RESEARCH ARTICLE

Highly efficient and versatile one-pot synthesis of substituted thienylidene compounds

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A novel, efficient, and very mild one-pot synthesis of methyl 2-[(Z)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate derivatives under kinetic control has been developed. The title compounds were prepared by the reaction of thioacetomorpholides with dimethyl acetylene-dicarboxylate (DMAD) in the presence of K₂CO₃ in a non-polar solvent with excellent yields.

Keywords: Substituted thienylidenes

1. Introduction

The ready availability of activated acetylenes allows their use in the synthesis, and permits the study, of new types of organic sulfur compounds [1, 2]. Reactions of acetylene compounds with sulfide anions are of great importance in the synthesis of the thiophenes [3, 4]. On the other hand, sulfur compounds, and especially vinyl sulfides, form the basis of drugs, highly active pesticides, and thermally stable and conductive materials [5, 6].

In connection with our work on thioamides, especially thioacetomorpholides, for the construction of new heterocyclic compounds [7], we report here a very mild, efficient, and one-pot synthesis of methyl 2-[(Z)-4-arylmorpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate derivatives, under kinetic control, from thioacetomorpholides, a process which, to the best of our knowledge, has not yet been described.

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2. Result and discussion

The thioacetomorpholides were found to react smoothly with dimethyl acetylenedicarboxylate (DMAD) in the presence of K₂CO₃ in a non-polar solvent such as toluene to produce methyl 2-[(Z)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate derivatives in good to excellent yields (82–94%) and in short reaction times (scheme 1). The reaction was carried out on a 2 mmol scale, in anhydrous toluene, and at a temperature between 40 and 50 °C. The reaction proceeded in low yields at 0–20 °C, and higher temperatures led to a complex mixture of unidentified coloured products.

We investigated the effects of varying the solvent in this reaction, by using toluene, dimethylformamide, and tetrahydrofuran. Table 1 summarizes the results for the three model compounds tested.

Toluene was the best choice for this reaction; dimethylformamide and tetrahydrofuran were also effective, but the reaction proceeded sluggishly with lower yields and the formation of side products. In a typical procedure 1a was treated with 1.1 molar equivalents of DMAD in toluene and the mixture was heated at 45 °C for 50 min to give the desired product 2a in 92% isolated yield.

To demonstrate the generality of this methodology, different substrates were used and the results are summarized in table 2.

We suggest that the thioamide first undergoes S-alkylation via a Michael addition to DMAD, then subsequent enamine nucleophilic attack leading to cyclization and formation of the methyl 2-[(Z)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate derivatives. It should be noted that, theoretically, the reaction could proceed via two different routes, giving thiophenes A or 4H-thiopyran-4-one derivatives B (scheme 2). Since the two possible structures A and B could not be distinguished by spectroscopic methods such as ¹H- and ¹³C-

![Scheme 1](image)

**Scheme 1.**

<table>
<thead>
<tr>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82-94%</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>DMF</th>
<th>THF</th>
<th>Toluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>50</td>
<td>53</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>2e</td>
<td>60</td>
<td>58</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>2g</td>
<td>75</td>
<td>43</td>
<td>56</td>
<td>82</td>
</tr>
</tbody>
</table>

*Reactions were carried using 2 mmol thioacetomorpholide, 2.1 mmol DMAD, and 0.522 g K₂CO₃ at 45 °C.

Isolated yields.
Table 2. Construction of methyl 2-[(Z)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophene-2-ylidene]acetate derivatives from thioacetomorpholides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar product of 2</th>
<th>Time (min)</th>
<th>Mp (°C)</th>
<th>Yield a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>50</td>
<td>167–169</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC₆H₄</td>
<td>60</td>
<td>191–193</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>4-BrC₆H₄</td>
<td>50</td>
<td>228–230</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>4-ClC₆H₄</td>
<td>65</td>
<td>232–234</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>4-MeOC₆H₄</td>
<td>60</td>
<td>168–170</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>4-PhC₆H₄</td>
<td>70</td>
<td>209–211</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>1-Naphthyl</td>
<td>75</td>
<td>208–210</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>2-Naphthyl</td>
<td>75</td>
<td>196–198</td>
<td>85</td>
</tr>
</tbody>
</table>

aYield refers to pure isolated products.

