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An Efficient Synthesis of Substituted 4-Aryl-3-Cyano-2-Amino Thiophenes by a Stepwise Gewald Reaction

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The title compounds were efficiently synthesised starting from aryl methyl ketones in 3 steps. Knoevenagel condensation of aryl methyl ketones with malononitrile gave the corresponding crotonitriles **(5a-f)**. Methyl groups of the crotonitriles **(5a-f)** were then efficiently brominated by refluxing and lightening the reaction media to give bromocrotonitriles **(6a-f)**. The bromocrotonitriles **(6a-f)** were finally cyclised by treatment with NaSH to give the title compounds.

Key Words: Aminothiophenes, bromocrotonitriles, substituted aminothiophenes.

Introduction

Highly substituted thiophenes (**1**) form an internal part of numerous natural products[1] and pharmaceuticals.[2] They are often used as novel conducting polymers[3] and as isosteric replacements for phenyl groups in medicinal chemistry.[4] The electronic and optical properties of polythiophene and its derivatives have been the subject of many papers.[5−11] Azo dyes with heterocyclic diazo components led to commercial products to replace the conventional azobenzene disperse dyes.[12−17] Some derivatives of **2** obtained from the coupling moieties of 2-aminothiophenes and 2-aminothiazoles were distinguished by their high colour strength and brilliant shades.[18,19]

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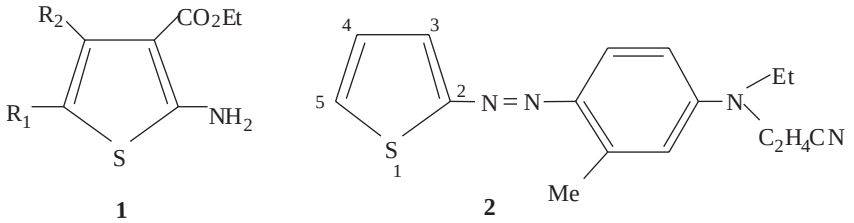


1 **2**

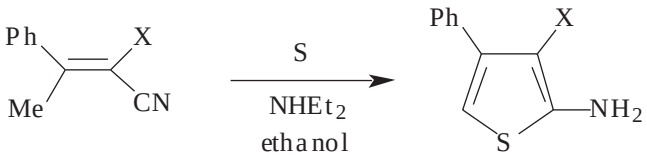
3 = CN, COOR, $CONH_2$

4 = H, Me

5 = R, Ph, Ac, CN

4,5 = (aryl)alkylene

Since the first reported preparation of 2-aminothiophene[20], the synthesis of highly functionalised aminothiophenes has been extensively studied.[21] There are 4 main synthetic approaches for 2-aminothiophenes, 3 of which utilise pre-existing thiophene rings, namely the reduction of nitro[22]/nitroso groups[23], rearrangements of carboxyclic acid derivatives[24,25], and nucleophilic displacements of mercapto[26]/iodo groups[27] with amines. The other method includes ring closure reactions from non-thiophene starting materials, and is less developed for the preparation of simple 2-aminothiophenes (Gewald reaction, Scheme 1).[28–31]



ylide-nitril aminothiophene

X= COOR; $C(O)NH_2$; CN

Scheme 1. Gewald reaction

In this study, we report an improved synthesis of the 3,4-disubstituted-2-aminothiophenes (**9a-f**) by a stepwise Gewald reaction.

Experimental Section

General. Melting points were determined on a Büchi model 530 apparatus and are uncorrected. Infrared spectra were recorded on a Mattson model 1000 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a 200 (50) MHz spectrometer. The mass spectra were recorded on Finnigan GC-MS instruments. Column chromatography was performed on silica gel (60-200 mesh) and activated alumina (70-230 mesh) from Merck Co. TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminium plates.

The preparation of crotonitriles 5a-f; typical procedure[32]

To a stirred solution of acetophenone (**3a**) (5.8 g, 0.048 mol) in 50 mL of dry and freshly distilled benzene were added ammonium acetate (6.96 g, 0.090 mol) and malononitrile **4** (3.2 g, 0.048 mol). The reaction mixture was refluxed for 6 h (**3b**, **3c, 3e** and **3f**: 12 h, **3d:** 8 h), and then cooled to room temperature. After the solvent was removed, the residue was diluted with water. The organic phase was extracted with ether (3

x 50 mL). The combined solutions were washed with water (2 x 10 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallised from $CHCl_3$ to give 2-(1-Phenyl-ethylidene)-malononitrile (**5a**) (6.4 g, 79%).

