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ONE-POT SYNTHESIS OF FUNCTIONALIZED TETRAHYDRO-1,4-THIAZEPINES

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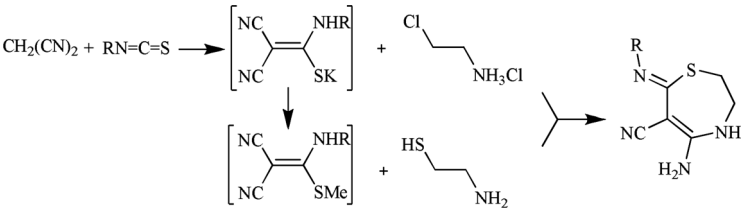
GRAPHICAL ABSTRACT



Abstract *One-pot synthesis of (5Z,7Z)-5-amino-7-(ethyl or arylimino)-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitriles from cyclocondensation of 2-((ethyl or arylamino)(mercapto)methylene)malononitrile potassium salts or their methylated derivatives with 2-chloroethylamine hydrochloride or cysteamine in dimethylformamide via two routes but a single intermediate is described.*

Keywords Heterocyclization; isothiocyanates; malononitrile; 1,4-thiazepine

INTRODUCTION

In connection with our interest in the synthesis of novel polyfunctionalized 1,4-thiazepines as potential precursors for the synthesis of biologically important fused 1,4-thiazepines, we previously described the reaction of sodium 2,2-dicyanoethene-1,1-bis(thiolate) and ethyl-2-cyano-3,3-dimercaptoacrylate dipotassium salts with 2-chloroethylamine hydrochloride in water to prepare the novel 5-amino-1,4-thiazepines[1,2] (Scheme 1).

To extend the scope of this reaction, we have explored the reaction of other substituted (methylene)malononitrile potassium salts with 2-chloroethylamine hydrochloride to synthesize the new (5Z,7Z)-5-amino-7-(ethyl or arylimino)-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitriles **8a–f** via two different routes.

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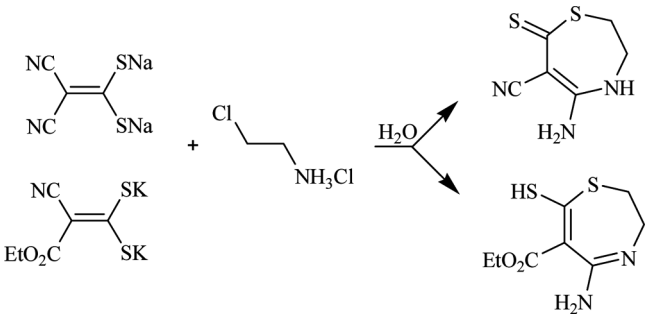
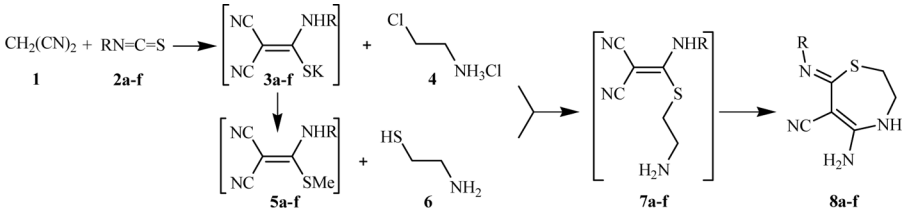


Scheme 1. Synthesis of 5-amino-1,4-thiazepines.

RESULTS AND DISCUSSION

The functionalized tetrahydro-1,4-thiazepines **8a–f** were obtained via two routes. In route **A,** a mixture of 2-((ethyl or arylamino)(mercapto)methylene)malononitrile potassium salts **3a–f** (which were prepared as intermediates from malononitrile **1** and isothiocyanates **2a–f**) and 2-chloroethylamine hydrochloride **4** in dimethylformamide (DMF) was first stirred at room temperature for 3 h, then heated at 60 °C for 12 h to afford the solid products **8a–f** (Scheme 2). In route **B,** similar treatment of the methylated salts **5a–f** with cysteamine **6** afforded the desired products **8a–f**. The yields of the products obtained are depicted in Table 1.



Scheme 2. Synthetic routes to (5Z,7Z)-5-amino-7-(ethyl or arylimino)-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitriles **8a–f**.

