Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2014, 3 (3): 1050-1054

(International Peer Reviewed Journal)

A Green Protocol Towards Rapid Synthesis of N, N'-Disubstituted Ureas In The Presence of p-Toulenesulphonic Acid

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Accepted on 7th April 2014

ABSTRACT

Rapid synthesis of symmetrically substituted ureas from urea and variously substituted anilines has been carried out in presence of p-toluenesulphonic acid monohydrate ($TsOH.H_2O$) in dry media. The reaction conditions are mild and the products were obtained in high yields (75-94 %).

Keywords: Anilines; Urea, Symmetrical ureas; $TsOH.H_2O$; MW.

INTRODUCTION

Ureas are very significant compounds in organic synthesis[1]. Urea is a functional moiety that is commonly found in natural products. Urea based organic compounds have fascinative pharmacotherapeutic profiles[1-3]. In particular, dissymmetric ureas have attracted attention due to their wide range of applications. Some urea derivatives are useful as active ingredients in antimicrobial, antifungal, algaecides agents, HIV-1 protease inhibitory activity, as anti-tuberculosis agents, anti-melanoma agents and anti-depressant etc.

Substituted urea derivatives of various anilines have been prepared by Curtis rearrangement, reductive alkylation of aromatic aldehydes from CS_2, palladium catalyzed reactions etc[1-3]. The drawbacks associated with the reported methods such as toxicity, and tedious purification procedures prompted us to develop practical and eco-friendly methods for the reaction. Now a days, microwave assisted organic synthesis has gained considerable importance because of its efficiency to lead to the formation of the pure products in high yields[4-8]. So, we decided to carry out the rapid synthesis of the ureas rather than under classical reaction conditions.

MATERIALS AND METHODS

Anilines were purchased from Sigma-Aldrich and Fluka Goldie. Urea was purchased from LobaChemie. $TsOH.H_2O$ was purchased fromFluka Goldie. Reactions were monitored by analytical thin layer chromatography (TLC) performed on glass plates precoated with silica gel G as supplied by Sisco Research Laboratories (SRL). ^{1}H-NMR was recorded on a 400MHz spectrometer (BrukerAvance II 400). The chemical shifts were determined using Tetramethylsilane (TMS) as internal standard at δ 0.0 or to the

signal of residual $CDCl_3$ δ 7.26. ^{13}C-NMR was recorded at 100 MHz, using $CDCl_3$ as solvent. All commercially available chemicals were used without further purifications.

General procedure for the synthesis of N,N'-disubstitutedureas in the presence of TsOH.H_2O: Urea (0.06g, 1 mmol) and aniline (0.182 mL, 2 mmol) were taken in a 10 mL Pyrex beaker and intimately mixed with the catalyst,TsOH.H_2O (100 mg). The reaction mixture was stirred for a few minutes at room temperature and then microwaved for 45s at 53 °C. TLC (CCl_4/ethylacetate, 4:1) was used to monitor the reaction progress. After the reaction was complete, the beaker was taken out and cooled. Water was added to the reaction vessel to isolate the product. The crude product was further purified by recrystallisation from ethanol in 77% yield. Same procedure was followed for the preparation of N, N'- disubstituted ureas from other substituted anilines. Structural confirmation of the products was done on the basis of spectroscopic analyses and by direct comparison with authentic samples.[10]

Spectroscopic characterization data

N, N'-diphenylurea^{1}H-NMR (DMSO-d_6): δ6.9-7.4 (m, 10H, ArH), 8.6 (br, 2H, NH);^{13}C-NMR (DMSO-d_6):δ 121.7, 118.7, 128.7, 139.7 (C-NH), 152.6 (C=O).

N,N'-bis(2-methylphenyl)urea:^{1}H NMR (DMSO-d_6): δ 2.3 (s, 6H, -CH_3), 6.8-7.5 (m, 8H, ArH), 7.9 (br, 2H, NH); ^{13}C NMR (DMSO-d_6):δ 120.3, 125.7, 124, 129.4, 129.6, 11.4 (-CH_3), 138.9 (C-NH), 152.2 (C=O).

N,N'-bis(4-methylphenyl)urea:^{1}H NMR (DMSO-d_6):δ2.3 (s, 6H, -CH_3), 7.0-7.5 (m, 8H, ArH), 7.5 (br, 2H, NH); ^{13}C NMR (DMSO-d_6):δ120.3, 133.3, 129.4, 20.9 (-CH_3), 135.2 (C-NH), 152.2 (C=O).

