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Gewald-type reaction of double activated 2,3-diarylcyclopropanes with elemental sulfur for synthesis of polysubstituted 2-aminothiophenes

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ABSTRACT

A new synthetic procedure for the polysubstituted 2-aminothiophenes was developed via Gewald type ring-opening reaction of 1,1-dicyano-2,3-diarylcyclopropanes with elemental sulfur in *N*,*N*-dimethylformamide in the presence of morpholine as base.

The donor–acceptor-substituted cyclopropanes are widely used as the versatile three carbon building blocks for the synthesis of versatile functionalized molecules.[1,2] Through the ring-opening reactions of the donor–acceptor cyclopropanes with various chemicals, for example electrophiles, nucleophiles, and radicals, such as aldehydes, imines, isocyanate, nitrones, acetylenes, and nitriles have been demonstrated to form valuable five-membered heterocycles, especially furan and pyrroles.[3–7] At present the direct transformation of the activated cyclopropanes to functionalized skeleton of thiophene with sulfur-containing reagents still remains a challenging subject mainly due to their low nucleophilicity. Reissig and co-workers[8] firstly reported the synthesis of 2-aminothiophene by reaction of cyanoacetates, elemental sulfur, and methyl 2-siloxycyclopropanecarboxylates, which were used as equivalents of carbonyl compounds. Chandrasekaran and co-worker[9] developed the regioselective ring-opening of cyclopropanes with tetrathiomolybdate as the sulfur transfer reagent to give dihydrothiophenes in excellent yield. Recently, Dong and co-workers[10] successfully developed a domino reaction of dimethylaminopropenoyl cyclopropanes initiated by Lawesson's reagent for convenient synthesis of 2,3-dihydrothieno[3,2-*c*]pyridines. On the other hand, 2-aminothiophene is arguably one of the most typical functionalized molecules in the present-day chemical and medical research of thiophene.[11] In 1965 Gewald et al. reported the synthesis of substituted 2-aminothiophenes via condensation of carbonyl compounds with methylene active nitriles and elemental sulfur in the presence of organic bases.[12] Since then this novel multicomponent reaction turned out to become a universal method for the synthesis of substituted 2-aminothiophenes and has gained prominence in recent years.[13,14] Under this background, and as also in the context of our investigations to develop more efficient ring-opening reactions for the sterically hindered polysubstituted cyclopropanes,[15] herein we wish to report the preliminary results on the Gewald-type reactions of 1,1-dicyano-2,3-diarylcyclopropanes with elemental sulfur for the synthesis of polysubstituted 2-aminothiophenes.

To optimize the reaction conditions, we examined the reaction of 1,1-dicyano-2-phenyl-3-*p*-nitrophenylcyclopropane[15a] **1a** with elemental sulfur in the presence of different bases and solvents. When pyridine, triethylamine, diethylamine, or piperidine were used as base, nearly no reaction was observed in refluxing methanol, but when morpholine was used, the product **1a** was obtained in about 20% yield. If the reaction was carried out in refluxing ethanol, triethylamine, diethylamine, and morpholine resulted in the products in 10%, 25%, and 20% yields, respectively. When DMF was used as solvent, triethylamine gave a complicate mixture of products, diethylamine and piperidine still gave low yields of product. The highest yield of product **1a** (73%) was obtained in the presence of morpholine as base. This result was concordance with the known facts that morpholine had been proved to be the most suitable base for the activation with sulfur and the subsequent sulfur

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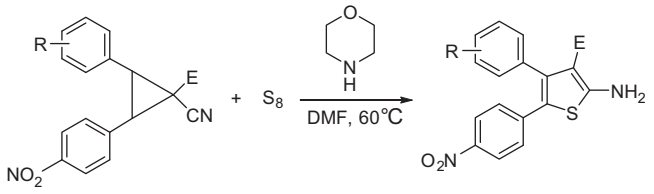
Table 1
Synthesis of polysubstituted 2-aminothiphenes **2a**–**2n**[a]



Entry	Compd	R	E	Yield[b] (%)
1	**2a**	H	CN	63
2	**2b**	*p*-CH_3	CN	63
3	**2c**	*p*-OCH_3	CN	56
4	**2d**	*o*-OCH_3	CN	53
5	**2e**	*p*-OPh	CN	48
6	**2f**	*p*-F	CN	81
7	**2g**	*p*-Cl	CN	68
8	**2h**	*m*-Cl	CN	70
9	**2i**	*p*-Br	CN	78
10	**2j**	H	CO_2Et	83
11	**2k**	*m*-CH_3	CO_2Et	79
12	**2l**	*p*-CH_3	CO_2Et	71
13	**2m**	*p*-Cl	CO_2Et	80
14	**2n**	*p*-Br	CO_2Et	78

