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4-Chloro-5*H*-1,2,3-dithiazol-5-one: a good α-thiocyanating agent for α,β-unsaturated β-amino esters

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Abstract

Treatment of 4-chloro-5*H*-1,2,3-dithiazol-5-one with 3-alkyl (or aryl)-3-amino-2-propenoate esters in DMSO at 120°C gave the corresponding 2-thiocyanated esters **4** (major) and 5-alkoxycarbonyl-4-alkyl (or aryl)-4-thiazolin-2-ones **5** (minor), whereas the esters bearing a strong electron-withdrawing group at C-3 under the same conditions afforded **5** and/or 4-substituted 5-alkoxycarbonyl-2-aminothiazoles **6**, depending on the electron-withdrawing groups.

Keywords: 4-chloro-5*H*-1,2,3-dithiazol-5-one; (*E*)-3-amino-2-thiocyanato-2-butenoate; 4-substituted 5-alkoxycarbonyl-2-aminothiazoles.

Thiocyanation of alkenes has been mostly achieved by treatment with in situ generated thiocyanogen [$(SCN)_2$] or thiocyanic acid.[1] Thiocyanated compounds are useful for the synthesis of 4,5-disubstituted 2-aminothiazoles, which are invaluable intermediates for the preparation of other thiazole derivatives.[2] However, the extreme sensitivity of thiocyanogen toward hydrolysis and polymerization as well as toxic effects limits its general use in many organic reactions.

In a continuation of our ongoing project for exploring the synthetic utility of 4-chloro-5*H*-1,2,3-dithiazoles, 4-chloro-5*H*-1,2,3-dithiazol-5-one (**1a**) was treated with ethyl 3-amino-2-butenoate (**2a**) in DMSO at 120°C with the expectation of forming a compound analogous to *N*-alkyl- and *N,N*-dialkylcyanothioformamides (**3**), which were prepared from 4-chloro-5*H*-1,2,3-dithiazole-5-thione (**1b**) and primary and secondary alkylamines.[3] However, the reaction afforded (*E*)-3-amino-2-thiocyanato-2-butenoate (**4a**) and 5-ethoxycarbonyl-4-methyl-4-thiazolin-2-one (**5a**) in 60 and 38% yields, respectively (Scheme 1).[4] Compound **4a** was reported to be prepared by the reaction of **2a** with $(SCN)_2$ in CH_2Cl_2 at 0°C in 78% yield.[1c] The spectroscopic data and mp of **4a** were in accordance with the literature. The stereochemistry of **4a** was determined based on the chemical shift of the NH_2 protons situated at δ 5.65 and 9.29 ppm.

To the best of our knowledge, this is the first example of thiocyanation of the C=C double bond by an organic sulfur compound. Compound **1a** is stable in the air and it can be readily prepared from

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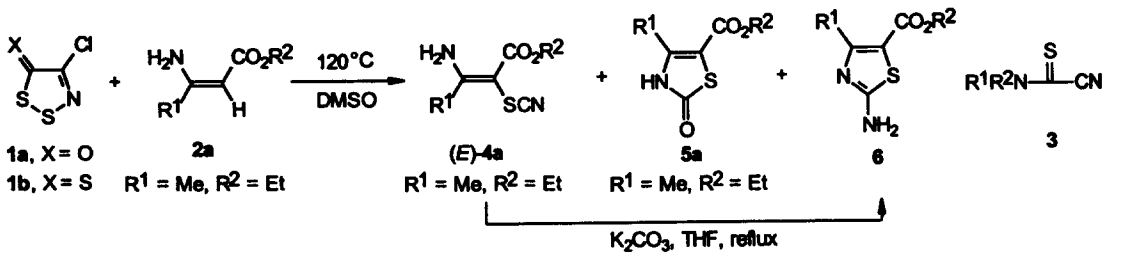


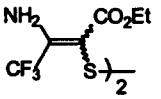
Scheme 1.

Table 1
Reaction times and yields of products **4**, **5**, and 2-aminothiazoles **6**

Entry	R^1	R^2	Time h	Product[a] (%) 4	mp ℃	Product[a] (%) 5	mp ℃	Product[a] (%) 6[c]	mp ℃
1	Me	Et	0.5	**a** 60	112-114[g] (lit.[1(c)] 114.5-115)	**a** 38	177-178 (lit.[7] 177-178)	**a** (93)[d] (98)[e]	177-178 (lit.[9] 178-179)
2			3	**a** 61		**a** 22			
3	Me	Me	0.5	**b** 50	99-100	**b** 35	219-220 (lit.[8] 218-219)	**b** (98)	224-226 (lit.[9] 231.5-233)
4	Me	*t*-Bu	1.5	**c** 30	87-88	**b** 13	169-170	**c** (76)	173-174
5	Me	Allyl	0.5	**d** 46	105-106	**c** 16	148-150	**d** (92)	148-150
6	*n*-Pr	Et	0.5	**e** 60	93-94	**d** 27	95-96	**e** (100)	136-138
7	*n*-Pe	Et	0.5	**f** 70	Liquid	**e** 25	76-77	**f** (100)	107-108
8	$PhCH_2CH_2$	Et	0.5	**g** 71	132-133	**f** 26	134-135	**g** (71)	120-122
9	CF_3	Et	2					**h** 97	176-177 (lit.[10] 170-172)
10			5[b]	**h** 13	102-104			**h** 70	
11	$2\text{-}FC_6H_4$	Et	2	**i** 72	92-94	**g** 34	142-143	**i** (100)[f]	153-156
12	$3\text{-}O_2NC_6H_4$	Et	5			**h** 43	178-180	**j** 55	228-229[h] (lit.[11] 228-230)

