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Synthesis of 2,5-diaroyl-3-arylthiophenes: novel tandem reactions mediated [3+2]-self annulation of bis(aroylmethyl) sulfides

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A series of 2,5-diaroyl-3-arylthiophenes were obtained from the [3+2]-self annulation of bis(aroylmethyl) sulfides in the presence of sodium hydroxide. This transformation occurs presumably via a tandem intermolecular condensation - ring closing intramolecular displacement-aromatization via air oxidation and elimination sequence.

Keywords: bis(aroylmethyl) sulfide; sulfur heterocycles; 2,3,5-trisubstituted thiophenes; tandem reaction; [3+2]-self condensation

1. Introduction

Bis(aroylmethyl) sulfides endowed with two activated methylenes, one sulfur and two carbonyls, are versatile synthons used for the construction of novel organic molecules (*1–6*). However, studies on the self-condensation of these compounds are lacking in the literature and the present work explores them in the presence of base. This study is attractive from mechanistic and synthetic viewpoints, as the bis(aroylmethyl) sulfides can undergo diverse novel tandem transformations starting from base-catalyzed intermolecular condensation and subsequent inter- or intramolecular condensation, aldol reaction, Michael addition or displacement, etc., which could furnish oligomers and/or sulfur heterocycles of varying ring sizes (*vide infra*). Interestingly, the reaction of bis(aroylmethyl) sulfides catalyzed by alcoholic sodium hydroxide displayed a product selectivity affording exclusively novel 2,5-diaroyl-3-arylthiophenes via tandem reactions.

Tandem reactions (*7–14*) being one pot multistep process, fall under the fold of green chemistry (*15*), as they result in a rapid building-up of complex, interesting, and/or unexpected structures in a convergent, efficient, and elegant manner without isolating and characterizing the intermediates. Incidentally, the thiophene ring system is an important pharmacophore, some of which are used as surgical anaesthetics in both humans and veterinary practices (*16*). Compounds bearing thiophene substructures possess many important biological activities such as antitumor (*17*), antioxidant

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(*18*), antifungal (*19*), anti-inflammatory (*20*), and antibacterial (*21*). This paper describes the synthesis of a series of new 2,5-diaroyl-3-arylthiophenes.

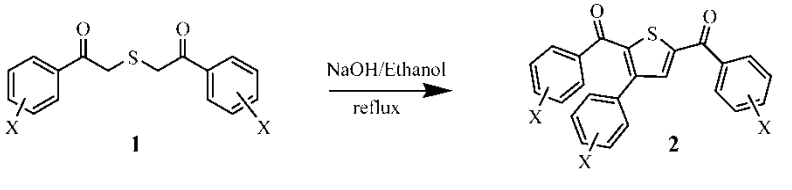
2. Results and discussion

In the present investigation, the reaction of bis(aroylmethyl) sulfides **1** with sodium hydroxide in a 1:4 molar ratio with ethanol at reflux for about 3 h afforded the corresponding unreported 2,5-diaroyl-3-arylthiophenes **2** in good yields (62–75%) considering the number of steps involved (Scheme 1, Table 1). Addition of **1** in two equal portions, one before and one after the addition of sodium hydroxide, led to an enhanced yield of the product, than adding **1** in a single lot. In the latter case, the yield is less than 50%.

Structure of 2,5-diaroyl-3-arylthiophenes **2** is in accord with the ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data as illustrated for **2b**. The ^{1}H NMR spectrum of **2b** has a singlet for the thiophene ring proton at 7.69 ppm, two pairs of doublets, each arising from a AX spin system of the 4-chlorobenzoyl rings, one at 7.89 and 7.52 ppm and another at 7.68 and 7.27 ppm, and a 4H singlet for the 4-chlorophenyl at 3-position of the thiophene ring appearing at 7.20 ppm. Aromatic carbons of **2b** produce 16 ^{13}C signals in the range of 128.7–144.8 ppm, while the carbonyl carbons appear at 186.4 and 188.4 ppm. The singlet at 7.69 ppm of the thiophene ring proton has a heteronuclear multiple bond correlation contour with the carbonyl at 186.4 ppm assigning the latter to the carbonyl linked to C-5 of the thiophene ring. Using similar straightforward considerations, all the hydrogens of **2b** could be unambiguously assigned.

