

## An Improved Synthesis of Urea Derivatives from *N*-Acylbenzotriazole via Curtius Rearrangement

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Several molecules incorporating the urea functionality have displayed a vital role in pharmaceutical, analytical, agricultural, polymer science and organic synthesis.<sup>1</sup> This moiety is found in a number of pharmacologically active molecules, for example carmustine, sorafenib, and many more, thus there is an increasing demand for functionalized ureas to be tested for a variety of applications and biological uses. A traditional and general synthetic method for preparing ureas involves the reaction of amines with phosgene, isocyanates or phosgene derivatives; however, these tend to be considerably toxic.<sup>2</sup> Ureas can also be obtained via reductive and oxidative carbonylation of amines in the presence of suitable transition-metal catalysts, such as palladium, tungsten, cobalt, copper and nickel. Unfortunately, using carbon monoxide as the source of the carbonyl moiety generally requires harsh conditions, such as high temperature and pressure.<sup>3a</sup> Carbon dioxide as a renewable carbon source or CH<sub>3</sub>OH as the C-1 source in the presence of ruthenium pincer complexes has also been used for this purpose;<sup>3b</sup> however, the stoichiometric use of expensive dehydrating reagents like di-*tert*-butyl azodicarboxylate, required to obtain the corresponding isocyanates, again limits the synthetic utility of the procedure.<sup>3c</sup> Hofmann and related Curtius, Lossen and Schmidt rearrangements are also well-known protocols to obtain the related urea derivatives, but all these processes have their drawbacks. Thus, the search for a versatile protocol for the synthesis of urea derivatives under mild reaction conditions remains a challenge for synthetic chemists.

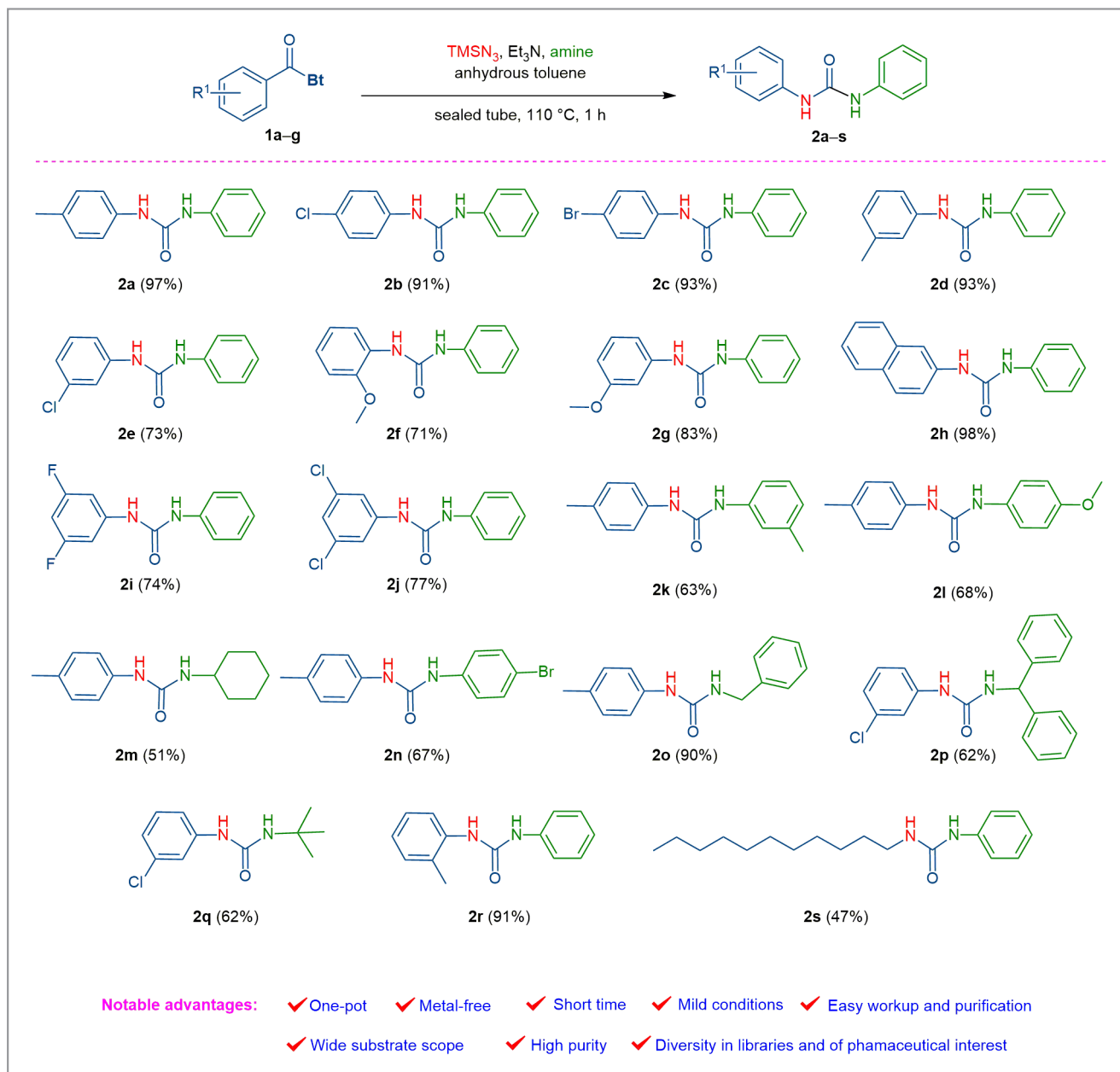
Over the last three decades, the benzotriazole group has been considered as one of the most successful synthetic auxiliaries for a number of reasons. In addition to its nature – benzotriazoles are mainly solid, non-toxic, moisture-insensitive, cost-effective, etc. – the triazole scaffold can be easily obtained under standard conditions, is sufficiently stable during the course of many reactions, can be activated for a number of transformations, and finally can be easily removed at the end of the reaction sequence.<sup>4</sup> *N*-Acylbenzotriazoles are considered as an alternative to acid chlorides in *N*-, *C*-, *O*- and *S*-acylations for the synthesis of amides, esters, acid azides, peptides, oxazolines, diketones, and thiazolines. The group of Dr. Vinod Tiwari at Banaras Hindu University (India) previously devised a method for synthesizing carbamates, thio-

