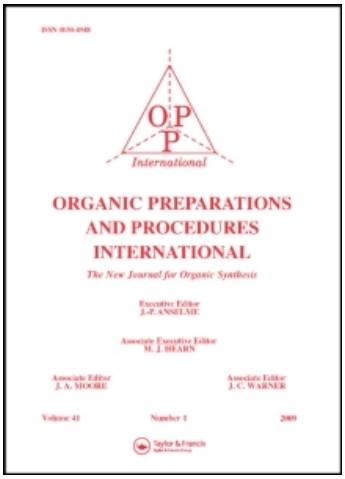

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AN EFFICIENT ONE POT SYNTHESIS OF N,N'-DISUBSTITUTED UNSYMMETRICAL UREAS AND CARBAMATES

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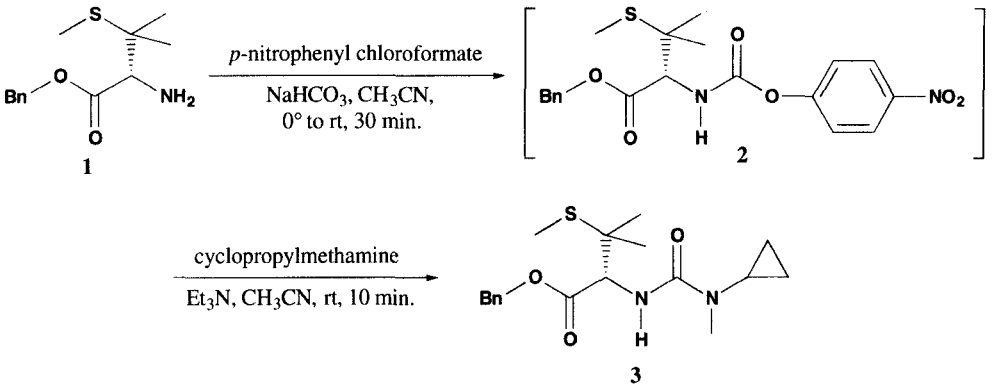
Unsymmetrical ureas have received considerable attention because of their potential as key structural fragments of synthetic drugs such as Abbott's HIV protease inhibitor **A77003**.[1] The traditional method for the general synthesis of ureas involves the reaction of amines with isocyanates,[2] of which the most widely used preparation method involves the use of phosgene.[3] However, the potential hazards associated with this reagent render it inappropriate for large scale production of isocyanate compounds. Another method developed for the preparation of isocyanates involves the use of carbamates such as phenyl carbamate[4] and *N*-trimethylsilyl-*N*-ethyl carbamate.[5] However, both approaches have drawbacks: in the former harsh conditions are required and in the latter an extra step, silylation, is required. Recently, Basha reported the synthesis of *N,N'*-disubstituted ureas from carbamates,[6] by initial treatment of an amine with a Grignard reagent such as ethylmagnesium bromide to form the magnesium salt, followed by the efficient displacement of an alkoxy group of a carbamate to provide the corresponding urea. Although this method is very simple, its obvious drawback is that neither amine should contain any functional group labile to Grignard reagents. In order to develop a mild method for the preparation of isocyanates and/or for the preparation of ureas, we reasoned that a better leaving group in the carbamate could be utilized to generate an isocyanate under mild conditions or could be displaced by a simple amine without being activated by Grignard reagents to produce the urea efficiently.

We have found that it is possible to generate *N,N'*-disubstituted ureas by addition of a simple amine to *p*-nitrophenoxy carbamates in the presence of triethylamine. As shown in the Scheme, the target urea **3** was synthesized from S- and O- protected L-penicillamine **1**. Coupling of amine **1** with commercially available *p*-nitrophenyl chloroformate under mildly basic conditions gave *p*-nitrophenoxy carbamate **2**. Although the carbamate **2** may be isolated by simple base work-up,[7] it was used *in situ* for the preparation of the target urea by the addition of cyclopropylmethylamine and triethylamine. Among various solvents examined, the formation of *p*-nitrophenoxy carbamate **2** was fastest

