

SYNLETT Spotlight 252

Urea: A Useful and Inexpensive Chemical for Organic Synthesis

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Ricardo Antonio Wanderley Neves Filho was born in Recife/PE, Brazil in 1984. He received his B.Sc. degree from the Federal University of Pernambuco (UFPE) in 2006. Presently, he is enrolled in the M.Sc. program in Chemistry at the same university and is doing research in synthetic organic chemistry under the supervision of Prof. Rajendra M. Srivastava at UFPE and Prof. Hugo Gallardo at the Federal University of Santa Catarina (UFSC). His research is focused on the synthesis of luminescent liquid crystalline compounds containing an oxadiazole moiety. He is grateful to Gustavo Gouveia for a kind revision of this Spotlight.

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In honor of Professor R. M. Srivastava on the occasion of his 70th birthday on March 16, 2008.

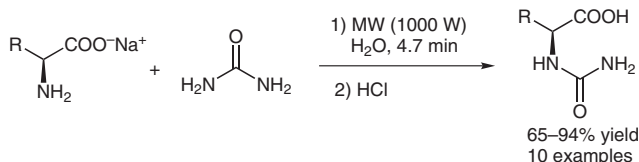
Introduction

Urea was the first organic compound to be synthesized from inorganic reagents. This easily accessible chemical has been used as building block in the synthesis of *N*-carbamoyl-L-amino acids,¹ cyclic carbonates,² and many nitrogen-containing heterocycles such as pyridines,³ pyrimidines,⁴ 3,4-dihydropyrimidinones,⁵ oxazines,⁶ 1,3-ox-

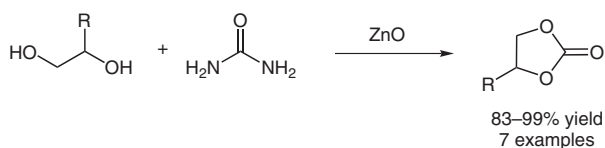
azin-3-ones,⁷ and iminosugars.⁸ Another application of urea in carbohydrate chemistry was described earlier.⁹ Urea is also employed as source of ammonia in the syntheses of triaryl amines,¹⁰ imides,¹¹ and amides.¹² Urea is an inexpensive, commercially available colorless crystalline compound, and is soluble in a large range of polar solvents including water. Its recent applications are given below.

Abstracts

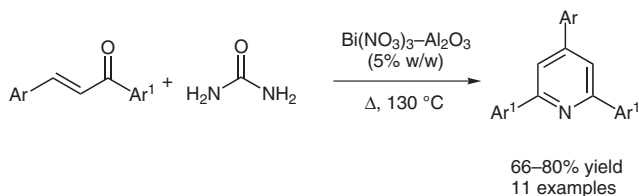
(A) *N*-Carbamoyl-L-amino acids are important synthetic intermediates for the synthesis of peptides and heterocycles. A microwave-assisted green synthesis of these compounds was described by Verardo et al.¹ The reaction between urea and amino acid sodium salts in water followed by acidification furnished the desired compounds in good yields and optical purity.



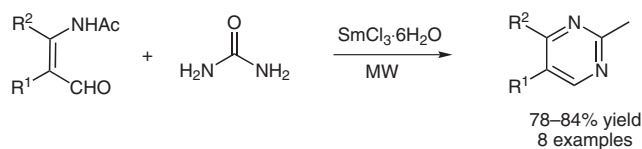
(B) Li et al.² described the high-yielding synthesis of cyclic carbonates using the reaction of urea and diols catalyzed by metal oxides. The interaction of urea with many metal catalysts was studied by FTIR spectroscopy and it was found that the strongest interaction occurs with ZnO. The products were obtained in excellent yields.



