A Safe and Efficient Method for Preparation of N,N'-Unsymmetrically Disubstituted Ureas Utilizing Triphosgene

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An unsymmetrically substituted urea is a frequent structural feature of many biologically active compounds such as enzyme inhibitors[1-4] and pseudopeptides.[5] Insertion of a urea moiety into a peptide backbone can be used to connect the two amino termini and thereby reverse the main chain direction. This change may be of interest for the chemistry of peptidomimetic drugs.

In connection with our work aimed at synthesis of HIV protease inhibitors equipotent toward both wild and mutant type, we required an unsymmetrically disubstituted urea **5** (Table 1).[6] The general procedures for the synthesis of unsymmetrical ureas involve the reaction of an isocyanate and primary amine.[7] Isocyanates are usually prepared by bubbling phosgene gas through a solution of an amine at elevated temperature.[8] An improved method for preparation of isocyanates involve reaction of amines with phogene in presence of base.[9] The hazards of handling of phosgene and drastic conditions detract from these procedures. Alternatively, methods for preparation of unsymmetrical ureas are based on a carbonic acid derivatives such as, *p*-nitrophenyl chloroformate,[10] 2,4,5-trichlorophenyl chloroformate,[11] or (phenoxycarbonyl)-tetrazole.[12] These methods require preparation of reagent, long reaction time, use of large excess of reagent, and need to isolate the reactive intermediate from excess of reagent by column chromatography.[12]

Our attempts to prepare compound **5** using *p*-nitrophenyl chloroformate resulted in a mixture of products with a persistent yellow color. Compound **5** could only be obtained in moderate (35%) yield after careful chromatography.

Recently, triphosgene [bis(trichloromethyl) carbonate], a crystalline solid which can be easily handled, was reported as a safe and stable replacement for phosgene.[13] During the preparation of an authentic sample of the symmetrical urea by the reaction of valine methyl ester hydrochloride with triphosgene in the presence of tertiary base (diisopropylethylamine) in dichloromethane, we observed that the first mol equiv of amine was consumed rapidly to give a nonpolar intermediate. The intermediate thus formed reacted slowly with the second equivalent of amine (valine methyl ester) and produced a symmetrical urea. We have now extended the observed different reactivity of triphosgene and the intermediate toward amine to a facile one-pot synthesis of unsymmetrically disubstituted ureas by sequential addition of two different amino components to a solution of triphosgene in dichloromethane. In a typical procedure an intermediate is first formed from one of the amines and triphosgene (molar ratio 1:0.37) in the presence of tertiary base. The second amino component (1 mol equiv) is then added to the above solution to provide unsymmetrically disubstituted urea (Scheme 1). The generality and selectivity of the reaction was explored by condensations with the amines containing multiple functionality, and the results are summarized in Table I. An unsymmetrical urea was the main product of the reaction.[14] The reaction exhibited high selectivity for N-nucleophiles; the amines (primary and or secondary) containing an unprotected primary (entry **2**) or secondary (entries **1** and **4**) hydroxy group could be used directly. The methyl, benzyl, and even acid-sensitive *tert*-butyl ester were unaffected. The less-sensitive amino component was always chosen for the first step of synthesis. All amino acid derivatives used were of the *S*-configuration. The products resulting from racemization of the α-center were not detected.

IR spectral analysis (thin film) of the intermediate prepared from valine methyl ester hydrochloride showed a peak at 2247 cm^{-1} indicating an isocyanate. There was only one carbonyl peak at 1749 cm^{-1} in the spectrum, corresponding to the ester moiety.

In conclusion, we have provided a convenient, one-pot procedure for the synthesis of N,N'-unsymmetrically disubstituted ureas utilizing commercially available triphosgene. The reaction is operationally simple, offers high yields, short reaction time, and high selectivity toward nitrogen nucleophiles. The isolation of reactive intermediate, the isocyanate, is unnecessary. Application of this methodology to the synthesis of various HIV-protease inhibitors is currently under investigation.

Experimental Section

Melting points are uncorrected. HPLC analyses were carried out using a Vydac C-18 reverse-phase column and methanol-water mixture as mobile phase. Purity of all the compounds was established by TLC and HPLC. All glassware was flame-dried and cooled under a stream of argon. The reactions were carried out under a positive pressure of Ar.

