Propenethioamides in the Synthesis of Heterocyclic Systems. Synthesis of Pyrrole and 1,4-Thiazepine Derivatives

Maria Teresa Cocco*, Cenzo Congiu, and Valentina Onnis

Dipartimento Farmaco Chimico Tecnologico, Università, Via Ospedale 72, I-09124 Cagliari, Italy

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The reaction of propenethioamides **1** with bromoketones **2** and **3** led in acidic medium to the formation of 1,4-thiazepines **6** and **7**. The pyrrole derivatives **4** and **5** were obtained by reaction of **1** with **2** and **3** in basic medium.

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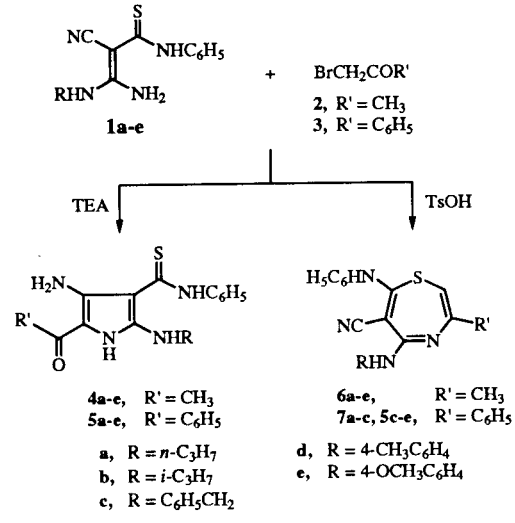
Recently we have reported on the utility of 3-aminopropenethioamides for the synthesis of some heterocyclic systems as isothiazoles and pyrimidinethiones [1,2]. Furthermore in a previous study we found that the *p*-toluenesulphonic acid catalyzed reaction of 3-amino-3-(dialkylamino)propenethioamides with 2-bromoacetophenone furnished 1,4-thiazepine derivatives, while in basic medium the 1,4-thiazepin-5-one or thiophene derivatives were obtained in almost quantitative yields [3]. These results indicated that the heterocyclic compound obtained was strongly affected by substitution pattern of the starting thioamide as well as the reaction conditions.

With the aim of exploring the synthetic possibilities of 3,3-diaminopropenethioamides and in connection with our interest towards the heterocyclic chemistry we here report on the reaction of α-bromoketones **2**, **3** with 3-amino-3-(alkyl or arylamino)propenethioamides **1** in order to verify the effect of the monosubstituted amino group on the regioselectivity of heterocyclization.

In the first approach we performed the reaction between compounds **1** and α-bromoketones **2** and **3** in chloroform

Scheme



in the presence of equimolecular amounts of triethylamine. In these reaction conditions we isolated only the pyrrole-3-carbothioamide derivatives **4** and **5**. The struc-

Table 1

Physical and Analytical Data of Compounds **4** and **5**

Compound No	R^1	R	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
4a	CH_3	n-C_3H_7	90	223-224 (2-Propanol)	$C_{16}H_{20}N_4OS$	60.73 60.68	6.37 6.35	17.71 17.68
4b	CH_3	i-C_3H_7	95	220-221 (2-Propanol)	$C_{16}H_{20}N_4OS$	60.73 60.76	6.37 6.40	17.71 17.74
4c	CH_3	$C_6H_5CH_2$	87	222-224 (2-Propanol)	$C_{20}H_{20}N_4OS$	65.91 65.85	5.53 5.50	15.37 15.34
4d	CH_3	4-$CH_3C_6H_4$	93	204-205 (Acetonitrile)	$C_{20}H_{20}N_4OS$	65.91 65.95	5.53 5.55	15.37 15.35
4e	CH_3	4-$OCH_3C_6H_4$	98	171-172 (2-Propanol)	$C_{20}H_{20}N_4O_2S$	63.14 63.19	5.30 5.27	14.73 14.70
5a	C_6H_5	n-C_3H_7	97	189-190 (Benzene)	$C_{21}H_{22}N_4OS$	66.64 66.60	5.86 5.88	14.80 14.77
5b	C_6H_5	i-C_3H_7	96	169-170 (Benzene)	$C_{21}H_{22}N_4OS$	66.64 66.69	5.86 5.84	14.80 14.76
5c	C_6H_5	$C_6H_5CH_2$	96	189-190 (Benzene)	$C_{25}H_{22}N_4OS$	70.40 70.35	5.20 5.22	13.14 13.10
5d	C_6H_5	4-$CH_3C_6H_4$	92	189-190 (Acetonitrile)	$C_{25}H_{22}N_4OS$	70.40 70.42	5.20 5.17	13.14 13.16
5e	C_6H_5	4-$OCH_3C_6H_4$	98	198-200 (Benzene)	$C_{25}H_{22}N_4O_2S$	67.85 67.80	5.01 4.99	12.66 12.63

