A Simple Method for the Synthesis of 5-Aryl-3-amino-2-alkoxycarbonylthiophenes

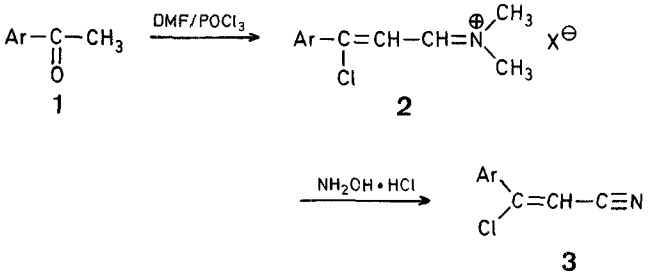
Horst HARTMANN

Sektion Chemie der Technischen Universität, DDR-8027 Dresden, Mommsenstr. 13, German Democratic Republic

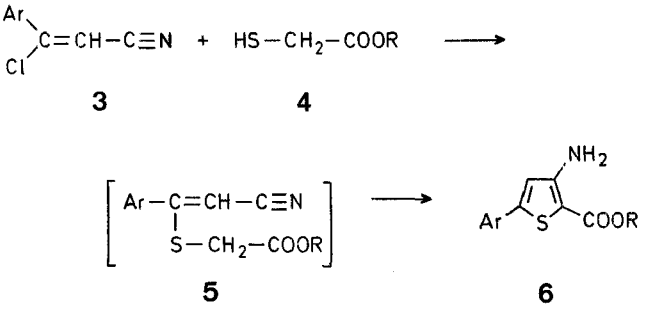
Jürgen LIEBSCHER

Sektion Chemie der Humboldt-Universität, DDR-1040 Berlin, Hessesche Str. 2, German Democratic Republic

Recently, we described a simple, one-pot synthesis of β-chlorocinnamonitriles **3** starting from acetophenones **1**, dimethylformamide, phosphoryl chloride, and hydroxylamine hydrochloride[1,2]. The reaction involves intermediate 3-chloro-2-propeniminium salts **2**[3], which are versatile synthons in organic chemistry, especially in the synthesis of heterocyclic compounds[4]. Thiophenes for example can be synthesized with ease by the reaction of the salts **2** with activated mercaptomethyl compounds[5].



Due to their structural resemblance to the iminium salts **2** the β-chlorocinnamonitriles **3** should exhibit a similar behaviour. As expected, the β-chlorocinnamonitriles **3** can be converted to 5-aryl-3-amino-2-alkoxycarbonylthiophenes **6** by the reaction with α-mercaptoacetic esters **4** in the presence of a base. Probably, the reactands interact by primary substitution of the chloro-substituent in **3** by the mercapto group of **4** followed by a Dieckmann-Thorpe cyclization of the resulting 3-aryl-3-alkoxycarbonylmethylmercaptoacrylonitriles **5**.



The best yields of **6** are achieved when alkali hydroxides in alcoholic solution are used as bases. However, also triethylamine in acetonitrile can be employed with success.

The compounds prepared are listed in the Table. They reveal characteristic absorption bands at about 3450 and 3350 cm^{-1} (NH_2) and 1660 cm^{-1} (COOR) in the I.R. spectra and at about 350 nm in the U.V. spectra. The H-atom in position 4 of the thiophene moiety gives rise to a singulett at about 6.8 ppm in the ^{1}H-N.M.R. spectra.

Table. 5-Aryl-3-amino-2-alkoxycarbonyl-thiophene **6** by Sodium Alkoxide-Catalyzed Condensation of **3** with **4**

