A Facile Synthesis of 2-Acyl-3-amino-5-phenacylthio-4-phenylthiophenes from Sodium Cyanophenyldithioacetate and α-Halo Ketones

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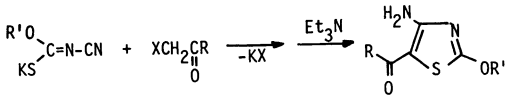
Synopsis. Various kinds of α-halo ketones readily reacted with sodium cyanophenyldithioacetate to provide 2-acyl-3-amino-5-phenacylthio-4-phenylthiophenes in good yields.

In the course of our intensive synthetic studies of heterocyclic compounds,[1,2] we found that 5-acyl-2-alkoxy-4-aminothiazoles were easily prepared by the reaction of potassium (alkoxythiocarbonyl)cyanamide with α-halo ketones (Scheme 1).[1] We have tried to



Scheme 1.

extend this process to a facile synthesis of 2-acyl-3-amino-5-mercapto-4-phenylthiophenes (**5**) using α-halo ketones (**2**) and sodium cyanophenyldithioaceate (**1**) instead of (alkoxythiocarbonyl)cyanamide salts as shown in Scheme 2. The starting material **1** was easily prepared from carbon disulfide and phenylacetonitrile in the presence of sodium hydride[3] and without purification the crude **1** was used for the synthesis of **5**.

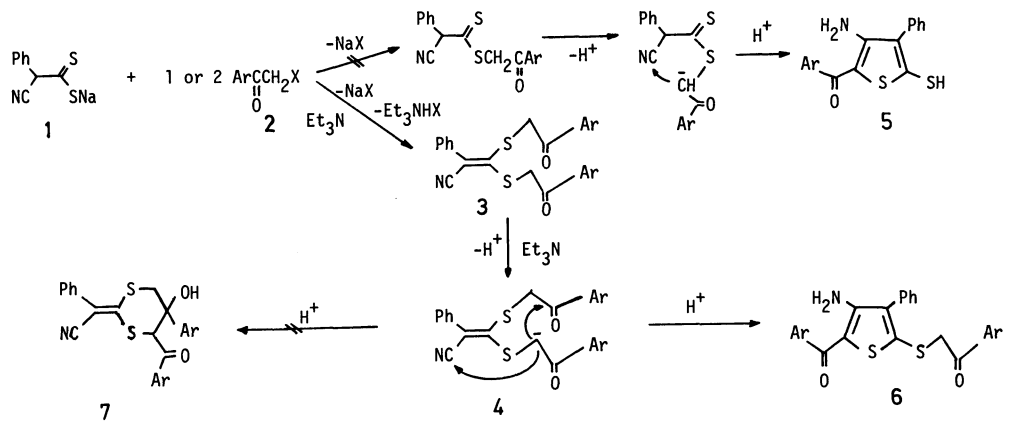
At first, in a procedure similar to the preparation of 2-acyl-3-aminothiazoles,[1] the reaction was carried out at room temperature using equimolar **1** and phenacyl bromide **2a** and subsequent cyclization was attempted by treatment with triethylamine under slightly warming. The product was not the desired compound **5a** but **6a**.

Since **6a** should be stoichiometrically formed from one mole of **1** and two moles of **2a**, the first condensation reaction was carried out using 2 equiv of **2a** in the presence of an equiv of triethylamine as a dehydrobrominating reagent,[4] and then base-catalyzed cyclization with additional triethylamine was performed. In this case, the thiophene **6a** could be obtained in an excellent yield. The structure of **6a** was confirmed by elemental analysis and spectral studies as follows: The parent peak (*m/z* 429) was observed in MS, and the IR absorption band of a cyano group in the starting **1** disappeared after the reaction, while that of an amino group newly appeared. In addition, the bands of two carbonyl groups (1700 and 1600 cm^{-1}) were also observed.

Thiophenes (**6b—g**) were prepared in good or excellent yields by the similar one-pot reaction from substituted phenacyl halides as shown in Table 1. In this reaction, any aldol condensation to form **7** did not occur and **6** was always a sole product.

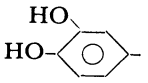
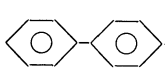
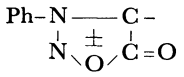
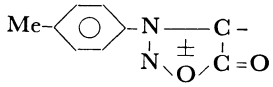
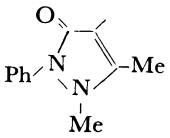
Since the reaction proceeds selectively under quite mild conditions, it seems to be useful for the preparation of aminothiophenes having unstable substituents. Although a number of sydnone compounds have been prepared because of their unique electronic structure and biological activities,[5] few works[1b,6] dealing with the successful synthesis of sydnones having heterocyclic substituents have been reported because of the instability of a sydnone ring. From this aspect, the reaction of **1** with 3-aryl-4-(bromoacetyl)sydnone was successfully tried under such mild conditions and pure aminothiophenes (**6h**, **6i**) having a sydnone ring were directly obtained in good yields without purification. In a similar manner, a thiophene derivative (**6j**) having an antipyrine ring was also prepared from the viewpoint of biological activity.