Table 2

Spectroscopic Data of Compounds **4** and **5**

Compound No	IR (cm^{-1})	^1H NMR δ (ppm)
4a	3410, 3320, 3160, 1665, 1620	[a] 0.91 (t, J = 7.8 Hz, 3H, CH_3), 1.57 (m, 2H, CH_2), 1.85 (s, 3H, CH_3), 3.22 (m, 2H, CH_2), 6.97, 7.25 (m, 5H, Ar), 7.61, 7.72 (s, 4H, NH_2 and NH), 10.85 (s, 1H, NH)
4b	3400, 3300, 1660, 1610	[a] 1.19 (d, J = 6.3 Hz, 6H, CH_3), 1.86 (s, 3H, CH_3), 3.88 (m, 1H, CH), 6.94, 7.25 (m, 5H, Ar), 7.54, 7.70 (s, 4H, NH_2 and NH), 10.89 (s, 1H, NH)
4c	3400, 3310, 1670, 1610	[a] 1.87 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 6.91, 7.22, 7.36 (m, 10H, Ar), 7.66, 7.83 (s, 4H, NH_2 and NH), 11.35 (br s, 1H, NH)
4d	3460, 3420, 3340, 3290, 1610	[a] 2.01 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 6.96, 7.15, 7.32 (m, 9H, Ar), 7.71 (s, 2H, NH_2)
4e	3460, 3400, 3290, 3140, 1630, 1600	[a] 1.98 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 6.92, 7.00, 7.13, 7.30 (m, 9H, Ar), 7.72 (s, 2H, NH_2), 11.05 (s, 1H, NH)
5a	3450, 3360, 3260, 1660, 1600	[b] 0.93 (t, J = 7.3 Hz, 3H, CH_3), 1.62 (m, 2H, CH_2), 3.08 (m, 2H, CH_2), 6.96, 7.22, 7.26, 7.54 (m, 10H, Ar)
5b	3400, 3300, 1650, 1610	[a] 1.20 (d, J = 6.3 Hz, 6H, CH_3), 3.90 (m, 1H, CH), 6.91, 7.20, 7.30, 7.41 (m, 10H, Ar), 7.83, 8.05 (s, 4H, NH_2 and NH), 10.81 (s, 1H, NH)
5c	3440, 3320, 1650, 1610	[b] 4.42 (s, 2H, CH_2), 6.96, 7.22, 7.33, 7.62 (m, 15H, Ar)
5d	3460, 3400, 3250, 3120, 1630	[b] 2.30 (s, 3H, CH_3), 4.94 (s, 2H, NH_2), 6.85, 7.02, 7.20, 7.38, 7.66 (m, 14H, Ar)
5e	3460, 3400, 3260, 3120, 1640	[a] 3.73 (s, 3H, CH_3), 6.97, 7.06, 7.26, 7.38, 7.49 (m, 14H, Ar), 8.24 (s, 2H, NH_2), 11.36 (br s, 1H, NH)

[a] In hexadeuteriodimethyl sulphoxide. [b] In deuteriochloroform.

tures of these compounds were assigned on the basis of their microanalyses, ir and ^1H nmr data showed in Tables 1 and 2. The ir spectra of **4** and **5** revealed the absence of CN absorbance band and the presence of characteristic absorbtion of CO, NH and NH_2 groups. The ^1H nmr spectra showed five deuterium oxide exchangeable protons, the one that lowerfield resonates was easily assigned to pyrrolic NH.

The possible pathway of the reaction may be explained assuming that the initial step involves the alkylation of the primary amino group. The formed intermediate undergoes subsequent intramolecular cyclization *via* selective nucleophilic attack of the active methylene to cyano group.

Subsequently the reaction of **1** with **2** and **3** was carried out in presence of a catalytic amount of *p*-toluenesulphonic acid. In these conditions the reaction of **1** with bromoacetone (**2**) gave the 1,4-thiazepine derivatives **6** (Tables 3 and 4), through an S-alkylated intermediate (non isolable). When the 2-bromoacetophenone (**3**) was instead used the 1,4-thiazepines **7a,b** were exclusively obtained from thioamides **1a,b**, while thioamides **1d,e** led only to pyrrole derivatives **5d,e**. On the other hand, under the same reaction conditions the thioamide **1c** reacted with **3** to afford a mixture of compouds **5c** and **7c** in 5:1 ratio.