Product No.	Ar	R	Yield [%]	m.p.[a] [°C]	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (KBr) [cm^{-1}] ν_{NH_2}	ν_{COOR}	U.V. (CH_3OH) λ_{max} [nm] (log ε)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
6a	C_6H_5	C_2H_5	66	101–104°	104–105°[6]	3400, 3350	1660	293 (4.25); 350 (3.95)	6.78 (s, 1H)
6b	4-Cl—C_6H_4	CH_3	76	139–141°	$C_{12}H_{10}ClNO_2S$ (267.6)	3420, 3340	1666	299 (4.30); 352 (3.98)	
6c	4-Cl—C_6H_4	C_2H_5	98 (77)[c]	106–107°	$C_{13}H_{12}ClNO_2S$ (281.6)	3430, 3338	1653	302 (4.35); 350 (3.96)	6.74 (s, 1H)
6d	4-Br—C_6H_4	CH_3	81	145–147°	$C_{12}H_{10}BrNO_2S$ (312.0)	3425, 3325	1658	314 (4.23); 354 (3.99)	
6e	4-Br—C_6H_4	C_2H_5	82	105–106°	$C_{13}H_{12}BrNO_2S$ (326.0)	3410, 3320	1670	316 (4.18); 355 (3.97)	6.76 (s, 1H)
6f	4-H_3CO—C_6H_4	CH_3	55	181–182°	$C_{13}H_{13}NO_3S$ (263.1)	3490, 3380	1658	307 (4.30); 341 (4.08)	
6g	4-H_3CO—C_6H_4	C_2H_5	70	119–120°	$C_{14}H_{15}NO_3S$ (277.1)	3430, 3337	1670	308 (4.32); 348 (4.12)	6.68 (s, 1H)
6h	4-C_6H_5—C_6H_4	CH_3	79	243–246°	$C_{18}H_{15}NO_2S$ (309.1)	3480, 3373	1668	312 (—); 350 (—)	
6i	4-C_6H_5—C_6H_4	C_2H_5	80	175–180°	$C_{19}H_{17}NO_2S$ (323.1)	3478, 3360	1650	310 (4.46); 355 (4.16)	6.82 (s, 1H)
6j	4-O_2N—C_6H_4	CH_3	84	218–219°	$C_{12}H_{10}N_2O_4S$ (278.1)	3472, 3345	1648	319 (—); 393 (—)	
6k	4-O_2N—C_6H_4	C_2H_5	86	140–147°	$C_{13}H_{12}N_2O_4S$ (292.1)	3448, 3355	1670	320 (4.15); 394 (3.82)	6.90 (s, 1H)
6l	2-$C_{10}H_7$	CH_3	70	159–161°	$C_{16}H_{13}NO_2S$ (283.1)	3480, 3362	1667	312 (4.35); 350 (4.04)	
6m	2-$C_{10}H_7$	C_2H_5	86	130–131°	$C_{17}H_{15}NO_2S$ (297.1)	3430, 3330	1655	311 (4.31); 351 (4.10)	6.89 (s, 1H)

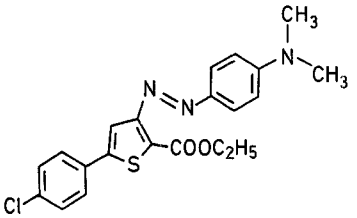
[a] Recrystallized from ethanol.

[b] All products gave satisfactory microanalyses: C, ±0.27; H, ±0.22; N, ±0.29; S, ±0.58; Hal, ±0.42; exception: **6i**, C, −0.51.

[c] Triethylamine-catalyzed condensation.

Hitherto known 3-aminothiophenes of a structure similar to the **6** have been synthesized by the reaction of α,β-dichloropropionitriles or α-chloroacrylonitriles with mercaptomethyl compounds[6,7,8]. These reactions, however, run presumably via intermediate cyanoacetylenes.

The 5-aryl-3-amino-2-alkoxycarbonylthiophenes **6** exhibit the typical properties of heteroaromatic amines: they can be diazotated to the appropriate diazonium salts which couple with aromatic amines or phenols to give azo compounds, such as the compound **7**.



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5-Aryl-3-amino-2-alkoxycarbonylthiophenes 6; General Procedure:
To a stirred solution of sodium (2.3 g, 0.1 mol) in methanol or ethanol (100 ml), the appropriate α-mercaptoacetic ester **4** (0.1 mol) is added at room temperature. After the addition is completed, the requisite β-chlorocinnamonitrile **3** (0.1 mol) is added. The mixture is heated under reflux for 10 min, cooled, diluted with water (300 ml), and filtered. The collected products are recrystalliced after drying (Table).

2-Ethoxycarbonyl-3-(4-dimethylaminophenylazo)-5-(4-chlorophenyl)-thiophene (7):
To a stirred solution of 2-ethoxycarbonyl-3-amino-5-(4-chlorophenyl)-thiophene (**6c**; 1.4 g, 5 mmol) in acetic acid (50 ml) containing hydrogen chloride (10%), a solution of sodium nitrite (0.35 g, 5 mol) in water (2 ml) is added at 0°C. After 10 min, *N,N*-dimethylaniline (1 g) is added at once. The mixture is stirred for 1 h, then diluted with water (100 ml), and filtered. The orange solid is dried and recrystallized from *n*-butanol containing a few drops of triethylamine; yield: 1.5 g (85%); m.p. 145–148°C.

$C_{21}H_{20}ClN_3O_2S$	calc.	C 60.9	H 4.9	Cl 8.6	N 10.1	S 7.8
(413.8)	found	60.0	4.6	9.1	10.2	8.2

U.V. (CH_3OH): λ_{max} = 284 (log ε = 4.40); 318 (4.27); 444 nm (4.50).

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