2-(1-Phenyl-ethylidene)-malononitrile (5a): (79%; from $CHCl_3$/Hexane, colourless crystals, mp 92 °C), (Lit[32]. 92 °C).^{13}C NMR: (50 MHz, $CDCl_3$)δ 177.39, 137.94, 134.25, 131.12, 129.34, 114.77, 114.71, 86.80, 26.27.

2-(1-Naphthalen-1-yl-ethylidene)-malononitrile (5b): (82%; from $CHCl_3$/Hexane, colourless crystals, mp 72-73 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.95 (m, 2H, ArH), 7.42-7.35 (m, 5H, ArH), 2.74 (s, 3H, CH_3) ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.97, 136.56, 135.74, 133.18, 131.11, 130.74, 129.69, 128.96, 127.13, 126.71, 125.79, 114.03, 113.71, 91.10, 27.87. IR (KBr film): 3062, 3021, 2235, 1588, 1513, 1429, 1371, 1260, 1177, 1025 cm^{-1}. EIMS m/z (%): 218 (M^+, 100), 203(64), 190(82), 176(21), 152(20), 128(19). Anal. calc. For $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84. Found C, 82.67; H, 4.65; N, 12.64.

2-(1-Naphthalen-2-yl-ethylidene)-malononitrile (5c): (85%; yellow crystals, mp 106-107 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.09 (bs, 1H, ArH), 7.98-7.55 (m, 6H, ArH), 2.74 (s, 3H, CH_3) ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.21, 136.74, 135.19, 134.50, 131.06, 130.66, 130.35, 129.86, 129.45, 129.25, 125.44, 115.01, 114.89, 86.68, 26.29. IR (KBr film): 3050, 2225, 1630, 1562, 1500, 1465, 1373, 1288, 1176, 1014 cm^{-1}. EIMS m/z (%):218 (M^+, 100), 203(10), 190(40), 153(12), 128(20). Anal. calc. For $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84. Found C, 82.43; H, 4.68; N, 13.03.

2-[1-(4-Methoxy-phenyl)-ethylidene]-malononitrile (5d): (82%; from $CHCl_3$/Hexane, colourless crystals mp 76-77 °C), (Lit[33]. 76 °C). ^{1}H NMR (200 MHz, $CDCl_3$):δ 7.62 (d, A part of AB system, J=9.0 Hz, 2H, ArH), 6.99 (d, B part of AB system, J=9.0 Hz, 2H, ArH), 3.87 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$):δ175.88, 165.12, 131.79, 129.92, 116.48, 115.62, 115.36, 84.03, 57.58, 25.78. IR (KBr film): 3025, 2844, 2221, 1601, 1547, 1431, 1266, 1189, 1023, 842 cm^{-1}. EIMS m/z (%): 197 (M^+, 100), 183(10), 155(18), 128(30).

2-(1-Biphenyl-4-yl-ethylidene)-malononitrile (5e): (70%; from $CHCl_3$/Hexane, light yellow crystals, mp 160-161 °C, Lit[34]. 164-165 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76−7.63 (m, 5H, ArH), 7.61-7.41 (m, 4H ArH), 2.68 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.62, 147.29, 141.31, 136.53, 131.08, 130.52, 130.10, 129.65, 129.19, 115.06, 114.92, 85.90, 26.10. IR (KBr film): 3068, 2970, 2220, 1574, 1485, 1412, 1374, 1312, 1197, 1131, 1081, 1004, 965 cm^{-1}. EIMS m/z (%): 244 (M^+, 100), 229(32), 189(10), 179(12), 152(20).

2-(1-Phenanthren-3-yl-ethylidene)-malononitrile (5f): (78%; from $CHCl_3$/Hexane, yellow crystals mp 164-165 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.97 (s, 1H, ArH), 8.69 (d, J=7.9 Hz, 1H, ArH), 7.97-7.67 (m, 7H, ArH), 2.79 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.19, 136.29, 135.47, 134.33, 132.10,132.04, 131.96, 131.47, 130.97, 129.60,129.62, 128.03, 126.58, 124.89, 124.57, 115.29, 115.01, 86.54, 26.37. IR (KBr film): 3056, 2952, 2228, 1566, 1428, 1285, 1239, 1181, 1150, 1035, 965 cm^{-1}. EIMS m/z (%): 268 (M^+, 100), 253(54), 240(40), 202(20), 178(18), 120(14), 106(30). Anal. calc. For $C_{19}H_{12}N_2$: C, 85.05; H, 4.51; N, 10.44. Found C, 84.97; H, 4.63; N, 10.58