Typical Procedure. Triphosgene (0.37 mmol, 110 mg) was dissolved in CH_2Cl_2 (2 mL). A mixture of valine methyl ester hydrochloride (1 mmol, 167.5 mg) and diisopropylethylamine (DIEA, 2.2 mmol, 378 μL) in CH_2Cl_2 (3.5 mL) was slowly added to the stirred solution of triphosgene over a period of 30 min using a syringe pump. After a further 5 min of stirring, a solution

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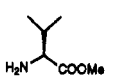
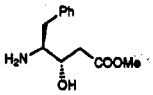
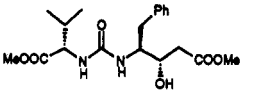
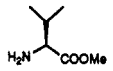
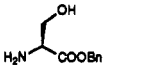
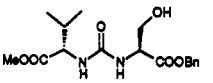
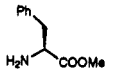
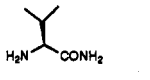
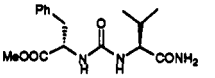
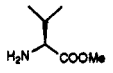
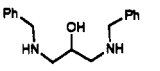
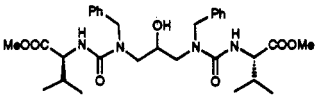
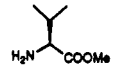
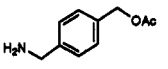
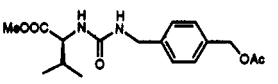
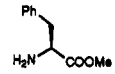
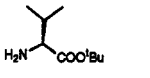
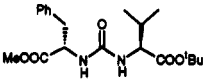
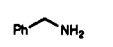
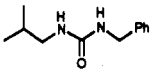
(14) Stochiometry and anhydrous conditions were found to be essential. Varying amounts (2–5%) of two possible symmetrical urea products were observed (HPLC).

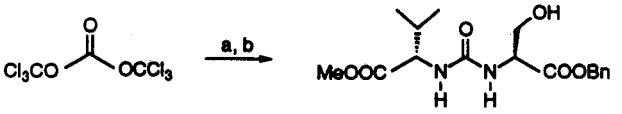
0022-3263/94/1959-1937$04.50/0

Table 1. Synthesis of N,N'-Unsymmetrical Ureas by Sequential Addition of Amines to Triphosgene[a]

no.	R	R'	product	mp, °C	yield,[b] %
1				101–102	85
2				145–147	89
3[c]				202–204 dec	88
4				viscous liquid	88
5				viscous liquid	89
6				84–86	90
7				81–83	91

[a] All reactions were carried out on 1-mmol scale in CH_2Cl_2 under Ar atmosphere. Amine R was always added first to the solution of triphosgene. The reaction provided the unsymmetrical urea as the sole product. Purity of the reaction product was established by TLC and HPLC. [b] Isolated yields. [c] Valinamide hydrochloride was dissolved in acetonitrile containing 2.2 mol equiv of DIEA.

Scheme 1.[a] Synthesis of an Unsymmetrical Urea by Sequential Addition of Amines to Triphosgene



[a] (a) Valine methyl ester hydrochloride (1 mmol), DIEA (2.2 mmol), and CH_2Cl_2, was added over 30 min to triphosgene (0.37 mmol) in CH_2Cl_2 at rt; (b) serine benzyl ester·HCl (1 mmol), DIEA (2.2 mmol), CH_2Cl_2, 10 min, rt.

of serine benzyl ester hydrochloride (1 mmol, 231.5 mg) and DIEA (2.2 mmol, 378 μL) in CH_2Cl_2 (2 mL) was added in one portion. The reaction mixture was stirred for 10 min at rt, evaporated to dryness, diluted with ethyl acetate, washed with 10% aqueous $KHSO_4$, 5% aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated to give pure unsymmetrical urea **2** (314 mg, 89%).

Compound **2** was crystallized from petroleum ether–ethyl acetate: mp 145–147 °C; ^1H NMR ($CDCl_3$) δ 0.89 (d, 3H, J = 7 Hz), 0.97 (d, 3H, J = 7 Hz), 2.15 (m, 1H), 3.76 (s, 3H), 3.86 (d, 2H, J = 3.6 Hz), 4.45 (bd, 1H), 4.54 (bt, 1H), 5.17 (s, 2H), 7.33 (s, 5H); LSIMS 353 $(M + H)^+$. Compounds **1** and **3–7** were similarly prepared and were characterized by ^1H NMR and mass spectroscopy.

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Supplementary Material Available: ^1H-NMR data for **1–7** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.