[a] Reaction conditions: cyclopropane (1.0 mmol), sulfur (1.5 mmol), morpholine (1.0 mmol), DMF, 60 °C, 48 h.
[b] Isolated yields.

addition in Gewald reaction.[16] Thus, we established the optimal conditions for the reaction of polysubstituted cyclopropanes **1** with elemental sulfur in DMF with morpholine as the base for about 48 h.[17]

Under these optimized reaction conditions, a series of 1,1-dicyano-2-aryl-3-*p*-nitrophenylcyclopropanes were used in the reaction. The results are summarized in Table 1. It can be seen that 2-aryl substituents bearing with electron-withdrawing fluoro, chloro, bromo groups in cyclopropanes gave higher yields of products than that of 2-aryl substituents with electron-donating methyl, methoxy, and phenoxy groups (Table 1, entries 1–9). The reactions of ethyl 1-cyano-2-aryl-3-*p*-nitrophenyl-cyclopropyl-1-carboxylate also reacted efficiently to afford polysubstituted 2-aminothiophenes **2j**–**2n** in good yields (Table 1, entries 10–14). These results showed that this reaction was quite general and had a very broad scope of substrates. The structures of the prepared polysubstituted 2-aminothiophenes **2a**–**2n** were fully characterized by ^1H and ^{13}C NMR, MS, IR spectra. The single crystal structures of compound **2c** and **2l** were determined by single-crystal X-ray diffraction (Figs. 1 and 2).[18] It is clear to see that the most stronger electron-withdrawing *p*-nitrophenyl group exists on the *ortho*-position of the newly-formed thiophenyl ring, while the aryl groups orient on the 3-position. This result indicated that the cyclopropyl ring was opened between the carbon atom with the *p*-nitrophenyl group and the carbon atom with the cyano group, which also suggested that this reaction was a highly regioselective reaction.

Although no detailed mechanism and experimental investigation were carried out in this Letter, a plausible reaction course for the formation of 2-aminothiophene is proposed in Scheme 1 on the basis of the established ring-opening reaction of the donor–acceptor substituted cyclopropanes and Gewald reaction.[3,14] Firstly, the double activated cyclopropane (**1**) underwent ring-opening to give an ionic intermediate (**A**) on heating. Secondly, an allylic carbanion (**B**) was formed by elimination

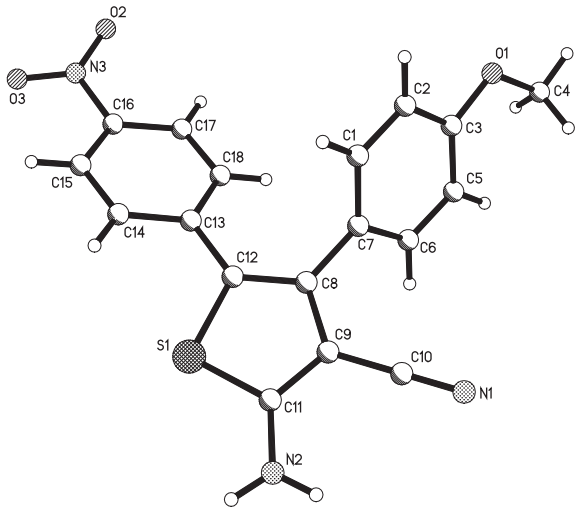


Figure 1. Molecular structure of compound **2c**.

