Journal Synthetic Chemistry

Short Communication

*J. Synth. Chem.*

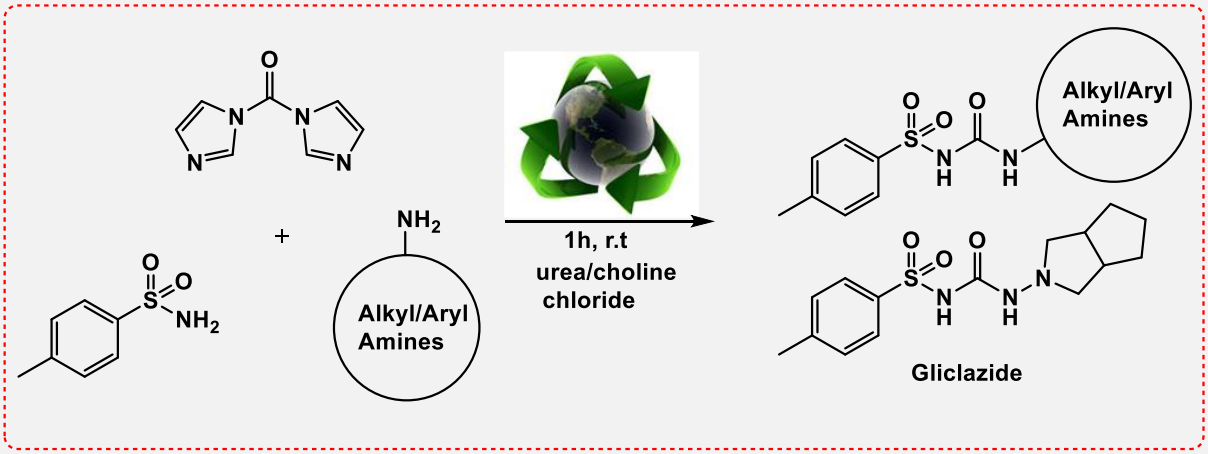
# Novel and Simple Process for the Synthesis and Characterization of Gliclazide in the Presence of Sustainable Natural Deep Eutectic Solvents

Ajmal R. Bhat *

Department of Chemistry, University of Delhi, Delhi, India.

**Corresponding author-mail:** Ajmalr.bhat@yahoo.com

**ABSTRACT:** The synthesis of sulfonyl urea derivatives from p-toluene sulfonamide with various amines using carbonyl diimidazole natural deep eutectic solvents and catalyst was reported as a novel and simple process. To evaluate the reaction conditions, various aromatic, aliphatic, and heterocyclic amines were utilized. Most of the amines were well tolerated and formed their corresponding sulfonyl urea derivatives in good to better yields. A 92% yield was achieved in the synthesis of the anti-diabetic medication gliclazide using this approach. This approach is easy to use, has little reaction time, and doesn't require chromatographic purification.




**KEYWORDS:** Sulfonamide urea's amines, P-toluene sulfonamide, Carbonyldiimidazole, Gliclazide, Natural Deep Eutectic Solvents.

## ■ Introduction

Sulfonyl urea appears frequently in the structural elements of many anti-diabetic medications. It is possible to make sulfonyl urea derivatives from 4-toluenesulfonyl azide [1], isocyanates [2], sulfonyl chlorides [3], and tosyl urea derivatives under a variety of conditions, as described in the literature [4,5]. On the other hand, the second-generation anti-diabetic medication gliclazide (**Figure 1**) also has sulfonyl urea as a core group. gliclazide functions as an oral diabetes medication. Both blood coagulation and hypoglycemia are improved. When insulin therapy fails, it is employed. Sulfonyl urea is also a component of other anti-diabetic medications, including glisoxepid, tolazamide, glibenclamide, glycopyramide, and tolbutamide (**Figure 1**). In sulfonyl urea derivatives, changes to the amine moiety rather than the sulfonamide moiety were attempted for the majority of the urea production. We suggested commencing the synthesis of sulfonyl urea derivatives from p-toluene sulfonamide in order to address the drawbacks of the earlier procedures.

**Received:** Nov 4, 2022
**Revised:** Nov 29, 2022
**Published:** Jul 4, 2022

**DOI:** 10.22034/jsc.2023.174119
**J. Synth. Chem.** 2022, 1, 171-176

For the creation of gliclazide, a number of synthesis techniques have been documented in the literature [6,7]. However, none of them have produced gliclazide directly from carbonyldiimidazole. These inquiries are still in their early stages, though. In a variety of organic syntheses, deep eutectic solvents (DESs) were used as simple, eco-friendly substitutes for transition metal-based catalysts and harmful organic solvents [1,8–11].

