Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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

Firouz Matloubi Moghaddam[a]; Hassan Zali Boeini[a]; Mojtaba Bagheri[a]; Peter Rüedi[b]; Anthony Linden[b]
[a] Department of Chemistry, Sharif University of Technology, Tehran, Iran [b] Institute of Organic Chemistry, University of Zürich, Zürich, Switzerland

To cite this Article Moghaddam, Firouz Matloubi , Boeini, Hassan Zali , Bagheri, Mojtaba , Rüedi, Peter and Linden, Anthony(2005) 'Highly efficient and versatile one-pot synthesis of substituted thienylidene compounds', Journal of Sulfur Chemistry, 26: 3, 245 — 250
To link to this Article: DOI: 10.1080/00268970500247680
URL: http://dx.doi.org/10.1080/00268970500247680

Journal of Sulfur Chemistry
Vol. 26, No. 3, June 2005, 245–250

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

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

FIROUZ MATLOUBI MOGHADDAM*†, HASSAN ZALI BOEINI†, MOJTABA BAGHERI†, PETER RÜEDI‡ and ANTHONY LINDEN‡

†Department of Chemistry, Sharif University of Technology, PO Box 11365-9516 Tehran, Iran
‡Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

(Received 1 May 2005; in final form 22 June 2005)

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 acetylenedicarboxylate (DMAD) in the presence of K_2CO_3 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].

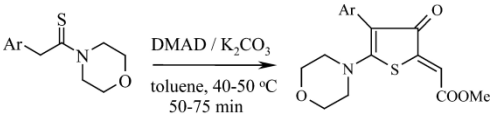
In connection with our work on thioamides, especially thioacetomorpholides, for the construction of new heterocyclic compounds [7], we report here a very mild, efficient, and one-pot synthesis of methyl 2-[(*Z*)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate derivatives, under kinetic control, from thioacetomorpholides, a process which, to the best of our knowledge, has not yet been described.

*Corresponding author. Email: matloubi@sharif.ir

Journal of Sulfur Chemistry
ISSN 1741-5993 print/ISSN 1741-6000 online © 2005 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/00268970500247680

2. Result and discussion

The thioacetomorpholides were found to react smoothly with dimethyl acetylenedicarboxylate (DMAD) in the presence of K_2CO_3 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.



1(a-h) **2(a-h)** 82-94 %

a: Ar= phenyl **b:** Ar= 4-MeC_6H_4 **c:** Ar= 4-BrC_6H_4
d: Ar= 4-ClC_6H_4 **e:** Ar= 4-$MeOC_6H_4$ **f:** Ar= 4-PhC_6H_4
g: Ar= 1-naphthyl **h:** Ar= 2-naphthyl

SCHEME 1.

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.

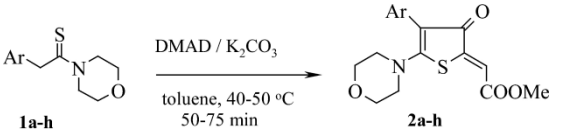
We suggest that the thioamide first undergoes *S*-alkylation *via* a Michael addition to DMAD, then subsequent enamine nucleophilic attack leading to cyclization and formation of the methyl 2-[(*Z*)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate derivatives. It should be noted that,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

Table 1. Investigation of the effects of varying the solvent on the reaction course.[a]

		Yield[b] (%)		
Entry	Time (min)	DMF	THF	Toluene
2a	50	53	73	92
2e	60	58	78	90
2g	75	43	56	82

[a]Reactions were carried using 2 mmol thioacetomorpholide, 2.1 mmol DMAD, and 0.522 g K_2CO_3 at 45 °C.
[b]Isolated yields.

