Heterocyclization of Propenethioamides: A Direct Synthesis of 1,4-Thiazepine Ring Systems

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The heterocyclization of 3-aminopropenethioamides **1** and **2** with 2-bromoacetophenone is reported. The *p*-toluenesulphonic acid catalyzed reaction gives a direct route to 1,4-thiazepines **3** and **5**, while in the presence of triethylamine thiophene **4** and 1,4-thiazepin-5-one **6** are obtained.

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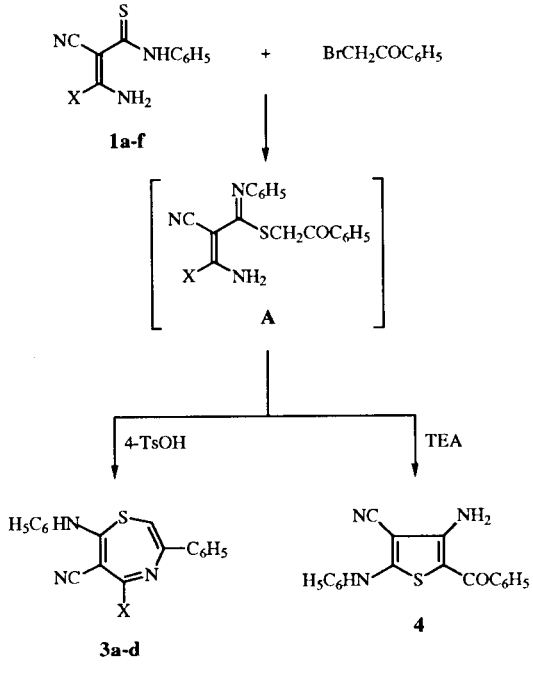
There is great interest at present in seven-membered heterocycles such as oxepins, azepines, thiepins and thiazepines. Among these the thiazepine system and its derivatives fused to the benzene ring, have been studied extensively in the last years for their biological activity. Several patents are reported in literature on the perhydro-1,4-thiazepine derivatives [1-5] and the 1,4-thiazepin-5-(2*H*)-one system [6-12], while to our knowledge little attention has been given to the 1,4-thiazepine system [13].

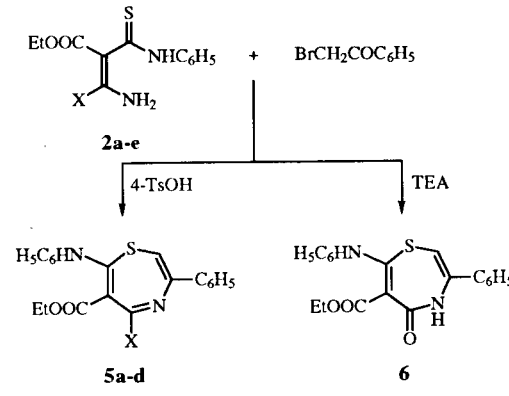
Continuing our interest in the synthesis of nitrogen heterocyclic systems, in this paper we describe an easy access path to these nuclei, using the 3-amino-3-(dialkylamino)propenethioamide derivatives **1** and **2** prepared by action of the aryl isothiocyanates on the 3-amino-3-(dialkylamino)propenenitriles or -propenoate esters [14] (Schemes 1 and 2) as starting materials.

Scheme 1



a, X = pyrrolidino
b, X = piperidino
c, X = morpholino
d, X = 4-ethoxycarbonylpiperazino
e, X = 4-phenylpiperazino
f, X = 4-methylpiperazino

Scheme 2



a, X = pyrrolidino
b, X = morpholino
c, X = 4-ethoxycarbonylpiperazino
d, X = 4-phenylpiperazino
e, X = 4-methylpiperazino

Thus the reaction of thioamides **1** and **2** with 2-bromoacetophenone in the presence of a catalytic amount of *p*-toluenesulphonic acid in chloroform at reflux leads to the 1,4-thiazepine derivatives **3** and **5**. The thiazepines **5** are initially isolated as hydrobromides since during the working up of the reaction mixture (basification with sodium hydroxide solution and extraction) an untreatable residue is obtained. The free thiazepines **5** can easily be obtained by treating the hydroalcoholic solution of the hydrobromides with sodium hydroxide solution.

