Pergamon

Tetrahedron, Vol. 52, No. 33, pp. 10841-10848, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00632-1

REGIOSELECTIVE SYNTHESIS AND S-DERIVATIZATION REACTIONS OF 4- AND 6-TRIFLUOROMETHYL - 3-CYANO-2(1H)-PYRIDINETHIONES

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Abstract: The regioselective synthesis of the title compounds was developed on the basis of condensation reactions of trifluoroacetylacetone and its methyl enacetal with cyanothioacetamide in the presence of bases. Thus, the condensation of trifluoroacetylacetone with cyanothioacetamide yields predominantly 4-trifluoromethyl-6-methyl-3-cyano-2(1H)-pyridinethiones, whereas the methyl enacetal of trifluoroacetylacetone gives exclusively the 6-trifluoromethyl-4-methyl isomer. S-Alkylation of the trifluoromethylpyridinethione salts can be achieved using methyl iodide or bromoacetophenone in DMF-water. Bromoacetophenone derivatives can be further transformed into 3-aminothieno-[2,3-b]pyridines in the presence of excess KOH. Copyright © 1996 Elsevier Science Ltd

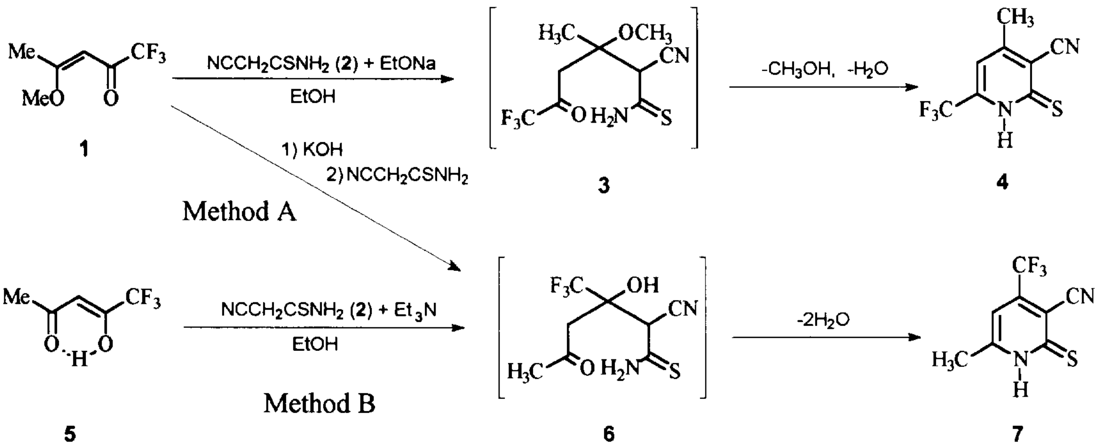
Interest in development of efficient synthetic approaches for preparation of functionalized 3-cyano-2(1H)-pyridinethiones is related to their use as versatile precursors in the preparation of dyes, herbicides, bactericides and other biologically active compounds.[1-3] However, in the vast volume of literature devoted to synthesis and transformations of this class of heterocyclic compounds, only a few publications have reported stereoselective synthesis of hydro-2(1H)-pyridinethiones,[4,5] and there is only one example of regiocontrolled synthesis of 3-cyano-2(1H)-pyridinethiones.[6] Thus, regiocontrolled synthesis of 4-methyl-6-phenyl-3-cyano-2(1H)-pyridinethiones and 6-methyl-4-phenyl-3-cyano-2(1H)-pyridinethiones can be achieved by varying the sequence of addition of morpholine and cyanothioacetamide to 1-acetyl-2-phenylacetylene. This regiocontrolled synthesis of 4-methyl-6-phenyl-3-cyano-2(1H)-

pyridinethione can be rationalized by assuming the formation of E-1-morpholino-1-phenyl-1-butene-3-one as a major intermediate, whereas the formation of isomeric 6-methyl-4-phenyl-3-cyano-2(1H)-pyridinethione is deemed to proceed through the Michael addition of cyanothioacetamide anion to the activated triple bond of the starting material.[6]

Here we report the first example of regiocontrolled synthesis of trifluoromethylcyano-2(1H)-pyridinethiones based on the reactions of trifluoroacetylacetone (**5**) and its methyl derivative (**1**) with cyanothioacetamide (**2**), and some further reactions of these 2(1H)-pyridinethiones.

