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1,2,3-Triarylpropenones as starting materials for 2-pyridinethiones

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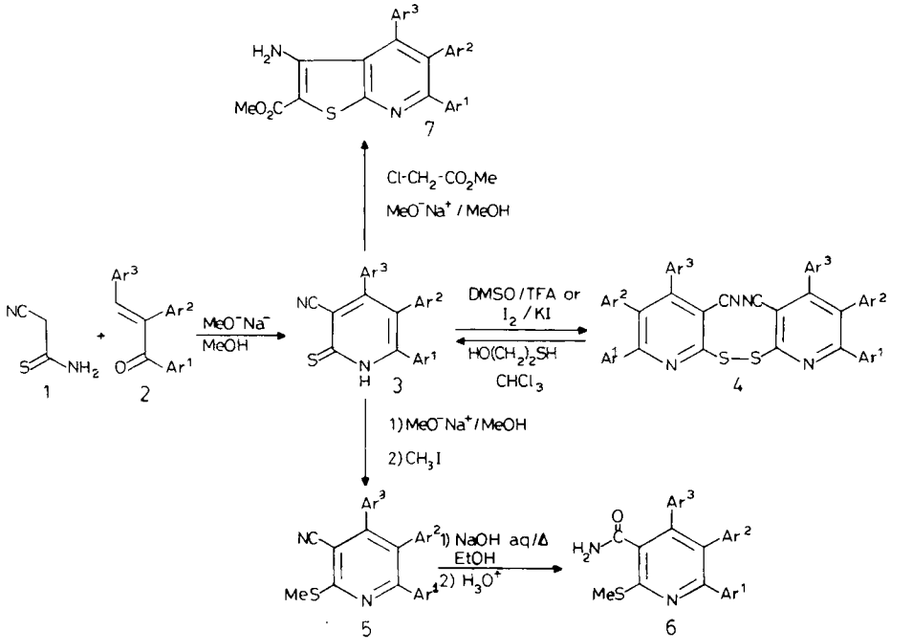
Abstract. 2-Pyridinethiones **3** are obtained in good yields from 1,2,3-triarylpropenones **2** by treatment with cyanothioacetamide **1**. Disulfides **4** result from oxydation of **3**. Pyridinethiones **3** undergo methylation at the sulfur atom, leading to (methylthio)pyridines **5**, which can be hydrolized to carboxamides **6**. Thieno[2,3-*b*]pyridines **7** are obtained from **3** upon reaction with methyl chloroacetate.

Introduction

1,2,3-Triarylpropenones have been known for a long time[1,2] and, since their discovery, several publications have appeared on these compounds, dealing with their preparation[3-5], their formation in ring-opening reactions[6], their spectral[7,8] and pharmacological[9] properties, their oxidation[10] and reduction[11,12], the formation of adducts[13,14] and reductive alkylation[15]. However, very little involving the use of 1,2,3-triarylpropenones in the synthesis of heterocyclic compounds has been published[14,16,17]. In a previous paper[18], we have reported on the synthesis of 4*H*-pyrans and furans from 1,2,3-triarylpropenones. We now wish to report the use of these compounds in the preparation of 2-pyridinethiones.

Results

1,2,3-Triarylpropenones **2**, upon treatment with cyanothioacetamide (**1**), undergo a *Michael* addition, followed by spontaneous cyclization and aromatization to 2-pyridinethiones **3**. The reaction is very simple to carry out in



Scheme 1

basic alcoholic solution and compounds **3** are isolated in good yields upon acidifying with hydrochloric acid (Table I). The 2-pyridinethione tautomer is probably favoured in **3**[19,20]; a broad band at 2650–3250 cm^{-1} is observed in the IR spectra, corresponding to the thioamide system. The cyano group gives rise to a band at 2230–2240 cm^{-1}. In the ^1H NMR spectra of compounds **3** (Table II), the aromatic protons appear at 6.6–7.5 ppm. The isolation of 2-pyridinethiones **3** as aromatic compounds is in contrast with the results obtained on the addition of cyanothioacetamide to ethyl 2,3-diphenylpropenoates[21], in which case a non-aromatic sodium salt is first isolated. Here an intramolecular hydrogen bond involving the ethoxycarbonyl group seems to exist. This could lead to stabilisation of the non-aromatic ring in a way not possible with a phenyl group as present in 1,2,3-triarylpropenones.

It must be pointed out that 2-pyridinethiones **3** are isolated from the reaction medium contaminated with a small amount of the corresponding dipyridiyl disulfide (**4**), however crystallization of the crude 2-pyridinethione, in the presence of a reducing agent 2-mercaptoethanol, affords compounds **3** in pure form. On the other hand, disulfides **4** can also be obtained pure by oxydation of the corresponding 2-pyridinethiones **3**. The reaction can be performed in good yields by using either iodine/potassium iodide in ethanol or dimethyl sulfoxide/trifluoroacetic acid (Table I).

