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Unexpected formation of novel pyrrole derivatives by the reaction of thioamide with dimethyl acetylenedicarboxylate

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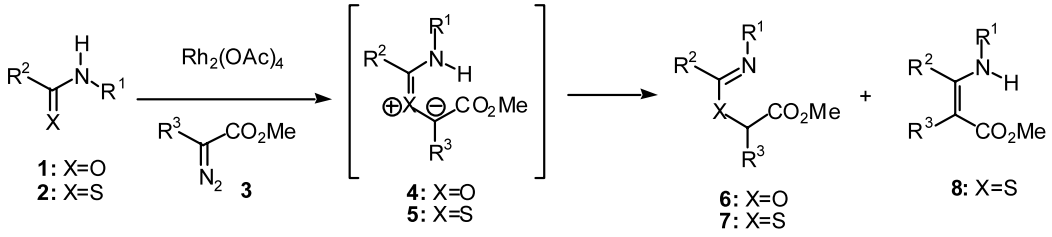
Abstract—The reaction of thioamides with DMAD gave the pyrrole derivatives in good yield and the thiophene derivatives as a byproduct. These were formed by 1,3-dipolar cycloaddition of themodynamicaly stable azomethine ylide or less stable thiocarbonyl ylide with DMAD, followed by elimination of thioaldehyde or imine derivatives. © 2003 Elsevier Science Ltd. All rights reserved.

1,3-Dipole is a useful reactive intermediate for constructing heterocycles by 1,3-dipolar cycloaddition with selective manner.[1] Carbonyl ylides[2,3] and thiocarbonyl ylides[4] have been widely studied in syntheic and theoretical view points. We have been shown the formation of carbonyl ylides or thiocarbonyl ylides by the rhodium(II) catalyzed-reaction of diazocarbonyl compounds with carbonyl compounds or thiocarbonyl compounds such as carbon disulfide,[5] isothiocyanate,[6,7] thioketene[8] and so on.[9] Besides, we have reported the formation of various mesoionic compounds condensed seven-membered ring via intermolecular selective *O*-alkylation of amide derivatives with ethyl diazoacetate through carbonyl ylide intermediate.[10,11] We have also studied the rhodium(II) acetate-catalyzed reactions of diazo compounds **3** with amides **1** or thioamides **2**.[12] The former reaction gave imidates **6** through stabilized carbonyl ylide intermediate **4**. The latter reaction gave thioimidates **7** and enamines **8** through thiocarbonyl ylide **5** (Scheme 1). Then, Corey reported the rhodium(II)-catalyzed reaction of diazoacetic esters with cyclic carbonyl and thiocarbonyl compounds are effective methods for the preparation of acetic esters of the corresponding enol forms.[13] In our study, trapping experiments of the thiocarbonyl ylide **5** with dimethyl acetylenedicarboxylate (DMAD) **9** were failed. But the reaction of thioamides with **9** gave the pyrrole derivatives **10** in good yields (Scheme 2). So, we were interested in the reaction mechanism. Reactions of acetylenic esters with thioamides are known to generate various heterocyclic compounds, thiazolidinones,[14–17] thiazolinones,[18,19] thiazinones,[14,20–22] thiazolotriazinediones,[21,23] and so on.[14] Recently, Bakulev et al. reported the reactions of 5-mercaptazoles and pyridine-2-thiones with DMAD.[24] Nevertheless, there is no precedent of pyrrole derivatives formation. In this letter, we describe the formation of trimethyl pyrrole-2,3,4-tricarboxylate derivatives by the reaction of DMAD with thioamide.

A solution of thioamide **2** (0.23 mmol) and DMAD **9** (2 or 5 equiv.) in the appropriate solvent (1.0 ml) was refluxed for 14 h. The reaction mixture was separated by silica gel column chromatography to give trimethyl pyrrole-2,3,4-tricarboxylate derivatives **10** as shown in Table 1. Treatment of **2** ($R^1=R^2=C_6H_5$) with 2 equiv. of DMAD gave the pyrrole **10** in low yield (entry 1).



Scheme 1.

