaction product. N, N'-disubstituted ureas are separated out which are of high purity. For instance, in case of product 3a, when a mixture of biuret (1mmol) and aniline (2 mmol) was heated under microwaves for 7-10 min at 45°C, N,N'-diphenyl urea was isolated as a pure product in 85% yield. Next, the method was extended to the synthesis of ureas from other aromatic amines substituted with electron-donating and electron-withdrawing groups. The results are given in table 1. As can be seen, the method is equally efficient for other substrates leading to the formation of the corresponding urea products (3b-g).

Table 1: Synthesis of N,N'-disubstituted ureas from biuret and aniline

Product ^a	Time ^b (min)	Yield ^c (%)	M.p/Lit.m.p.(°C)
3a 	8-10	87	239-240/238
3b 	7	93	266/266
3c 	7-8	76	171/172
3d 	9	90	131-132/132
3e 	9-10	91	194/195
3f 	10	71	171/170-172

^a All products were identified by IR, ¹H NMR and by comparison of melting point with those of the authentic samples . ^c Isolated yields

APPLICATIONS

The urea derivatives have great applications as described above.

CONCLUSIONS

N,N'- disubstituted ureas have been synthesized by reacting biuret with anilines in 1:2 molar ratio. The products were obtained in good to excellent yields by a rapid, economic and environment friendly method[24] as no organic solvent was used throughout the reaction. The desired ureas were obtained under mild and convenient conditions with a simple work-up.

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