**AASCIT Journal of Chemistry**
2015; 2(4): 97-101
Published online August 10, 2015 (http://www.aascit.org/journal/chemistry)

American Association for Science and Technology

# Green Synthesis of Symmetrical 1, 3-Disubstituted Urea Derivatives from Biuret and Different Substituted Anilines in the Presence of NaCl

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## Citation
Rashmi Singh, G. Vinoth Kumar. Green Synthesis of Symmetrical 1, 3-Disubstituted Urea Derivatives from Biuret and Different Substituted Anilines in the Presence of NaCl. *AASCIT Journal of Chemistry.* Vol. 2, No. 4, 2015, pp. 97-101.

## Abstract

Rapid synthesis of symmetrical 1, 3- disubstituted urea derivatives from biuret and different substituted anilines has been carried out in presence of Sodium chloride (NaCl) in dry media. Diverse substituted anilines were reacted with biuret in 2:1 molar ratio to give the corresponding urea derivatives. The reaction conditions were clement, solvent free, mild and the products were attained in good to excellent yields. Structural confirmations of all the products were done on the basis of spectroscopic analyses- $^{1}$H NMR, $^{13}$C NMR, IR and by assessment of their melting points with those of authentic samples.

## Keywords
Anilines,
Dry Media,
1, 3-Disubstituted Urea Derivatives,
Sodium Chloride,
Urea

Received: June 30, 2015
Revised: July 17, 2015
Accepted: July 18, 2015

## 1. Introduction

Discoveries of innovations in performing chemical reactions without affecting the environment are an emerging trend in order to reduce the reaction time and to enhance the yields of chemical reactions considerably. Several greenery efforts such as using ionic liquids [1,2] as reaction media, conducting chemical reactions in dry media [3] have been taken in order to achieve these principles. Applying afore mentioned methodologies of performing chemical reactions of organic synthesis, provide a clean, efficient and economical technology for carrying out the green chemistry processes. In order to improve the potentiality of dry media and ionic liquids, conducting the reactions under microwave irradiation have been applied drastically in several Friedel-Crafts [4] and Diels-Alder reactions [5] Ureas are one of the most important tools of synthesizing organic compounds smoothly. Several organic reactions participating derivatives of urea with alcohols, ketones, formaldehyde, diamines, alkylene oxides, unsaturated compounds, aldehyde-ammonia, aldehyde-ammine derivatives and several other organic compounds have already been carried out for synthesizing novel organic compounds drastically [6,7]. A number of urea and thiourea derivatives have captivative pharmacotherapeutic characteristics [8,9]. In particular, dissymmetric ureas have appealed consideration due to their expansive range of applications. Some urea derivatives are valued as active components in antimicrobial, antifungal, algaecides agents, HIV-1 protease inhibitory activity [10], as anti-tuberculosis agents, anti- melanoma agents [11,12]. The inadequacies associated with the traditional methods such as toxicity, and tedious purification procedures prompted us to develop practical and ecological methods for the reaction. In recent years, microwave assisted organic synthesis has gained considerable prominence because of its efficiency to lead to the formation of the pure products in high yields [13-17]. Particularly, the dry media (solventless) reactions doped with a catalyst are predominantly applied in microwave assisted synthetic techniques over other types of reactions [18-24]. The required activation energies for the progress of microwave assisted chemical reactions are achieved through dielectric heating. This heating method reduces the reaction duration of several organic reactions from days or hours to few minutes or seconds [25]. In addition to this concept, heterogeneous catalysts play a vital role in the synthetic reactions using dry media leading to the significant rate enhancements of microwave assisted chemical processes. In this study, the widely and inexpensively available commercial chemical, sodium chloride was used as heterogeneous catalyst because of its better efficiency in the view of rate and yield [26]. So, the rapid microwave assisted synthesis of the urea derivatives under dry media performed in solvent free conditions was focused in this present study which inevitably lead to a proficient, cost-effective, clean and green chemistry rather than under established reaction situations.