The structure of compounds **3** and **5** is determined on the basis of analytical and spectral data. Therefore the ir spectra show two weak absorptions in the region between 3320 and 3080 cm^{-1} and the presence of the CN and CO group stretching absorption for compounds **3** and **5** respectively. Besides the resonances of the different substituents, the ^1H nmr spectra present a singlet between 6.37 and 6.86 ppm due to H-2.

The ^1H nmr spectra of the compounds **5** present two distinct multiplets, each integrating one proton, for the methylene of the ethoxycarbonyl group, and three or four

Table 1

Physical and Analytical Data of Compounds **3** and **5**

Compound No.	X	Y	Yield (%)	Mp (°C) (solvent)	Formula	Analysis % Calcd./Found C	H	N
3a	pyrrolidino	CN	93	219-220 (ethanol)	$C_{22}H_{20}N_4S$	70.94 70.89	5.41 5.39	15.04 15.00
3b	piperidino	CN	97	218-220 (acetonitrile)	$C_{23}H_{22}N_4S$	71.47 71.50	5.74 5.72	14.50 14.51
3c	morpholino	CN	88	240-241 (ethanol)	$C_{22}H_{20}N_4OS$	68.02 67.95	5.19 5.17	14.42 14.39
3d	4-ethoxycarbonyl piperazino	CN	78	198-200 (ethanol)	$C_{25}H_{25}N_5O_2S$	65.33 65.30	5.48 5.50	15.24 15.21
5a	pyrrolidino	$COOC_2H_5$	80	173-175 (benzene)	$C_{24}H_{25}N_3O_2S$	68.70 68.77	6.00 5.98	10.02 10.06
5b	morpholino	$COOC_2H_5$	75	179-180 (cyclohexane)	$C_{24}H_{25}N_3O_3S$	66.18 66.13	5.79 5.81	9.65 9.68
5c	4-ethoxycarbonyl piperazino	$COOC_2H_5$	93	174-175 (cyclohexane)	$C_{27}H_{30}N_4O_4S$	64.01 64.08	5.97 5.95	11.06 11.09
5d	4-phenyl piperazino	$COOC_2H_5$	94	80-81 (cyclohexane)	$C_{30}H_{30}N_4O_2S$	70.56 70.50	5.92 5.90	10.97 10.95