The preparation of bromocrotonitriles 6a-f; typical procedure

To a stirred solution of crotonitriles **5a** (1.1 g, 6.55 mmol) in 25 mL of CCl_4 was added dropwise a solution of bromine (0.53 g, 3.313 mmol) in 5 mL of CCl_4 at room temperature over 20 min. The reaction flask was irradiated with a 500-W sunlamp for 2 h (**5e** and **5f**: 2 h; **5b**: 6 h; **5c** and **5d**: 4 h). After evaporation of the solvent, the residue was filtered over silica gel (10 g) after eluting with hexane/chloroform (9:1). Removal of the solvent and recrystallisation from hexane/chloroform (4:1) gave **6a** (1.41 g, 88%).

2-(2-Bromo-1-phenyl-ethylidene)-malononitrile (6a): (88%; colourless crystals, mp 111-112 °C, Lit[35]. 113-116 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.65-7.50 (m, 5H, ArH), 4.56 (s, 2H, CH_2Br). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.45, 134.90, 131.39, 130.95, 129.86, 113.56, 112.79, 88.65, 30.73. IR (KBr film): 3039, 2981, 2233, 1585, 1573, 1488, 1438, 1315, 1284, 1207, 1195, 1083, 998 cm^{-1}. EIMS m/z (%): 246/248 (M^+, 14), 166/168(42), 140/142(100).

2-(2-Bromo-1-napthalen-1-yl-ethylidene)-malononitrile (6b): (85%; from $CHCl_3$/Hexane, yellow crystals, mp 103-104 ^{o}C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05-8.02 (m, 2H, ArH), 7.99-7.48 (m, 5H, ArH), 4.86 (s, 2H, CH_2Br). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.73, 135.69, 134.02, 132.68, 131.26, 129.99, 129.09, 128.98, 128.88, 125.55, 113.18, 112.89, 93.25, 31.87. IR (KBr film): 3056, 2968, 2236, 1582, 1516, 1447, 1335, 1258, 1220, 1170, 1023, 912 cm^{-1}. EIMS m/z (%): 296/298 (M^+, 24), 216/218(66), 188/190(100). Anal. calc. For $C_{15}H_9BrN_2$: C, 60.63; H, 3.05; N, 9.43. Found C, 60.54; H, 3.12; N, 9.37

2-(2-Bromo-1-napthalen-2-yl-ethylidene)-malononitrile (6c): (82%; from $CHCl_3$, light yellow crystals, mp 152-153 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18 (m, 1H, ArH), 8.01-7.90 (m, 3H, ArH), 7.69-7.61 (m, 3H, ArH), 4.62 (s, 2H, CH_2Br). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.61, 136.99, 134.52, 132.19, 131.48, 131.32, 131.23, 131.02, 129.96, 129.83, 125.39, 114.23, 113.54, 88.77, 30.57. IR (KBr film): 3031, 2981, 2233, 1627, 1585, 1500, 1438, 1365, 1211, 1168, 1126 cm^{-1}. EIMS m/z (%): 296/298 (M^+, 60), 216/218(64), 188/190(100). Anal. calc. For $C_{15}H_9BrN_2$: C, 60.63; H, 3.05; N, 9.43. Found C, 60.81; H, 3.02; N, 9.30

2-[2-Bromo-1-(4-methoxy-phenyl)-ethylidene]-malononitrile (6d): (87%; from $CHCl_3$/Hexane, colourless crystals, mp 104-105 °C, Lit[36]. 106-108 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39 (d, A part of AB system J=9.0 Hz, 2H, ArH), 7.02 (d, B part of AB system J=9.0 Hz, 2H, ArH), 4.53 (s, 2H, CH_2Br), 3.88 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.16, 165.74, 132.41, 126.91, 116.90, 115.24, 114.35, 85.57, 57.45, 30.69. IR (KBr film): 3056, 2968, 2844, 2236, 1605, 1516, 1451, 1312, 1266, 1181, 1023, 958 cm^{-1}. EIMS m/z (%): 276/278 (M^+, 64), 196/198(58), 180/182(100).