Methylation of pyridinethiones **3** takes place at the sulfur atom, leading to (methylthio)pyridines **5** (see Table I). Spectral data of compounds **5**, including the peak of the methylthio group at 2.66–2.73 ppm, are shown in Table II. Usually, 2-(methylthio)pyridines can be transformed into 2-pyridinones by treatment with alkali. However, when such a treatment is applied to (methylthio)pyridines **5**, the methylthio group is unaffected. Instead, the cyano group undergoes basic hydrolysis to a carbamoyl group, and 3-carbamoyl-2-(methylthio)pyridine **6** is obtained as the reaction product. It is easily identified on the basis of its spectral properties (Table II).

As a final reaction, 2-pyridinethiones **3** were transformed into a fused heterocyclic system. When compounds **3** are reacted with methyl chloroacetate, a ring-closing reaction involving the sulfur atom and the cyano group takes place, leading to a series of thieno[2,3-*b*]pyridines **7** (Tables I and II).

Table I Physical data of compounds **3–7**.

Compound	Ar^3	Ar^1, Ar^2	M.p. (°C) Yield (%)	Formula (Mol. mass)	Elemental analysis	C	H	N	S	Cl
3a	C_6H_5	C_6H_5 C_6H_5	269–270 (68)	$C_{24}H_{16}N_2S$ (364.5)	Calc.	79.09	4.42	7.68	8.80	
					Found	78.80	4.64	7.42	9.05	
3b	*p*-CH_3-C_6H_4	C_6H_5 C_6H_5	263–264 (72)	$C_{25}H_{18}N_2S$ (378.5)	Calc.	79.33	4.79	7.40	8.47	
					Found	79.10	5.00	7.64	8.26	
3c	*p*-CH_3O-C_6H_4	C_6H_5 C_6H_5	278–279 (76)	$C_{25}H_{18}N_2OS$ (394.5)	Calc.	76.11	4.60	7.10	8.13	
					Found	75.72	4.81	7.10	8.35	
3d	*p*-Cl-C_6H_4	C_6H_5 C_6H_5	281–282 (90)	$C_{24}H_{15}N_2ClS$ (398.9)	Calc.	72.26	3.79	7.02	8.04	8.89
					Found	72.40	3.80	7.07	8.07	8.66
4a	C_6H_5	C_6H_5 C_6H_5	246–247 (97[a], 38[b])	$C_{48}H_{30}N_4S_2$ (726.9)	Calc.	79.31	4.16	7.71	8.82	
					Found	79.09	4.50	7.63	8.78	
4b	*p*-CH_3-C_6H_4	C_6H_5 C_6H_5	225–226 (96[a], 35[b])	$C_{50}H_{34}N_4S_2$ (754.9)	Calc.	79.55	4.54	7.43	8.49	
					Found	79.29	4.36	7.62	8.73	
4c	*p*-CH_3O-C_6H_4	C_6H_5 C_6H_5	249–250 (96[a], 74[b])	$C_{50}H_{34}N_4O_2S_2$ (786.9)	Calc.	76.32	4.35	7.11	8.14	
					Found	76.31	4.70	6.78	7.82	
4d	*p*-Cl-C_6H_4	C_6H_5 C_6H_5	220–221 (99[a], 32[b])	$C_{48}H_{28}Cl_2N_4S_2$ (795.8)	Calc.	72.44	3.54	7.04	8.06	8.92
					Found	72.55	3.42	6.93	8.40	8.81
5a	C_6H_5	C_6H_5 C_6H_5	265–266 (99)	$C_{25}H_{18}N_2S$ (378.5)	Calc.	79.33	4.79	7.40	8.47	
					Found	79.14	5.01	7.10	8.75	
5b	*p*-CH_3-C_6H_4	C_6H_5 C_6H_5	238–239 (83)	$C_{26}H_{20}N_2S$ (392.5)	Calc.	79.56	5.14	7.14	8.17	
					Found	79.34	5.20	7.23	8.23	
5c	*p*-CH_3O-C_6H_4	C_6H_5 C_6H_5	202–203 (63)	$C_{26}H_{20}N_2OS$ (408.5)	Calc.	76.44	4.93	6.86	7.85	
					Found	76.15	4.69	6.91	7.89	
5d	*p*-Cl-C_6H_4	C_6H_5 C_6H_5	197–198 (86)	$C_{25}H_{17}ClN_2S$ (412.9)	Calc.	72.72	4.15	6.78	7.76	8.58
					Found	72.45	4.36	6.77	8.25	8.17
6a	C_6H_5	C_6H_5 C_6H_5	262–263 (53)	$C_{25}H_{20}N_2OS$ (396.5)	Calc.	75.73	5.08	7.06	8.09	
					Found	76.00	5.36	7.22	7.69	
7a	C_6H_5	C_6H_5 C_6H_5	288–289 (54)	$C_{27}H_{20}N_2O_2S$ (436.5)	Calc.	74.29	4.62	6.42	7.35	
					Found	74.01	4.82	6.51	7.47	
7c	*p*-CH_3O-C_6H_4	C_6H_5 C_6H_5	263–264 (37)	$C_{28}H_{22}N_2O_3S$ (466.5)	Calc.	72.08	4.75	6.00	6.87	
					Found	71.78	5.10	6.07	7.21	
7d	*p*-Cl-C_6H_4	C_6H_5 C_6H_5	272–273 (34)	$C_{27}H_{19}ClN_2O_2S$ (470.9)	Calc.	68.86	4.07	5.95	6.81	
					Found	68.59	4.00	6.02	6.95	