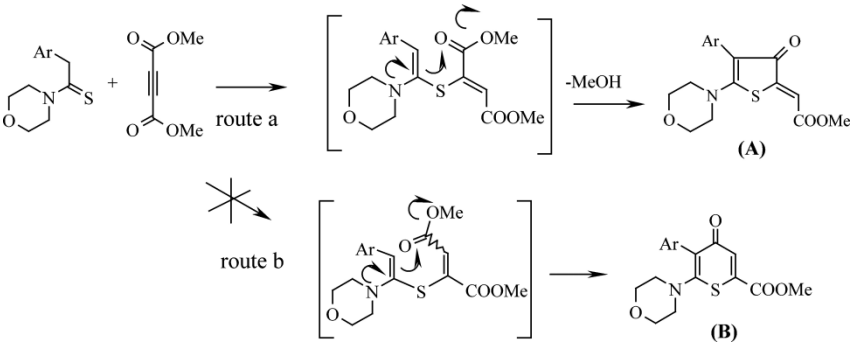
Table 2. Construction of methyl 2-[(*Z*)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophene-2-ylidene]acetate derivatives from thioacetomorpholides.



1a-h **2a-h**

Entry	Ar product of 2	Time (min)	Mp (°C)	Yield[a] (%)
1	Ph	50	167–169	92
2	4-MeC_6H_4	60	191–193	94
3	4-BrC_6H_4	50	228–230	83
4	4-ClC_6H_4	65	232–234	85
5	4-$MeOC_6H_4$	60	168–170	90
6	4-PhC_6H_4	70	209–211	84
7	1-Naphthyl	75	208–210	82
8	2-Naphthyl	75	196–198	85

[a]Yield refers to pure isolated products.



SCHEME 2.

^{13}C-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.

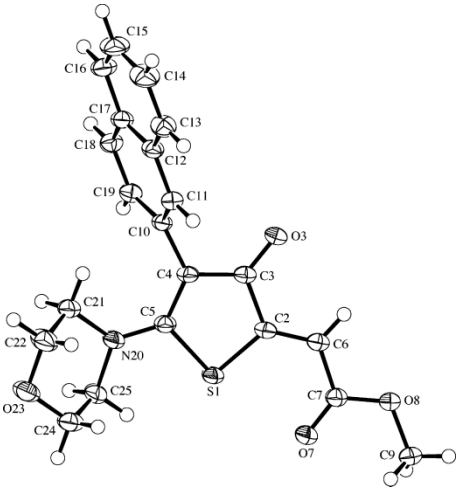


Figure 1. ORTEP [9] representation of the molecule **2h** (50% probability ellipsoids; H-atoms given arbitrary displacement parameters for clarity).

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_α 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 $1.2U_{eq}$ of its parent atom ($1.5U_{eq}$ 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 $\Sigma w(F_o^2 - F_c^2)^2$. 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. $C_{21}H_{19}NO_4S$, $M = 381.44$, 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 49 948, 2θ range for cell determination 4–60°, $a = 17.7576(4)$, $b = 6.1996(1)$, $c = 18.3061(4)$ Å, $\beta = 113.753(1)°$, $V = 1844.60(7)$ Å^3, $T = -113$ °C, $D_X = 1.373$ g cm^{-3}, μ(Mo-K_α) $= 0.203$ mm^{-1}, $2\theta_{(max)} = 60°$, transmission factors (min; max) 0.876; 0.982, total reflections measured 49 140, 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 Δ_{max}/σ 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 K_2CO_3 (4 mmol, 0.552 g). Then dimethyl acetylenedicarboxylate (DMAD, 2.1 mmol) was added dropwise 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; ^{1}H-NMR ($CDCl_3$; 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); ^{13}C-NMR ($CDCl_3$; 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; ^{1}H-NMR ($CDCl_3$; 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); ^{13}C-NMR ($CDCl_3$; 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; ^{1}H-NMR ($CDCl_3$; 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); ^{13}C-NMR ($CDCl_3$; 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, 1652, 1548, 1315 (cm^{-1}).