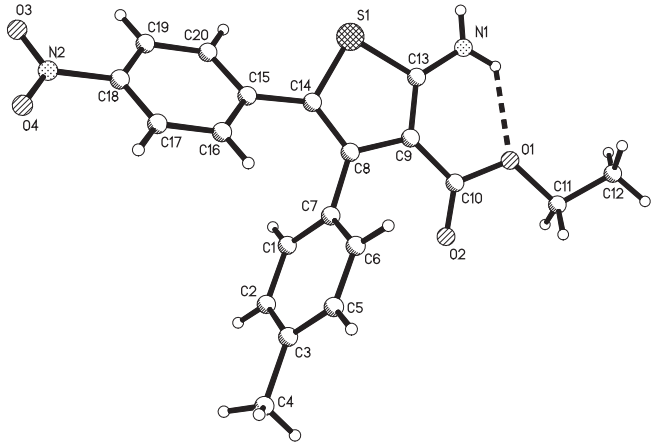
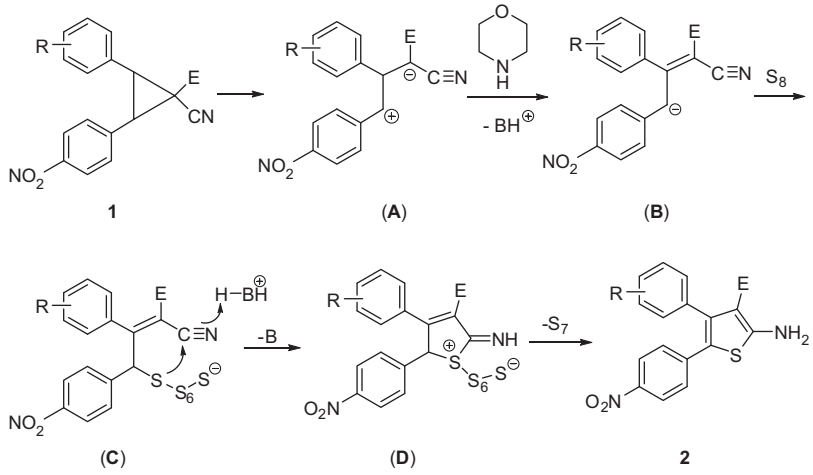


Figure 2. Molecular structure of compound **2l**.

reaction with morpholine and 1,3-H shift process. Then carbanium ion was preferably formed on the carbon atom bearing with the electron-withdrawing *p*-nitrophenyl group, which consequently also determined the regioselective ring-opening of the cyclopropyl ring. Thirdly, the reaction of carbanion with elemental sulfur gave intermediate (**C**). Then the intramolecular addition of the sulfur to the cyano group yielded the ring intermediate (**D**). Finally, through the imine-enamine tautomerization and elimination of excess sulfur atom, the intermediate (**D**) was transformed to 2-aminothiophene **2** as the final product.

In conclusion, an efficient synthetic procedure for the polysubstituted 2-aminothiophenes was developed by Gewald-type reaction of the donor–acceptor cyclopropanes with elemental sulfur. This protocol not only provides an effective methodology for the preparation of functionalized pyrroles, but also provides new examples of the Gewald reaction in organic synthetic chemistry. The potential uses of this reaction in synthetic and medicinal chemistry might be quite significant. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.



Scheme 1. The proposed formation mechanism of 2-aminothiophene.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.043.