The carbonyl carbon of aroyl group at C-5 appears upfield relative to the other carbonyl suggesting more effective conjugation of the former with the thienyl ring than the latter. This is understandable as the aroyl at C-5 could be coplanar with the thienyl ring, while the aroyl at C-2 is likely to be non coplanar due to its steric interaction with the C-3 aryl. However, the solid state structure determined from a single crystal X-ray crystallographic study of **2b** (Figure 1) (*22*) discloses that both the aroyl groups are equally inclined to the thienyl ring (dihedral angles 28.4° and 24.7° for the aroyls at C5 and C2, respectively).

The mechanism (Scheme 2) for the formation of **2** from **1** occurs initially by an intermolecular condensation affording the triketone **3**, which upon reaction with base can generate carbanions,



Scheme 1.

Table 1. Yields and melting points of **2**.

Product	X	Mp (°C)	Yield (%)
2a	H	156	68
2b	*p*-Cl	174	75
2c	*p*-Br	154	69
2d	*p*-Me	122–124	64
2e	*p*-MeO	134	62
2f	*m*-Cl	158	62

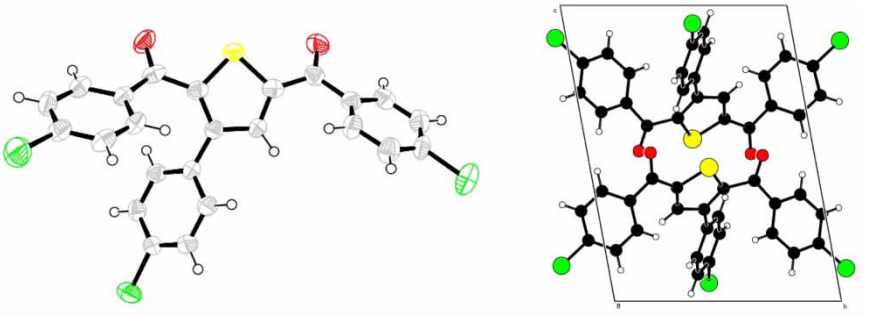


Figure 1. ORTEP and packing diagrams of **2b**.

6, **12** and **15** (Schemes 2 and 3). The formation of 2,5-diaroyl-3-arylthiophenes suggests that the carbanion **6** undergoes ring-closing intramolecular displacement leading to 2,5-diaroyl-3-aryl-4,5-dihydrothiophenes **7**. This ring closure requires (*Z*)-configuration for the carbanion **6**, although its precursor **5** could be in equilibrium with **3** having (*E*)-configuration. The intermediate **3** is expected to be more stable and hence predominate in the equilibrium than **5**, as the bulky aroyl and aryl groups are *trans* in the former.

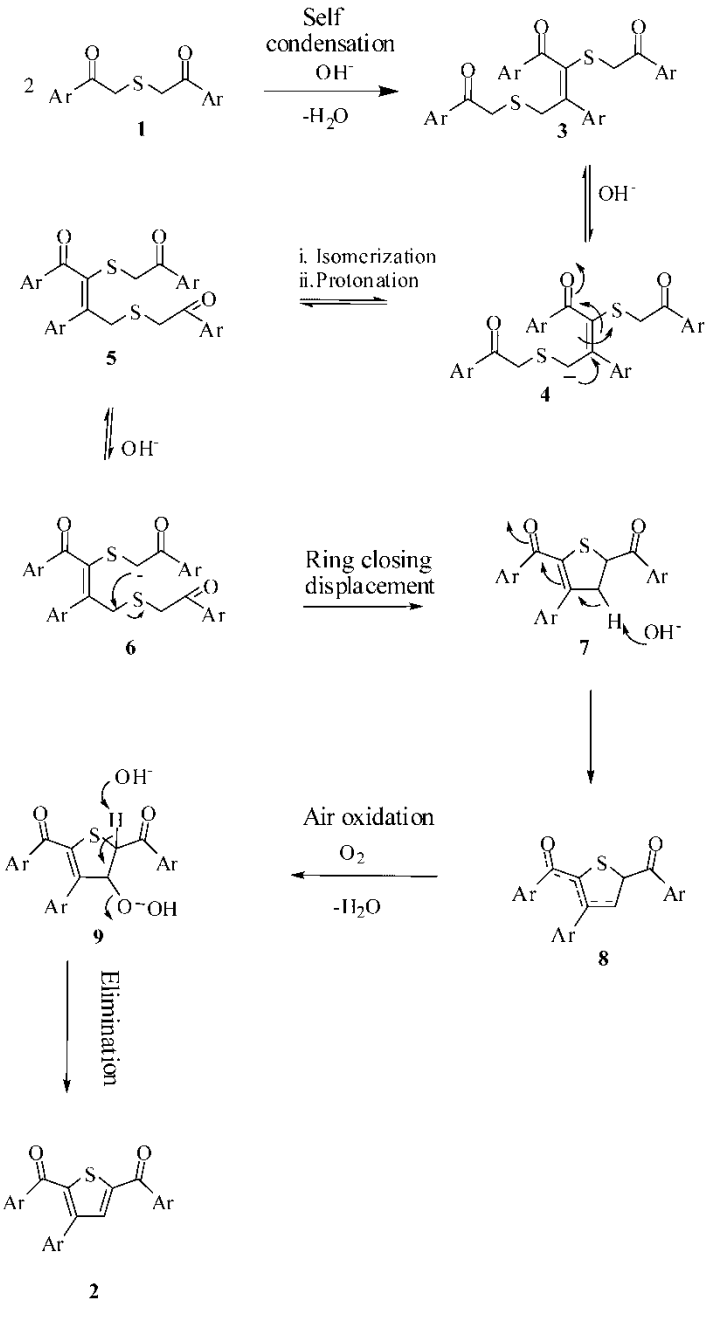
Good yields of **2** (62–75%) suggest that the equilibrium is shifted from **3** to **5** during the reaction via carbanion **4**, which can undergo (*E*)–(*Z*)-isomerization. Thus, the yield of **2** is likely to be unaffected by the position of equilibrium between **3** and **5**. Probably, **7** is transformed into the 2,5-diaroyl-3-arylthiophenes **2**, by air-oxidation via formation and elimination of hydroperoxide, the aromatic stability of the thiophene ring being the driving force. The ring-closure of the carbanion **6** to **7** is likely to be favored more by entropy than the other reactions of the carbanion **6** and those of carbanions **12** and **15** (Scheme 3). This accounts for the absence of formation of four-, six-, and eight-membered ring sulfur heterocycles and oligomers.

