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Influence of solvent and substituents on the reaction of *N*-alkylthioacetamides with dimethyl acetylenedicarboxylate: synthesis of functionalized thiophenes containing an exocyclic double bond

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ABSTRACT

The reaction of thioacetamides with dimethyl acetylenedicarboxylate affords 3-oxothien-2-ylidene or 4-oxothiazol-2,5-ylidene derivatives based on the structure of the thioacetamides and the solvent employed. The structural features of the 3-oxothien-2-ylidenes are discussed.

Thiophenes containing double bonds attract attention as photochromic molecular switches[1] and as models of D–π–A (donor–spacer–acceptor) systems.[2] There are a number of methods in the literature for the preparation of thiophenes containing exocyclic double bonds (Scheme 1). In general, these compounds are synthesized from isothiocyanates (pathway A)[3,4] or by the oxidation of thiophenes (pathway B).[5–7]

In this Letter, we report a method for the preparation of the thiophenes containing exocyclic double bonds by reaction of *N*-monosubstituted thioacetamides with dimethyl acetylenedicarboxylate (DMAD) (pathway C). In reactions of *N,N*-disubstituted thioacetoamides with DMAD the formation of thiazoles does not occur, as was reported previously by us.[8] Although there are a number of possible pathways for the reaction between acetylenedicarboxylates and *N*-substituted thioamides,[9–11] formation of thiophenes is now reported.

In the present work we report that reactions between cyanothioacetamides **1a–d** and DMAD **2** proceed via different pathways depending on the structure of **1** and the solvent. To establish the influence of the solvent, heterocyclization reactions were conducted in ethanol or acetic acid (Scheme 2).

Thiophenes **5c,d** were formed as the major products from cyanothioacetamides with bulky substituents on nitrogen **1c,d**.[12–14] However, in the case of the cyanothioacetamides **1c,d** it was shown that the main products were (2-cyanomethylen-4-oxothiazolidin-5-ylidene)acetic acid methyl esters **4c,d** when the reaction was conducted in ethanol (Table 1). The thiazoles **4** and thiophenes **5** were easily separated by recrystallization from acetic acid. With cyanothioacetamides **1a,b** the formation of thiophene derivatives was not observed.[15,16]

The percentage increase in the formation of the thiophenes can be due to the formation of iminium intermediate **3** when acetic was used as the solvent.

At the same time *N,N′*-dialkylmalonodithioamides **6a–d** react with DMAD to afford only 3-oxothien-2(3*H*)-ylidene derivatives **8a–d** (Scheme 3) in 40–65% yields.[17–19] This result is additional to earlier work when the reaction was carried out in acetone and only the formation of thiazoles was observed.[11] Malonothioacetamides **6a–d** are more reactive in comparison with cyanothioacetamides **1a–d**, therefore the reaction proceeds even at room temperature.

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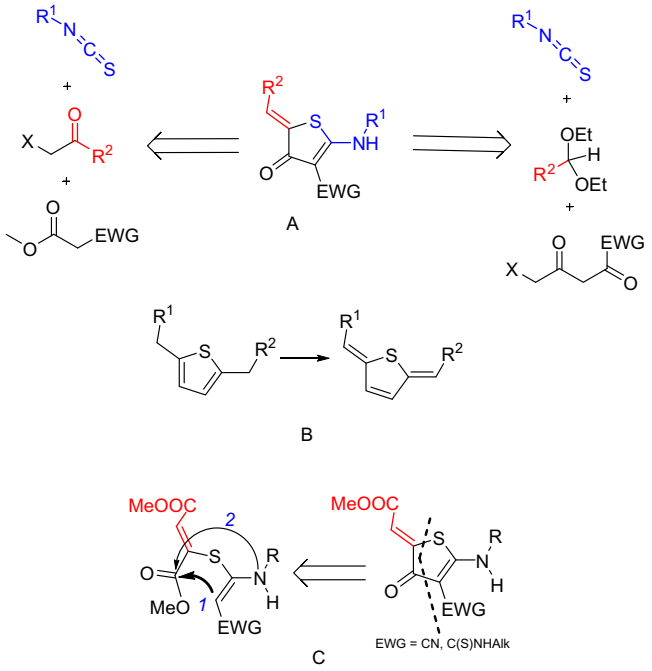