Under acidic conditions reactions it exist competition between the sulfur atom and the primary amino group of

Table 3

Physical and Analytical Data of Compounds **6** and **7**

Compound No	R^1	R	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
6a	CH_3	*n*-C_3H_7	70	149-150 (2-Propanol)	$C_{16}H_{18}N_4S$	64.40 64.34	6.08 6.05	18.78 18.83
6b	CH_3	*i*-C_3H_7	92	146-147 (Cyclohexane)	$C_{16}H_{18}N_4S$	64.40 64.44	6.08 6.10	18.78 18.74
6c	CH_3	$C_6H_5CH_2$	60	137-138 (2-Propanol)	$C_{20}H_{18}N_4S$	69.34 69.30	5.24 5.26	16.17 16.20
6d	CH_3	4-$CH_3C_6H_4$	58	214-215 (Acetonitrile)	$C_{20}H_{18}N_4S$	69.34 69.39	5.24 5.22	16.17 16.20
6e	CH_3	4-$OCH_3C_6H_4$	91	234-235 (Acetonitrile)	$C_{20}H_{18}N_4OS$	66.28 66.30	5.01 5.03	15.46 15.43
7a	C_6H_5	*n*-C_3H_7	80	178-179 (2-Propanol)	$C_{21}H_{20}N_4S$	69.97 70.01	5.61 5.59	15.54 15.51
7b	C_6H_5	*i*-C_3H_7	90	190-191 (2-Propanol)	$C_{21}H_{20}N_4S$	69.97 69.92	5.59 5.56	15.54 15.60
7c	C_6H_5	$C_6H_5CH_2$	13	189-190 (2-Propanol)	$C_{25}H_{20}N_4S$	73.50 73.46	4.93 4.95	13.71 13.75

Table 4

Spectroscopic Data of Compounds **6** and **7**

Compound No	IR (cm^{-1})	^1H NMR (DMSO-d_6) δ (ppm)
6a	3480, 3370, 2170, 1630, 1595	1.00 (m, 3H, CH_3), 1.60 (m, 2H, CH_2), 1.74 (s, 3H, CH_3), 3.00 (m, 2H, CH_2), 5.20 (s, 2H, NH), 6.53 (s, 1H, H-2), 7.37, 7.52 (m, 5H, Ar)
6b	3460, 3390, 3360, 2150, 1620, 1590	1.08 (d, J = 5.9 Hz, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.56 (m, 1H, CH), 5.17 (s, 2H, NH), 6.52 (s, 1H, H-2), 7.38, 7.53 (m, 5H, Ar).
6c	3370, 2170, 1590	1.75 (s, 3H, CH_3), 4.34 (s, 2H, CH_2), 5.48 (s, 2H, NH), 6.58 (s, 1H, H-2), 7.20, 7.32, 7.41, 7.54 (m, 10H, Ar)
6d	3480, 3360, 3110, 2160, 1630, 1590	1.78 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 5.17 (s, 2H, NH), 6.67 (s, 1H, H-2), 6.72, 7.07 (d, J = 8.3 Hz, 4H, Ar), 7.45, 7.56 (m, 5H, Ar).
6e	3460, 3350, 3110, 2170, 1630, 1595	1.85 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 6.82 (s, 1H, H-2), 6.88, 7.48, 7.56 (m, 11H, Ar and NH)
7a	3350, 2150, 1630, 1595	0.98 (m, 3H, CH_3), 1.59 (m, 2H, CH_2), 3.02 (m, 2H, CH_2), 5.27 (s, 2H, NH), 6.81 (s, 1H, H-2), 7.09, 7.17, 7.30 (m, 10H, Ar)
7b	3480, 3360, 2140, 1625, 1595	1.09 (d, J = 5.9 Hz, 3H, CH_3), 3.57 (m, 1H, CH), 5.22 (s, 2H, NH), 6.77 (s, 1H, H-2), 7.08, 7.17, 7.29 (m, 10H, Ar)
7c	3470, 3380, 3120, 2170, 1635, 1600	4.36 (s, 2H, CH_2), 5.58 (s, 2H, NH), 6.86 (s, 1H, H-2), 7.12, 7.20, 7.34, 7.46 (m, 15H, Ar)

thioamides **1** toward the nucleophilic substitution. In light of these facts utilizing the less reactive bromoacetone (**2**) the *S*-alkylation is favoured in all the examined cases. On the contrary in the reaction of 3-arylamino substituted thioamides **1d,e** with the more reactive 2-bromoacetophenone (**3**) the nucleophilic attack is on the amino group.

Thus we could achieve the regioselective heterocyclization starting from the appropriate thioamide by utilizing α-bromoketones in acidic or basic medium. The synthetic strategies utilized here would be applicable to the synthesis of other types of pyrrole or thiazepine derivatives.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ir spectra were obtained in Nujol with a Perkin-Elmer 398 spectrophotometer. The ^1H nmr spectra were recorded 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-(benzylamino)-2-[(phenylamino)thioxamethyl]-2-propenenitrile (**1c**) [2] was prepared with a previously described procedure.