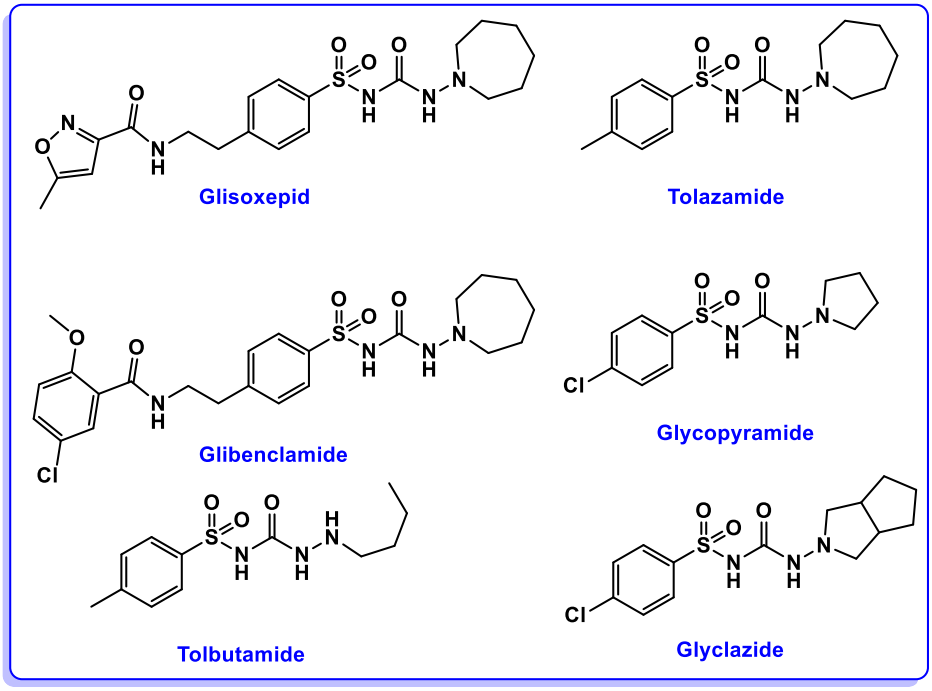
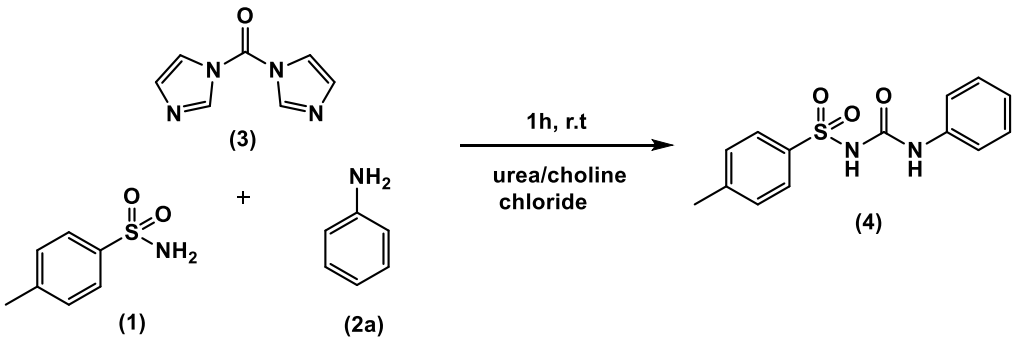



**Fig. 1**. APIs containing sulfonyl urea moiety.

On the other hand, DESs function as reusable, ecologically friendly catalysts in a variety of organic synthesis processes[12–15] because of their high liquid because they are easily separated from reaction mixtures, have a high liquid dispersibility, are inexpensive, and are simple to prepare and modify on the surface.