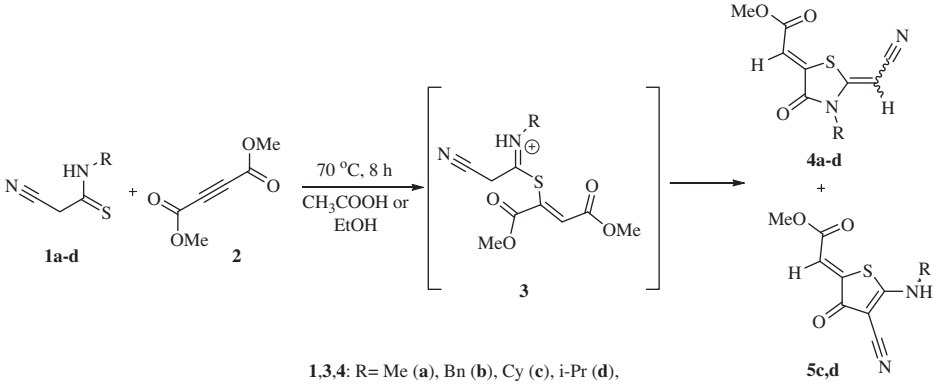
Scheme 1. General pathways toward thiophenes containing exocyclic double bonds.

Table 1
Synthesis of thiazoles **4** and thiophenes **5**

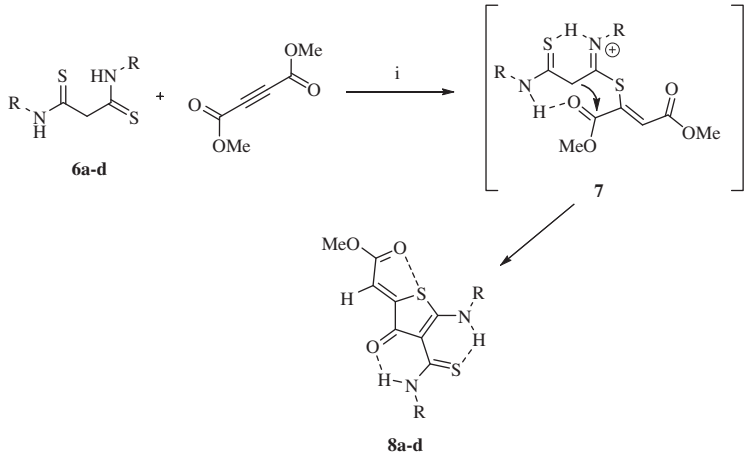
R	Solvent[a]	Product ratio **4**:**5**[b]	Yield[c] (%)
(a) Me	EtOH	1:0	50
	CH_3COOH	1:0	51
(b) Bn	EtOH	1:0	62
	CH_3COOH	1:0	56
(c) Cy	EtOH	4:1[d]	37
	CH_3COOH	2:3	75
(d) *i*-Pr	EtOH	2:1[d]	57
	CH_3COOH	1:3	53

[a] All reactions were carried out using equimolar amounts of each compound in 10 ml of solvent, 70 °C, 8 h.
[b] Ratio of the thiazole **4** and thiophene **5**.
[c] Isolated yield of the thiazoles **4** and thiophenes **5**.
[d] Ratio determined from the ^{1}H NMR spectrum of the crude product.

It is worth noting that the second thioamide group was unaffected even when 2 equiv of DMAD were used. Presumably the reaction route is governed by formation of iminium derivative 7 as a result of intermolecular hydrogen bond formation thanks to the presence of the second thioamide group (see Scheme 3). According to X-ray crystal data[20] the thiophene **8a** has a planar structure which is stabilized by two intramolecular hydrogen bonds (N_2–$H_2\cdots S_2$ and N_1–$H_1\cdots O_2$), and three weak interactions exist due to the presence of nearby located heteroatoms: O_3 and



Scheme 2. Synthesis of thiazoles **4** and thiophenes **5**.



