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LETTERS

Reductive Alkylation of Urea: A Practical Route to Substituted Ureas

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Abstract: Conditions are disclosed for the formation of either mono- or di-substituted ureas by reductive alkylation, which are readily adaptable to large scale preparations. Dehydrating agents such as acetyl chloride or trimethylsilyl chloride effectively promote the condensation of ureas and aldehydes. Reduction of the adducts affords the mono- or di-substituted ureas in high yields.

The synthesis of substituted ureas is a fundamental task in organic chemistry because of their many applications in the fields of chemicals, agriculture and medicine.[1, 2] Although the synthesis of substituted ureas has been extensively documented, most of the methods reported suffer various disadvantages, thus limiting their general application.[1] For example, the most widely utilized isocyanate route relies on the use of highly toxic and ecologically hazardous phosgene or its derivatives. Therefore, the search for new or improved procedures continues unabated, driven by the need for higher efficiency and ecological constraints. Recently, a mild and environmentally benign reductive alkylation method was reported from Merck for the preparation of N,N'-disubstituted ureas.[3] This report prompted us to disclose our findings which had been developed independently and successfully applied to the synthesis of one of our drug candidates on a multi-kilogram scale.

Although reductive alkylation of amines had been extensively reported,[4] there was no report of reductive alkylation of urea at the beginning of this work. However, imine formation had been inferred to occur between urea and aldehydes or ketones in a few publications.[5] Therefore, we speculated that substituted ureas could be obtained via the interaction of urea and aldehydes under proper reducing conditions.

Subjecting urea directly to reductive alkylation with benzaldehyde under conditions typically used for reductive alkylation of amines[4] was not successful. The conversion was low with about 10% consumption of the aldehyde, and the products consisted of a 3:7 mixture of *N*-benzylurea and benzyl alcohol. This poor result was attributed to incomplete formation of the urea/aldehyde adduct. Analysis of a mixture of 4-*t*-butylbenzaldehyde and urea by ^{1}H NMR spectroscopy indicated the presence of the equilibrium shown in eq 1. It is completely reversible with adduct formation being favored at lower temperature.

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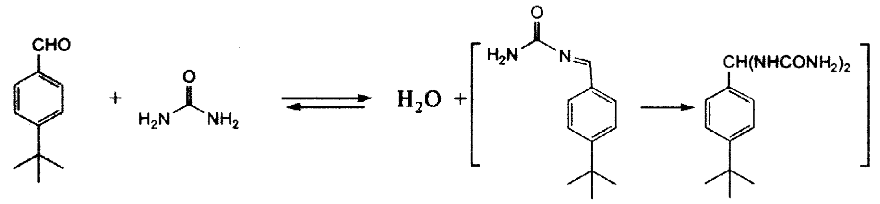
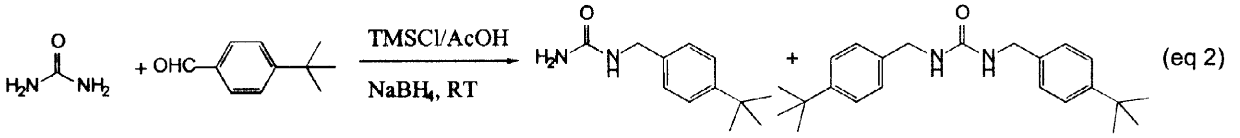


(eq 1)

20 °C, 2 h	56	44
50 °C	65	35
60 °C	75	25
cooled to 20 °C	58	42

We then tested a variety of dehydrating agents to shift this equilibrium to the adduct side. Among those examined, AcCl, Me_3SiCl, Cl_3SiH and $MeSiCl_2H$ were found to be quite effective. For example, the aldehyde/adduct ratio changed to 8:92 with 1 equivalent of acetyl chloride after one hour at room temperature. The aldehyde was completely consumed in the presence of either AcCl or Me_3SiCl, and the alcohol resulting from direct reduction of the aldehyde dropped to $\leq$ 5%. The bifunctional reagents, $MeSiCl_2H$ and Cl_3SiH, serving as both dehydrating and reducing agents, offered comparable yields in this reductive alkylation of urea. However, the product isolation was difficult due to the amorphous silica gel formation. Thus, we chose AcCl and Me_3SiCl for further optimizing the reaction due in part to operational convenience, especially on large scale.[6] It is interesting to note that acetyl chloride has been routinely used as a dehydrating/activating agent in the condensation of an amide/carbamate and an aldehyde with a dialkylphosphite *en route* to an α-aminophosphonic acid,[7] and trimethylsilyl chloride has been shown to catalyze the condensation of an amide with an aldehyde.[8]

The reductive alkylation of mono-substituted ureas appeared faster than of urea (eq 2). Therefore, in order to achieve optimal selectivity for mono-alkylation, up to 20 equivalents of urea was used.[9] The excess urea was easily removed during aqueous workup, allowing pure mono-substituted ureas to be obtained by recrystallization.