2-(1-Biphenyl-4-yl-2-bromo-ethylidene)-malononitrile (6e): (83%; from $CHCl_3$, light yellow crystals, mp 163-164 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75-7.62 (m, 5H, ArH), 7.53-7.43 (m, 4H, ArH), 4.60 (s, 2H, CH_2Br). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.75, 147.98, 141.09, 133.56, 131.15, 130.73, 130.61, 129.93, 129.25, 114.75, 113.81, 88.05, 30.61. IR (KBr film): 3037, 2979, 2875, 2228, 1582s, 1485, 1447, 1324, 1216, 1189, 1079, 946 cm^{-1}. EIMS m/z(%): 322/324 (M^+, 32), 242/244(68), 214/216(100). Anal. calc. For $C_{17}H_{11}BrN_2$: C, 63.18; H, 3.43; N, 8.67. Found C, 63.21; H, 3.55; N, 8.80.

2-(2-Bromo-1-phenanthren-3-yl-ethylidene)-malononitrile (6f): (80% ; from $CHCl_3$/Hexane, light red crystals, mp 164-165 ^{o}C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.07 (d, J_4=1.8 Hz, 1H, ArH), 8.68 (d, J=7.8 Hz, 1H, ArH), 8.01 (d, J=8.4 Hz, 1H, ArH), 7.94 (d, J=7.4 Hz, 1H, ArH), 7.89 (d, J=8.9 Hz, 1H,

ArH), 7.79-7.64 (m, 4H, ArH), 4.71 (s, 2H, CH_2Br). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.23, 136.74, 134.38, 132.59, 132.52, 132.03, 131.79, 131.02, 131.00, 129.82, 129.79, 128.01, 129.59, 125.76, 124.62, 113.86, 104.05, 88.32, 30.76. IR (KBr film): 3048, 2991, 2883, 2221, 1612, 1547, 1408, 1354, 1293, 1247, 1200, 1123, 1035, 969 cm^{-1}. EIMS m/z (%): 346/348 (M^+, 38), 266/268(100), 252/254(68), 240/242(98). Anal. calc. For $C_{19}H_{11}BrN_2$: C, 65.73; H, 3.19; N, 8.07. Found C, 65.79; H, 3.35; N, 8.18.

The preparation of aminothiophenes 9a-f; typical procedure[35]

Bromocrotonitrile **6a** (0.94 g, 3.84 mmol) was dissolved in a solution of dioxane (5 mL) and absolute ethanol (20 mL). The stirred solution was cooled to 0 °C, and then a suspension of NaSH (0.24 g, 4.29 mmol) in absolute ethanol (10 mL) was added dropwise over 30 min. The resulting reaction mixture was stirred for an additional 1 h at room temperature. After removal of the solvent, the residue was dissolved in hexane/ethylacetate (7:3) and the solution filtered over of 20 g neutral Al_2O_3 (activity-IV). After removing the solvent, the residue was crystallised from chloroform to yield **9a** (655 mg, 85%).

2-Amino-4-phenyl-thiophene-3-carbonitrile (9a): (85%; colourless crystals, mp101-102 °C, Lit[35]. 100-102 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 7.61-7.31 (m, 5H, ArH), 6.35 (s, 1H, H_5), 5.24 (bs, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.65, 142.01, 136.23, 130.78, 130.22, 129.19, 117.83, 107.97, 90.63. IR (KBr film): 3421, 3309, 3101, 2210, 1631, 1504, 1442, 1396, 1195, 941 cm^{-1}. EIMS m/z (%): 200 (M^+, 100), 172(18), 155(36), 128(10). Anal. calc. For $C_{11}H_8N_2S$: C, 65.97; H, 4.03; N, 13.99. Found C, 66.10; H, 4.33; N, 13.79.

2-Amino-4-naphthalen-1-yl-thiophene-3-carbonitrile (9b): (76%; from $CHCl_3$, colourless crystals, mp 152-153 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 7.98-7.48 (m, 7H, ArH), 6.37 (s, 1H, H_5), 4.92 (bs, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.43, 140.72, 135.79, 134.09, 133.73, 130.86, 130.39, 129.30, 128.43, 128.06, 127.43, 127.20, 117.14, 110.49, 93.47. IR (KBr film): 3415, 3300, 3092, 2215, 1638, 1515, 1415, 1384, 1207, 784 cm^{-1}. EIMS m/z (%): 250 (M^+, 100), 233(10), 216(15), 207(24), 190(20), 163(14). Anal. calc. For $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found C, 72.01; H, 4.01; N, 11.32.