13C-NMR, the decisive assignment was confirmed by an X-ray crystal-structure analysis of the crystalline compound 2h (table 2, entry 8; figure 1).

Conclusions

In conclusion, we have developed a new, general, efficient, and versatile method for the preparation of novel methyl 2-[(Z)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate derivatives. The usefulness of this methodology lies in the fact that the reactions proceed under mild conditions and kinetic control, in a short time, and in excellent yields. Furthermore this is a one-pot procedure using the starting materials, which are also available by known procedures [8].

3. Experimental

All compounds gave satisfactory spectroscopic data.
3.1 Crystal structure determination of compound 2h

Crystals of 2h were obtained from EtOH. All measurements were performed on a Nonius KappaCCD area-detector diffractometer [10] using graphite-monochromated Mo-K$_\alpha$ radiation ($\lambda = 0.71073$ Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below and a view of the molecule is shown in figure 1. Data reduction was performed with HKL Denzo and Scalepack [11]. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method [12] was applied. The space-group was uniquely determined by the systematic absences. Equivalent reflections were merged. The structure was solved by direct methods using SIR92 [13], which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 $U_{eq}$ of its parent atom (1.5 $U_{eq}$ for the methyl group). The refinement of the structure was carried out on $F^2$ using full-matrix least-squares procedures, which minimized the function $\sum w(F_o^2 - F_c^2)^2$. The largest peak of residual electron density is within 1.0 Å of the S-atom. All calculations were performed using the SHELXL97 program [14].

3.1.1 Crystal data for 2h. C$_{21}$H$_{19}$NO$_4$S, $M = 381.44$, orange prism, crystal dimensions 0.10 $\times$ 0.25 $\times$ 0.25 mm, monoclinic, space-group $P2_1/c$, $Z = 4$, reflections for cell determination 49498, 2$\theta$ range for cell determination 4–60°, $a = 17.7576(4)$, $b = 6.1996(1)$, $c = 18.3061(4)$ Å, $\beta = 113.753(1)^\circ$, $V = 1844.60(7)$ Å$^3$, $T = -113^\circ$C, $D_X = 1.373$ g cm$^{-3}$, $\mu$(Mo-K$_\alpha$) = 0.203 mm$^{-1}$, 2$\theta$(max) = 60°, transmission factors (min; max) 0.876; 0.982, total reflections measured 49140, symmetry-independent reflections 5393, reflections with $I > 2\sigma(I)$ 4132, reflections used in refinement 5393, parameters refined 245; $R(F) [I > 2\sigma(I)\] reflections = 0.0489, $wR(F^2)$ [all data] = 0.1328 ($w = [\sigma^2(F_o^2) + (0.0601P)^2 + 1.1135P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.035, final $\Delta_{\text{max}}/\sigma$ 0.001, $\Delta \rho$ (max; min) = 1.01; $-0.32$ e Å$^{-3}$. CCDC-275008 contains the supplementary
crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3.2 General procedure for the one-pot preparation of compounds 2a–2h

To a stirred solution of thioacetomorpholide (2 mmol) in toluene (5 ml) was added K₂CO₃ (4 mmol, 0.552 g). Then dimethyl acetylenedicarboxylate (DMAD, 2.1 mmol) was added drop-wise over 10 minutes. The reaction mixture was heated at 40–50°C for about 50 minutes. The solvent was evaporated off and the residue was subjected to column chromatography (silica gel; hexane:ethyl acetate, 1:1) to afford the corresponding products.

3.2.1 Spectroscopic data for compounds 2a–2h

2a: yellow crystals (EtOH), mp 167–169°C; ¹H-NMR (CDCl₃; 500 MHz) δ 7.42 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 6.8 Hz, 2H), 6.97 (s, 1H), 3.89 (s, 3H), 3.73 (t, J = 4.5 Hz, 4H), 3.51 (t, J = 4.5 Hz, 4H); ¹³C-NMR (CDCl₃; 125 MHz) δ 185.3, 170.2, 167.7, 146.8, 134.5, 130.5, 129.0, 127.8, 115.2, 108.9, 66.7, 52.7, 51.5; IR (KBr) ν 2485, 1700, 1645, 1315 (cm⁻¹).