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17. *Typical procedure:* A mixture of polysubstituted cyclopropane (1.0 mmol), elemental sulfur (1.5 mmol), and morpholine (1.0 mL) in 10 mL of *N,N*-dimethylformamide was stirred at 60 °C for 48 h. Then the reaction was quenched by adding water. The resulting precipitates were collected by filtration and subjected to preparative thin-layer chromatography with light petroleum and ethyl acetate (*V*/*V* = 3:1) as developing agent to give pure product for analysis. *2-Amino-5-(4-nitrophenyl)-4-phenylthiophene-3-carbonitrile* (**2a**)*:* Orange solid, 63%, mp 172–174 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 9.0 Hz, 2H, ArH), 7.39 (m, 3H, ArH), 7.29–7.28 (m, 2H, ArH), 7.21 (d, *J* = 9.0 Hz, 2H, ArH), 5.22 (s, 2H, NH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 165.2, 162.3, 145.1, 134.0, 138.5, 133.8, 129.1, 129.0, 128.6, 128.1, 123.8, 116.5, 115.6, 88.0; IR (KBr) *v*: 3723, 3314, 3217, 2211, 1627, 1589, 1511, 1339, 1234, 1107, 853, 743, 699; HRMS (ESI) Calcd for $C_{17}H_{11}N_3NaO_2S$ ([M+Na]$^+$): 344.0464, Found: 344.0466. *2-Amino-4-(2-methylphenyl)-5-(4-nitrophenyl)-thiophene-3-carbonitrile* (**2d**)*:* Orange Solid, 53%, mp 184–186 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.03 (d, *J* = 9.0 Hz, 2H, ArH), 7.70 (s, 2H, ArH), 7.44 (t, *J* = 7.8 Hz, 1H, ArH), 7.20 (d, *J* = 9.0 Hz, 2H, ArH), 7.16 (d, *J* = 8.4 Hz, 1H, ArH), 7.08 (d, *J* = 7.2 Hz, 1H, ArH), 6.98 (s, *J* = 7.8 Hz, 1H, NH_2), 3.69 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.4, 156.8, 144.9, 140.4, 135.8, 130.7, 130.5, 127.1, 123.9, 122.6, 120.9, 117.1, 115.5, 112.1, 89.0, 55.4; IR (KBr) *v*: 3399, 3318, 3218, 2209, 1641, 1590, 1513, 1341, 1234, 1187, 847, 754; HRMS (ESI) Calcd for $C_{18}H_{13}N_3NaO_3S$ ([M+Na]$^+$): 374.0570. Found: 374.0570. *2-Amino-4-(3-chlorophenyl)-5-(4-nitrophenyl)-thiophene-3-carbonitrile* (**2h**)*:* Orange solid, 70%, mp 242–244 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.08 (d, *J* = 7.8 Hz, 2H, ArH), 7.84 (s, 2H, NH_2), 7.72 (d, *J* = 7.2 Hz, 1H, ArH), 7.51 (d, *J* = 7.2 Hz, 1H, ArH), 7.47 (t, *J* = 7.2 Hz, 3H, ArH), 7.39 (s, 1H, ArH), 7.24 (d, *J* = 7.8 Hz, 2H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 165.3, 145.3, 139.6, 136.5, 135.8, 133.5, 131.7, 130.8, 128.8, 128.6, 128.3, 128.1, 124.0, 123.8, 117.2, 115.5, 87.7; IR (KBr) *v*:3721, 3416, 3317, 3217, 2209, 1644, 1591, 1513, 1324, 1109, 848, 779, 750; HRMS (ESI) Calcd for $C_{17}H_{10}ClN_3NaO_2S$ ([M+Na]$^+$): 378.0074, Found: 378.0075. *Ethyl 2-amino-4-(3-methylphenyl)-5-(4-nitrophenyl)-thiophene-3-carboxylate* (**2k**)*:* Red solid, 79%, mp 158–160 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.94 (d, *J* = 8.4 Hz, 2H, ArH), 7.19 (t, *J* = 7.2 Hz, 1H, ArH), 7.14 (d, *J* = 7.2 Hz, 1H, ArH), 7.10 (d, *J* = 8.4 Hz, 2H, ArH), 7.00 (s, 1H, ArH), 6.94 (d, *J* = 7.2 Hz, 1H, ArH), 6.40 (s, 2H, NH_2), 3.95 (s, 2H, CH_2), 2.32 (s, 3H, CH_3), 0.82 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 165.7, 163.4, 145.3, 141.1, 140.1, 137.5, 137.2, 130.3, 128.3, 128.1, 128.0, 126.7, 123.5, 118.0, 108.9, 59.6, 21.4, 13.5; IR (KBr) *v*: 3695, 3452, 3337, 2982, 1668, 1580, 1526, 1484, 1331, 1266, 1108, 850; HRMS (ESI) Calcd for $C_{20}H_{18}N_2NaO_4S$ ([M+Na]$^+$): 405.0879, Found: 405.0881. *Ethyl 2-amino-4-(4-bromophenyl)-5-(4-nitrophenyl)-thiophene-3-arboxylate* (**2n**)*:* Red solid, 78%, mp 144–146 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.02 (d, *J* = 8.4 Hz, 2H, ArH), 7.85 (s, 2H, NH_2), 7.53 (d, *J* = 8.4 Hz, 2H, ArH), 7.14 (d, *J* = 8.4 Hz, 4H, ArH), 3.88 (q, *J* = 7.2 Hz, 2H, CH_2), 0.81 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 164.7, 164.3, 144.9, 140.7, 138.0, 136.5, 131.8, 130.8, 128.3, 123.7, 120.5, 116.4, 106.0, 58.9, 13.4; IR (KBr) *v*: 3528, 3443, 3390, 3329, 1667, 1644, 1586, 1524, 1493, 1412, 1338, 1244, 1109, 1013, 849; MHRMS (ESI) Calcd for $C_{19}H_{15}BrN_2NaO_4S$ ([M+Na]$^+$): 468.9828, Found: 468.9834.
18. Single crystal data for compound **2c** (CCDC 965174), **2l** (CCDC 965174) have been deposited in the Cambridge Crystallographic Data Center. These data can be obtained free of charge via www.ccdc.ac.ck./data_request/cif.