[a] Isolated yields.
[b] Reaction temperature: 70 ℃. In addition to **4h** and **6h**, bis(2-amino-1-ethoxycarbonyl-3,3,3-(trifluoro)propenyl) disulfide (**7**)[6] was isolated in 10% yield.
[c] Number in the parentheses represents yields of **6**, which were obtained from heating **4** and K_2CO_3 in THF for 1.5 days at either reflux (entries 1-8) or rt (entry 11).
[d,f] Reaction times were 36 h, 5 days, and 10 days, respectively.
[g,h] Solvents for the recrystallization were CH_2Cl_2 and a mixture of CH_2Cl_2 and *n*-hexane, respectively. Other compounds were recrystallized from a mixture of EtOAc and *n*-hexane.

4,5-dichloro-4*H*-1,2,3-dithiazolium chloride (Appel's salt) and either $NaNO_3$ or water with an excellent yield.[5] The preliminary results obtained from the reactions of **1a** with β-enamino esters are summarized in Table 1.



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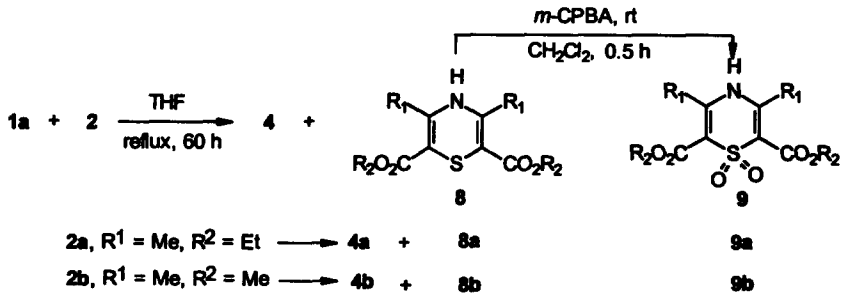
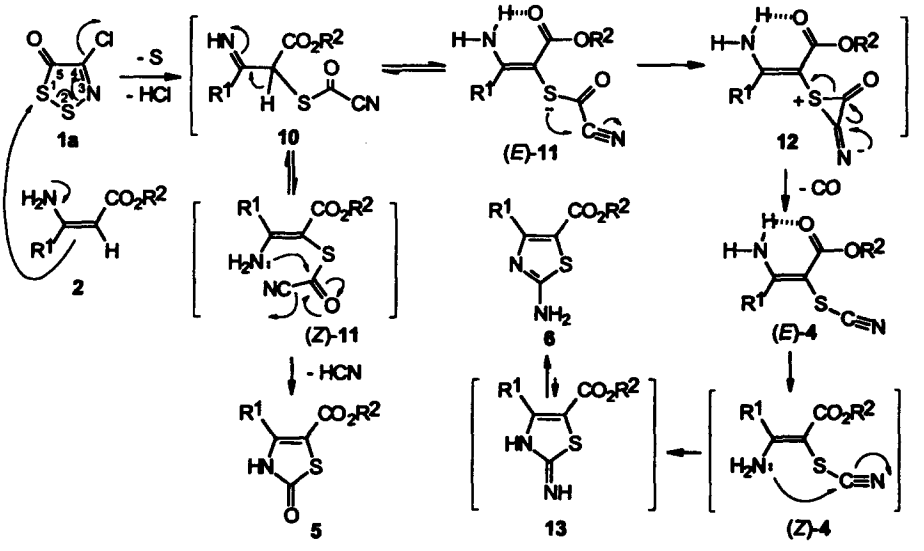
The reaction was found to be sensitive to the solvent. Thus treatment of **1a** with **2a** in THF at reflux gave **4a** (14%) and 1,4-thiazine **8a** (37%).[12] Similarly the reaction with **2b** gave **4b** (47%) and **8b** (21%) (Scheme 2). Treatment of **8a** and **8b** with *m*-CPBA in CH_2Cl_2 at room temperature gave sulfones **9a**[13] (39%) and **9b** (40%), respectively.