carbamates, and symmetric ureas from *N*-acylbenzotriazoles via Curtius rearrangement, yet this method has limitations, particularly for the synthesis of unsymmetrical ureas.<sup>5</sup>

“Thus, a practical, mild, metal-free, one-pot and high-yielding method to synthesize urea derivatives with the aid of *N*-acylbenzotriazoles as a synthetic auxiliary via generation of *N*-acylazides was the ultimate goal of our present investigation,” said Dr. Tiwari, who added: “We believe that the acyl azide, upon heating, first converted into the corresponding isocyanate intermediate via Curtius rearrangement, which further reacts with amines under mild conditions to afford libraries of symmetric, unsymmetric, *N*-acyl and cyclic urea derivatives.”

Their synthetic strategy begins with the *N*-acylbenzotriazoles **1**, prepared from the corresponding carboxylic acids by reaction with thionyl chloride, NBS/PPh<sub>3</sub> or PySSPy/PPh<sub>3</sub> and 1*H*-benzotriazole in dichloromethane.<sup>6</sup> “Although the reaction of *N*-acylbenzotriazoles with NaN<sub>3</sub> afforded the corresponding carbamates, thiocarbamates, and symmetric ureas in average to good yields via Curtius rearrangement,<sup>5</sup> the method was not equally applicable for the production of unsymmetrical ureas, which therefore became our next objective,” explained Dr. Tiwari. A number of reactions with a diverse range of reagents were attempted, ending with the conclusion that *N*-acylbenzotriazole **1a** (1.0 equiv) on treatment with aniline (1.0 equiv), TMSN<sub>3</sub> (1.0 equiv) and triethylamine (1.0 equiv) in anhydrous toluene at 110 °C afforded the required unsymmetrical urea derivative **2a** in 83% yield. “After achieving this result, conditions were further optimized in terms of reagent and base equivalents, solvent medium, reaction time, and temperature to establish the optimum yield of compound **2a** (isolated in 97% yield) when *N*-acylbenzotriazole **1b** (1.0 equiv) was heated at 110 °C with 1.0 equivalent of aniline, 1.1 equivalents of TMSN<sub>3</sub> and 2.0 equivalents of triethylamine in anhydrous toluene for 60 minutes,” said Dr. Tiwari.

In order to determine the scope of the protocol, a library comprising diverse urea derivatives **2a–s** was developed simply by varying the *N*-acylbenzotriazole **1** and the amine under optimized reaction conditions (Scheme 1). “The reaction yield is not entirely dependent on the nature and position of the substituent present on the benzene ring of *N*-acylbenzotriazoles, or on the nature of amines used,” remarked Dr.