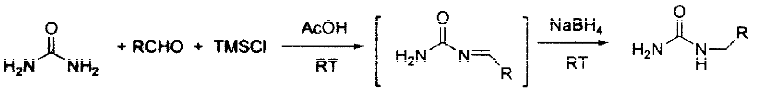


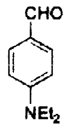
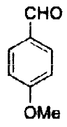
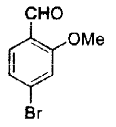
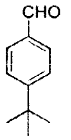
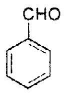
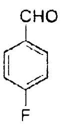
(eq 2)

molar ratio		mono-	di-
1	1	36	64
5	1	88	12
20	1	94	6

Good yields of mono-substituted products were obtained for a variety of aromatic aldehydes (Table 1). Electronic and steric factors seem to have little effect on the reaction. The low yield for benzylurea (entry 5, Table 1) is due to its high solubility in water. Unfortunately, complicated mixtures were obtained for α,β-unsaturated aldehydes (i.e. cinnamaldehyde) and enolizable aldehydes under these conditions.

Table 1: Mono-alkylation of Urea

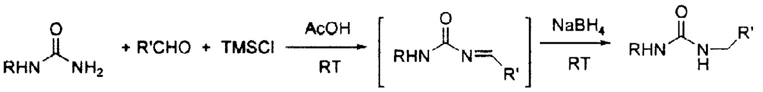


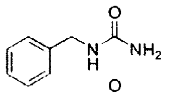
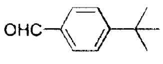
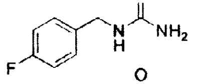
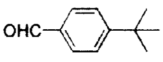
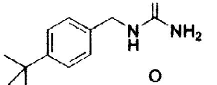
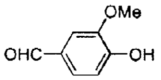
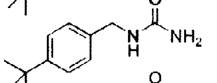
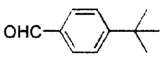
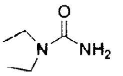
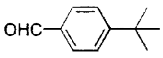
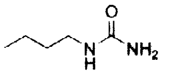
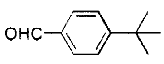
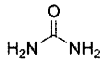
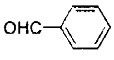
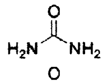
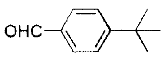
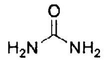
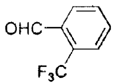
Entry	1	2	3	4	5	6
Aldehyde						
Yield (%)[a]	82	75	87	75	60	92

a) isolated yields

The reductive alkylation of mono-substituted ureas, giving dialkylated products, is much more facile. No over-alkylation is observed. Therefore, neither the starting mono-substituted urea nor the aldehyde needs to be in excess.[10] As shown in Table 2, high yields can be obtained for a wide range of non-enolizable, non-conjugated aldehydes and ureas. A symmetrically disubstituted urea is efficiently formed by reacting urea itself with two equivalents of an aldehyde (entries 7, 8, 9, Table 2).

Table 2: Formation of Disubstituted Ureas:



Entry	Urea	Aldehyde	Yield(%)[a]
1			78
2			70
3			85
4			89
5			65
6			86
7[b]			85
8[b]			75
9[b]			75

a) isolated yields; b) two equivalents of aldehydes were used.

In conclusion, a highly efficient reductive alkylation method for the formation of mono- and di-substituted ureas has been found. The presence of a dehydrating agent such as acetyl chloride or trimethylsilyl chloride is essential for the initial condensation between an urea and an aldehyde. The dehydrating agents used in this work offer more choices for solvents in which the reductive alkylation is carried out and, thus, promise a broader scope of the method as compared to the Merck protocol.[3] Further, the simplicity in product isolation and mild reaction conditions make this method easily adaptable to large-scale preparations.

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References and Notes:

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(5) (a) Kato, T.; Chiba, T.; Sasaki, M.; Yakugaku, D.; Yakugaku, Z. *J. Pharm. SOS. JAR.* **1981**, *101*, 182. (b) Butler, A. R.; Hussain, I.; Leitch, E. *J. Chem. Soc. Perkin Trans. II 1980*, 106. (c) Gompper,R.; Noth, H.; Rattay, W.; Schwarzensteiner, M.; Spes, P.; Wagner, H. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1039.

(6) Although acetyl chloride and trimethylsilyl chloride were interchangable as dehydrating agent, trimethylsilyl chloride generally offered cleaner reaction mixtures (but not necessarily higher yields) and was used in obtaining the results shown in the two tables.

(7) (a) S. Chen; Coward, J. K. *Tetrahedron Lett.* **1996**, *37*, 4335; (b) Yuan, C.; Chen, S.; Wang, G. *Synthesis*, **1991**, 490; (c) Yuan, C.; Wang, G.; Chen, S. *Synthesis*, **1990**, 522.

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(9) The mono-/di- ratio did not show significant change from 10 equivalents to 20 equivalents of urea. However, 20 equivalents of urea is recommended to ensure the general applicability of the method.

(10) However, 1.2 to 1.5 equivalents of one of the starting reagents (depends on their availability) were normally used to ensure convenient reaction times.