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A convenient synthesis of symmetrical *N*,*N*′-dialkylureas by the reactions of 4-chloro-5*H*-1,2,3-dithiazol-5-one with alkylamines

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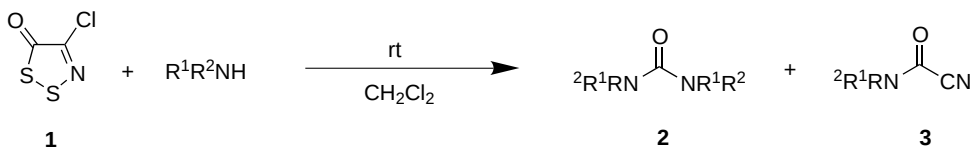
Abstract—Treatment of 4-chloro-5*H*-1,2,3-dithiazol-5-one with primary and secondary alkylamines (>2 equiv.) in CH_2Cl_2 at rt afforded symmetrical *N*,*N*′-disubstituted ureas in moderate to good yields. Similarly, the reactions with amino acid ester hydrochlorides in the presence of Et_3N (>3 equiv.) under the same conditions gave symmetrical ureas.

Substituted ureas have been the subject of much attention owing to their biological activity and wide variety of applications.[1] Most syntheses of ureas involve the reaction of amine either with compounds that incorporate an NCO linkage such as isocyanates,[2] formamides,[3] carbamates[2,4] and reactive imidazole ureas,[2,5] or with carbonyl compounds like phosgene,[2] triphosgene,[6] chloroformates,[7] carbonates,[6,8] *S*,*S*-dimethyl dithiocarbonates,[9] or CO itself in the presence of sulfur,[10] carbon dioxide in the presence of metal complexes,[11] phosphorus compounds[12] and *N*,*N*′-dicyclohexylcarbodiimide.[13]

In recent years, much attention has been paid to more efficient synthesis of ureas without the use of poisonous and dangerous phosgene or carbon monoxide. For symmetrical *N*,*N*′-dialkylureas, carbon dioxide was reacted with amines in the presence of carbodiimides and tertiary amines.[13] However, a large excess of carbon dioxide, whose pressure is dependent on the experimental procedure and variable temperature, should be maintained throughout the reaction. Another method involved the reaction of alkylamines with *S*,*S*-dimethyl dithiocarbonate (DMDTC).[9] This method involves dimethyl sulfate, known as a suspected human carcinogen, for the preparation of DMDTC.[9]

Recently, the reaction of 1,1′-carbonylbisbenzotriazole with alkylamines has been reported to give symmetrical and unsymmetrical ureas. However, phosgene was used to prepare the starting bisbenzotriazole.[14] *N*-Boc protected primary amines reacted with alkylamines in THF at 65°C to give symmetrical and unsymmetrical ureas. A strong base, i.e. *t*-BuLi, *n*-BuLi and NaH, was used in the reactions.[15] The method of choice may perhaps be the DMAP-catalyzed reaction of amines (alkyl or aryl) with di-*tert*-butylcarbonate, yielding symmetrical and unsymmetrical *N*,*N*′-disubstituted ureas[16] and the reaction involving triphosgene, a soft and stable replacement for phosgene.[17]

In the course of our study on the development of the potential synthetic utility of 4-chloro-5*H*-1,2,3-dithiazol-5-one (**1**),[18] we found that compound **1**, a stable crystalline solid at rt, which is readily prepared starting from



1 **2** **3**

Scheme 1.

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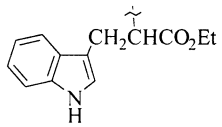
S_2Cl_2 (or SCl_2) and $ClCH_2CN$ in two steps[19] and easy to handle, may be utilized as a substitute for the foregoing carbonyl compounds for the synthesis of ureas.

Treatment of **1** with primary and secondary alkylamines (4 equiv.) in CH_2Cl_2 (15 mL) at rt gave the corresponding symmetrical ureas **2** (Scheme 1). Yields of **2** produced from primary alkylamines (entries 1–6) are higher than those from secondary alkylamines (entries 7–9).