Scheme 3. Reagents and conditions: (i) CH_3COOH or EtOH + 1 equiv CH_3COOH, rt, 40 °C, 4 h.

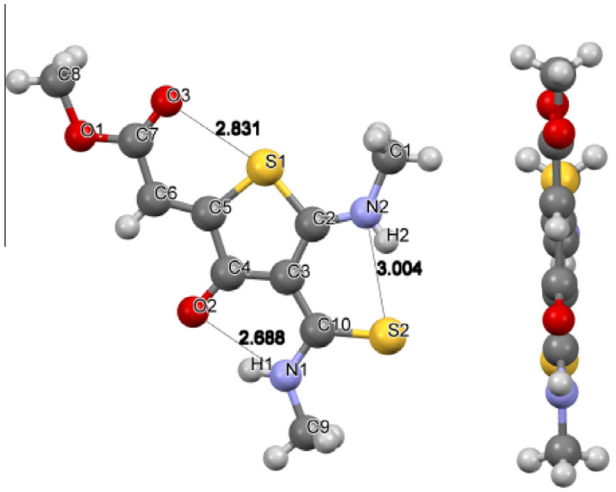
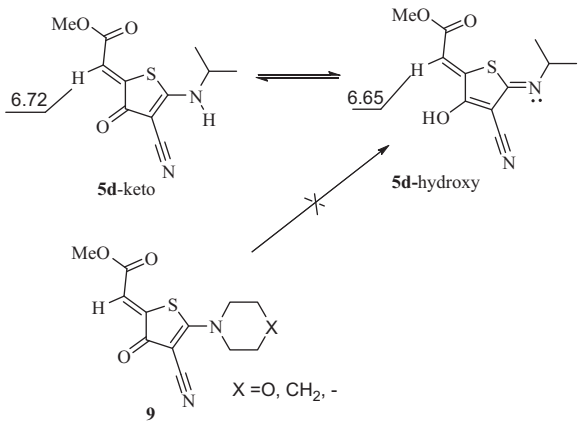


Figure 1. Molecular structure and selected geometric parameters (Å) of compound **8a**.



Scheme 4. The equilibrium of thiophene **5b** in solution.

S_1, N_2 and S_2, O_2 and N_1 (see Fig. 1). In all probability, intramolecular hydrogen bonds exist in intermediate **7** that similarly facilitate the direction of further condensation.

The thiophenes **8a–d** have groups which can undergo further heterocyclizations to form bicyclic heterocyclic system.[21–24]

In the ^{1}H NMR spectra of thiazoles **4a–d** and thiophenes **5c,d**, we observed doubling of the signals of all groups, including the signals assigned to the exocyclic double bond hydrogen atoms (5–7 ppm), which indicates that isomers were formed, unlike with thiophenes **8a–d**. The tautomeric equilibrium of (2-methylen-4-oxo-thiazolidin-5-ylidene)acetic acid ethers has been described previously.[25] In the earlier work, tautomerism of (*Z*)-methyl 2-[4-cyano-5-(dialkylamino)-3-oxothien-2(3*H*)-ylidene]acetic acids esters **9** was not observed.[8] We propose that isomerization of thiophenes **5c,d** could occur via tautomerism (Scheme 4).

An additional ^{1}H NMR experiment in which the spectra of thiophene **5d** were recorded over a temperature range from rt to 100 °C (Fig. 2) was done. In the ^{1}H NMR spectra of compound **5b** recorded in DMSO-d_6 at 80 °C and 100 °C the doubling of the signals disappeared, while in the spectra **8c** recorded in $CDCl_3$, doubling of the signals was not observed, even on cooling to −60 °C. Hence, isomerization is via tautomerism and not the formation of regioisomers during cyanothioacetamides heterocyclization with DMAD.