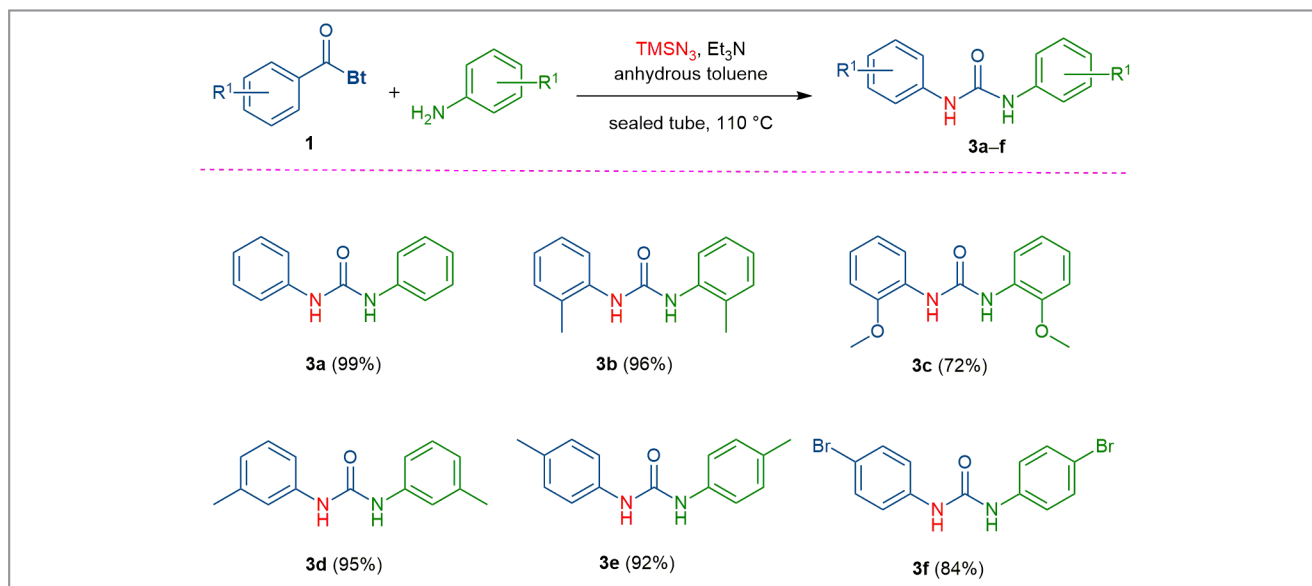


**Scheme 1** Synthesis of unsymmetric/symmetric/cyclic and *N*-acyl urea derivatives **3–6** from *N*-acylbenzotriazole **2** via Curtis rearrangement using  $\text{TMSN}_3$ . Molar ratios: *N*-Acylbenzotriazole **1** (1.0 equiv),  $\text{TMSN}_3$  (1.1 equiv),  $\text{Et}_3\text{N}$  (2.0 equiv), aniline derivative (1.0 equiv).

Tiwari. He continued: “A similar reaction of **2a** with propargyl amine under optimized conditions resulted in *N*-(prop-2-yn-1-yl)benzamide as the sole product instead of the respective urea.”

To improve further the practical utility of this methodology, the protocol was extended for the synthesis of symme-

tric urea **3** and *N*-acylurea derivatives **4**. For the synthesis of symmetric ureas **3a–f** (Scheme 2), aromatic *N*-acylbenzotriazoles and anilines having the same aromatic rings present on aryl *N*-acylbenzotriazoles were selected under the above optimized conditions. Likewise, 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-phenylethane-1,2-dione (**1o**) on reaction with aniline



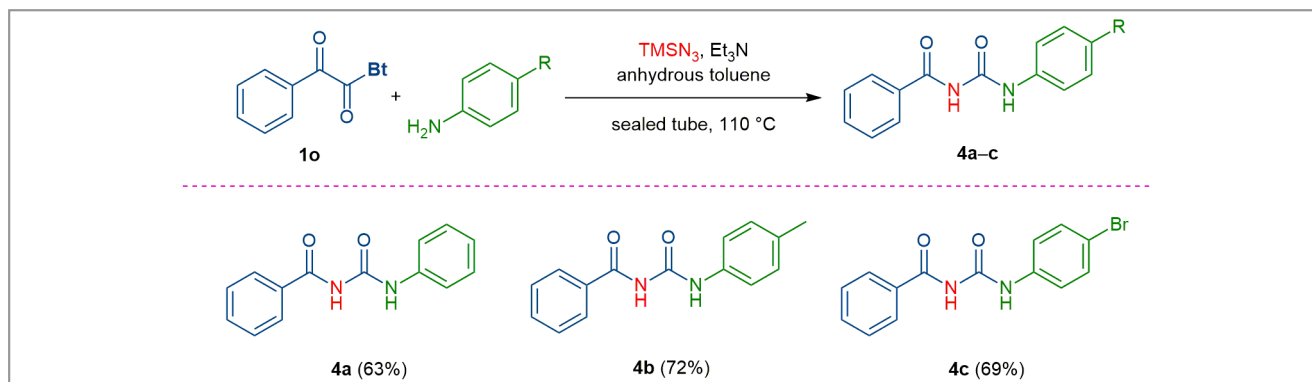
**Scheme 2** Symmetric ureas **3a-f** from *N*-acylbenzotriazole **1** via Curtius rearrangement. Molar ratios: *N*-Acylbenzotriazole **1** (1.0 equiv),  $\text{TMSN}_3$  (1.1 equiv),  $\text{Et}_3\text{N}$  (2.0 equiv), aniline derivative (1.0 equiv).

under the optimum reaction conditions afforded *N*-acyl ureas **4a-c** in satisfactory yields (Scheme 3).