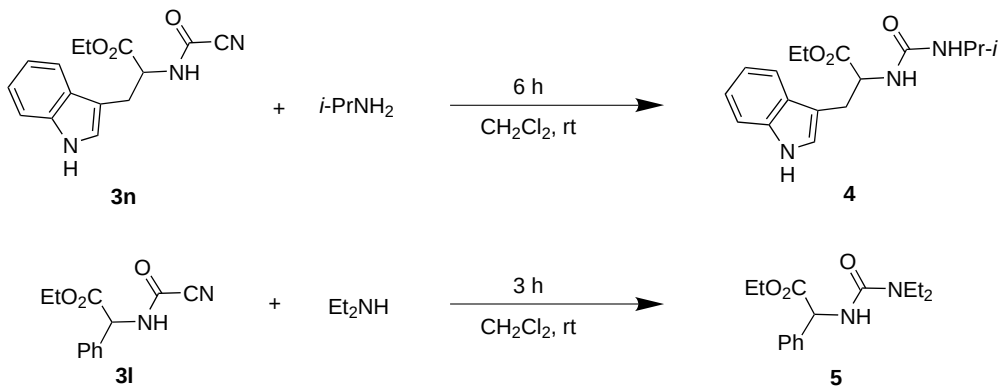
Similarly, treatment of a mixture of **1** and Et_3N (2 equiv.) in CH_2Cl_2 (15 mL) with amino acid ester hydrochlorides (2 equiv.) at rt afforded cyanoformamides **3** and unreacted **1** in addition to **2**[20] (entries 10–15). However, by using a large excess of Et_3N (>3 equiv.), yields of **2** increased with expense of **3** and no unreacted starting material **1** remained. Yields of **2**, **3** and unreacted **1**, and reaction times are summarized in Table 1.

The increased yields with the amounts of Et_3N may be due to complete removal of hydrogen chloride originating from the amino acid ester hydrochlorides and hydrogen chloride produced in the course of the reaction as a byproduct.

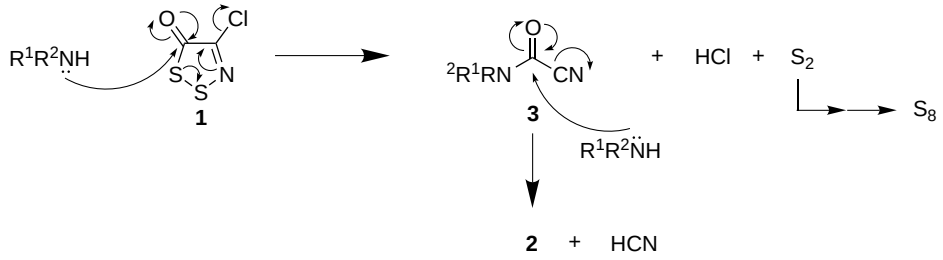
Table 1. Yields of **2**, **3**, and unreacted **1**, and reaction times

Entry	R^1	R^2	TEA mmol	Time h		Compd	Yield[a](%) **2**	**3**	**1**
1	*i*-Pr	H		15		**a**	78		
2	*t*-Bu	H		14		**b**	99		
3	*n*-Pentyl	H		13		**c**	93		
4	*n*-Hexyl	H		14		**d**	66		
5	Bn	H		5		**e**	79		
6	Piperonyl	H		7		**f**	75		
7	Allyl	Allyl		15		**g**	41		
8	Et	Et		17		**h**	37		
9	*n*-Pr	*n*-Pr		40		**i**	50		
10	$-CH_2CO_2Et\cdot HCl$	H	4 (2)	2	(2)	**j**	63 (35)	(37)	(17)
11	$MeCHCO_2Et\cdot HCl$	H	3 (2)	1	(1.5)	**k**	69 (46)	(28)	(15)
12	$BnCHCO_2Et$	H	1 (0)	24	(120)	**l**	77 (31)	18 (28)	(28)
13	*i*-$BuCHCO_2Me\cdot HCl$	H	3 (2)	72	(24)	**m**	68 (33)	10 (15)	(26)
14		H	1 (0)	48	(16)	**n**	87 (40)	(49)	(0)
15	$MeS(CH_2)_2CHCO_2Et\cdot HCl$	H	3 (2)	6	(3)	**o**	56 (51)	9 (19)	(0)

[a]Isolated yields. Number in the parenthesis represents data when amino acid hydrochlorides were treated with insufficient amounts of Et_3N. No Et_3N was used for entries 1-9.