Only one previous study is available in the literature on the synthesis of only one 2,5-diaroyl-3-arylthiophene, *viz*, bis-2,5-(4-methylbenzoyl)-3-phenylthiophene in 68% yield from the reaction of bis((4-methylbenzoyl)methyl) sulfide with phenylglyoxal in the presence of a base. It is pertinent to note that the tandem reactions of the present study also afford comparable yields (62–75%), thus providing a complementary protocol for the synthesis of these thiophenes via [3+2]-annulation of two molecules of bis(aroylmethyl) sulfides, in contrast to the literature method requiring two reactants, bis(aroylmethyl) sulfide and benzil (*23*). The other previous related study involves the synthesis of 2,5-diaroylthiophene lacking 3-aryl by the reaction of bis(aroylmethyl) sulfides with glyoxal (*24*).

In conclusion, this study describes a tandem protocol for the [3+2]-self annulation of bis(aroylmethyl) sulfides affording new 2,5-diaroyl-3-arylthiophenes for the first time.

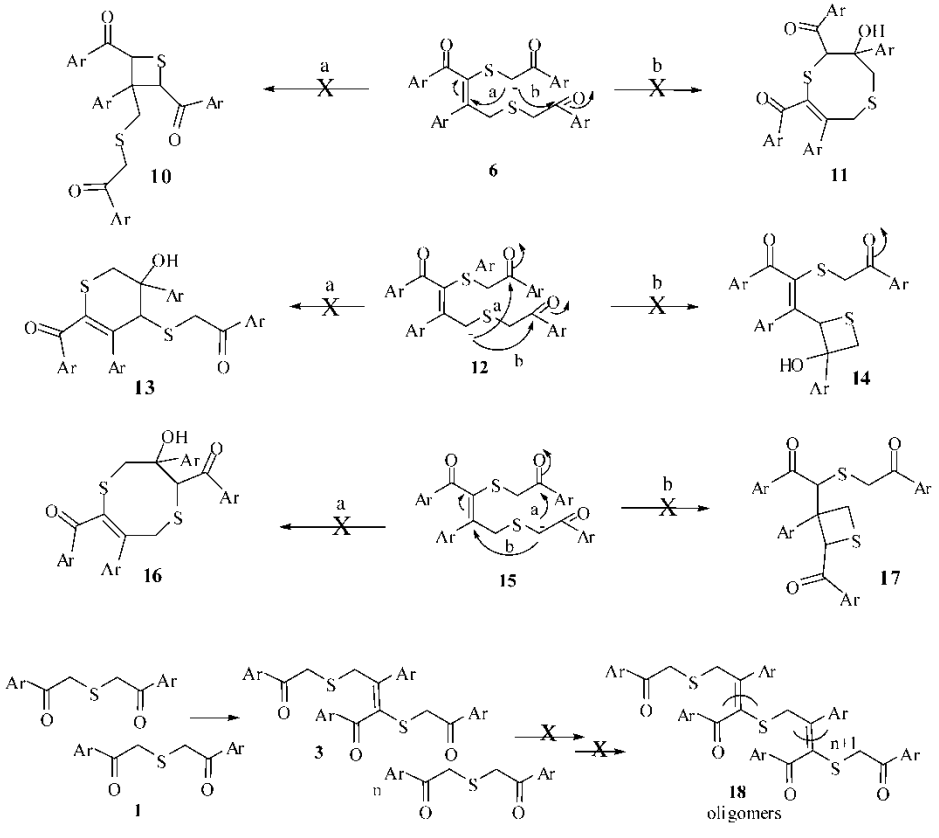
3. Experimental

All the chemicals were of reagent grade quality and used without further purification. All the melting points were recorded in open capillaries and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$ using TMS as internal standard at 25 °C. The related 2D NMR spectra were also recorded on the same instrument. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in Hertz. Microanalysis was carried out on a Perkin-Elmer instrument. Infrared (IR) spectra were recorded on a JASCO FT-IR instrument using KBr pellets. The single



Scheme 2.

crystal X-ray data were collected on a Nonius MACH3 kappa diffractometer with MoK_{α} radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods from SHELXS-86 and refined by full matrix least squares on F^2 by SHELXL-93. The crystal data for **2b** have been deposited with the Cambridge Crystallographic Centre as supplementary publication (CCDC number 646678). All the chromatographic separations were performed on 60–120-mesh silica gel using petroleum