2-Amino-4-naphthalen-2-yl-thiophene-3-carbonitrile (9c)[37]: (74%; from $CHCl_3$/Hexane, colourless crystals, mp 129-130 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 8.09 (s, 1H, ArH), 7.92-7.48(m, 6H, ArH), 6.47 (s, 1H, H_5), 4.94 (bs, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.55, 141.98, 135.39, 134.99, 133.52, 130.52, 130.31, 129.67, 128.49, 128.38, 128.09, 127.15, 117.83, 108.38, 90.84. IR (KBr film): 3428, 3326, 3122, 3054, 2204, 1640, 1619, 1514, 1402, 1198 cm^{-1}. EIMS m/z (%): 250 (M^+, 100), 223(10), 216(10), 207(30), 190(12), 151(10), 125(10). Anal. calc. For $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found C, 71.79; H, 4.30; N, 11.48.

2-Amino-4-(4-methoxy-phenyl)-thiophene-3-carbonitrile (9d)[37]: (81%; from $CHCl_3$/Hexane, white crystals, mp 154-155 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 7.52 (d, A part of AB system, J=8.9 Hz, 2H, ArH), 6.94 (d, B part of AB system, J=8.9 Hz, 2H, ArH), 6.23 (s, 1H, H_5), 4.86 (bs, 2H, NH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.22, 121.68, 141.78, 130.31, 128.88, 117.83, 116.23, 106.82, 90.98, 57.33. IR (KBr film): 3449, 3326, 3210, 3114, 2201, 1624, 1508, 1393, 1254, 1157, 1023, 946 cm^{-1}. EIMS m/z (%): 230 (M^+, 100), 215(42), 187(26), 143(10), 115(12).

2-Amino-4-biphenyl-4-yl-thiophene-3-carbonitrile (9e): (82%; from $CHCl_3$, light yellow crys-

tals, mp 192-193 °C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.78-7.64 (m, 5H, ArH), 7.54-7.39 (m, 4H, ArH), 7.32 (bs, 2H, NH_2), 6.63 (s, 1H, H_5). ^{13}C NMR (50 MHz, DMSO-d_6): δ 168.29, 141.29, 139.69, 135.27, 130.76, 129.36, 129.15, 128.66, 128.34, 118.47, 106.93, 106.89, 84.89. IR (KBr film): 3372, 3314, 3210, 2209, 1651, 1509, 1408, 1293, 1200, 1123, 1081, 1004, 939 cm^{-1}. EIMS m/z (%): 276 (M^+, 100), 248(10), 231(22), 216(10), 189(8), 152(8), 138(12), 110(20). Anal. calc. For $C_{17}H_{12}N_2S$: C, 73.88; H, 4.38; N, 10.14. Found C, 73.62; H, 4.40; N, 9.86.