[a] Yield by method a. [b] Yield by method b (see experimental).

Table II Spectral data of compounds **3–7**.

Compound	Aromatic hydrogens	^{1}H NMR				IR				Mass spectra
		CH_3	OCH_3	SCH_3	NH_2.	NH_2	NH	CN	CO	
3a	7.2–6.9 (m, 10H) 6.73 (s, 5H)						3200–2700	2240		364(M+, 100), 363(94), 329(21), 178(10), 165(10), 151(11), 105(24), 77(20), 46(10), 45(23).
3b	7.20 (s, 5H); 7.03 (s, 5H); 6.88 (s, 4H).	2.20 (s, 3H)					3200–2650	2230		378(M+, 100), 377(80), 363(18), 343(11), 164(8), 151(7).
3c	7.4–6.6 (m, 14H)		3.66 (s, 3H)				3250–2650	2230		394(M+, 100), 393(82), 363(9), 350(5), 317(5), 316(8), 189(5), 158(5).
3d	7.5–6.8 (m, 14H)						3220–2650	2230		398(M+ 100), 397(71), 363(14), 328(13), 327(10), 181(12), 164(13), 151(9).
4a	7.4–6.6 (m, 30H)							2220		726(M+, 81), 725(78), 696(37), 695(88), 694(99), 693(98), 669(32), 668(74), 366(20), 365(76), 364(100), 363(99), 361(23), 347(23), 331(19), 330(28), 329(81),328(19), 314(23), 302(20), 301(24), 227(23), 216(27), 165(23), 151(22), 77(44), 66(25), 44(20).
4b	7.4–6.7 (m, 28H)	2.26 (s, 6H)						2220		
4c	7.4–6.6 (m, 28H)		3.73 (s, 6H)					2220		786(M+, 2), 785(4), 784(4), 755(18), 754(52), 753(100), 752(56), 729(6), 728(15), 727(28), 407(7), 395(9), 394(28), 393(27), 378(5), 377(18), 101(29), 100(23), 64(9), 44(14).
4d	7.4–6.6 (m, 28H)							2230		
5a	7.4–6.7 (m, 15H)			2.73 (s, 3H)				2220		378(M+, 43), 377(100), 329(4), 181(7), 180(5), 164(4), 151(4), 105(4), 77(4).
5b	7.5–6.7 (m, 14H)	2.25 (s, 3H)		2.70 (s. 3H)				2220		
5c	7.4–6.6 m, 14H)		3.75 (s, 3H)	2.70 (s, 3H)				2220		
5d	7.3–6.6 (m, 14H)			2.66 (s, 3H)				2240		412(M+, 66), 411(100), 378(7), 377(21), 181(7), 180(6), 164(6), 102(11), 101(47), 100(38), 99(16).
6a	7.3–6.6 (m, 15H)			2.56 (s, 3H)	7.6 (bs, 2H)		3440–3180		1660	
7a	7.5–6.5 (m, 15H)	3.83 (s, 3H)			5.6 (bs, 2H)	3490–3360			1670	
7c	7.4–6.6 (m, 14H)	3.83 (s, 3H)	3.75 (s, 3H)		5.6 (bs, 2H)	3500–3460			1670	
7d	7.4–6.6 (m, 14H)	3.83 (s, 3H)			5.5 (bs, 2H)	3500–3270			1675	471(M+, 100), 470(11), 441(6), 440(20), 439(13), 438(38), 412(53), 410(11), 374(6), 220(11), 187(11).