In summary, we have developed a novel pathway for *N*-substituted thioacetamide heterocyclization with DMAD. Several

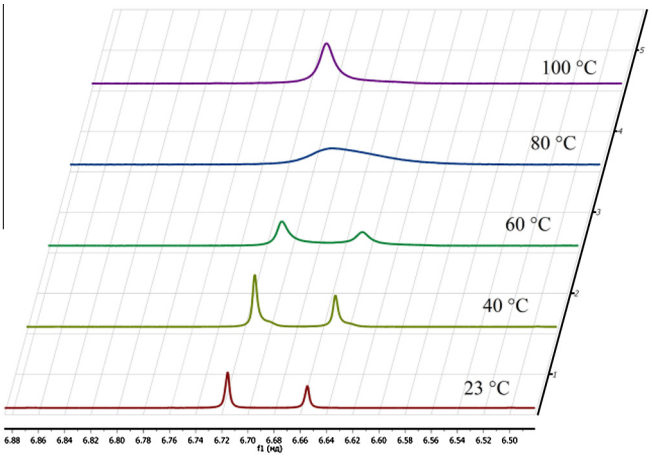


Figure 2. Spectra of the exocyclic double bond hydrogen atom in thiophene **5d** at different temperatures.

novel 3-oxo-3*H*-thien-2-ylidenes were prepared. It was shown that formation of 3-oxo-3*H*-thien-2-ylidenes in acetic acid was favored due to the hindered substituent at nitrogen and the presence of a second thioamide group. The thioamide group leads to a planar stable structure of 2-[4-(methylcarbamothioyl)-3-oxothien-2(3*H*)-ylidene]acetate. It was revealed that 2-[2-(cyanomethylene)-4-oxothiazolidin-5-ylidene]acetates exist in a solution together with the hydroxy forms as a result of tautomerism.

Acknowledgments

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12. *General procedure.* To a suspension of cyanthioacetomide (1.2 mmol) in 20 ml of glacial AcOH was added (0.095 ml, DMAD, 1.2 mmol) at 40 °C. The mixture was stirred at 70 °C for 8 h. The resulting precipitate was filtered to give the pure solid product. Thiazole derivatives were obtained by dilution of the filtrate with water, filtration, and recrystallization from ethanol if neccesary.
13. *(Z)-Methyl 2-[4-cyano-5-(isopropylamino)-3-oxothien-2(3H)-ylidene]acetate* (**5d**). Yield 34%, yellow crystals; mp 270–271 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): (the keto-form (61%)) 1.32 (s, 6H, CH_3), 3.79 (s, 3H, CH_3), 3.89–3.97 (m, 1H, CH), 6.72 (s, 1H, =CH), 10.43 (s, 1H, NH); hydroxy-form (39%) 1.30 (s, 6H, CH_3), 3.78 (s, 3H, CH_3), 4.40–4.48 (m, 1H, CH), 6.65 (s, 1H, =CH), 10.28 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): (mixture of isomers) 21.91, 22.31, 48.52, 50.99, 52.58, 77.00, 78.10, 114.04, 114.11, 115.26, 115.49, 144.42, 145.30, 165.87, 166.05, 170.66, 173.90, 180.77, 182.81. Anal. calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10; S, 12.71; found: C, 52.10; H, 4.70; N, 11.15; S, 12.85. MS (EI, 70 eV), *m*/*z* (%): 252 $[M]^+$ (83).
14. *(Z)-Methyl 2-[(Z)-2-(cyanomethylene)-3-cyclohexyl-4-oxothiazolidin-5-ylidene]acetate* (**5c**). Yield 30%, pale yellow powder; mp 259–261 °C. ^{1}H NMR

(400 MHz, DMSO-d_6, 25 °C): 1.36–1.19 (3H, m, CHCy), 1.80–1.59 (5H, m, CHCy), 2.14–2.10 (2H, m, CHCy), 3.78 (3H, s, OCH_3), 4.09 (1H, m, CHCy), 6.04 (1H, s, CH), 6.74 (1H, s, =CH). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): 24.97, 25.70, 27.99, 115.06, 53.09, 56.89, 74.28, 117.25, 140.63, 154.87, 164.23, 166.60. Anal. calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; S, 10.97; found: C, 57.55; H, 5.50; N, 9.60; S, 10.92. MS (EI, 70 eV), *m*/*z* (%): 292 $[M]^+$ (60).