N,N'-bis(2-methoxylphenyl)urea:^{1}H NMR (DMSO-d_6):δ3.1 (s, 6H, -OCH_3), 6.9-7.4 (m, 8H, ArH), 7.5 (br, 2H, NH); ^{13}C NMR (DMSO-d_6):δ 114.3, 125.1, 121.0, 121.4, 123.8, 153.9 (C-O), 56.0 (O-CH_3), 152.2 (C=O).

N,N'-bis(4-methoxylphenyl)urea:^{1}H NMR (DMSO-d_6):δ2.3 (s, 6H, -OCH_3), 7.0-7.5 (m, 8H, ArH), 7.5 (br, 2H, NH); ^{13}C NMR (DMSO-d_6):δ114.3, 121.3, 157.4 (C-O), 56 (-CH_3), 130.5 (C-NH), 152.2 (C=O).

N,N'-bis(2-aminophenyl)urea:^{1}H NMR (DMSO-d_6): δ 4.0 (s, 4H, -NH_2), 6.4-7.3 (m, 8H, ArH), 7.6 (br, 2H, NH); ^{13}C NMR (DMSO-d_6):δ121.3, 118.7, 124.9, 115.3, 138.6 (C-N), 124.8 (C-NH), 152.2 (C=O).

N,N'-bis(3-aminophenyl)urea:^{1}H NMR (DMSO-d_6):δ4.0 (s, 4H, -NH_2), 6.2-7.0 (m, 8H, ArH), 7.5 (br, 2H, NH); ^{13}C NMR (DMSO-d_6):δ110.7, 129.7, 124.9, 110.3, 107.0, 146.9 (C-NH_2), 139 (C-NH), 152.2 (C=O).

N,N'-bis(4-aminophenyl)urea:^{1}H NMR (DMSO-d_6):δ4.0 (s, 4H, -NH_2), 6.4-7.3 (m, 8H, ArH), 7.5 (br, 2H, NH); ^{13}C NMR (DMSO-d_6):δ121.2, 115.3, 142.3 (C-NH_2), 128.2 (C-NH), 152.2 (C=O).

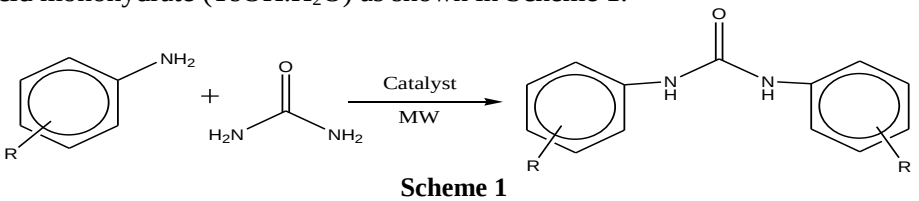
N,N'-bis(2-chlorophenyl)urea:^{1}H NMR (DMSO-d_6):δ7-7.8 (m, 8H, ArH), 6.5-7.1 (m, 8H, ArH), 9 (br, 2H, NH); ^{13}C NMR (DMSO-d_6):δ121.8, 126.8, 125.5, 129.1, 125.7 (C-Cl), 138.6 (C-NH), 152.2 (C=O).

N,N'-bis(4-nitrophenyl)urea:^{1}H NMR (DMSO-d_6):δ7.9-8.1 (m, 8H, ArH), 7.3 (br, 2H, NH);^{13}C NMR (DMSO-d_6):δ123.8, 121.3, 144.0 (C-NO_2), 144.3 (C-NH), 152.2 (C=O).

N,N'-bis(phenylamino)urea:^{1}H NMR (DMSO-d_6):δ 6.6-7.1 (m, 10H, ArH), 6.0 (d, 2H, NH), 4.0 (d, 2H, NH); ^{13}C NMR (DMSO-d_6):δ112.0, 129.0, 118.9, 142.2 (C-N), 156.4 (C=O).

RESULTS AND DISCUSSION

We report herein an operationally simple protocol for the synthesis of substituted urea derivatives from urea and variously substituted anilines in the presence of an easy to handle organic acid catalyst, p-toluenesulphonic acid monohydrate ($TsOH.H_2O$) as shown in Scheme 1.