## 2. Materials and Methods

### 2.1. General Methods

Anilines were purchased from Sigma-Aldrich and Fluka Goldie. Biuret was purchased from LobaChemie. Sodium chloride (NaCl) was purchased from Fluka Goldie. The reactions were carried out in a Synthwave 402 Prolabo microwave reactor with an open system of reaction vessel (freq. 2450 MHz). Visualization of the resulting chromatograms was done by looking under iodine chamber followed by dipping in a solution of carbon tetrachloride ($CCl_4$) and ethyl acetate. All the reactions were examined 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 400 MHz spectrometer (Bruker Avance Π 400). The chemical shifts were determined using Tetramethylsilane (TMS) as internal standard at δ 0.0 or to the signal of residual DMSO-d$_6$.$^{13}$C-NMR was recorded at 100 MHz, using DMSO-d$_6$ as solvent. All commercially accessible chemicals were used without further refinements.

### 2.2. Experimental Section

#### 2.2.1. General Procedure for the Synthesis of 1, 3- Disubstituted Urea Derivatives in the Presence of Sodium Chloride (NaCl)

Biuret (0.103g, 1 mmol) and aniline (0.18 mL, 2 mmol) were taken in a 10 mL Pyrex beaker and intimately assorted with the catalyst, NaCl (200 mg). The reaction mixture was stirred for a few minutes at room temperature and then subjected to microwave irradiations at 140 °C. TLC ($CCl_4$ / ethyl acetate, 4:1) was used to monitor the reaction advancement. After accomplishment of reaction, reaction mixture was cooled and the product was extracted using water. It was filtered, dried and recrystallized from ethanol. N, N'-diphenylurea was obtained in 92% yield. Identical procedure was followed for the preparation of N, N'-disubstituted urea derivatives from other substituted anilines. Structural confirmation of the products was done on the basis of spectroscopic analyses and by direct comparison with authentic samples [27, 28].

#### 2.2.2. Spectroscopic Characterization Data

*N, N'-diphenylurea:* Mp. 236 °C (lit. 236°C); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm, δ): 6.9-7.4 (m, 10H, ArH), 8.6 (br, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm, δ ): 121.7, 118.7, 128.7, 139.7 (C-NH), 152.6 (C=O); IR (KBr, cm$^{-1}$): 3328 (N-H), 3128 (C-H), 1650 (C=O).

*N, N'-bis(2-methylphenyl)urea:* Mp. 235 °C (lit. 235°C); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm, δ): 2.4 (s, 6H, -$CH_3$), 6.4-7.9 (m, 8H, ArH), 7.9 (br, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm, δ): 120.3, 125.7, 124, 129.4, 129.6, 11.4 (-$CH_3$), 138.9 (C-NH), 152.2 (C=O); IR (KBr, cm$^{-1}$): 3304 (N-H), 2922 (C-H), 1641 (C=O).

*N, N'-bis(4-methylphenyl)urea:* Mp. 232 °C (lit. 232°C); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm, δ): 2.3 (s, 6H, -$CH_3$), 5.9-7.8 (m, 8H, ArH), 8.2 (br, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm, δ): 121.4, 133.3, 129.4, 20.9 (-$CH_3$), 135.2 (C-NH), 153.1 (C=O); IR (KBr, cm$^{-1}$): 3306 (N-H), 3030 (C-H), 1640 (C=O).

*N, N'-bis(2-methoxyphenyl)urea:* Mp. 221°C (lit. 220°C); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm, δ): 3.1 (s, 6H, -$OCH_3$), 6.8-7.6 (m, 8H, ArH), 7.7 (br, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm, δ): 114.3, 125.1, 121.0, 121.4, 123.8, 154.2 (C-O), 56.0 (O-$CH_3$), 152.1 (C=O); IR (KBr, cm$^{-1}$): 3319 (N-H), 2829 (C-H), 1647 (C=0).

*N, N'-bis(4-methoxyphenyl)urea:* Mp. 224°C (lit. 224°C); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm, δ): 2.3 (s, 6H, -$OCH_3$), 7.0-7.9 (m, 8H, ArH), 7.4 (br, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm, δ): 114.3, 121.3, 157.4 (C-O), 56 (-$CH_3$), 130.5 (C-NH), 152.9 (C=O); IR (KBr, cm$^{-1}$): 3309 (N-H), 2829 (C-H), 1642 (C=0).