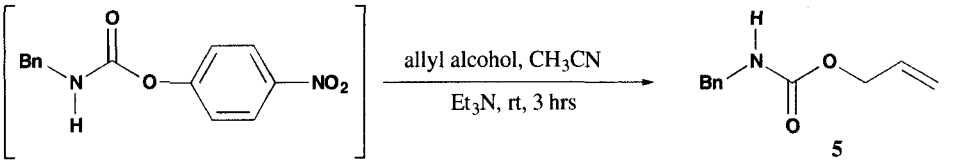


1 2 3

in acetonitrile and solid $NaHCO_3$ was the base of the choice among various bases examined. The formation of ureas from *p*-nitrophenoxy carbamates proceeded via isocyanate intermediate. The addition of triethylamine to intermediate **2** produced the isocyanate[8] and the *p*-nitrophenolate, which was characterized by its deep yellow color. Also, *p*-nitrophenoxy carbamates of the secondary amines, which cannot generate the isocyanate intermediate, do not produce ureas under our reaction conditions.

Recently, Ghosh *et al.* reported a convenient synthesis of functionalized carbamates utilizing di(2-pyridyl) carbonate (DPC) or N,N'-disuccinimidyl carbonate (DSC).[9,10] They developed a mild and convenient method for the preparation of various carbamates of amines with a host of alcohols. However, in both the cases the mixed active carbamates must be isolated. As it was reported that the reaction of alcohols with isocyanates gave carbamates, we decided to utilize the above mentioned isocyanate intermediate. Thus, we report herein the scope of *p*-nitrophenyl chloroformate promoted, one-pot alkoxycarbonylation of various amines.

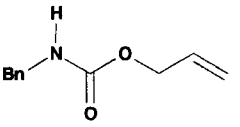
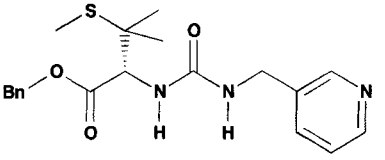
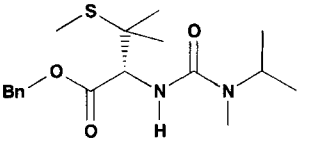
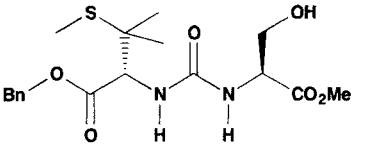
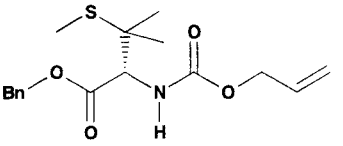
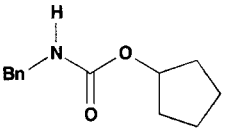
A solution of allyl alcohol and triethylamine in CH_3CN was added to the intermediate **4**, which was prepared from the reaction of benzylamine and *p*-nitrophenyl chloroformate, and the resulting solution was stirred for 3 hrs to afford the desired carbamate **5** in good yield.



5

In the case of hindered tertiary alcohols, the formation of carbamate was unsuccessful under a variety of conditions. Further studies are currently in progress to extend the scope of this method for tertiary alcohols. This simple, one-pot procedure was applied to a series of amines and alcohols (Table 1).[11] These conditions are suitable for functionally diverse alcohols and amines. Reaction of intermediate **2** with L-serine methyl ester (entry 4) demonstrated the selectivity of this reaction between amine and alcohol. Thus, we have developed a simple and practical method for the preparation of *N,N'*-disubstituted unsymmetrical urea and carbamates. Application of this methodology in the synthesis of various biologically active ureas and carbamates is currently under investigation.

TABLE 1. Synthesis of N,N'-Disubstituted Unsymmetrical Ureas and Carbamates.

Entry	Amine	Amine or Alcohol	Product		Yield (%)
1	$PhCH_2NH_2$	allyl alcohol		**5**	88
2	**1**	3-pyridylmethylamine		**6**	97
3_	**1**	isopropylmethylamine		**7**	96
4	**1**	L-Ser-OMe		**8**	96
5	**1**	allyl alcohol		**9**	80
6	$PhCH_2NH_2$	cyclopentanol		**10**	48

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on a Jeol GSX500 spectrometer with chemical shifts expressed in δ units (ppm) relative to tetramethylsilane. FAB Mass spectra were recorded on a Jeol JMS-DX300 Mass Spectrometer. Thin-layer chromatography was conducted with E. Merck silica gel 60 F_{254} plates. Column chromatography was performed using E. Merck silica gel 60 (230-400 mesh). Unless otherwise noted, reactions were conducted under a nitrogen atmosphere.