Table 2

Spectroscopic Data of Compounds **3** and **5**

Compound No.	IR ν (cm^{-1})		^1H NMR δ (ppm)
3a	3320, 3110, 2170, 1565	[a]	1.72 (m, 4H, $(CH_2)_2$), 3.25 (m, 4H, CH_2NCH_2), 6.63 (br s, 1H, NH), 6.78 (s, 1H, H-2), 7.06-7.27 (m, 10H, Ar)
3b	3300, 3080, 2180, 1555	[a]	1.44 (m, 6H, $(CH_2)_3$), 3.28 (m, 4H, CH_2NCH_2), 6.82 (s, 1H, H-2), 7.08-7.29 (m, 10H, Ar)
3c	3300, 3100, 2160, 1570	[b]	3.19 (m, 4H, CH_2NCH_2), 3.65 (m, 4H, CH_2OCH_2), 6.37 (s, 1H, H-2), 6.96-7.36 (m, 10H, Ar)
3d	3320, 3130, 2170, 1695, 1570	[a]	1.13 (t, 3H, CH_3, J = 7.3 Hz), 3.03 (m, 4H, CH_2NCH_2), 3.53 (m, 4H, CH_2NCH_2), 3.98 (q, 2H, CH_2, J = 7.3 Hz), 6.86 (s, 1H, H-2), 7.03-7.58 (m, 10H, Ar)
5a	3310, 3130, 1640, 1575	[a]	1.07 (t, 3H, CH_3, J = 7.3 Hz), 1.54, 2.11, 2.75, 2.93 [m, 8H, $(CH_2)_2N(CH_2)_2$], 3.89, 4.11 (m, 2H, CH_2), 5.71 (br s, 1H, NH), 6.76 (s, 1H, H-2), 7.03-7.33 (m, 10H, Ar)
5b	3320, 3100, 1640, 1575	[a]	1.09 (t, 3H, CH_3, J = 7.3 Hz), 2.51, 2.85, 2.93, 3.17 (m, 8H, CH_2NCH_2 and CH_2OCH_2), 3.91, 4.07 (m, 2H, CH_2), 6.25 (br s, 1H, NH), 6.77 (s, 1H, H-2), 7.03-7.32 (m, 10H, Ar)
5c	3300, 3080, 1675, 1635, 1575	[a]	1.09 (m, 6H, $2CH_3$), 2.31, 2.70, 3.02, 3.18 [m, 8H, $(CH_2)_2N(CH_2)_2$], 3.99 (m, 4H, $2CH_2$), 6.68 (br s, 1H, NH), 6.80 (s, 1H, H-2), 7.03-7.32 (m, 10H, Ar)
5d	3300, 3080, 1640, 1570	[a]	1.07 (t, 3H, CH_3, J = 7.3 Hz), 2.57, 2.86, 2.95, 3.12, 3.21 [m, 8H, $(CH_2)_2N(CH_2)_2$], 3.93, 4.05 (2q, 2H, CH_2, J = 7.3 Hz), 6.35 (br s, 1H, NH), 6.80 (s, 1H, H-2), 6.73, 6.83, 7.12 (m, 15H, Ar)

[a] Hexadeuteriodimethyl sulphoxide as solvent. [b] Deuteriochloroform as solvent.

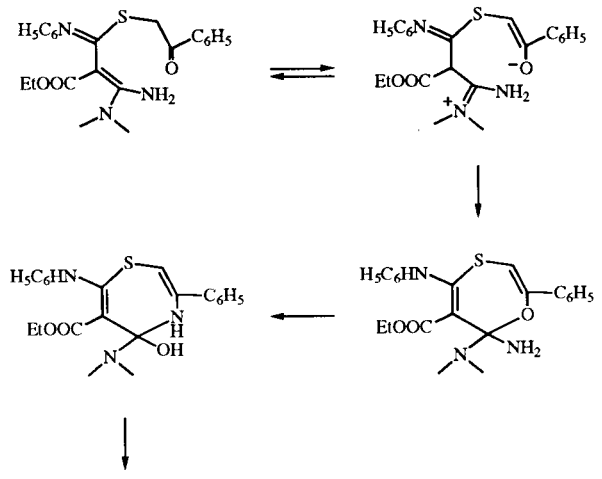
multiplets for the methylene protons of the cyclic amine in *ortho*. This fact suggests that the heterocyclic amine is probably on a plane almost perpendicular to the plane of the 1,4-thiazepine ring. For this reason the protons of the amino group are differently affected by COOR. At the same time the non-equivalence of the protons of OCH_2 can be due both to steric hindrance and to the repulsive effects that can give rise to partial restricted rotation. In fact by heating at 60° the two multiplets collapse.

The 1,4-thiazepines **3** and **5** are presumably formed *via* the non-isolatable intermediate adduct **A** that depending on the reaction conditions and the nature of thioamide cyclizes differently. In acid medium the adduct **A** forms the 1,4-thiazepines **3** and **5** by 7-*exo-trig* cyclization.

The treatment of the thioamides **1** with 2-bromoacetophenone in chloroform and in presence of triethylamine leads to only one product in high yields identified as thiophene **4**, whose structure has been deduced from spectral evidence. Compound **4** is assumed to be formed by the intermediate **A** *via* the nucleophilic attack of the active methylene CH_2COAr to the amidinic group followed by the elimination of heterocyclic amine. In basic medium instead the reaction of the thioamides **2** with 2-bromoacetophenone leads to the 1,4-thiazepin-5-one derivative

6. The formation of compound **6** can be explained *via* the intermediate **A**. In this case cyclization probably occurs *via* the open chain amidinium enolate anion, which after rearrangement and elimination of the aminic group, leads to the derivative **6** as shown in Scheme 3.