15. *General procedure.* To a suspension of *N*-substituted cyanothioacetamide (1.1 mmol) in 20 ml of glacial AcOH was added (0.160 ml, DMAD, 1.1 mmol) at room temperature. The mixture was stirred at temperature 70 °C for 8 h, then diluted with ice-cold water (20 ml), stirred for 30 min, and filtered. The precipitate was dried over P_2O_5 under reduced pressure.
16. *(Z)-Methyl 2-(2-(cyanomethylene)-3-benzyl-4-oxothiazolidin-5-ylidene)acetate (***4b***).* Yield: 0.2 g (63%); mp 119–120 °C, pale yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): 3.82 (s, 3H, OCH_3), 5.00 (s, 2H, CH_2), 5.82 (s, 1H, CH), 6.90 (s, 1H, CH), 7.38–7.29 (m, 5H, Ar-H); Anal. calcd for $C_{15}H_{12}N_2O_3S$: C, 60.02; H, 4.02; N, 9.33; S, 10.58; found: C, 59.99; H, 4.03; N, 9.33; S, 10.68. MS (EI, 70 eV), *m*/*z* (%): 300 $[M]^+$ (8.9).
17. *General procedure.* To a suspension of malonthioamide (1.2 mmol) in 20 ml of glacial AcOH was added (0.095 ml, DMAD, 1.2 mmol) at 40 °C. The mixture was stirred at 40 °C for 4 h. In the cases of thiophenes **4a**,**b**, filtration gave compound as yellow fibers after washing with AcOH (10 ml) and then of distilled water (50 ml). The precipitate was dried over P_2O_5 under reduced pressure. In the cases of thiophenes **4c**,**d**, the mixture was diluted with of ice-cold water (20 ml) then mixture was stirred for 30 min and filtered. The precipitate was recrystallized from ethanol, filtered, washed with ethanol 1 ml, and dried over P_2O_5 under reduced pressure.
18. *(Z)-Benzyl 2-[5-(benzylamino)-4-(methylcarbamothioyl)-3-oxothien-2(3H)-ylidene]acetate (***8b***).* Yield: 0.18 g (65%), yellow fibrous precipitate; mp 148–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): 3.85 (s, 3H, CH_3), 4.81 (d, 2H, *J* = 6.4, CH_2), 4.89 (d, 2H, *J* = 5.2, CH_2), 3.82 (s, 3H, CH_3), 6.94 (s, 1H, =CH), 7.29–7.43 (m, 10H, 2Ph), 11.83 (s, 1H, NH); 13.68 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): 46.30, 49.57, 52.01, 101.36, 115.85, 126.88, 127.08, 127.27, 127.59, 128.09, 128.43, 135.01, 136.64, 143.19, 165.40, 177.24 (S=C), 181.36 (COOMe), 184.99 (C=O). Anal. calcd for $C_{22}H_{20}N_2O_3S_2$: C, 66.24; H, 4.75; N, 6.60; S, 15.11; found: C, 66.25; H, 4.80; N, 6.60; S, 15.10. MS (EI, 70 eV), *m*/*z* (%): 424 $[M]^+$ (33).
19. *(Z)-Methyl 2-[5-(isopropylamino)-4-(isopropylcarbamothioyl)-3-oxothien-2(3H)-ylidene]acetate (***8d***).* Yield: 0.2 g (65%), yellow crystals; mp 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): 1.31 (d, *J* = 6,4 Hz, 6H, CH_3), 1.46 (d, *J* = 6,4 Hz, 6H, CH_3), 3.86 (s, 3H, OCH_3), 3.92–4.04 (m, 1H, CH), 4.62–4.73 (m, 1H, CH), 6.92 (s, 1H, =CH), 11.52 (s, 1H, NH), 13.52 (s, 1H, NH. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 21.58, 22.97, 44.88, 50.43, 52.53, 101.41, 115.95, 114.93, 166.92, 176.33, 182.31, 184.12. Anal. calcd for $C_{14}H_{20}N_2O_3S_2$: C, 51.19; H, 6.14; N, 8.53; S, 19.53; found: C, 51.20; H, 6.10; N, 8.50; S, 19.55. MS (EI, 70 eV), *m*/*z* (%): 328 $[M]^+$ (30).
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