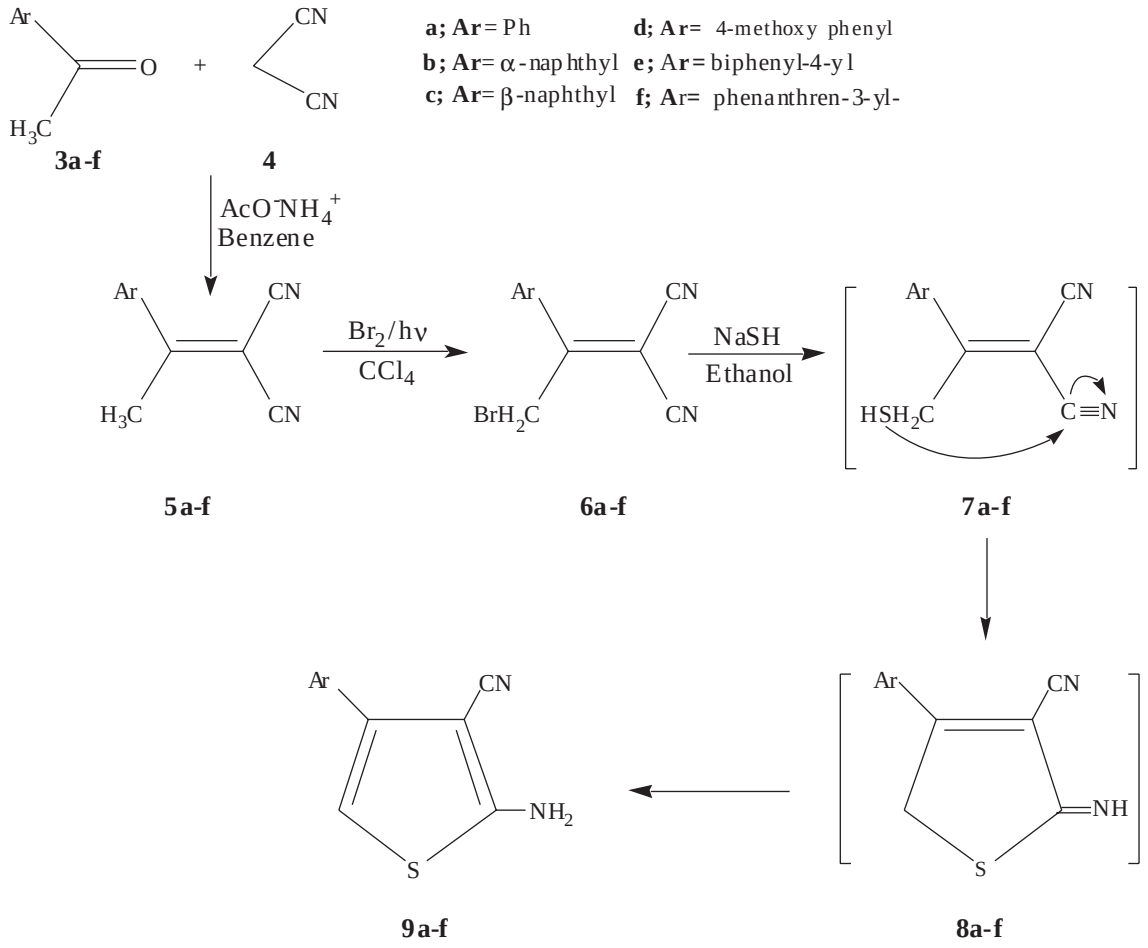
2-Amino-4-phenanthren-3-yl-thiophene-3-carbonitrile (9f): (76%; from $CHCl_3$, brown crystals, mp 155-156 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.97 (bs, 1H, ArH), 8.74 (d, J=7.5 Hz, 1H, ArH), 7.96-7.76 (m, 2H, ArH), 7.74-7.58 (m, 5H, ArH), 6.55 (s, 1H, H_5), 4.92 (bs, 2H, NH_2). ^{13}C NMR (50 MHz, CDCl3): δ 165.67, 142.21, 134.30, 134.12, 133.73, 132.44, 132.33, 131.05, 130.62, 129.49, 128.87, 128.41, 127.84, 127.52, 124.84, 123.26, 118.03, 108.37, 90.79. IR (KBr film): 3306, 3202, 3048, 2221, 1651, 1516, 1420, 1381, 1285, 1200, 1035, 958 cm^{-1}. EIMS m/z (%): 300 (M^+, 100), 275(10), 260(16), 178(12), 125(15). Anal. calc. For $C_{19}H_{12}N_2S$: C, 75.97; H, 4.03; N, 9.33. Found C, 76.15; H, 4.06; N, 9.50.

Results and Discussion

In our methodology, we focused on the reaction of bromocrotonitriles **6a-f** with NaSH for a facile synthesis of 2-aminothiophenes. For this purpose, we prepared crotonitriles **5a-f** by the condensation of malononitrile with acetophenone derivatives by employing a known literature procedure.[32] Allylic bromination of crotonitriles was reported to result in low yields.[35,36] Crotonitriles may be efficiently brominated in allylic position by treatment with potassium tert-butoxide and then molecular Br_2.[38] Another allylic bromination procedure for crotonitriles was reported by refluxing in CCl_4.[39] In the present work, the reaction of crotonitriles **5a** and **5d** with NBS/AIBN at reflux temperature gave bromocrotonitriles **6a** and **6d** in moderate yields (56%and 39%). However, when the crotonitriles **5a-f** were subjected to bromination under a project lamp (500 W mercury) at reflux temperature bromocrotonitriles **6a-f** were obtained in high yields (80-88%). Bromocrotonitriles **6a-f** were directly then converted into the desired 3,4-disubstituted-2-aminothiophenes **9a-f** by anhydrous NaHS-promoted cyclisation. It is noteworthy that all the bromocrotonitriles **6a-f** were completely cyclised to aminothiophene in high yields ranging from 74% to 85%.

Importantly, HS^- reacts with **6a-f** to afford unstable intermediates **7a-f,** and then **8a-f,** which are converted to **9a-f** under the experimental conditions (Scheme 2).

In conclusion, the present work provides a facile synthesis of substituted-2-aminothiophenes via a stepwise Gewald reaction. In particular, the allylic bromination of acrilonitriles was improved. Thus, the methodology represents an improvement over the other methods in terms of total reaction yields.



Scheme 2

Acknowledgements

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