Scheme 3



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This is supported by the fact that compounds **5** are not modified by treatment with sodium hydroxide solution. Moreover, preliminary hydrolysis of the amidinic group of the thioamide **2** should be ruled out, since in the same reaction conditions and in absence of 2-bromoacetophenone, triethylamine is ineffective on the thioamides.

Unexpectedly, in the case of the thioamides **1e,f** in both acid and basic medium only thiophene **4** is obtained, while the analogous **2e** only leads to the derivative **6**.

EXPERIMENTAL

Melting points were determined on a Köfler hot stage and are uncorrected. The ir spectra were obtained in Nujol with a Perkin-Elmer 398 spectrophotometer. The ^{1}H nmr spectra were recorded for hexadeuteriodimethylsulphoxide solution with a Varian Unity 300 spectrometer; chemical shifts are reported in ppm from hexamethyldisiloxane as an internal standard and are given in δ units. The elemental analyses (C, H, N) were carried out with a Carlo Erba model 1106 Elemental analyzer. The 3-amino-3-(dialkylamino)-2-[(phenylamino)thioxamethyl]-2-propenenitriles **1a-d,f** and ethyl 3-amino-3-(dialkylamino)-2-[(phenylamino)thioxamethyl]-2-propenoates **2a-c,e** [14], ethyl 3-amino-3-(4-phenylpiperazino)propenoate [15] were prepared by previously described procedures.

3-Amino-3-(4-phenylpiperazino)propenenitrile.

A solution of 3-amino-3-ethoxypropenenitrile (1.10 g, 10 mmoles) and 1-phenylpiperazine (1.2 g, 10 mmoles) in absolute ethanol (20 ml) was stirred for 24 hours at room temperature. The formed precipitate was filtered off, washed with diethyl ether and recrystallized from ethanol to give the title compound, yield 87%, mp 184-185°; ir: ν 3420, 3320, 3230, 2170, 1650, 1600, 1570 cm^{-1}; ^{1}H nmr: δ 3.09, 3.23 (m, 8H, piperazinyl), 3.30 (s, 1H, =CH), 5.92 (s, 2H, NH_2), 6.76, 6.91, 7.18 (m, 5H, Ar).

Anal. Calcd. for $C_{13}H_{16}N_4$: C, 68.39; H, 7.06; N, 24.54. Found: C, 68.45; H, 7.04; N, 24.57.

3-Amino-3-(4-phenylpiperazino)-2-[(phenylamino)thioxamethyl]-2-propenenitrile (**1e**).

Phenyl isothiocyanate (1.35 g, 10 mmoles) was added to a stirred solution of 3-amino-3-(4-phenylpiperazino)propenenitrile (2.28 g, 10 mmoles) in anhydrous acetonitrile (50 ml). The mixture was stirred at room temperature for 5 hours. The resulting precipitate was flltered, mp 195-196° (from 1-propanol), yield 80%; ir: ν 3260, 2170, 1605, 1595, 1515 cm^{-1}: ^{1}H nmr: δ 3.15, 3.40 (m, 8H, piperazinyl), 6.76, 6.90, 7.00, 7.18, 7.36 (m, 10H, Ar), 7.85, 8.75 (br s, 2H, NH_2), 9.63 (s, 1H, NH).

Anal. Calcd. for $C_{20}H_{21}N_5S$: C, 66.08; H, 5.82; N, 19.27. Found: C, 66.13; H, 5.81; N, 19.30.

Ethyl 3-Amino-3-(4-phenylpiperazino)-2-[(phenylamino)thioxamethyl]-2-propenoate (**2d**).