Slow addition of **1** to an ethanol solution of the sodium salt of cyanothioacetamide (**2**) (prepared *in situ* from cyanothioacetamide and sodium ethoxide) gives 4-methyl-6-trifluoromethyl-3-cyano-2(1H)-pyridinethione **4** in 94% isolated yield. Examination of the ^{1}H and ^{19}F NMR spectra showed at least 95% isomeric purity of the product. *The same reaction conducted in a different manner (addition of cyanothioacetamide (2) to the solution of KOH and 1 in EtOH) results in the formation of isomeric 6-methyl-4-trifluoromethyl-3-cyano-2(1H)-pyridinethione 7 in 89% isolated yield and at least 97% isomeric purity (Method A).* The formation of **7** can be rationalized by assuming initial hydrolysis of **1** to the potassium salt of trifluoroacetylacetone in the presence of excess of KOH. Indeed, compound **7** can be prepared in 88% yield and more than 99% isomeric purity by direct reaction of trifluoroacetylacetone and cyanothioacetamide in the presence of catalytic amounts of triethylamine (Method B).[7]

Scheme 1



We suggest that the observed differences in regioselectivity is a result of different directions of the initial nucleophilic attack (Michael-type addition of cyanothioacetamide anion to the enol double bond) with the formation of intermediate **3** in the synthesis of **4**, and intermediate **6** in the synthesis of **7** (Scheme 1). In the case of trifluoroacetylacetone **(5)** the predominant enol form has the double bond adjacent to the CF_3 group as shown in Scheme 1, and addition of cyanothioacetamide anion leads to isomer **7**. In the case of methyl enacetal **1** the double bond is fixed in the position adjacent to the methyl group which results in the formation of isomer **4** (Scheme 1).

The structure of the new compounds was elucidated by means of NMR, IR and UV-VIS spectroscopy (Table 1 and 2). Analysis of the spectra showed that compounds **4** and **7** exist in the same tautomeric form with the exocyclic C=S bond (as depicted in Scheme 1). The proposed positions of methyl and trifluoromethyl groups in isomers **4** and **7** were in agreement with the observed chemical shifts and long range $J_{H\text{-}^{13}C}$ and $J_{F\text{-}^{13}C}$ constants in ^{13}C NMR spectra (Table 2).

We observe unusual differences between the UV-VIS spectra of compound **4** and its anion. The absorption maxima of the anion experienced an abnormal shift to shorter wavelengths, and the maximum at 415 nm sharply decreased its intensity (Table 1). It should be noted that 2(1H)-pyridinethiones without trifluoromethyl groups display reverse tendencies.[6]

Table 1. Yields, melting points, ^{19}F and ^{1}H NMR, IR and UV-VIS spectral data of the compounds **4** and **7**