Although our attempts to prepare 3-amino-2-acetylthiophene derivative from α-chloroacetone (**2l**) and **1** failed, the reaction was successfully carried out using 3-chloro-2,4-pentanedione instead of **2l** to provide **6k** in a moderate yield. The product **6k** seemed to be formed by elimination of ketene from the cyclized



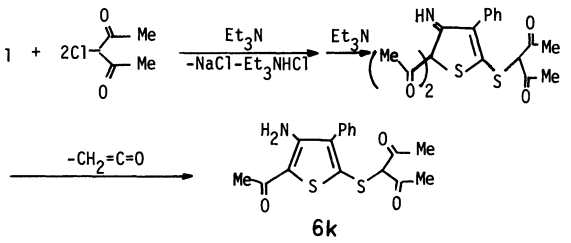
Scheme 2.

TABLE 1. SYNTHESIS OF 2-ACYL-3-AMINO-5-PHENACYLTHIO-4-PHENYLTHIOPHENES (**6**)[a)]

	6	Yield	Mp	MS	IR (KBr)	
	Ar	%	θ_m/°C	*m/z*	ν_{NH}/cm^{-1}	$\nu_{C=O}$/cm^{-1}
6a	Ph	Quant	164—165	429(M^+)	3500, 3400	1700, 1600
6b	*p*-ClC_6H_4	Quant	182—183	499(M^++2), 497(M^+)	3520, 3330	1600, 1590
6c	*p*-BrC_6H_4	Quant	179—180	588(M^+), 586(M^+)	3500, 3340	1700, 1600, 1585
6d	*p*-MeC_6H_4	82	133—134	457(M^+)	3520, 3320	1690, 1680, 1610
6e	*p*-$MeOC_6H_4$	97	174—175	489(M^+)	3520, 3340	1675, 1600
6f		78	247—248(dec)	—[b)]	3640, 3480, 3300	1650, 1600
6g		79	182(dec)	581(M^+)	3500, 3350	1680, 1600
6h		Quant	115(dec)	—[b)]	3460, 3400, 3300	1780, 1660, 1580
6i		74	143—144(dec)	—[b)]	3750, 3660, 3470, 3330	1780, 1670, 1590
6j		Quant	118—119	—[b)]	3500, 3400, 3300	1660, 1640

a) Satisfactory analyses (±0.3% for C,H, and N) were obtained. b) No molecular ion peak was observed.

intermediate as shown in Scheme 3.



Scheme 3.

Experimental

*Typical Procedure for the Preparation of Thiophenes. Preparation of 3-Amino-2-benzoyl-5-phenacylthio-4-phenylthiophene (**6a**)*: To a stirred suspension of 2.15 g (10 mmol) of sodium cyanophenyldithioacetate (**1**)[3)] and 1.4 ml (10 mmol) of triethylamine in 30 ml of ethanol was gradually added a solution of 4.00 g (20 mmol) of phenacyl bromide in 20 ml of ethanol at room temperature. After about 2 h of stirring, additional triethylamine (1.4 ml) was added and the reaction mixture was refluxed for 1 h or stirred for 10 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. The residue was mixed with water, and insoluble solid was collected by filtration. 4.29 g (quant). Recrystallization from DMF–ethanol provided pure **6a** as light yellow needles. Mp 164—165 °C. IR (KBr) 3500, 3400 (ν_{NH}), 1700, and 1600 cm^{-1} ($\nu_{C=O}$). ^{1}H NMR (DMSO-d_6) δ= 3.27 (s, 2H, SCH_2), 4.70 (s, 2H, NH_2), and 7.10—8.07 (m, 15H, C_6H_5). MS: *m/z* 429 (M^+). Found: C, 69.79; H, 4.28; N, 3.27%. Calcd for $C_{25}H_{19}NO_2S_2$: C, 69.90; H, 4.46; N, 3.26%.

*Preparation of 2-Acetyl-3-amino-4-phenyl-5-(diacetylmethylthio)thiophene (**6k**)*: In a similar manner, **6k** was obtained from 3-chloro-2,4-pentanedione and **1** in 57% yield. Recrystallization from aq ethanol provided pure **6k** as yellow needles. Mp 125 °C. IR (KBr) 3390, 3280, 3200 (ν_{NH}), 1605, 1590 cm^{-1} ($\nu_{C=O}$). ^{1}H NMR (DMSO-d_6) δ=2.22 (s, 3H, CH_3), 2.40 (s, 6H, CH_3COCH), 3.44 (broad s, 1H, SCH), 6.90 (broad s, 2H, NH_2), and 7.38—7.80 (m, 5H, C_6H_5). MS: *m/z* 347 (M^+). Found: C, 58.60; H, 4.79; N, 4.14%. Calcd for $C_{17}H_{17}NO_3S_2$: C, 58.77; H, 4.93; N, 4.03%.

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4) The open-chain intermediate **3a** which showed IR absorpotion of a cyano group around 2200 cm^{-1} was isolated and it underwent cyclization quantitatively by treatment with triethylamine.

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