Phenyl isothiocyanate (1.35 g, 10 mmoles) was added to a stirred solution of ethyl 3-amino-3-(4-phenylpiperazino)-propenoate (2.75 g, 10 mmoles) in anhydrous acetonitrile (20 ml). The resulting mixture was stirred at room temperature for 5 hours and then the resulting precipitate was separated by filtration, mp 165-166° (from acetonitrile), yield 70%; ir: ν 3340, 3150, 1655, 1605, 1580 cm^{-1}; ^{1}H nmr: δ 1.08 (t, 3H, CH_3), 3.20, 3.65 (m, 8H, piperazinyl), 3.96 (q, 2H, CH_2), 6.77, 6.94, 7.20, 7.73 (m, 10H, Ar), 8.34, 8.76 (s, 2H, NH_2), 12.06 (s, 1H, NH).

Anal. Calcd. for $C_{22}H_{26}N_4O_2S$: C, 64.36; H, 6.38; N, 13.65. Found: C, 64.40; H, 6.36; N, 13.68.

Reaction of Propenethioamides **1** with 2-Bromoacetophenone.

A mixture of compound **1** (2.5 mmoles), and 2-bromoacetophenone (0.5 g, 2.5 mmoles) in dry chloroform (20 ml) was refluxed for 1 hour in presence of a catalytic amount of *p*-toluenesulphonic acid. In the case of compounds **1a-d** after cooling, the reaction solution was washed with 20% aqueous sodium hydroxide (10 ml) and water (10 ml). The organic layer was dried over sodium sulfate and then evaporated *in vacuo* to give the 1,4-thiazepines **3a-d** (Table 1). In the case of compounds **1e,f** the solid precipitated from the hot reaction mixture was filtered off, washed with water, dried and identified as **4**, yield 97%, mp 264-265° (from ethanol); ir: ν 3360, 3250, 3180, 3090, 2200, 1625, 1600, 1585, 1550 cm^{-1}; ^{1}H nmr: δ 7.13-7.52 (m, 10H, Ar), 7.98 (s, 2H, NH_2), 10.50 (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16. Found: C, 67.74; H, 4.08; N, 13.20.

Reaction of Propenethioamides **2** with 2-Bromoacetophenone.

A mixture of compound **2** (2.5 mmoles) and 2-bromoacetophenone (0.5 g, 2.5 mmoles) in dry chloroform (20 ml) was refluxed for 1 hour in the presence of a catalytic amount of *p*-toluenesulphonic acid. In the case of compounds **2a-d** the reaction mixture was concentrated to dryness, and the residue treated with water (50 ml) to obtain compounds **5** as hydrobromides. These salts were dissolved in 50% aqueous ethanol (5 ml) and treated with 20% aqueous sodium hydroxide (5 ml) to give the 1,4-thiazepines **5a-d** (Table 1).

In the case of compound **2e**, the solid that precipitated from

the hot reaction mixture was collected by filtration, washed with water, dried and identified as 1,4-thiazepin-5-one derivative **6**, yield 98%, mp 144-145° (from 2-propanol); ir: ν 3500, 3310, 3270, 1655, 1585, 1560, 1550 cm^{-1}; ^1H nmr: δ 1.32 (t, 3H, CH_3), 4.35 (q, 2H, CH_2), 7.06-7.52 (m, 6H, Ar + H-2), 8.99 (br s, 1H, NH), 10.12 (s, 1H, NH).

Anal. Calcd. for $C_{20}H_{18}N_2O_3S$: C, 65.53; H, 4.95; N, 7.65. Found: C, 65.50; H, 4.94; N, 7.67.

Reaction in Triethylamine of Propenethioamides **1** and **2** with 2-Bromoacetophenone.

A solution of **1** or **2** (2.5 mmoles), 2-bromoacetophenone (0.5 g, 2.5 mmoles) and triethylamine (0.35 ml, 2.5 mmoles) in anhydrous chloroform (40 ml) was stirred at room temperature for 24 hours. After removal of the solvent, the residue was washed with water, filtered and recrystallized from the appropriate solvent to give compound **4** and **6** respectively.

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