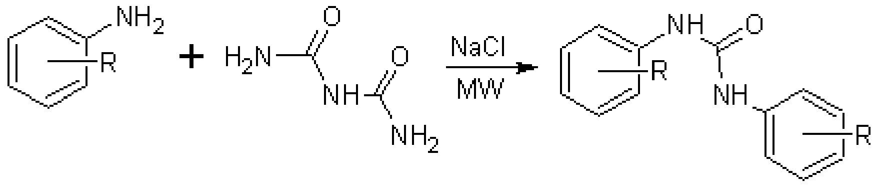
*N, N'-bis(2-chlorophenyl)urea:* Mp. 234°C (lit. 234°C); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm, δ): 7-7.8 (m, 8H, ArH), 8.6 (br, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm, δ): 121.8, 126.8, 125.5, 129.1, 125.7 (C-Cl), 138.6 (C-NH), 153.5 (C=O); IR (KBr, cm$^{-1}$): 3295 (N-H), 876 (C-Cl), 1635 (C=0).

*N, N'-bis(4-nitrophenyl)urea:* Mp. 238 °C (lit. 238°C); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm, δ): 6.6-8.3 (m, 8H, ArH), 9.5 (br, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm, δ): 123.8, 121.3, 144.0 (C-$NO_2$), 144.3 (C-NH), 154.1 (C=O); IR (KBr, cm$^{1}$): 3344 (N-H), 1324 (N=0), 1650 (C=0).

*N, N'-bis(phenylamino)urea:* Mp. 171 °C (lit. 172°C); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm, δ): 7.1-7.9 (m, 10H, ArH), 6.7 (d, 2H, NH), 5.9 (d, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$, ppm, δ): 112.0, 129.0, 118.9, 142.2 (C-N), 156.4 (C=O); IR (KBr, cm$^{-1}$): 3316 (N-H), 1645 (C=0).

## 3. Results and Discussion

In this study, an operationally simple protocol is reported for the synthesis of symmetrical substituted urea derivatives from biuret and different substituted anilines (electron-donating and electron withdrawing) in the presence of an easy to handle catalyst, Sodium chloride (NaCl) as shown in Figure 1.

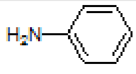
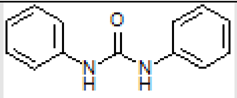
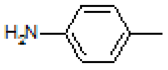
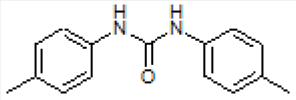
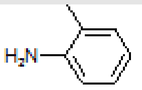
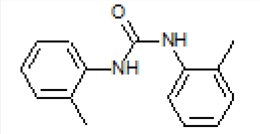
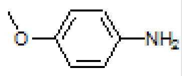
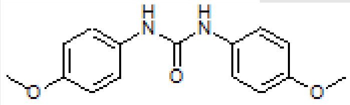
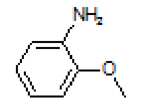
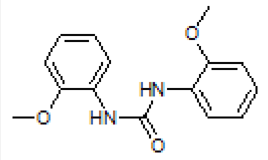
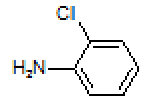
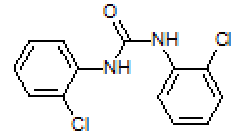


a: R=H, b: R=4-Me, c: R=2-Me, d: R=4-OMe , e: R=2-OMe, f: R=2-Cl, g: R=4-$NO_2$

***Fig. 1.*** *Microwave assisted reactions under dry media between biuret and substituted anilines.*

Initially, biuret and aniline taken in 1:2 molar ratio were subjected to microwave irradiation in an open vessel at a moderate temperature of 70°C, the desired product was indeed formed, but it was attained in low yield which is in line with the results reported in the literature. Evidently, the yield of the product was required to be elevated. Hence, when the reaction was carried out in the presence of NaCl and by elevating the temperature, the product was attained in about 75-95% 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 identical reaction conditions such as 4-methyl aniline, 2-methyl aniline, 4-methoxyaniline, 2-methoxyaniline, 2-chloroaniline, and 4-nitroaniline. Phenylhydrazine was also endeavored. The yields of the products formed are gathered in table 1.