**Scheme 1**. Synthesis of sulfonyl urea from para toluene sulfonamide and primary amine.



**DOI:** 10.22034/jsc.2023.174119
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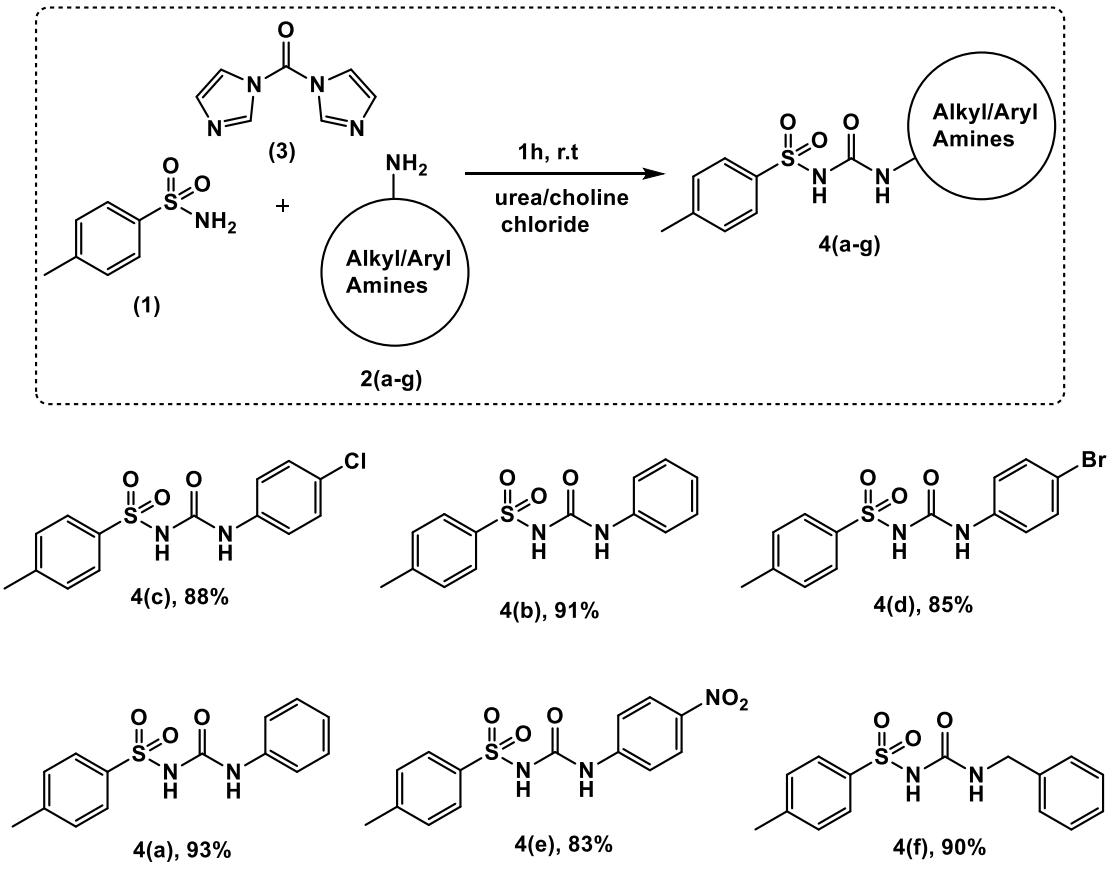
Because it makes it simpler to recover and reuse a catalyst after a reaction is complete and reduces separation issues and environmental challenges. [16–18] For a wide range of applications in various types of organic transformations, from laboratory to industrial operations, a variety of functional DESs have drawn increasing attention in this field. We would like to describe the synthesis of sulfonyl urea derivatives starting from p-toluene sulfonamide with various amines using carbonyldiimidazole in toluene in the current article. As a result of our ongoing interest in creating new processes for the synthesis of physiologically active chemicals we want to create a brand-new process for making sulfonyl urea.

## ■ Result and discussion

Here, we present a straightforward and easy method for synthesizing sulfonyl urea using carbonyldiimidazole as the starting material. In order to do this, we used urea choline chloride to evaluate the model reaction involving p-toluene sulfonamide **1**, aniline **2a**, and carbonyldiimidazole (**3)** (**Scheme 1**).

**Table 1.** Synthesis of sulfonyl urea's [a, b]




[a] Reaction conditions: all the reaction were carried out using p-toluene sulfonamide (1 mmol), amine (1 mmol), carbonyldiimidazole (1 mmol), 1h, r.t. [b] Isolated yields.

This outcome prompted us to use several amines to test the applicability and universality of the current methodology. The results of applying the improved technology to screen a variety of amines are shown in



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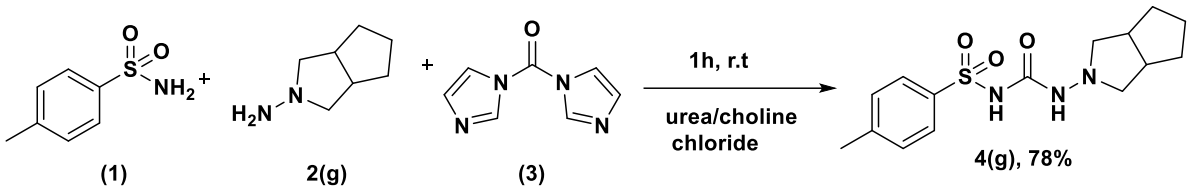
**Table 1**. The reactions all went off without a hitch, resulting in good to superior yields. Compounds **4a** and **4b** in **Table 1** readily participated in the reaction and produced good yields. In Table 1, compounds **4d** to **4f**, heterocyclic and heteroaromatic compounds demonstrated good participation in the reaction by providing the corresponding product in good yields. Following the successful synthesis of the sulfonyl urea derivatives mentioned above, we concentrated on applying this technology to the production of the anti-diabetic medication gliclazide. When 3-Amino-3-azabicyclo[3.3.0]octane **2g** and p-toluene sulfonamide **1** reacted in DES with each other using carbonyldidimidazole as a catalyst and reagent, 78% of gliclazide was produced. Reaction mixture was filtered once the reaction was finished, and water was then added to the reaction mixture to produce the required result as solid material (**Scheme 2**).