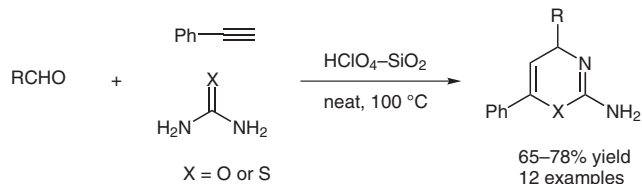
(C) Recently the synthesis of 2,4,6-triarylpyridines was described by Kumar et al.³ The one-pot reaction of urea and benzylideneacetophenones supported on Bi(NO₃)₃–Al₂O₃ under heating afforded the desired compounds in good yields. The superiority of urea in this reaction was demonstrated by comparison with other amino reagents.



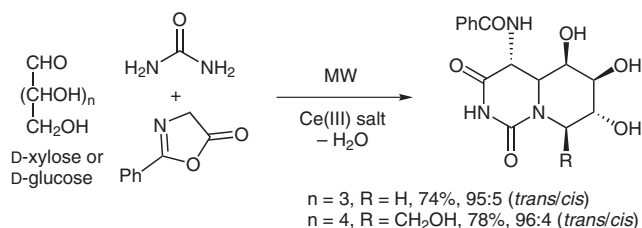
(D) Barthakur et al.⁴ developed a new one-pot protocol to access annelated pyrimidines by the Lewis acid catalyzed reaction of β -formyl enamides with urea under solvent-free conditions. The desired compounds were obtained in good yields after a short reaction time. The reactions work well using β -formyl enamides containing aromatic or aliphatic moieties. Ester as well as amide groups survive the reaction conditions.



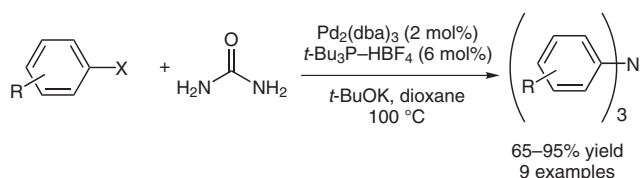
(E) Mandal et al.⁶ developed a new three-component Diels–Alder cycloaddition using phenyl acetylene, aldehyde, and urea or thiourea as reactants and $\text{HClO}_4\text{--SiO}_2$ as catalyst under solvent-free conditions. The 2-amino-4*H*-1,3-oxazines were obtained as sole products in good yields. The high yields and easy handling of the reagents and simple work-up make this reaction an attractive approach for obtaining these heterocycles.



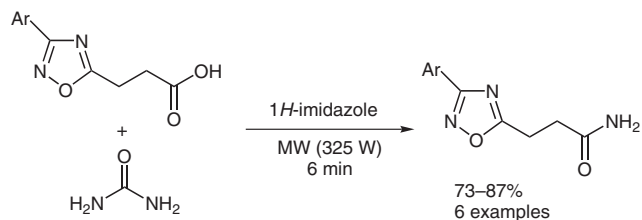
(F) Iminosugars are compounds with great pharmacological importance. Yadav et al.⁸ reported that the reaction of 2-phenyl-1,3-oxazol-5-one, urea, and unprotected aldoses following the Biginelli protocol under solvent-free conditions leads to the formation of functionalized iminosugars in good yields and high *trans* diastereoselectivity.



(G) Recently, Artamkina et al.¹⁰ developed a new method for triarylamine synthesis using a palladium-catalyzed C–N bond formation (Buchwald–Hartwig reaction). Urea was used to generate ammonia in situ which reacts with inactivated aryl halides in the presence of a catalytic amount of $\text{Pd}_2\text{dba}_3/t\text{-Bu}_3\text{P-HBF}_4$ and a strong base to afford selectively the triarylated compounds in good yields.



(H) In 2006, Neves Filho and Srivastava described the clean microwave-induced synthesis of six 1,2,4-oxadiazole-based propionamides. The reaction of the corresponding carboxylic acids, urea, and imidazole under microwave irradiation and solvent-free conditions (Khalafi–Nezhad protocol) led to the formation of the desired amides in good yields in six minutes.¹²



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