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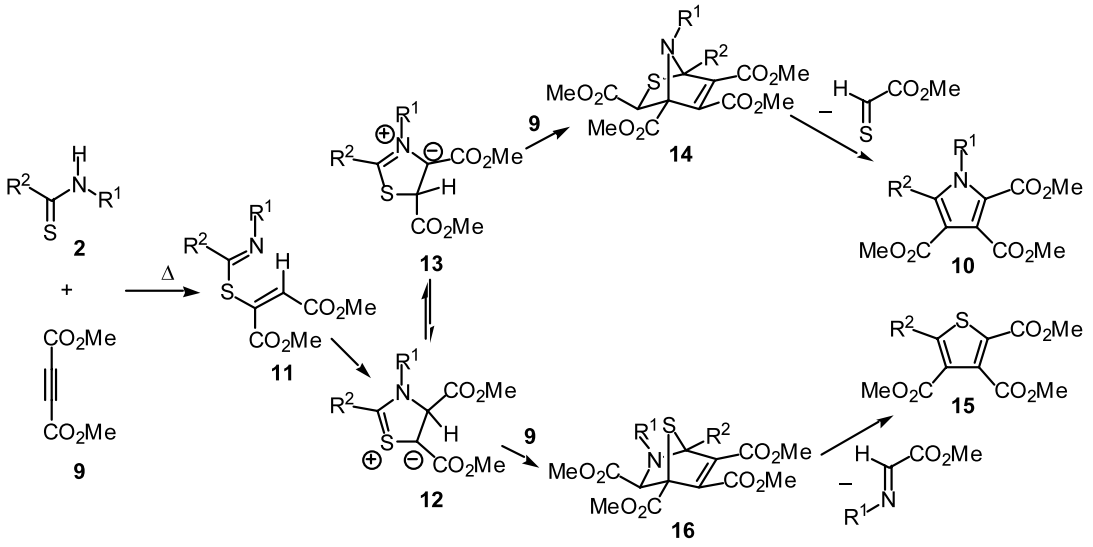
But the yields were high in the case of using 5 equiv. of DMAD (entries 2–14). 1,2-Dichloroethane and toluene were good solvents for the reaction. The structure of **10** was determined by ^{1}H and ^{13}C NMR, elemental analysis, MS, and IR.[25]

The reaction of *N*-methylthiobenzamide also gave the corresponding 1-methylpyrrole derivative in 56% yield. But the same reaction of thiobenzamide did not give any pyrrole. This result indicated alkyl group on substituent R^1 was also applicable to the reaction.

The possible formation mechanism of pyrrole **10** is indicated in Scheme 2. Thioamide **2** added to DMAD **9** to give 1:1 adduct, which has undergone N–H proton-migration to generate **11**, and further intramolecular cyclization to give thiocarbonyl ylide **12**. The ylide **12** was converted thermodynamically stable azomethine ylide **13** by proton transfer from 4 position to 5, which cycloadded with DMAD **9** to give 1,3-dipolar cycloadduct **14**. Finally, the pyrrole **10** was formed by elimination of thioaldehyde. The last step was aromatization similar to trapping some mesoionic compounds with acetylenic compounds followed by extrusion of carbon dioxide or isocyanate.[26]

In order to get information of reaction mechanism, we examined the reaction mixture precisely. We also isolated the thiophene derivative **15** from the reaction mixture of entry 2 in 6% yield. The structure of **15** ($R^2 = C_6H_5$) was identified by ^{1}H and ^{13}C NMR, IR and HRMS.[27] The ^{1}H NMR spectra of **15** exhibited three signals corresponding to three methoxycarbonyl groups at 3.66, 3.88, and 3.98 ppm, and a multiplet of aromatic five protons at 7.40–7.44 ppm. The signals of three carbonyl carbons appeared at 160.66, 162.10, and 165.31 ppm. The IR spectra showed three carbonyl absorptions at 1741, 1727, and 1709 cm^{-1}. A peak of $[M]^+$ required $C_{16}H_{14}O_6S$; 334.0511 was found at $m/z =$ 334.0511 in the high-resolution mass spectrum. The thiophene **15** was formed by 1,3-dipolar cycloaddition



Scheme 2.