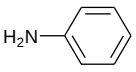
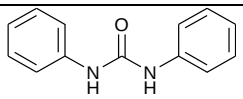
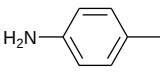
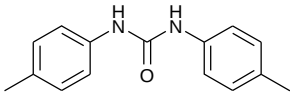
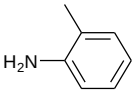
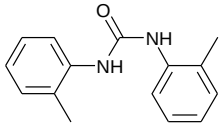
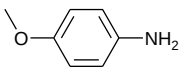
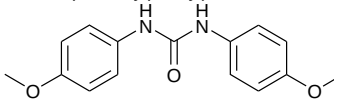
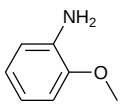
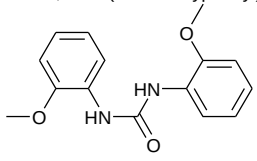


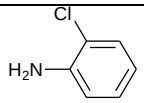
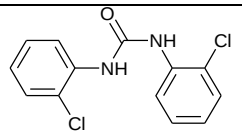
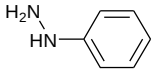
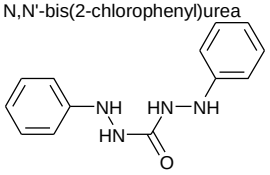
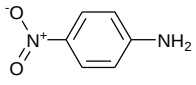
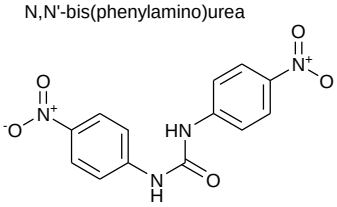
Scheme 1

Initially, urea and aniline taken in 1:2 molar ratio were subjected to microwave irradiation in an open vessel at a moderate temperature of 53^0C, the desired product was indeed formed, but it was obtained in low yield of 55% which is in line with the results reported in the literature[9]. Obviously, the yield of the product required to be raised. From the point of view of the mechanism, we envisaged that the reaction was most likely to be acid-catalyzed as the reaction would be initiated by the nucleophilic attack of the nitrogen of the amine on the electrophilic carbon of the carbonyl group of the urea.

Hence, when the reaction was carried out in the presence of $TsOH.H_2O$, the product was obtained in about 77 % yield under the identical reaction conditions. The method was then extended to other aromatic anilines substituted with electron donating and electron withdrawing substituents under the same reaction conditions such as 4-methyl aniline, 2-methyl aniline, 4-methoxyaniline, 2-methoxyaniline, 2-chloroaniline, and 4-nitroaniline. Phenylhydrazine was also attempted. The yields of the products formed are collected in table 1.

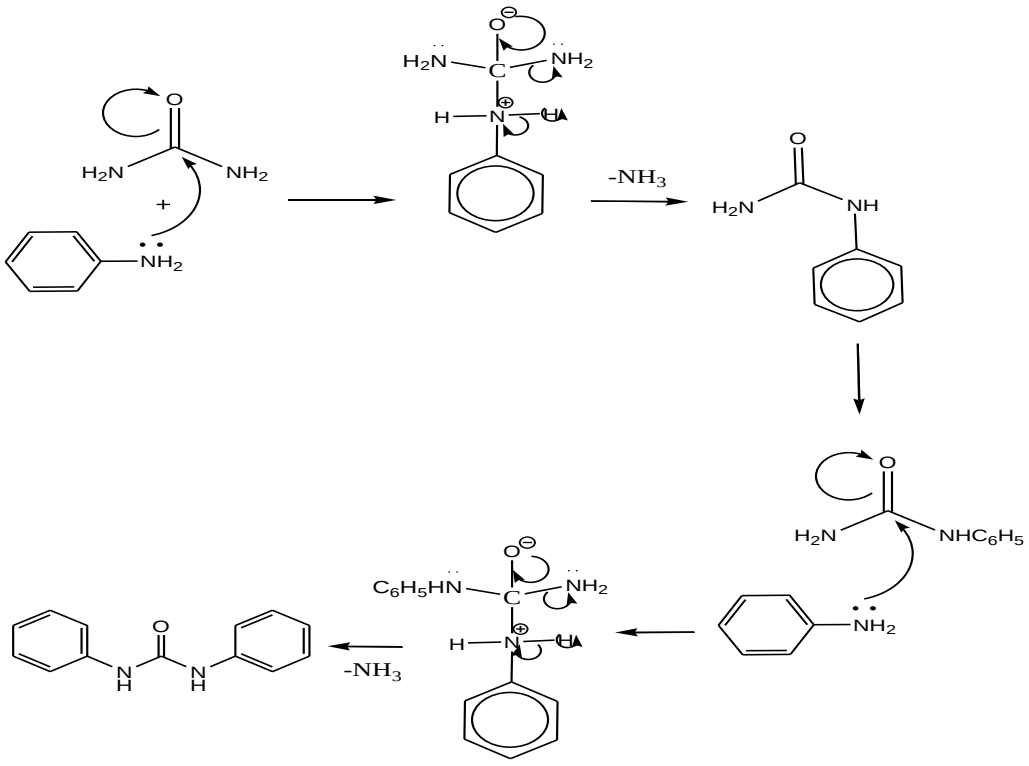
Table-1. Microwave-assisted synthesis of N, N'- disubstituted ureas from urea and various anilines (1:2) in the presence of $TsOH.H_2O$at 53 °C.

