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A High Yielding, One-pot Synthesis of Substituted Ureas from the Corresponding Amines Using *Mitsunobu*'s Reagent[#]

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Summary. A *Mitsunobu*-based protocol has been developed for the synthesis of symmetrically and unsymmetrically substituted ureas from a variety of primary and secondary amines using gaseous carbon dioxide, in good to excellent yields. This protocol is mild and efficient compared to other reported methods.

Keywords. *Mitsunobu*'s reagent; Carbon dioxide; Amines; Substituted ureas.

Introduction

Substituted ureas are very important class of compounds that display a wide range of interesting applications [1]. They have extensively been used as agrochemicals [2], pharmaceuticals [3], intermediates in organic synthesis [4], for protection of amino groups [5], and as linkers in combinatorial chemistry [6]. These uses require their preparation by convenient and safe methodology. Traditionally, their synthesis involves a reaction of amines with phosgene [7], its derivatives [8], carbonyl-imidazoles [9], or carbon monoxide [10] using various kinds of metal and non-metal catalysts. Moreover, a process for preparing 1,3-disubstituted ureas through reacting a cyclic carbonic acid ester with an amine over a proper catalyst was disclosed [11]. However, This method is too expensive to use on a large scale. The transformation of amines through catalytic carbonylation to produce disubstituted ureas provides an alternative environmental benign method and has been investigated over many years using various kinds of metallic catalysts [12]. However, these methods failed due to the problems of regenerating the catalysts from the products. Moreover, their formation using CO_2 employed harsh reaction conditions, such as long reaction times, use of expensive strongly basic reagents, tedious work-up, and low yields [13]. Consequently, there is continued interest in developing new and convenient methods for the synthesis of substituted ureas using mild reaction conditions.

Our group [14] has been engaged over several years with the development of new methods for the synthesis of carbamates, dithiocarbamates and related compounds using cheap, abundantly available, and safe reagents like CO_2 and CS_2. Recently, we have reported [15] the synthesis of carbamates, dithiocarbamates, *O*,*S*-dialkyl-dithiocarbonates (xanthates), and dialkyl carbonates from the corresponding alcohols using *Mitsunobu*'s reagent. Based on our recent work, we report herein a chemoselective, highly efficient, and mild synthesis of symmetrical and unsymmetrical ureas from corresponding amines using *Mitsunobu*'s reagent.

Results and Discussion

We carried out the synthesis of substituted symmetrical and unsymmetrical ureas by mild carba-

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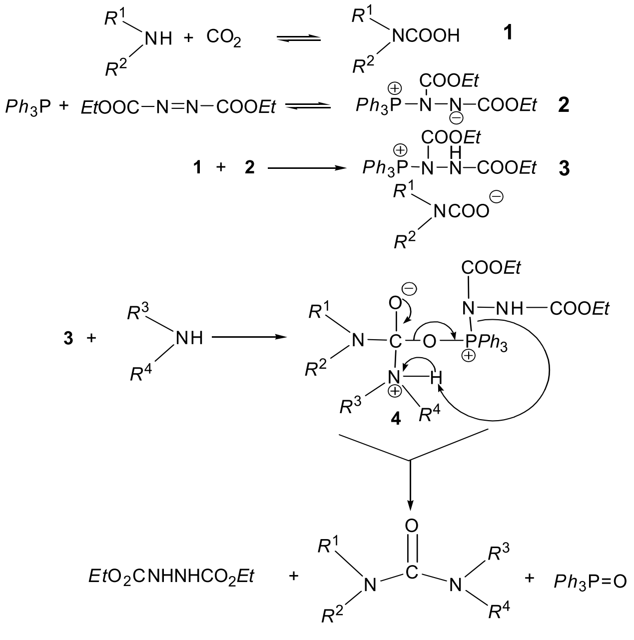
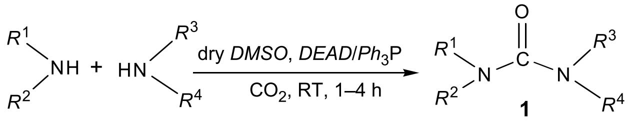
mation of amines with gaseous carbon dioxide in the presence of *Mitsunobu*'s reagent. We assume that the unstable carbamic acid **1** [16] generated from an amine and CO_2 reacts with the *Mitsunobu* zwitterion **2** formed from Ph_3P and diethyl azodicarboxylate, to furnish the stabilized zwitter-ionic species **3**, which in turn would react with a second molecule of desired amine to form the highly reactive ionic species **4**. This ionic species **4** would further undergo electronic rearrangement to afford the desired substituted urea derivative as shown in Scheme 1. Various symmetrical and unsymmetrical substituted urea derivatives were prepared in high yields and their spectroscopic confirmation was achieved from the reported values as mentioned in Table 1.



