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Conversion of Carbonimidodithioates into Unsymmetrical Di- and Tri- substituted Ureas including Urea Dipeptides

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Abstract: **Selective hydrolysis of carbonimidodithioates (3) leads to the thiocarbamates (4), which can be easily transformed to the unsymmetrical ureas (5) by treatment with the appropriate amines. This constitutes a synthesis of ureas without the use of phosgene or carbon monoxide.** © 1998 Elsevier Science Ltd. All rights reserved.

A spate of recent publications has dealt with the synthesis of unsymmetrical di- , tri-, and tetra substituted ureas.[1-7] This prompts us to record our results on a new route to such molecules.

The synthesis of unsymmetrical ureas essentially invloves two steps: i) reaction of an amine with a one-carbon reagent at the carbon dioxide oxidation level to form a reactive molecule still possessing a leaving group attached to the carbonyl, and ii) treatment of this intermediate with another amine to form the unsymmetrical urea. Two types of reagents have been evolved for this purpose. In the first type (Scheme 1), the two leaving groups in the reagent (**1**) are identical; the success of the scheme is critically dependent on the second step being much slower than the first, so that the formation of a symmetrical urea is minimised. Phosgene (**1**; X=Cl) is a classical example of this type of reagent.[8] The reaction of an amine with an isocyanate (either preformed, or generated *in situ*[9]) can be regarded as an extension of this concept. Several other reagents of the type COX_2 have now been introduced for the synthesis of unsymmetrical ureas.[1,2,3,10,11] In the alternate strategy, the reagent (**2**) has two different leaving groups attached to the carbonyl; the rate of displacement of X is faster than that of Y (Scheme 2). An example of such a reagent is phenyl chloroformate.[4] Other analogs have also been reported.[5,6,12]

Apart from these two general approaches, a few special syntehtic routes have also been described for unsymmetrical ureas. These include the ruthenium - catalysed insertion of an amine into formanilides[13] and desulfurization of thioureas.[7] It is to be noted that the ultimate starting material for most of the reagents of the type COX_2 or COXY would be phosgene or carbon monoxide.

We now report a simple and mild method for the synthesis of unsymmetrical di- and tri- substituted ureas, including urea dipeptides. This route does not involve the use of phosgene or carbon monoxide at any stage (Scheme 3). The reaction of primary amines or amino acid esters with CS_2 followed by methylation with MeI leads to the carbonimidodithioates (**3**),[14] which can be hydrolysed to the corresponding S-methyl

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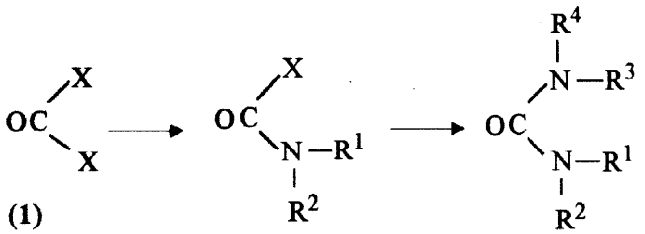
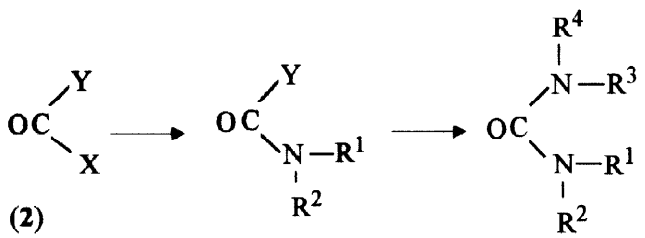
thiocarbamates (4) in excellent yields in the presence of $ZnCl_2$ in MeCN - H_2O (3:1).[15] Treatment of these with 2 equivalents of another amine (primary or secondary) in MeCN at 30 °C or 80 °C leads to the unsymmetrical ureas (5 a to r) in 60-89% yield (Table 1).[16] The second amine molecule can also be an amino acid ester, leading in such cases to the urea dipeptides (5 p, q, r)[1].