Table 1. Reaction of thioamide with DMAD

Entry	R^1	R^2	DMAD (equiv.)	Solvent	Yield of **10** (%)[a]
1	C_6H_5	C_6H_5	2	Toluene	5
2	C_6H_5	C_6H_5	5	Toluene	61
3	C_6H_5	C_6H_5	5	1,2-Dichloroethane	61
4	C_6H_5	C_6H_5	5	Acetonitrile	60
5	*p*-CH_3O-C_6H_4	C_6H_5	5	Toluene	70
6	*p*-CH_3O-C_6H_4	C_6H_5	5	1,2-Dichloroethane	66
7	*p*-CH_3-C_6H_4	C_6H_5	5	Toluene	65
8	*p*-Cl-C_6H_4	C_6H_5	5	Toluene	68
9	*p*-NO_2-C_6H_4	C_6H_5	5	Toluene	65
10	*p*-NO_2-C_6H_4	C_6H_5	5	1,2-Dichloroethane	54
11	C_6H_5	*p*-CH_3O-C_6H_4	5	Toluene	61
12	C_6H_5	*p*-CH_3-C_6H_4	5	Toluene	65
13	C_6H_5	*p*-Cl-C_6H_4	5	Toluene	64
14	C_6H_5	*p*-NO_2-C_6H_4	5	Toluene	62

[a] Isolated yields after column chromatography.

of the less stable cyclic thiocarbonyl ylide **12** with DMAD, followed by elimination of imine (Scheme 2). The generation of **15** is evidence for the formation of thiocarbonyl ylide intermediate **12**, which supports the formation mechanism of pyrrole derivatives **10** as indicated in Scheme 1. It is clear that pyrroles **10** were generated via 1,3-dipolar cycloaddition of DMAD with azomethine ylide **13** converted from less stable thiocarbonyl ylide **12**.

In conclusion, the reaction of thioamides with DMAD gave the novel trimethyl pyrrole-2,3,4-tricarboxylate derivatives in good yield through the cyclic azomethine ylide intermediate. We rationalized the formation mechanism of pyrroles by the isolation of the thiophene-2,3,4-tricarboxylate derivatives. Further studies for the scope and limitation of the reaction are now under progress.

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25. *Trimethyl 1,5-diphenylpyrrole-2,3,4-tricarboxylate* ***(10)*** ($R^1=R^2=C_6H_5$): mp 171.5°C; IR (KBr) 2954, 1747 (C=O), 1722 (C=O), 1717 (C=O), 1449, 1287, 1223, 1202, 1177, 1068, 1040, 763, and 703 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$, Me_4Si) $\delta=3.63$ (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.02–7.10 (m, 4H, arom. H), and 7.15–7.28 (m, 6H, arom. H); ^{13}C NMR (100.4 MHz; $CDCl_3$, Me_4Si) $\delta=51.56$ (q, OCH_3), 51.94 (q, OCH_3), 52.84 (q, OCH_3), 112.55 (s, arom. C), 121.46 (s, arom. C), 125.57 (s, arom. C), 127.49 (d, arom. CH), 128.30 (d, arom. CH), 128.40 (d, arom. CH), 128.67 (d, arom. CH), 128.68 (d, arom. CH), 129.50 (s, arom. C), 130.72 (d, arom. CH), 137.21 (s, arom C), 143.40 (s, arom. C), 159.35 (s, C=O), 163.06 (s, C=O), and 166.50 (s, C=O); MS m/z (EI) 393 (M^+, 73%) and 362 (M^+–OCH_3, 100%). Anal. calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.09; H, 4.93; N, 3.61%.
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27. *Trimethyl 5-phenylthiophene-2,3,4-tricarboxylate* ***(15)*** ($R^2=C_6H_5$): mp 90–91°C; IR (KBr) 2955, 1741 (C=O), 1727 (C=O), 1709 (C=O), 1542, 1460, 1437, 1266, 1222, 1101, 1039, 1002, and 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, Me_4Si) $\delta=3.66$ (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), and 7.40–7.44 (m, 5H, arom. H); ^{13}C NMR (100.4 MHz, $CDCl_3$, Me_4Si) $\delta=52.12$ (q, OCH_3), 52.82 (q, OCH_3), 53.11 (q, OCH_3), 127.07 (s, arom. C), 128.29 (d, arom. CH), 128.96 (s, arom. C), 129.48 (d, arom. CH), 129.69 (d, arom. CH), 131.81 (s, arom. C), 140.76 (s, arom. C), 155.74 (s, arom. C), 160.66 (s, C=O), 162.10 (s, C=O), and 165.31 (s, C=O). HRMS. Calcd for $C_{16}H_{14}O_6S$: m/z 334.0511 found 334.0511 (EI); MS m/z (EI) 334 (M^+, 59%) and 303 (M^+–OCH_3, 100%).