N,N'-Disubstituted Ureas (3).- To a suspension of $NaHCO_3$ (1.35g, 16 mmol) in acetonitrile (50 mL), *p*-nitrophenyl chloroformate (2.01g, 10 mmol) and S-methyl-O-benzyl L-penicillamine (2.35g, 10 mmol) were added successively at 0°. After 30 min at room temperature, a solution of cyclopropyl-methylamine (0.75g, 10.5 mmol) and triethylamine (2.53g, 25 mmol) in acetonitrile (15 mL) was

added to the reaction mixture at room temperature. The resulting mixture was stirred until no *p*-nitrophenoxy carbamate remained by TLC (10 min). The mixture was then concentrated, diluted with ethyl acetate (100 mL) and washed successively with aqueous K_2CO_3 solution (100 mL), 1N HCl (100 mL) and dried over $MgSO_4$. Removal of the solvent, followed by chromatography over silica gel (20% EtOAc-hexane) afforded the urea **3** as a sticky oil (3.09g, 92%). ^{1}H NMR ($CDCl_3$): δ 0.83 (m, 2H), 0.94 (m, 2H), 1.41 (s, 3H), 1.44 (s, 3H), 2.03 (s, 3H), 2.60 (m, 1H), 2.99 (s, 3H), 4.54 (d, 1H), 5.25 (dd, 2H), 6.30 (d, 1H), 7.43 (m, 5H); FAB MS; 351 (M+1).

Anal. Calcd for $C_{18}H_{26}N_2O_3S$: C, 61.68, H, 7.48, N, 8.00. Found: C, 61.72, H, 7.46, N, 8.02

TABLE 2. Elemental Analyses and ^{1}H NMR Data of Compounds **5-10**

Cmpd	Elemental Analyses (Found) C	H	N	^{1}H NMR Data (δ)
5	61.25 (61.27)	5.57 (5.56)	6.00 (6.01)	4.61 (d, 2H), 4.72 (dd, 2H), 5.17 (m, 2H), 5.24 (br, 1H), 6.03 (m, 1H), 7.41 (m, 5H)
6	61.99 (61.99)	6.51 (6.50)	10.85 (10.87)	1.30 (s, 6H), 1.98 (s, 3H), 4.38 (m, 2H), 4.55 (d, 1H), 5.15 (dd, 2H), 5.70 (s, 1H), 5.84 (s, 1H), 7.20 (m, 1H), 7.35 (m, 5H), 7.63 (d, 1H), 8.50 (d, 2H)
7	61.33 (61.30)	8.01 (8.00)	7.95 (7.97)	1.05 (d, 6H), 1.28 (d, 6H), 1.90 (s, 3H), 2.82 (s, 3H), 4.41 (d, 1H), 5.10 (dd, 2H), 5.31 (br, 1H), 7.20 (m, 5H)
8	54.25 (54.27)	6.58 (6.57)	7.03 (7.05)	1.28 (d, 6H), 2.81 (s, 3H), 3.28 (m, 3H), 3.78 (s, 3H), 4.24 (d, 1H), 4.47 (m, 1H), 4.92 (s, 2H), 5.24 (br, 1H), 5.62 (br, 1H), 7.18 (m, 5H)
9	60.56 (60.54)	6.88 (6.87)	4.16 (4.17)	1.40 (s, 6H), 2.06 (s, 3H), 4.42 (d, 1H), 4.63 (d, 2H), 5.17-5.43 (m, 2H), 5.23 (dd, 2H), 5.65 (d, 1H), 6.01 (m, 1H), 7.40 (m, 5H)
10	63.85 (63.87)	6.51 (6.50)	5.32 (5.33)	1.38-1.79 (m, 8H), 4.78 (s, 2H), 4.98 (m, 1H), 5.23 (br, 1H), 7.22 (m, 5H)

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7. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 3H), 1.42 (s, 3H), 2.03 (s, 3H), 4.43 (d, 1H), 5.21 (dd, 2H), 6.03 (d, 1H), 7.32-7.73 (m, 7H), 8.23 (d, 2H).

8. The isocyanate could be isolated by the traditional[2b] work-up. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 3H), 1.42 (s, 3H), 2.03 (s, 3H), 3.90 (s, 1H), 5.21 (dd, 2H), 7.45 (m, 5H).

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11. All new compounds gave satisfactory spectroscopic and analytical results. All the compounds listed in Table 2 were sticky oils except compound **8**, whose mp. is 206-208°.

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