**Scheme 2.** Urea choline chloride mediated synthesis of Gliclazide from paratoluene sulfonamide.

## ■ Summary and Outlook

In conclusion, using urea choline chloride as a naturally occurring deep eutectic solvent and catalyst, we have established an effective technique for the synthesis of sulfonamide urea's from p-toluene sulfonamide. The process is straightforward, and the product was purified-free and isolated in good yields. A wide variety of substrates can be used in the method, which provides substituted sulfonyl urea derivatives in yields ranging from good to excellent. This approach resulted in a satisfactory yield for the production of gliclazide. The gentle reaction conditions, reusable reaction medium, large-scale synthesis, lack of column chromatography, and straightforward work-up and purification procedures are all visible benefits of this synthetic method.

## ■ Experimental

All reagents and solvents are commercially available and were purchased. The progress of reactions was monitored by thin-layer chromatography (TLC) using Merck silica gel (70–230 mesh) plates. Melting points were obtained in open capillary tubes on an electro-thermal 9200 apparatus. $^{1}$HNMR (300 MHz) spectra were determined on a Bruker 300 DRX Advance instrument. Elemental analyses for C, H, and N were performed using a Heraus CHN rapid analyzer.

### Preparation of DESs system

Deep eutectic solvents based on urea-choline chloride were created in accordance with the prior study [19]. Daily preparation of the deep eutectic solvent (ChCl-Urea) involved weighing, mixing, and boiling urea and choline chloride in a 2:1 molar ratio until a clear liquid formed. This liquid was then employed without additional purification. (**Scheme 3**).



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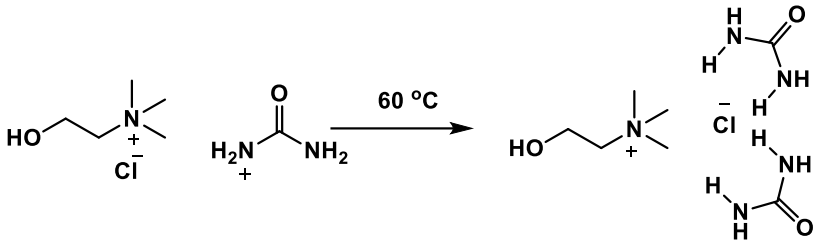


**Scheme 3**. Deep eutectic solvent production

**General Procedure for the preparation of compounds 4(a-g)**

A mixture of p-toluene sulfonamide **1,** amine **2(a-g)** and carbonyldiimidazole **3**, were dissolved in a choline chloride–urea-based deep eutectic solvent (2 mL), and were mixed and vigorously stirred at room temperature for 1h and the reaction progress was monitored by TLC (Ethyl acetate: n-Hexane, 1:2), after completion of the reaction, water was added DES (ChCl–Urea) is soluble in water and comes into the water layer and The white solid was separated by filtration recrystallization in EtOH to afford pure white solids crystals.

**N-((hexahydrocyclopenta[c]pyrrol-2(1H)-yl)carbamoyl)-4-methylbenzenesulfonamide (4g):** White solid; Yield = 78%; m.p: 164-167 °C; (m.p: 165-169 °C) [3], $^1$HNMR (300 MHz, $CDCl_3$) ppm: 1.38-1.59 (m, 2H, CH), 1.59-1.61(m, 4H, CH), 2.23-2.26 (m, 2H, CH), 2.37 (s, 3H, CH3), 3.26-3.31 (m, 2H, CH2), 3.62-3.66 (m, 2H, CH2), 7.34 (s, 2H, ArH), 7.39 (d, J= 7 Hz, 2H, ArH), 7.84 (s, 1H, NH), 7.86 (s, 1H, NH). Anal Calcd for $C_{15}H_{21}N_3O_3S$: C, 55.71; H, 6.54; N, 12.99 %. Found: C, 55.64; H, 6.51; N, 12.83%.

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