The formation of compounds **4**–**6** may be rationalized as a nucleophilic attack of the enamino carbon (α-C) on S-1 of **1a**, followed by extrusion of sulfur and chloride ion to give an intermediate **10**, which tautomerizes to give a pair of stereoisomers (*E*)-**11** and (*Z*)-**11** (Scheme 3). The intramolecular nucleophilic attack of sulfur of (*E*)-**11** on a cyano carbon to give an intermediate **12**, followed by extrusion of CO gives (*E*)-**4**. Isomerization of (*E*)-**4** yielding (*Z*)-**4**, followed by an intramolecular cyclization would



Scheme 2.

give 2-aminothiazoles **6** via an imino compound **13**. It is envisaged that a similar type of intramolecular cyclization occurs in the reactions for the formation of 2-imino-4-thiazolines from α-bromoketimines and KSCN,[14] 2-amino-2-thiazolines from phenylpropiolic acid chloride, amine, and KSCN,[15] and 2-aminothiazoles from enolizable ketones and NH_2SCN[16] notwithstanding the isolation of α-thiocyanato enamines. Alternatively, the intramolecular cyclization of (*Z*)-**11** would lead to 4-thiazolin-2-ones **5**. It seems that hydrogen-bonding between the N-H proton and the carbonyl oxygen of (*E*)-**11** may be responsible for the formation of a major product (*E*)-**4**.



Scheme 3.

In summary, we have developed a method for α-thiocyanation of β-amino α,β-unsaturated esters utilizing an organo sulfur compound, i.e., 4-chloro-5*H*-1,2,3-dithiazol-5-one without using $(SCN)_2$, HSCN, or inorganic thiocyanates. A study on the scope of this reaction is in progress.

Acknowledgements

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4. Typical procedure: To a solution of **1a** (249 mg, 1.62 mmol) in DMSO (10 mL) was added ethyl 3-amino-2-butenoate **2a** (839 mg, 6.50 mmol). The mixture was heated for 20 min at 120°C. The reaction was continued until no spot corresponding to **1a** had been observed on TLC (silica gel, EtOAc/*n*-hexane=1:4). The reaction mixture was cooled to rt, followed by addition of water (50 mL), which was extracted with CH_2Cl_2 (30 mL×3). The extracts were dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on a silica gel column (70–230 mesh, 3.5×20 cm). Elution with a mixture of EtOAc and *n*-hexane (1:4) gave unreacted **2a**. Subsequent elution with the same solvent mixture (1:2) gave ethyl 3-amino-2-thiocyanato-2-butenoate (**4a**) (182 mg, 60%): mp 112–114°C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J*=7.2 Hz, 3H), 2.40 (s, 3H), 4.23 (q, *J*=7.2 Hz, 2H), 5.65 (s, 1H), 9.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.35, 23.29, 60.79, 75.94, 113.46, 160.30, 168.38; IR (KBr) 3408, 3288, 2128, 1658, 1616 cm^{-1}; MS (*m/z*) 186 (M^+,71%), 141 (39), 113 (65), 87 (100). Anal. calcd for $C_7H_{10}N_2O_2S$: C, 45.15; H, 5.41; N, 15.04; S, 17.22. Found: C, 45.01; H, 5.22; N, 14.86; S, 17.24; and 5-ethoxycarbonyl-4-methyl-4-thiazolin-2-one (**5a**) (116 mg, 38%): mp 177–180°C (EtOAc–*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J*=7.2 Hz, 3H), 2.48 (s, 3H), 4.27 (q, *J*=7.2 Hz, 2H), 10.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.83, 61.75, 105.57, 142.65, 162.13, 174.53; IR (KBr) 3128, 1690, 1597, 1261 cm^{-1}; MS (*m/z*) 187 (M^+,100%), 159 (53), 142 (59), 113 (65). Anal. calcd for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48; S, 17.13. Found: C, 44.95; H, 4.83; N, 7.43; S, 17.18.
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6. Compound **7**: yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J*=7.1 Hz, 6H), 4.15 (q, *J*=7.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.55, 61.65, 93.79, 120.43 (q, *J*=278.63 Hz), 152.48 (q, *J*=29.89 Hz), 170.08; IR (neat) 3424, 2280, 1654, 1594 cm^{-1}; MS (*m/z*) 428 (M^+, 22%), 215 (47), 169 (89), 141 (100), 122 (16). Anal. calcd for $C_{12}H_{14}N_2F_6O_4S_2$: C, 33.65; H, 3.29; N, 6.54; S, 14.97. Found: C, 33.54; H, 3.35; N, 6.53; S, 14.64.
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12. Compound **8a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J*=7.2 Hz, 6H), 2.21 (s, 6H), 4.20 (q, *J*=7.2 Hz, 4H), 5.40 (s, 1H); IR (neat) 3312, 3224, 3080, 2976, 1696, 1622, 1477, 1358, 1278 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.68, 20.51, 61.35, 95.85, 150.30, 164.33. Anal. calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16; S, 11.82. Found: C, 53.25; H, 6.46; N, 4.97; S, 11.55.
13. Compound **9a**: mp 167–168°C (CH_2Cl_2–*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, *J*=7.0 Hz, 6H), 2.47 (s, 6H), 4.32 (q, *J*=7.0 Hz, 4H), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.55, 20.48, 62.33, 112.15, 150.30, 162.26; IR (KBr) 3296, 1704, 1666, 1619, 1491, 1243, 1117, 1072 cm^{-1}. Anal. calcd for $C_{12}H_{17}NO_6S$: C, 47.51; H, 5.65; N, 4.62; S, 10.57. Found: C, 47.29; H, 5.65; N, 4.61; S, 10.67.
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