Scheme 3.

ether–ethyl acetate as eluant. Bis(aroylmethyl) sulfides **1** were prepared in high yields by the reaction of α-haloketones with sodium sulfide (*3*).

3.1. *General procedure for the preparation of 2,5-diaroyl-3-arylthiophenes (2)*

Bis(aroylmethyl) sulfide **1** (3 mmol) was dissolved in ethanol (20 ml) to which freshly powdered sodium hydroxide (12 mmol) was added and the solution heated until it turned red (approximately 10 min). Then another equivalent of **1** (3 mmol) was added and the reaction mixture was refluxed for 3 h. The progress of the reaction was monitored using thin-layer chromatography. After completion of the reaction, the reaction mixture was poured into crushed ice and the solid separated was washed with petroleum ether and recrystallized from petroleum ether–ethyl acetate mixture to give thiophene **2**.

3.1.1. *(5-Benzoyl-3-phenyl-2-thienyl)(phenyl)methanone (**2a**)*

Mp. 156 °C; IR (KBr): 1625, 1654 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.07–7.27 (3H, m), 7.39–7.44 (4H, m), 7.51–7.56 (2H, m), 7.61–7.74 (2H, m), 7.66–7.75 (3H, m), 7.93–7.96 (2H, m); δ_C (75 MHz; $CDCl_3$) 128.1, 128.3, 128.6, 129.0, 129.3, 129.8, 131.4 132.8, 133.1, 134.5, 135.8, 136.5, 137.3, 142.7, 144.8, 145.8, 187.9, 190.0; (found: C, 78.22; H, 4.40. $C_{24}H_{16}O_2S$ requires C, 78.24; H, 4.38).

3.1.2. *[5-(4-Chlorobenzoyl)-3-(4-chlorophenyl)-2-thienyl](4-chlorophenyl)methanone (**2b**)*

Mp. 174 °C; IR (KBr) 1633, 1648 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.20 (4H, s), 7.27 (2H, d, J = 8.4 Hz), 7.52 (2H, d, J = 8.7 Hz), 7.61 (1H, s), 7.68 (2H, d, J = 8.7 Hz), 7.89 (2H, d, J = 8.4 Hz); δ_C (75 MHz; $CDCl_3$) 129.1, 129.2, 129.5, 130.5, 131.1, 131.6, 132.6, 133.2, 135.1, 135.2, 135.7, 135.8, 140.0, 140.5, 144.9, 145.2, 186.9, 188.8; (found: C, 61.13; H, 2.75. $C_{24}H_{13}Cl_3O_2S$ requires C, 61.10; H, 2.78).