***Table 1.*** *Microwave-assisted synthesis of N, N'-disubstituted urea derivatives from biuret and various anilines (1:2) in the presence of Sodium Chloride (NaCl) at 140 °C.*

| Sr. no | Substrate | Product | Yield (%) | Time (min) | M.P. (°C) Obs. Lit. |
|---|---|---|---|---|---|
| 1. | <br>Aniline | <br>N,N'-diphenylurea | 92 | 07 | 235 236 |
| 2. | <br>4-methylaniline | <br>N,N'-bis(4-methylphenyl)urea | 95 | 07 | 232 232 |
| 3. | <br>2-methylaniline | <br>N,N'-bis(2-methylphenyl)urea | 93 | 07 | 234 235 |
| 4. | <br>4-methoxyaniline | <br>N,N'-bis(4-methoxyphenyl)urea | 85 | 08 | 224 224 |
| 5. | <br>2-methoxyaniline | <br>N,N'-bis(2-methoxyphenyl)urea | 82 | 08 | 221 220 |
| 6. | <br>2-chloroaniline | <br>N,N'-bis(2-chlorophenyl)urea | 79 | 10 | 233 234 |

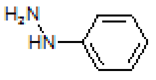
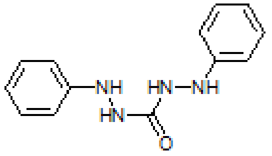
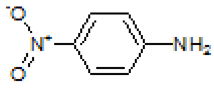
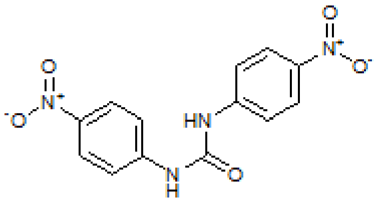
| Sr. no | Substrate | Product | Yield (%) | Time (min) | M.P. (°C) Obs. Lit. |
|---|---|---|---|---|---|
| 7. |  Phenylhydrazine |  N,N'-bis(phenylamino)urea | 86 | 07 | 171 172 |
| 8. |  4-nitroaniline |  N,N'-bis(4-nitrophenyl)urea | 75 | 10 | 237 238 |

Table 1. summarizes that the maximum rate was achieved while using the electron donating methyl substituent in para position (most basic) and least rates were observed while using the least basic electron withdrawing chloro and nitro group substituted in the aromatic ring of the anilines (Figure 1). But unsubstituted aniline shows lesser rate than electron donating methyl substituted aniline. A nitro group is strongly withdrawing due to resonance, a chloro group is weakly electron withdrawing due to inductive effects, a methyl group is a weak electron donor and a methoxy group a strong electron donor due to resonance. This fact prove that the reaction between biuret and aniline is less favor by electron withdrawing chloro and nitro substituents which are attached to the ortho or para positions of aniline respectively. As a result of substituting electron donating substituents in its ortho or para positions, the resonance structures of aniline are more strengthened tremendously leading to the enhancement of rate of the reaction between biuret and aniline. Favoring of the reactions are more strengthened while attaching the electron donating methyl and methoxy substituents in para positions rather than ortho (Table 1.). However, although the methoxy substituent is a stronger electron donar than methyl group, lesser rates for methoxy substituted aniline was observed rather than methyl substituted anilines and even lesser than unsubstituted aniline. These observations of reduction in rates may be due to the phenomenon of steric hinderence. Because, the methoxy group is bulkier than methyl. This group may hinder the incoming biuret substrate effectively leading to the reduction of reaction rates.

***Role of heterogeneous catalysis***

Based on the adsorption of the reactants on inert solid supports, at solvent free conditions, the microwave irradiated reactions has gained substantial importance in recent times [29]. The reactions occurred rapidly in the presence of NaCl catalyst than without using any catalysts performed in previous studies [30]. Moreover, the absence of solvents made the procedure as eco-friendly, which is the essential need of the hour. Further, NaCl as catalyst substantiated to be environmentally benevolent as no chemical wastes were produced and was economical as well.

## 4. Conclusion

N, N'-disubstituted urea derivatives have been synthesized by reacting biuret with substituted anilines in 1:2 molar ratio. The products were obtained in good to excellent yields by a rapid, pecuniary and environment friendly process [28, 30-32] as no organic solvent was used throughout the reaction. The anticipated ureas were obtained under clement and manageable conditions with a simple work-up.

## Acknowledgements

The authors would like to thank M. D. University, Rohtak and Bharathiar University, Coimbatore, India for their valuable support to this study.

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