Experimental

Melting points were determined on a Büchi 510 apparatus in capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer in potassium bromide pellets. The ^{1}H NMR spectra were determined on a Varian T-60A at 60 MHz. Chemical shifts are quoted in δ values using TMS as the internal standard. A Varian MAT 711 spectrometer was used for recording mass spectra. Microanalyses were performed by Centro Nacional de Química Orgánica de Madrid. The reactions and purity of compounds were monitored by TLC on silica-gel plates (Merck 60-F_{254}), using mixtures of toluene/ethyl acetate or chloroform/ethanol as the eluent.
Cyanothioacetamide (**1**) was obtained from malononitrile, using the method reported by *Howard* et al.[22], and from Aldrich. 1,2,3-Triarylpropenones (**2**) were prepared using previously reported procedures[1,2,23].

4,5,6-Triaryl-3-cyano-2-pyridinethiones (**3**). *General procedure*

Cyanothioacetamide **1** (5 mmol) was added to a solution of sodium methoxide in methanol (prepared from 5 mmol of sodium in 7 ml of dry methanol). The appropriate 1,2,3-triarylpropenone **2** (5 mol) was added to the solution and the reaction mixture stirred at room temperature for 50 h. It was then neutralized with hydrochloric acid and poured into cold water. A precipitate separated and was collected by filtration and recrystallized from ethanol. A few drops of 2-mercaptoethanol must be added to the ethanol prior to crystallization to avoid the oxydative dimerization of pyridinethiones **3** to disulfides **4**.

2,2'-Bis(4,5,6-triaryl-3-cyanopyridyl) disulfides (**4**). *General procedure*

Method a). The appropriate 2-pyridinethione **3** (1 mmol) was dissolved in 5 ml of dimethyl sulfoxide and a few drops of trifluoroacetic acid were added. The corresponding disulfide **4** precipitated after 24-h standing at room temperature. The solid was collected by filtration and recrystallized from ethanol.

Method b). The corresponding 2-pyridinethione **3** (1 mmol) was suspended in 20 ml of ethanol. A solution of iodine (30 mg) and potassium iodide (20 mg) in a small amount of ethanol (*ca.* 5 ml) was added to the reaction mixture, which was then stirred at room temperature for 50 h. A solid precipitated and was collected by filtration and washed with a large amount of distilled water. The solid was recrystallized from ethanol.

Transformation of 2,2'-bis(3-cyano-4,5,6-triphenylpyridyl) disulfide (**4a**) *into 3-cyano-4,5,6-triphenyl-2-pyridinethione* (**3a**).

Disulfide **4a** (0.164 g; 0.22 mol) was suspended in 20 ml of chloroform and 0.101 g (1.3 mmol) of 2-mercaptoethanol was added. The reaction mixture was stirred at room temperature for 10 h and the solution was then washed twice with distilled water and dried over magnesium sulfate. The solvent was removed under vacuum and the residue recrystallized from ethanol. Yield 97%.

4,5,6-Triaryl-3-cyano-2-(methylthio)pyridines (**5**). *General procedure*

The appropriate 2-pyridinethione **3** (5 mmol) was dissolved with stirring in a solution of sodium methoxide in methanol (previously prepared from 25 mmol of sodium and 75 ml of methanol). To the resulting solution, 8 mmol of methyl iodide were added and the solution maintained at room temperature for 2–3 h, after which time a precipitate separated which was then filtered off and recrystallized from ethanol.

Transformation of 3-cyano-4,5,6-triphenyl-2-(methylthio)pyridine (**5a**) *into 3-carbamoyl-4,5,6-triphenyl-2-(methylthio)pyridine* (**6a**)

(Methylthio)pyridine **5a** (0.214 g; 0.56 mmol) was suspended in *ca.* 28 ml of ethanol and 15 ml of a 60% aqueous solution of sodium hydroxide. The reaction mixture was refluxed for 30 h and the solution then evaporated to remove the ethanol. The remaining solution was poured into water and neutralized with acetic acid. The precipitate which separated was collected by filtration and recrystallized from ethanol. Yield 53%.

3-Amino-4,5,6-triaryl-2-(methoxycarbonyl)thieno[2,3-b]pyridines (**7**). *General procedure*

The appropriate 4,5,6-triaryl-3-cyano-2-pyridinethione **3** (0.40 mmol) was suspended in dry methanol (*ca.* 20 ml) in which 9 mg of sodium had been previously dissolved. Methyl chloroacetate (0.44 mmol) was then added and the mixture maintained at room temperature for *ca.* 24 h, after which time, a yellow precipitate separated, which was filtered off and recrystallized from methyl acetate or chloroform.

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