Table 1. Comparing yields of compounds **8a–f** obtained by routes **A** and **B**

			Yield (%)	
Entry	R	Substrate	Method A	Method B
1	C_2H_5	**8a**	32	48
2	C_6H_5	**8b**	35	50
3	*p*-ClC_6H_4	**8c**	38	55
4	*p*-BrC_6H_4	**8d**	40	58
5	*p*-$NO_2C_6H_4$	**8e**	44	61
6	*m*-MeC_6H_4	**8f**	33	50

A comparison between the results obtained from both routes leads us to the conclusion that route **A** is 66% to 72% as efficient as route **B**. While route **B** has greater yields, it also requires use of toxic methyl iodide and cysteamine, which has an unpleasant odor. This probably makes it less advantageous from an operational standpoint. It is worth noting that both routes share the same intermediate, 2-((2-aminoethylthio)(ethyl or arylamino)methylene)malononitriles **7a–f**. The multistep reactions can account for the poor yields of the final products.

The structures of compounds **8a–f** were confirmed from their spectral and micro analytical data. Their ^{1}H NMR spectra in acetone-d_6 showed triplet signals due to S-CH_2 groups at 2.88–3.03 ppm ($J \sim 6.8$ Hz) and doublet triplet signals due to N-CH_2 at 3.64–3.78 ppm ($J \sim 6.0$ Hz). After adding D_2O, the latter signals appeared as triplets with the same coupling constants as their neighboring methylen groups. Two broad signals at 6.61–7.39 and 8.62–9.13 ppm are attributed to NH_2 and NH groups respectively. The infrared (IR) spectra of the products showed two different absorption bands at 3270–3432 cm^{-1} and 3215–3282 cm^{-1} assignable to NH and NH_2 groups, bands at 2183–2208 cm^{-1} belonging to C≡N groups, and absorption bands at 1579–1648 cm^{-1} belonging to C=N imine groups.

EXPERIMENTAL

Materials

All the reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from Merck and used as received. Melting points were recorded on an Electrothermal type 9100 melting-point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. The IR spectra were obtained on a 4300 Shimadzu spectrometer, and only noteworthy absorptions are listed. The mass spectra were observed on a Varian Mat CH-7 at 70 ev. Elemental analyses (C, H, N, S) were performed on a Thermo Finnigan Flash EA microanalyzer.

General Procedure for the Synthesis of Functionalized Tetrahydro-1,4-thiazepines 8a–f

Method A. A suspension of **1** (10 mmol, 0.66 g), isothiocyanates **2a–f** (10 mmol), and potassium carbonate (10 mmol, 1.4 g) in DMF (20 ml) was stirred for 3 h at 25 °C before 2-chloroethylamine hydrochloride (10 mmol, 1.16 g) was added to it all at once. Then it was stirred for another 2 h before it was heated at 60 °C for 12 h. The mixture was neutralized with acetic acid (0.3 ml), and the solvent was removed at room temperature. The residue was dissolved in ethanol (10 ml) and added dropwise to brine 20% (30 ml). The solid was filtered off, washed with water (2 × 10 ml), and recrystallized from acetonitrile (12–23 ml) as white needles to give **8a–f**.

Method B. A suspension of **1** (10 mmol, 0.66 g), isothiocyanates **2a–f** (10 mmol), and potassium carbonate (10 mmol, 1.4 g) in DMF (20 ml) was stirred for 3 h at 25 °C before methyl iodide (10 mmol, 0.6 ml) was added dropwise on

stirring for 1 h. Then cysteamine **6** (10 mmol, 0.77 g) was added at once, and the mixture was heated at 60 °C for 12 h. The products were purified as in method A.

Data

(5Z,7Z)-5-Amino-7-(ethylimino)-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (8a). Mp 197–198 °C; IR (KBr) 3300, 3282, 2183, 1586 cm^{-1}; ^1H NMR (acetone-d_6, 100 MHz) δ: 1.23 (t, $J = 7.1$ Hz, 3H, CH_3), 3.03 (t, $J = 7.3$ Hz, 2H, S-CH_2), 3.45 (q, $J = 7.1$ Hz, 2H, N-CH_2CH_3), 3.76 (dt, $J \sim 6.1$ Hz, 2H, N-CH_2), 6.61 (s, 3H, NH, NH_2); mass (70 eV) 196 m/z. Anal. calcd. for $C_8H_{12}N_4S$ (196.27): C, 48.96; H, 6.16; N, 28.55; S, 16.33. Found: C, 48.88; H, 6.24; N, 28.67; S, 16.21.