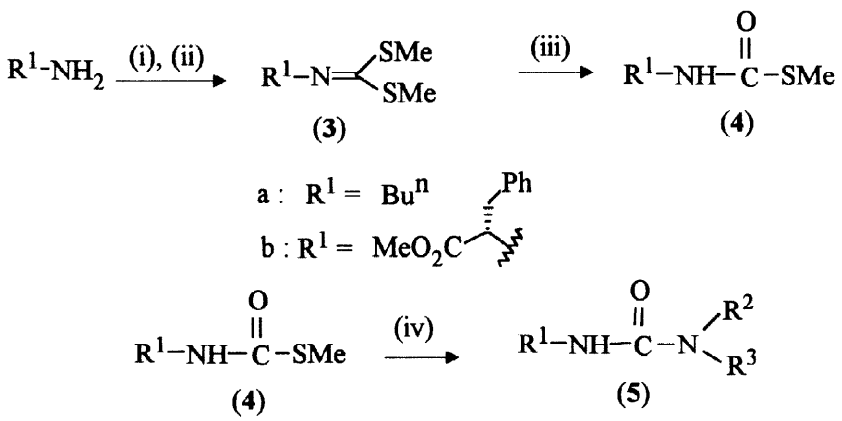
Scheme 1



Scheme 2

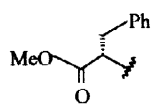
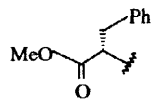
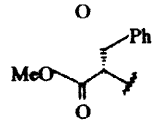
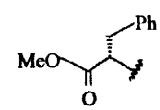
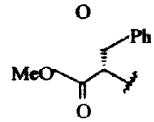
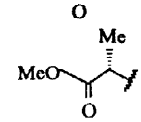
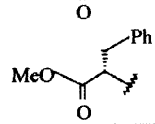
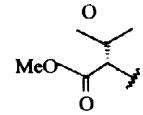


Scheme 3



(i) CS_2, Et_3N, CH_2Cl_2; (ii) MeI; (iii) $ZnCl_2$, MeCN-H_2O (3:1); (iv) MeCN, HNR^2R^3 30 °C or 80 °C

Table 1. Isolated and purified yields of urea derivatives (5)

Product (5)	R^1	R^2	R^3	conditions	Yeld (%)
a	n-Bu	H	n-Pr	30 °C, 8h	80
b	n-Bu	H	allyl	30 °C, 10h	76
c	n-Bu	H	$PhCH_2$	30 °C, 12h	75
d	n-Bu	H	Ph-CH(Me)-	30 °C, 12h	73
e	n-Bu	H	cyclohexyl	30 °C, 10h	82
f	n-Bu	H	Ph	80 °C, 12h	60
g	n-Bu	Me	Ph	80 °C, 12h	63
h	n-Bu	- (CH_2)$_4$ -		30 °C, 6h	89
i	n-Bu	- (CH_2)$_5$ -		30 °C, 6h	89
j	n-Bu	- $CH_2CH_2OCH_2CH_2$ -		30 °C, 10h	64
k	n-Bu	Et	Et	30 °C, 10h	78
l	n-Bu	i-Pr	i-Pr	30 °C, 10h	67
m	n-Bu	n-Bu	n-Bu	30 °C, 8h	72
n		- (CH_2)$_4$ -		30 °C, 6h	69
o		H	cyclohexyl	30 °C, 8h	85
p		H		80 °C, 12h	79
q		H		80 °C, 12h	81
r		H		80 °C, 12h	79

It is obvious that for the preparation of urea dipeptides, it would be preferable to consume just one equivalent of the second amino acid ester. Accordingly, freshly prepared methyl esters (1 eq) of (S) - phenylalanine, (S) -alanine and (S) - valine were reacted with the thiocarbamate (**4b**) derived from (S) - phenylalanine methyl ester. The products (**5** p, q, r) were obtained in just marginally lower yields (Table2).

Table 2. Yields of products (5 p, q, r) with 1 equivalent of the amino acid ester.

Product	yield %
5p	75
5q	77
5r	75

A typical procedure involved the treatment of a solution of thiol carbamate (**4b**) (1mmol, 253 mg) in MeCN (2 ml) with valine methyl ester (1 mmol, 131mg) in MeCN (2 ml) at 80 °C for 18h. After complete disappearance of the starting material (tlc), the solvent was removed under reduced pressure. The reaction mixture was diluted with EtOAc (50 ml) and after an aqueous acidic work up and chromatographic purification furnished 252 mg (75 %) of the urea peptide (**5r**) as a colorless oil.[17]

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16. All products were fully characterized by their spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR, MS).
17. Data for the compound **5r**: IR (neat), 3326, 2956, 2860, 1638, 1595, cm^{-1} ^{1}H-NMR ($CDCl_3$), δ 0.80(d, 3H, J = 8.0Hz), 0.90(d, 3H, J = 8.0 Hz), 2.10(m, 1H), 3.0(t, 2H, J = 7.0Hz), 3.60(s, 6H), 4.40(dd, 1H, J = 8.9Hz, J = 7.0Hz), 4.80(q, 1H, J = 8.0), 5.4(d, NH, J = 8.0Hz), 5.6(d, NH, J = 8.0Hz), 7.0-7.30(m, 5H); ^{13}C-NMR ($CDCl_3$), 174.58, 73.53, 157.20, 136.43, 129.66, 128.61, 127.13,58.13, 54.27, 52.32, 39.12, 31.78, 19.20, 18.00; MS (m/z), 336(M+), 304, 277, 245, 233, 202, 191,175,162(100%), 146, 130, 115.