Sr. no	Substrate	Product	Yield (%)	Time (sec)	M.P.(°C) Obs.	M.P.(°C) Lit[1-3]
1.	 Aniline	 N,N'-diphenylurea	77	45	235	236
2.	 4-methylaniline	 N,N'-bis(4-methylphenyl)urea	90	40	232	232
3.	 2-methylaniline	 N,N'-bis(2-methylphenyl)urea	87	40	234	235
4.	 4-methoxyaniline	 N,N'-bis(4-methoxyphenyl)urea	94	42	224	224
5.	 2-methoxyaniline	 N,N'-bis(2-methoxyphenyl)urea	88	43	221	220

6.	 2-chloroaniline	 N,N'-bis(2-chlorophenyl)urea	78	65	233	234
7.	 Phenylhydrazine	 N,N'-bis(phenylamino)urea	76	42	171	172
8.	 4-nitroaniline	 N,N'-bis(4-nitrophenyl)urea	75	68	237	238

A possible mechanism involving the nucleophilic attack of aniline on to the electrophilic carbon of the carbonyl group is shown in Scheme 2. Clearly, the mechanism can be anticipated to be acid-catalysed whence, the carbonyl carbon becomes more electrophilic consequent to the carbonyl oxygen getting protonated by the acid used in both the steps shown which involve the attack of the nitrogen on to the carbonyl carbon.

The results are described in table 1. The method developed involves the irradiation of a mixture of urea and a substituted aniline.



Scheme 2

APPLICATIONS

The prepared ureas have significant biological profiles.

CONCLUSIONS

As can be seen, the method developed for the synthesis of the symmetrically substituted ureas from anilines and ureas over p-toluenesulphonic acid gives good yields of the products and is eco-friendly and convenient.

ACKNOWLEDGEMENT

We are thankful to the department for providing the facilities.

REFERENCES

[1] C. Sun, *Bioorgan. Med. Chem.*, **2006**, 14, 8574.
[2] M. E. McDonnell, S P Zhang, N Nassen, A E Dubin, S L Dax, *Bio Org & Med Chem Lett*, **2004**,14, 531
[3] F. Bigi, R Maggi,G Sartori, E Zambonin, *Chem Commun*,**1998**, 4, 513 and references therein.
[4] S. K. Dewan, *Indian J. Chem.*, **2006**, 45B, 2337.
[5] S. K. Dewan, R. Singh and A. Kumar, *Synthetic Commun.*, **2004**, 34, 2025.
[6] S. K. Dewan and R. Singh, *Synthetic Commun.***, *2003***, *33, 3081*.
[7] S. K. Dewan and R. Singh, *Synthetic Commun.*, ***2003***, *33, 3085*.
[8] S. K. Dewan, R. Singh and A. Kumar, *Arkivoc*, **2006**, 2, 41.
[9] M. M. Mojtahedi, M R Saidi, M Bolourtchian, *J Chem Research (S),* **1999**, 710
[10] S K Dewan ,Rashmi, J Applicable Chemistry, **2014**, 3(2), 639- 641.