Scheme 1



Scheme 2

Conclusion

We have developed a convenient and efficient protocol for the one-pot, four-component coupling of various primary and secondary amines *via* a *Mitsunobu* zwitterion. This reaction generates the corresponding substituted ureas in high yields. Furthermore, this method exhibits substrate versatility, mild reaction conditions, and experimental convenience. This

Table 1. Conversion of amines into substituted areas of general formula **1**[a]

Entry	R^1	R^2	R^3	R^4	Time/h	Yield[b]/%	Ref.
1	*n*-Hexyl	H	*n*-Hexyl	H	2	94	[17]
2	2-Phenethyl	H	2-Phenethyl	H	2	96	[18]
3	Benzyl	H	Benzyl	H	2.5	85	[17]
4	*n*-Octyl	H	*n*-Octyl	H	2	96	[18]
5	*i*-Amyl	H	*i*-Amyl	H	2.5	84	[17]
6	*n*-Dodecyl	H	*n*-Dodecyl	H	1	98	[19]
7	Cyclohexyl	H	Cyclohexyl	H	2.5	81	[17]
8	*n*-Butyl	*n*-Butyl	*n*-Butyl	*n*-Butyl	3	84	[19]
9	$R^1 = R^2 =$ Piperidine		$R^3 = R^4 =$ Piperidine		4	88	[13c]
10	$R^1 = R^2 =$ Pyrolidine		$R^3 = R^4 =$ Pyrolidine		4	90	[13c]
11	$R^1 = R^2 =$ Morpholine		$R^3 = R^4 =$ Morpholine		4	86	[13c]
12	1-Methylbenzyl	H	1-Methylbenzyl	H	2.5	82	[18]
13	*n*-Hexyl	H	*n*-Dodecyl	H	2	93	[17]
14	*p*-Methoxybenzyl	H	*p*-Methoxybenzyl	H	2.5	86	[17]
15	*p*-Anisidine	H	*p*-Anisidine	H	3	76	[17]
16	*n*-Hexyl	H	*n*-Propyl	*n*-Propyl	3	83	[17]
17	Cyclohexyl	H	$R^3 = R^4 =$ Pyrolidine		4	80	[17]
18	Cyclohexyl	H	*n*-Propyl	*n*-Propyl	3	81	[17]

[a] All the products were characterized by IR, NMR, and mass spectral data

[b] Isolated yields

synthesis protocol is believed to offer a more general method for the formation of C–N bonds essential to numerous organic syntheses.

Experimental

Chemicals were procured from Merck, Aldrich and Fluka chemical companies. Reactions were carried out under an atmosphere of nitrogen. IR spectra (4000–200 cm^{-1}) were recorded on Bomem MB-104-FTIR spectrophotometer where as NMRs were scanned on AC-300F, NMR (300 MHz), instrument using $CDCl_3$ and some other deuterated solvents and *TMS* as internal standard. Elemental analysis were made by Carlo-Erba EA 1110-CNNO-S analyzer and agreed favorably with calculated values.

Typical Experimental Procedure

N,N′-Di-n-hexylurea (**1**) *n*-Hexylamine (1 cm^3, 7.56 mmol) was taken in 25 cm^3 dry *DMSO* and gaseous CO_2 was bubbled through it for 30 min at room temperature. To this, a mixture of 1.98 g triphenylphosphine (7.56 mmol) and 1.31 cm^3 diethyl azodicarboxylate (7.56 mmol) was added slowly in 2–3 small portions. Next, 1 cm^3 *n*-hexylamine (7.56 mmol) was added. The reaction was stirred at room temperature until completion (2 h) as confirmed by TLC. The reaction mixture was then poured into 50 cm^3 distilled water and extracted with ethyl acetate thrice. The organic layer was separated and dried over anhydrous sodium sulfate and then concentrated to afford 1.62 g (94%) *N*,*N*′-di-*n*-hexylurea identical in all respects with those described in Ref. [17].

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