3-Amino-3-(alkyl or arylamino)-2-[(phenylamino)thioxamethyl]-2-propenenitriles **1a-e**.

A solution of 3-amino-3-ethoxypropenenitrile (1.10 g, 10 mmoles) and the corresponding amine (10 mmoles) in anhydrous acetonitrile was stirred at room temperature. After 24 hours phenyl isothiocyanate (1.35 g, 10 mmoles) was added and the stirring was continued for 5 hours. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from the solvent indicated.

3-Amino-2-[(phenylamino)thioxamethyl]-3-(1-propylamino)-2-propenenitrile (**1a**).

This compound was obtained in a yield of 77%, mp 95-96° (from benzene); ir: ν 3440, 3310, 3250, 2180, 1630 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.89 (t, J = 7.3 Hz , 3H, CH_3), 1.51 (m, 2H, CH_2), 3.18 (m, 2H, CH_2), 7.09, 7.27 (m, 5H, Ar), 7.87 (s, 2H, NH_2), 9.29, 10.22 (s, 2H, NH).

Anal. Calcd. for $C_{13}H_{16}N_4S$: C, 59.97; H, 6.19; N, 21.52. Found: C, 60.02; H, 6.17; N, 21.56

3-Amino-2-[(phenylamino)thioxamethyl]-3-(2-propylamino)-2-propenenitrile (**1b**).

This compound was obtained in a yield of 70%, mp 126-127° (from benzene); ir: ν 3430, 3270, 2180, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.14 (d, J = 6.3 Hz, 6H, CH_3), 3.85 (m, 1H, CH), 7.07, 7.26 (m, 5H, Ar), 10.51 (d, J = 6.1 Hz, 1H, NH).

Anal. Calcd. for $C_{13}H_{16}N_4S$: C, 59.97; H, 6.19; N, 21.52. Found: C, 59.92; H, 6.21; N, 21.56

3-Amino-3-[(4-methylphenyl)amino]-2-[(phenylamino)thioxamethyl]-2-propenenitrile (**1d**).

This compound was obtained in a yield of 88%, mp 192-193° (from acetonitrile); ir: ν 3440, 3310, 2190, 1620, 1605 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.32 (s, 3H, CH_3), 5.29 (br s, 2H, NH_2), 7.10, 7.21, 7.35 (m, 9H, Ar), 8.29 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{16}N_4S$: C, 66.21; H, 5.23; N, 18.17. Found: C, 66.27; H, 5.21; N, 18.21

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

This compound was obtained in a yield of 71%, mp 203-205° (from acetonitrile); ir: ν 3350, 3300, 2180, 1625, 1590 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.73 (s, 3H, OCH_3), 6.97, 7.15, 7.30 (m, 9H, Ar), 8.15 (br s, 2H, NH_2), 9.55, 10.96 (s, 2H, NH).

Anal. Calcd. for $C_{17}H_{16}N_4OS$: C,62.94; H, 4.97; N, 17.27. Found: C, 63.00; H, 4.95; N, 17.24.

Pyrrole Derivatives **4** and **5**. General Procedure.

A solution of **1** (2.5 mmoles), the appropiate bromoketone (2.5 mmoles) and triethylamine (0.35 ml, 2.5 mmoles) in chloroform (20 ml) was stirred at room temperature for 24 hours. After removal of the solvent, the residue was washed with water, fil-

tered and recrystallized from the appropriate solvent to give compounds **4** and **5** (Table 1).

Reactions of Propenethioamides **1** with Bromoacetone (**2**).

A mixture of compound **1** (2.5 mmoles) and bromoacetone (0.34 g, 2.5 mmoles) in dry chloroform (20 ml) was refluxed for 1 hour in presence of a catalytic amount of *p*-toluenesulphonic acid. Then the reaction mixture was concentrated to dryness, and the residue treated with water (50 ml) to obtain compounds **6** 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 **6a-e** (Table 3)

Reactions of Propenethioamides **1** with 2-Bromoacetophenone (**3**).

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. Then the reaction mixture was concentrated to dryness, and the residue treated with water (50 ml). In the case of compounds **1a** and **1b** the corresponding 1,4-thiazepines **7a** and **7b** were obtained. In the case of compounds **1d** and **1e** the pyrrole derivatives **5d** and **5e** were respectively isolated. In the case of compound **1c** the solid that precipitated from the hot reaction mixture was separated by filtration and identified as 1,4-thiazepine derivative **7c**, yield 13%; while from the solution elaborated as above described compound **5c** was isolated in 85% yield.

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