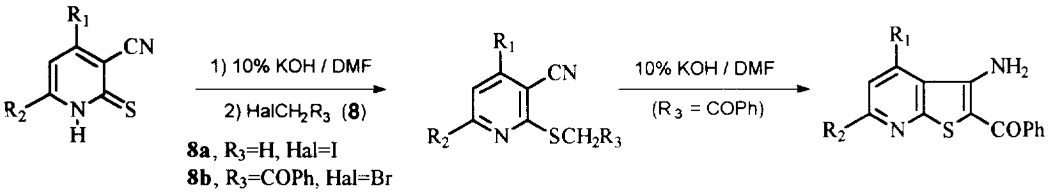
Compound	Yield	mp, °C	^{1}H NMR δ, ppm (in DMSO-D_6)	IR, ν cm^{-1} (in KBr)	^{19}F NMR δ, ppm (in DMSO-D_6)	Solvent	UV-VIS λ_{max} nm	E
4	94%	213-	2.45 s		- 63.44 s	0.1N KOH	297	11600
		215	(3H, CH_3)	2240 (C≡N)			372	1860
		dec.	7.00 s	1610 (NH_2)				
			(1H, 5-Py)			0.1N HCl	308	11700
			14.20 br.s			or MeOH	415	3300
			(1H,NH)					
7	89%	129-	2.64 s	2240 (C≡N)	- 67.48 s	0.1N KOH	290	12100
	(A)	131	(3H, CH_3)	1590 (NH_2)			358	2900
			7.87 s					
	88%		(1H, 5-Py)			0.1N HCl	305	12200
	(B)		14.50 br.s			or MeOH	398	2300
			(1H, NH)					

Table 2. ^{13}C NMR data (δ, ppm in DMSO-D_6; J, Hz) of the compounds **4** and **7**

Compound	C-2 (C=S)	C-3	C-4	C-5	C-6	CH_3	CF_3	CN
4	159.1s	111.4s	158.4q	120.0m $^1J_{CH}$ 165.3 $^3J_{CF}$ 2.9	148.0q $^2J_{CF}$ 35.0	19.9q	120.2m $^1J_{CF}$ 275.0	112.4s
7	179.0s	109.6d $^3J_{CF}$ 6.7	142.6m $^2J_{CF}$ 32.7 $^2J_{CH}$ 2.47	109.3d $^1J_{CH}$ 179.0	157.7q	19.6q	121.1q $^1J_{CF}$ 276.7 $^3J_{CH}$ 4.1	113.8s

The salts of **4** and **7** were found to react smoothly with alkylating agents such as CH_3I and bromoacetophenone in water-DMF to give the corresponding S-alkyl derivatives **9a-d** in high yields (Scheme 2 and Table 3). In the presence of excess of KOH, the acetophenone derivatives **9c,d** undergo self-condensation with the formation of 3-aminothieno[2,3-b]pyridines **10a,b** in high yields (Table 3). We also noticed that isomer **9c**, having CF_3 group adjacent to the cyano group, undergoes this condensation slower than isomer **9d**, suggesting an effect of the neighboring CF_3 group in **9c** on the reactivity of this cyano group.

Scheme 2



7, $R_1=CF_3$, $R_2=CH_3$
4, $R_1=CH_3$, $R_2=CF_3$

9a, $R_1=CF_3$, $R_2=CH_3$, $R_3=H$;
9b, $R_1=CH_3$, $R_2=CF_3$, $R_3=H$;
9c, $R_1=CF_3$, $R_2=CH_3$, $R_3=COPh$;
9d, $R_1=CH_3$, $R_2=CF_3$, $R_3=COPh$

10a, $R_1=CF_3$, $R_2=CH_3$;
10b, $R_1=CH_3$, $R_2=CF_3$

The spectral characteristics of compounds **9a-d** and **10a,b** shown in Table 3 are in agreement with the proposed structures (Scheme 2). Thus, in IR spectra of **9a-d** we observed the strong absorption band of the -CN group (2213-2225 cm^{-1}). In the compounds **10a,b** this peak was not observed. Instead, we observed the typical absorptions of the NH_2 group (stretching and deformation modes). Analysis of the IR spectra of **10a,b** also indicated the existence of intramolecular hydrogen bonding (based on shifts in the C=O absorptions compared with **9a,b**) which leads to overlap of the C=O and NH_2 bands. Analogous effects were observed in selenopheno[2,3-b]pyridines, where the existence of hydrogen bonding was confirmed by X-Ray analysis.[1]