3.1.3. *[5-(4-Bromobenzoyl)-3-(4-bromophenyl)-2-thienyl](4-bromophenyl)methanone (**2c**)*

Mp. 154 °C; IR (KBr) 1629, 1650 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.10 (2H, d, J 8.7), 7.36 (2H, d, J 8.4), 7.43 (2H, d, J 8.7), 7.56 (2H, d, J 8.4), 7.67 (3H, m), 7.80 (2H, d, J 8.7); δ_C (75 MHz; $CDCl_3$) 122.9, 128.3, 128.9, 130.4, 130.8, 131.2, 131.7, 132.1, 133.2, 135.2, 135.4, 135.8, 141.3, 142.3, 144.6, 144.8, 186.6, 188.5; (found: C, 47.60; H, 2.14. $C_{24}H_{13}Br_3O_2S$ requires C, 47.63; H, 2.17).

3.1.4. *[5-(4-Methylbenzoyl)-3-(4-methylphenyl)-2thienyl](4-methylphenyl)methanone (**2d**)*

Mp. 122–124 °C; IR (KBr) 1630, 1655 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 2.27 (3H, s), 2.33 (3H, s), 2.45 (3H, s), 7.02 (2H, d, J 7.8), 7.08 (2H, d, J 7.8), 7.17 (2H, d, J 8.1), 7.32 (2H, d, J 7.8), 7.66 (2H, d, J 8.1), 7.73 (1H, s), 7.85 (2H, d, J 8.1); δ_C (75 MHz; $CDCl_3$) 21.2, 21.7, 128.7, 128.9, 129.1, 129.3, 129.6, 130.2, 131.9, 134.3, 134.7, 135.6, 137.9, 142.1, 143.8, 144.3, 144.6, 145.4, 187.7, 189.8; (found: C, 78.99; H, 5.43. $C_{27}H_{22}O_2S$ requires C, 79.02; H, 5.40).

3.1.5. *[5-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-2-thienyl](4-methoxyphenyl) methanone (**2e**)*

Mp. 134 °C; IR (KBr) 1631, 1658 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 3.75 (3H, s), 3.81 (3H, s), 3.91 (3H, s), 6.74–6.78 (3H, m), 7.00 (2H, d, J 9.0), 7.21–7.25 (3H, m), 7.70–7.76 (3H, m), 7.98 (2H, d, J 9.0); δ_C (75 MHz; $CDCl_3$) 55.1, 55.4, 55.5, 111.1, 113.4, 113.8, 127.3, 128.4, 128.7, 129.5, 130.0, 131.3, 131.7, 132.4, 135.0, 141.4, 144.4, 159.3, 163.6. 186.2, 188.4; (found: C, 70.75; H, 4.81. $C_{27}H_{22}O_5S$ requires C, 70.72; H, 4.84).

3.1.6. *[5-(3-Chlorobenzoyl)-3-(3-chlorophenyl)-2-thienyl](3-chlorophenyl)methanone (**2f**)*

Mp. 158 °C; IR (KBr) 1633, 1648 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.10–7.21 (4H, m), 7.33–7.41 (2H, m), 7.49–7.60 (2H, m), 7.70–7.73 (2H, m), 7.80–7.83 (2H, m), 7.91 (1H, s); δ_C (75 MHz; $CDCl_3$) 127.3, 127.6, 127.7, 128.4, 128.8, 129.1, 129.4, 129.5, 129.7, 129.9, 132.9. 134.2, 134.4, 135.0, 135.5, 136.0, 138.0, 138.5, 138.7, 142.6, 143.0, 144.8, 188.1, 188.5; (found: C, 61.06; H, 2.74. $C_{24}H_{13}Cl_3O_2S$ requires C, 61.10; H, 2.78).

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(22) *Crystal data for* **2b**. $C_{24}H_{13}Cl_3O_2S$, $M = 471.75$, triclinic, space group P–1, $a = 7.605(10)$ Å, $b = 10.382(9)$ Å, $c = 14.031(10)$ Å, $V = 1053.9(9)$ Å^3, $Z = 2$, $f(000) = 480$, $\mu = 0.553$ mm^{-1}, Dc $= 1.487$ mg/m^3. The reflections collected were 4603 of which 3682 unique [$R_{(\text{int})} = 0.0239$]; 1977 reflections $I > 2\sigma(I)$, $R_1 = 0.0444$ and $wR_2 = 0.1204$ for 1977[$I > 2\sigma(I)$], $R_1 = 0.1042$ and $wR_2 = 0.1823$ for all (3682) intensity data. Goodness-of-fit 1.008, residual electron density in the final Fourier map was 0.289 and -0.331 e Å^{-3}. Complete crystallographic data, as a CIF file, have been deposited with the Cambridge Crystallographic Data Centre (CCDC number is 646678).
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