Scheme 2.



Scheme 3.

Compound **1** was reacted with *p*-anisidine in the presence of pyridine (4 equiv.) under the same conditions to give **3** ($R^1 = p$-$MeOC_6H_4$, $R^2 = H$) in 39% yield along with unreacted **1** (28%), while *p*-chloroaniline which is a deactivated aromatic amine, did not react with **1** with quantitative recovery of the starting material **1**.

Despite unsatisfactory yields of **3**, unsymmetrical ureas were prepared from cyanoformamides **3** and primary of secondary alkylamines. For example, treatment of cyanoformamide **3n** with *i*-propylamine (6 equiv.) for 5 h in CH_2Cl_2 at rt afforded unsymmetrical urea **4** (83%) (Scheme 2). Similarly, unsymmetrical urea **5** (97%) was prepared from cyanoformamide **3l** and diethylamine (5 equiv.) under the same conditions.

The mechanism for the formation of ureas **2** may be explained by a nucleophilic attack of alkylamine to the carbonyl carbon of **1**, followed by extrusion of S_2 concomitant with the liberation of chloride ion, yielding cyanoformamide **3** (Scheme 3). Displacement of cyanide ion by another molecule of alkylamine would give **2**.

In conclusion, we have developed a convenient method for the synthesis of symmetrical *N*,*N*′-dialkylureas from 4-chloro-5*H*-1,2,3-dithiazol-5-one and primary and secondary alkylamines, and amino acid esters. Cyanoformamides may be utilized for the synthesis of unsymmetrical *N*,*N*′-dialkylureas. The method described herein offers the advantage of producing desired ureas under the mild conditions without the use of poisonous and dangerous materials.

Acknowledgements

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20. Typical procedure: To a suspension of leucine methyl ester hydrochloride (302 mg, 1.66 mmol) in CH_2Cl_2 (15 mL) was added 4-chloro-5*H*-1,2,3-dithiazol-5-one (**1**) (121 mg, 0.788 mmol), followed by addition of Et_3N (168 mg, 1.66 mmol). The mixture was stirred for 24 h at rt. After removal of the solvent in vacuo, the residue was chromatographed on a silica gel (70–230 mesh, 2×10 cm). Elution with *n*-hexane gave sulfur (22 mg, 44%). Subsequent elution with a mixture of *n*-hexane and EtOAc (5:1) gave unreacted **1** (31 mg, 26%). Continuous elution with same solvent mixture (3:1) gave *N*-[(2-methoxycar-

bonyl-3-methyl)butyl]cyanoformamide (**3m**) (23 mg, 15%): IR (neat) 3296, 2240, 1741, 1693, 1536, 1437, 1347, 1267, 1226, 1203, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.95 (d, $J=6.2$ Hz, 6H, $2CH_3$), 1.62–1.76 (m, 3H, CH_2, CH), 3.80 (s, 3H, OCH_3), 4.63–4.70 (m, 1H, CH), 7.05 (s, br, 1H, NH). Anal. calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.40; H, 7.05; N, 14.25. Elution with EtOAc gave bis[(1-methoxycarbonyl-3-methyl)butyl]urea (**2m**) (82 mg, 33%): mp 85°C (CH_2Cl_2–*n*-hexane); IR (KBr) 3344, 1747, 1619, 1568, 1456, 1434, 1366, 1248, 1194, 1168, 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.92 (d, $J=6.4$ Hz, 12H, $4CH_3$), 1.47–1.60 (m, 4H, $2CH_2$), 1.60–1.72 (m, 2H, 2CH), 3.73 (s, 6H, $2OCH_3$), 4.44–4.52 (m, 2H, 2CH), 5.45 (d, $J=8.5$ Hz, 2H, 2NH). Anal. calcd for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.79; H, 8.91; N, 8.90.