Table 3. Yields, melting points, ^1H NMR, IR and UV-VIS spectral data for the compounds **9a-d** and **10a,b**

R_1	R_2	R_3	Compound	Yield %	mp, °C	IR, cm^{-1} in KBr	^1H NMR, δ, ppm in DMSO-D_6
CF_3	CH_3	H	**9a**	62	68-69	2215 (C≡N)	2.65s (6H, SCH_3, CH_3) 7.12s (1H, 5-Py)
CH_3	CF_3	H	**9b**	71	75-76	2215 (C≡N)	2.55s (3H, CH_3) 2.65s (3H, CH_3) 7.25s (1H, 5-Py)
CF_3	CH_3	COPh	**9c**	92	90-91	2223 (C≡N) 1684 (C=O)	2.62s (3H, CH_3) 4.73s (2H, SCH_2) 7.15s (1H, 5-Py) 7.50-8.10m (5H, C_6H_5)
CH_3	CF_3	COPh	**9d**	88	94-95	2228 (C≡N) 1680 (C=O)	2.60s (3H, CH_3) 4.72s (2H, SCH_2) 7.30s (1H, 5-Py) 7.50-8.10m (5H, C_6H_5)
CF_3	CH_3	-	**10a**	86	157-158	3482,3238 (NH_2) 1608 (C=O, NH_2)	2.63s (3H, CH_3) 7.18s (2H, NH_2) 7.56s (1H, 5-Py) 7.30-7.80m (5H,C_6H_5)
CH_3	CF_3	-	**10b**	73	147-148	3495,3110 (NH_2) 1600 (C=O, NH_2)	2.95s (3H, CH_3) 7.20s (2H, NH_2) 7.60s (1H, 5-Py) 7.30-7.90m (5H,C_6H_5)

In summary, we have developed a regioselective synthesis of 4- and 6-trifluoromethyl-pyridinethiones.

EXPERIMENTAL SECTION

General. IR spectra were recorded on a Perkin-Elmer-457 spectrometer for samples in potassium bromide pellets. UV-VIS spectra were measured using a Spekord UV-VIS spectrometer. ^{1}H NMR spectra were run at 250 MHz (Bruker WM-250) in DMSO-D$_6$ using TMS as internal standard. All chemical shifts are quoted in ppm with coupling constants J expressed in hertz (Hz). ^{13}C NMR spectra were recorded with a Bruker WM-250 (62.5 MHz) spectrometer in DMSO-D$_6$ using TMS as internal standard. ^{19}F NMR spectra were run at 235 MHz (Bruker WM-250) in DMSO-D$_6$ using CFCl$_3$ as internal standard. The yields of compounds **4**, **7**, **9a-d**, and **10a-b**, together with their melting points, spectral and microanalytical data, are compiled in Tables 1-4.

3-Cyano-4-methyl-6-trifluoromethyl-2(1H)-pyridinethione (4). A solution of cyanothioacetamide (**2**) (10.0 g, 0.1 mole) and EtONa (6.8 g, 0.1 mole) in EtOH (80 ml) was heated with stirring at 60°C for 20 min, during which time the methyl enolacetal of trifluoroacetylacetone (**1**) (16.6 g, 0.1 mole) was added dropwise. After the addition was complete, the reaction mixture was stirred at 20°C for an additional 30 min, cooled and neutralized with 10% HCl to pH=6 at 0°C. The precipitate was collected by filtration and washed with EtOH and hexane to yield an analytically pure sample of **4** (Tables 1,2 and 4).

3-Cyano-6-methyl-4-trifluoromethyl-2(1H)-pyridinethione (7).

Method A. A solution of KOH (5.6 g, 0.1 mole) and trifluoroacetylacetone methyl enacetal (**1**) (16.6 g, 0.11 mole) in EtOH (50 ml) was stirred at 20°C for 15 min. Cyanothioacetamide (**2**) (10.0g, 0.1 mole) was added by small portions to this solution at the same temperature. The reaction mixture was stirred for additional 10 min at 20°C and then poured into 0.1N HCl (200 ml). The precipitate was collected by filtration and recrystallized from EtOH to yield an analytically pure sample of **7** (Tables 1,2 and 4).