(5Z,7Z)-5-Amino-2,3,4,7-tetrahydro-7-(phenylimino)-1,4-thiazepine-6-carbonitrile (8b). Mp 127–128 °C; IR (KBr) 3312, 3279, 2192, 1579 cm^{-1}; ^1H NMR (acetone-d_6, 100 MHz) δ: 2.93 (t, $J = 6.8$ Hz, 2H, S-CH_2), 3.64 (dt, $J \sim 6.3$ Hz, 2H, N-CH_2), 6.90 (s, 2H, NH_2), 7.25 (m, 5H, Ph), 8.62 (s, 1H, NH); mass (70 eV) 244 m/z. Anal. calcd. for $C_{12}H_{12}N_4S$ (244.32): C, 58.99; H, 4.95; N, 22.93; S, 13.13. Found: C, 59.12; H, 4.88; N, 22.79; S, 13.21.

(5Z,7Z)-7-(4-Chlorophenylimino)-5-amino-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (8c). Mp 251–252 °C; IR (KBr) 3300, 3231, 2197, 1602 cm^{-1}; ^1H NMR (acetone-d_6, 100 MHz) δ: 3.00 (t, $J = 6.6$ Hz, 2H, S-CH_2), 3.72 (dt, $J \sim 5.9$ Hz, 2H, N-CH_2), 7.04 (s, 2H, NH_2), 7.19, 7.34 (dd, 4H, Ph), 8.71 (s, 1H, NH); mass (70 eV) 278 m/z. Anal. calcd. for $C_{12}H_{11}ClN_4S$ (278.76): C, 51.70; H, 3.98; N, 20.10; S, 11.50. Found: C, 51.56; H, 3.89; N, 20.21; S, 11.40.

(5Z,7Z)-7-(4-Bromophenylimino)-5-amino-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (8d). Mp 264–265 °C; IR (KBr) 3270, 3247, 2189, 1595 cm^{-1}; ^1H NMR (acetone-d_6, 100 MHz) δ: 3.00 (t, $J = 6.7$ Hz, 2H, S-CH_2), 3.72 (dt, $J \sim 6.1$ Hz, 2H, N-CH_2), 7.02 (s, 2H, NH_2), 7.22, 7.54 (dd, 4H, Ph), 8.74 (s, 1H, NH); mass (70 eV) 323 m/z. Anal. calcd. for $C_{12}H_{11}BrN_4S$ (323.21): C, 44.59; H, 3.43; N, 17.33; S, 9.92. Found: C, 44.64; H, 3.47; N, 17.47; S, 9.79.

(5Z,7Z)-7-(4-Nitrophenylimino)-5-amino-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (8e). Decomp. 243–244 °C; IR (KBr) 3324, 3215, 2208, 1648 cm^{-1}; ^1H NMR (acetone-d_6, 100 MHz) δ: 3.02 (t, $J = 6.4$ Hz, 2H, S-CH_2), 3.78 (dt, $J \sim 5.6$ Hz, 2H, N-CH_2), 7.39 (s, 2H, NH_2), 7.45, 7.24 (dd, 4H, Ph), 9.13 (s, 1H, NH); mass (70 eV) 289 m/z. Anal. calcd. for $C_{12}H_{11}N_5O_2S$ (289.31): C, 49.82; H, 3.83; N, 24.21; S, 11.08. Found: C, 49.94; H, 3.75; N, 24.18; S, 11.08.

(5Z,7Z)-7-(m-Tolylimino)-5-amino-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (8f). Mp 144–145 °C; IR (KBr) 3432, 3263, 2190, 1594 cm^{-1}; ^1H NMR (acetone-d_6, 100 MHz) δ: 2.34 (s, 3H, CH_3), 2.88 (t, $J = 6.5$ Hz, 2H, S-CH_2), 3.74 (dt, $J \sim 5.8$ Hz, 2H, N-CH_2), 6.93 (s, 2H, NH_2), 7.08 (m, 4H, Ph), 8.65 (s, 1H, NH); mass (70 eV) 258 m/z. Anal. calcd. for $C_{13}H_{14}N_4S$ (258.34): C, 60.44; H, 5.46; N, 21.69; S, 12.41. Found: C, 60.54; H, 5.38; N, 21.56; S, 12.52.

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