2d: yellowish orange crystals (EtOH), mp 232–234 °C, ^{1}H-NMR ($CDCl_3$; 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); ^{13}C-NMR ($CDCl_3$; 125 MHz) δ 185.2, 170.5, 167.6, 146.4, 133,6, 132.9, 131.7, 129.2, 115.5, 107.6, 66.7, 52.8, 51.6; IR (KBr) ν 2853, 1654, 1546, 1315 (cm^{-1}).

2e: orange crystals (EtOH), mp 168–170 °C; ^{1}H-NMR ($CDCl_3$; 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); ^{13}C-NMR ($CDCl_3$; 125 MHz) δ 185.2, 169.6, 167.3, 146.6, 132.2, 131.5, 126.4, 114.3, 108.5, 96.5, 66.6, 55.4, 52.5, 51.3; IR (KBr) ν 2945, 1692, 1646, 1545, 1315 (cm^{-1}).

2f: orange crystals (EtOH), mp 209–211 °C; ^{1}H-NMR ($CDCl_3$; 500 MHz) δ 7.65 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.36–7.39 (m, 3H), 6.97 (s, 1H), 3.91 (s, 3H), 3.74 (t, J = 4.1 Hz, 4H), 3.57 (t, J = 4.1 Hz, 4H); ^{13}C-NMR ($CDCl_3$; 125 MHz) δ 185.3, 170.2, 167.6, 146.7, 141.0, 140.5, 133.4, 130.8, 129.2, 127.8, 127.6, 115.4, 108.5, 96.6, 66.5, 52.6, 51.6; IR (KBr) ν 2915, 1692, 1654, 1545, 1315 (cm^{-1}).

2g: yellowish orange crystals (EtOH), mp 208–210 °C; ^{1}H-NMR ($CDCl_3$; 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); ^{13}C-NMR ($CDCl_3$; 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, 96.6, 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

[1] X. Lu, C. Zhang, Z. Xu. *Acc. Chem. Res.*, **34**, 535 (2001).
[2] L. Brandsma. *Preparative Acetylenic Chemistry*, Elsevier, Oxford (1988).
[3] S. Patai, Z. Rappoport (Eds.). *The Chemistry of Functional Groups. Supplement S: The Chemistry of Sulfur-containing Functional Groups*, p. 659, Wiley, New York (1993).
[4] S. Oae. *Chemistry of Organic Sulfur Compounds*, p. 416, Khimiya, Moskva (1975).
[5] B.A. Trofimov. *Zh. Org. Khim.*, **31**, 1368 (1995).
[6] L.M. Belen'kii (Ed.). *Polutchenie i Svoistva Organicheskikh Soedinenii Sery*, p. 560, Khimiya, Moskva (1998).
[7] (a) F. Matloubi Moghaddam, H. Zali Boinee. *Tetrahedron Lett.*, **44**, 6253 (2003); (b) F. Matloubi Moghaddam, H. Zali Boinee. *Tetrahedron*, **60**, 6085 (2004).
[8] (a) F. Matloubi Moghaddam, M. Ghaffarzadeh, M. Dekamin. *J. Chem. Res. (S)*, 228 (2000); (b) F. Matloubi Moghaddam, M. Ghaffarzadeh. *Synth. Commun.*, **31**, 317 (2001).
[9] C.K. Johnson. *ORTEPII*, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee (1976).
[10] R. Hooft. *KappaCCD Collect Software*, Nonius BV, Delft, The Netherlands (1999).
[11] Z. Otwinowski, W. Minor. *Methods Enzymol.*, **276**, 307 (1997).
[12] R.H. Blessing. *Acta Crystallogr., Sect A*, **51**, 33 (1995).
[13] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M.C. Burla, G. Polidori, M. Camalli. *SIR92, J. Appl. Crystallogr.*, **27**, 435 (1994).
[14] G.M. Sheldrick. *SHELXL97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany (1997).