Method B. A suspension of cyanothioacetamide (**2**) (10.0 g, 0.1 mole), trifluoroacetylacetone (**5**) (15.3 g, 0.1 mole) and triethylamine (0.5 ml) in EtOH (80 ml) was heated under reflux for 2 min. The reaction mixture was then cooled and stirred at 20°C for an additional 6 h. The precipitate was collected by filtration, washed with EtOH and hexane to yield an analytically pure sample of **7** (Tables 1,2 and 4). The samples of compound **7** prepared by methods A and B had the same IR spectra, their mixture did not exhibit melting point depression.

3-Cyano-6(4)-methyl-2-methylthio-4(6)-trifluoromethylpyridines (9a,b), and 2-benzoylmethylthio-3-cyano-6(4)-methyl-4(6)-trifluoromethylpyridines (9c,d). General procedure: A suspension of cyanopyridinethiones (**4** or **7**) (2.2 g, 10 mmol) in DMF (15 ml) was stirred at 20°C for 10-30 min, during which time methyl iodide (1.4 g, 10 mmol) (**9a,b**) or bromoacetophenone (2.0 g, 10 mmol) (**9c,d**) and 10% KOH solution in water (5.6 g, 10 mmol) were added dropwise. The reaction mixture was stirred at 20°C for an additional 30 min and then diluted with water (10-15 ml). The precipitate was collected by filtration and recrystallized from EtOH (Tables 3 and 4).

3-Amino-2-benzoylthieno[2,3-b]pyridines (10a,b). General procedure: A 10% aqueous solution of KOH (3.0g, 5.3 mmol) was added to a suspension of benzoylmethyl-thiopyridines (**9c,d**) (3.4 g, 10 mmol) in DMF (15 ml). The reaction mixture was stirred at 20°C for an additional 3 h and then diluted with water (10 ml). The precipitate was collected by filtration and recrystallized from EtOH (Tables 3 and 4).

Table 4. Elemental analysis data for the compounds **4**, **7**, **9a-g** and **10a,b**

Com-po-und	Found, %					Formula	Calculated, %				
	C	H	F	N	S		C	H	F	N	S
4	43.79	2.04	26.48	12.57	15.11	$C_8H_5F_3N_2S$	44.04	2.29	26.15	12.84	14.68
7	43.81	2.02	26.53	12.53	15.13	$C_8H_5F_3N_2S$	44.04	2.29	26.15	12.84	14.68
9a	46.29	2.66	-	12.43	13.66	$C_9H_7F_3N_2S$	46.55	3.02	-	12.07	13.79
9b	46.31	2.69	-	12.40	13.61	$C_9H_7F_3N_2S$	46.55	3.02	-	12.07	13.79
9c	56.95	3.03	-	8.51	9.83	$C_{16}H_{11}F_3N_2OS$	57.14	3.27	-	8.33	9.52
9d	56.93	3.04	-	8.49	9.79	$C_{16}H_{11}F_3N_2OS$	57.14	3.27	-	8.33	9.52
10a	57.33	3.31	-	8.17	9.27	$C_{16}H_{11}F_3N_2OS$	57.14	3.27	-	8.33	9.52
10b	57.38	3.23	-	8.13	9.23	$C_{16}H_{11}F_3N_2OS$	57.14	3.27	-	8.33	9.52

ACKNOWLEDGEMENT

This research was sponsored by the Newly Independant States - Industry Partnership Program (NIS-IPP), Division of Defense Programs, U.S. Department of Energy under contract DP-15.

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(*Received in USA* 20 *May* 1996; *revised* 1 *July* 1996; *accepted* 3 *July* 1996)