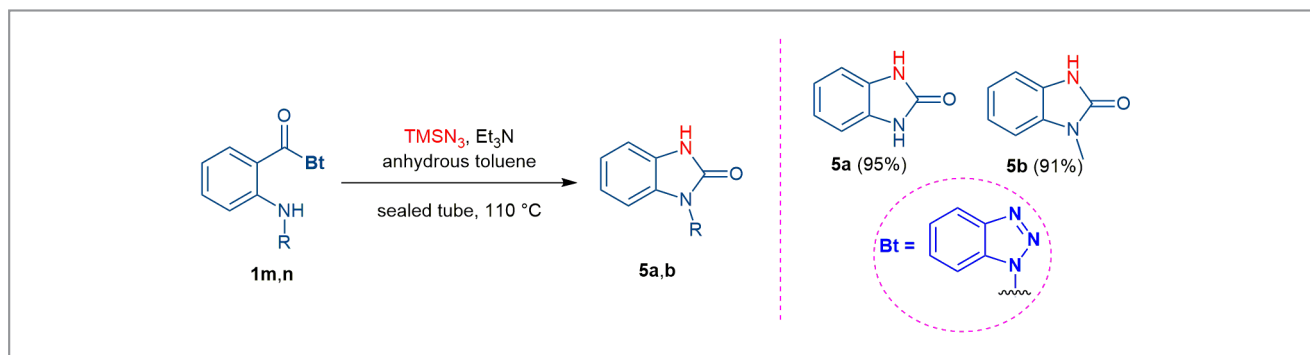
Finally, the authors successfully exploited the protocol in order to obtain cyclic ureas simply by reacting *N*-acylbenzotriazoles **1m,n** under optimized conditions, affording cyclic ureas **5a,b** in excellent yields via intramolecular cyclization through isocyanate intermediates (Scheme 4). "A plausible mechanism to explain the formation of ureas **2-5** involves an acyl azide intermediate formed by the nucleophilic addition of an azide ion to the carbonyl carbon of acyl benzotriazole through the displacement of benzotriazole as leaving group,"

explained Dr. Tiwari. He continued: "The acyl azide intermediate further undergoes Curtius rearrangement to afford the isocyanate intermediate with the subsequent loss of molecular nitrogen, finally captured by an amine to produce the final urea derivatives."

Dr. Tiwari concluded: "The key step of this new method relies on the good leaving group nature of the benzotriazole moiety, which was exploited for the synthesis of a number of different ureas. In many cases, column chromatography was avoided and thus, the devised protocol can certainly be considered for its practical use in both academia and industry."



**Scheme 3** *N*-Acylureas **4a-c** from 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-phenylethane-1,2-dione (**1o**). Molar ratios: *N*-Acylbenzotriazole **1** (1.0 equiv),  $\text{TMSN}_3$  (1.1 equiv),  $\text{Et}_3\text{N}$  (2.0 equiv), aniline derivative (1.0 equiv).



**Scheme 4** Cyclic urea derivatives **5a,b** from *N*-acylbenzotriazoles **1m,n** via Curtius rearrangement. Molar ratios: *N*-Acylbenzotriazole **1** (1.0 equiv),  $\text{TMSN}_3$  (1.1 equiv),  $\text{Et}_3\text{N}$  (2.0 equiv), aniline derivative (1.0 equiv).

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Dr. V. K. Tiwari

**Vinod K. Tiwari** is associated with Banaras Hindu University (BHU), India since 2005 where he is an associate professor of organic chemistry. After completing his MSc from BHU in 1998, he qualified CSIR-UGC-NET, GATE, SET, and then began his doctoral research at CSIR-Central Drug Research Institute, Lucknow, India followed by postdoctoral experience at the University of Florida (USA), the University of California-Davis (USA), and Universitat Konstanz (Germany). He was offered the post of Lecturer at Bundelkhand University, Jhansi, India (2004–2005) before being appointed to his current post at BHU. With more than 20 years of research and 15 years of teaching experience, Dr. Tiwari has supervised 11 PhD theses and contributed significantly to 130 peer-reviewed publications, several patents and invited book chapters. His research has been recognized with many prestigious honors, awarded by Indian Chemical Society, Chemical Research Society of India, Indian Science Congress Association, Indian Council of Chemists, and more. His current research focuses on various aspects of carbohydrate chemistry and the development of novel synthetic methodologies.