2b: orange crystals (EtOH), mp 191–193°C; ¹H-NMR (CDCl₃; 500 MHz) δ 7.23 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 6.97 (s, 1H), 3.89 (s, 3H), 3.71 (t, J = 4.5 Hz, 4H), 3.52 (t, J = 4.5 Hz, 4H), 2.39 (s, 3H); ¹³C-NMR (CDCl₃; 125 MHz) δ 185.6, 169.9, 167.3, 146.8, 137.6, 131.3, 130.3, 129.8, 115.1, 109.0, 66.8, 52.7, 51.5, 21.7; IR (KBr) ν 2853, 1692, 1647, 1545, 1315 (cm⁻¹).

2c: orange crystals (EtOH), mp 228–230°C; ¹H-NMR (CDCl₃; 500 MHz) δ 7.54 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.94 (s, 1H), 3.90 (s, 3H), 3.73 (t, J = 4.4 Hz, 4H), 3.57 (t, J = 4.4 Hz, 4H); ¹³C-NMR (CDCl₃; 125 MHz) δ 184.9, 170.3, 167.5, 146.3, 133.3, 132.1, 121.8, 115.5, 107.6, 96.6, 66.6, 52.7, 51.6; IR (KBr) ν 2845, 1692, 1654, 1546, 1315 (cm⁻¹).

2d: yellowish orange crystals (EtOH), mp 232–234°C; ¹H-NMR (CDCl₃; 500 MHz) δ 7.39 (d, J = 7.8 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 6.94 (s, 1H), 3.90 (s, 3H), 3.73 (t, J = 4.7 Hz, 4H), 3.52 (t, J = 4.7 Hz, 4H); ¹³C-NMR (CDCl₃; 125 MHz) δ 185.2, 170.5, 167.6, 146.4, 133.6, 132.9, 131.7, 129.2, 115.5, 107.6, 115.2, 66.7, 52.8, 51.6; IR (KBr) ν 2853, 1654, 1546, 1315 (cm⁻¹).

2e: orange crystals (EtOH), mp 168–170°C; ¹H-NMR (CDCl₃; 500 MHz) δ 7.19 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.92 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.71 (t, J = 4.4 Hz, 4H), 3.52 (t, J = 4.4 Hz, 4H); ¹³C-NMR (CDCl₃; 125 MHz) δ 185.2, 170.3, 167.5, 146.3, 133.6, 132.9, 131.7, 129.2, 115.5, 107.6, 96.6, 52.8, 51.6; IR (KBr) ν 2845, 1692, 1654, 1546, 1315 (cm⁻¹).

2f: orange crystals (EtOH), mp 208–210°C; ¹H-NMR (CDCl₃; 500 MHz) δ 7.88 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.69–7.71 (m, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.50–7.53 (m, 2H), 7.41 (d, J = 6.6 Hz, 1H), 6.97 (s, 1H), 3.92 (s, 3H), 3.41–3.54 (m, 8H); ¹³C-NMR (CDCl₃; 125 MHz) δ 185.2, 169.8, 167.6, 146.6, 134.3, 132.8, 129.3, 129.0, 128.8,
126.8, 126.5, 126.1, 125.9, 115.4, 106.7, 66.7, 52.6, 51.0; IR (KBr) ν 2853, 1692, 1653, 1545, 1315 (cm\(^{-1}\)).

**2h:** orange crystals (EtOH), mp 196–198 °C; \(^1\)H-NMR (CDCl\(_3\); 500 MHz) δ 7.85–7.88 (m, 3H), 7.81 (s, 1H), 7.50–7.51 (m, 2H), 7.39 (d, \(J = 8.0\) Hz, 1H), 6.98 (s, 1H), 3.91 (s, 3H), 3.70 (t, \(J = 4.4\) Hz, 4H), 3.52 (t, \(J = 4.4\) Hz, 4H); \(^13\)C-NMR (CDCl\(_3\); 125 MHz) δ 185.1, 170.3, 167.4, 146.7, 133.8, 132.9, 129.4, 128.4, 128.3, 128.2, 128.1, 126.6, 126.5, 115.3, 108.7, 96.6, 66.5, 52.6, 51.6; IR (KBr) ν 2945, 1692, 1653, 1545, 1315 (cm\(^{-1}\)).

**References**