

## A FACILE PREPARATION OF $\beta$ -ALKYL- $\beta$ -PHENYLTHIO- $\alpha,\beta$ -UNSATURATED CARBONYL COMPOUNDS IN A SYNTHESIS OF ALKYL SUBSTITUTED THIOPHENE-2-CARBOXYLIC ESTERS

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**Abstract**— A facile two-step or three-step one-flask procedure for a synthesis of  $\beta$ -alkyl- $\beta$ -phenylthio- $\alpha,\beta$ -unsaturated carbonyl compounds (**3a-j**) from readily prepared 3-methoxy-1-phenylthio-1-propyne (**1**) is described. Condensation of **3a-j** with methyl thioglycolate readily affords a number of 3-alkyl- and 3,5-dialkylthiophene-2-carboxylic methyl esters.

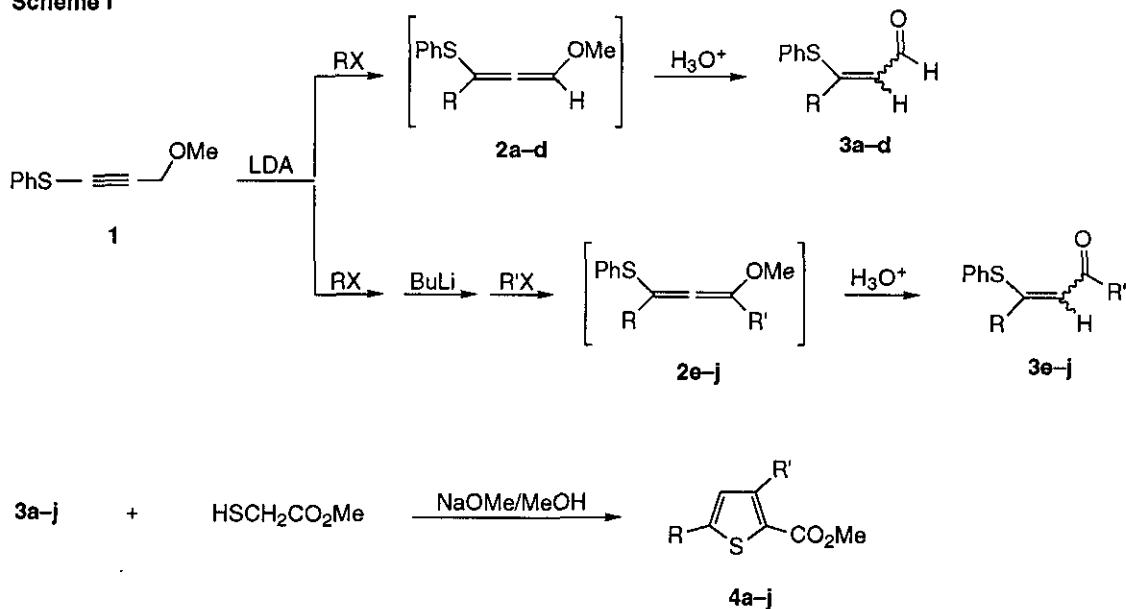
$\beta$ -Thiosubstituted  $\alpha,\beta$ -unsaturated enones (vinylogous thiol esters), besides their use as a blocking group,<sup>1</sup> have been shown to be of interest as multifunctional synthons in organic synthesis.<sup>2-3</sup> However, the use of this class of compounds in heterocyclic synthesis hitherto has not been examined too much, probably due to the non-availability of expedient methods for their synthesis. To the best of our knowledge, only scattered examples of their exploitation for furan,<sup>4</sup>  $\alpha$ -pyrone,<sup>5</sup> pyrazole,<sup>6</sup> and pyrimidine<sup>6</sup> syntheses have been reported in the literature. As a part of our interest in studying the synthetic utility of 3-methoxy-1-phenylthio-1-propyne (**1**),<sup>7</sup> we now report a facile procedure for synthesizing a group of  $\beta$ -alkyl- $\beta$ -phenylthio- $\alpha,\beta$ -unsaturated carbonyl compounds<sup>8</sup> which, in turn, react with the methyl thioglycolate affording 3-alkyl- and 3,5-dialkylthiophene-2-carboxylic methyl esters in good yields (Scheme I).<sup>9</sup>

The synthesis of  $\beta$ -alkyl- $\beta$ -phenylthio- $\alpha,\beta$ -unsaturated aldehydes (**3a-c**) and ketones (**3d-h**) was performed by a sequence of alkylation and hydrolysis from **1**<sup>10</sup> which was readily prepared by phenylsulfenylation of methyl propargyl ether.<sup>7</sup> When compound (**1**) was treated with lithium diisopropyl amide (LDA) (1 equiv.) in THF at -78 °C followed by the addition of ethyl iodide (1.2 equiv.), the alkylated allene product (**2a**) (R = Et) was produced in 70% yield (Kugelrohr distillation, 110 °C/3 mm Hg). Simple acid treatment of a THF solution of **2a** with 0.1% HCl afforded a mixture of *Z*- and *E*- stereoisomeric 3-phenylthio-2-penten-1-ones (**3a**) (9:1, 92% combined yield), which were separable by silica gel flash chromatography. The highly

regioselective alkylation of **1** was confirmed by the nmr spectra of **2a** and the following hydrolysis product (**3a**).<sup>10-11</sup> In fact, the allenic intermediate (**2a**) has no need to be isolated in the synthesis of **3**. A more convenient way to afford the same ratio of the *Z*- and *E*- **3a** in a better overall yield (84%) was achieved by the acid hydrolysis of the alkylation mixture where the solvent and regenerated diisopropylamine were removed under reduced pressure before addition of the acid. Likewise, the  $\beta$ -alkyl- $\beta$ -phenylthio- $\alpha,\beta$ -unsaturated aldehydes (**3b-d**) were also produced by this facile two-step one-flask procedure (Table 1).

The same strategy was successfully applied on the synthesis of  $\beta$ -phenylthio- $\alpha,\beta$ -unsaturated ketones. Treatment of **1** in THF with LDA (1 equiv.), alkyl iodide (1 equiv.), *n*-BuLi (1 equiv.), and alkyl iodide (1.5 equiv.) sequentially followed by the hydrolysis gave the desired ketones (**3e-j**) in good overall yields, presumably via the allenic intermediates (**2e-j**) (Scheme I) (Table 1).

Scheme I



Condensation of the vinylogous thiol esters (**3a-j**) thus obtained with the methyl thioglycolate to give the thiophenes was carried out in NaOMe/MeOH (2 equiv.) at reflux (Scheme 1). Methyl 5-ethylthiophene-2-carboxylate (**4a**) was found to be produced in 75 and 64% yields from the *Z*- and *E*- stereoisomeric enones (**3a**), respectively. Similarly, reaction of the mixture of *E/Z* enones (**3b-j**) with NaOMe under the same conditions smoothly afforded the corresponding 3-alkyl and 3,5-dialkyl substituted thiophenes (**4b-j**) (Table 1). In summary, a facile two-step or three-step one-flask synthesis of  $\beta$ -alkyl substituted  $\beta$ -phenylthio- $\alpha,\beta$ -unsaturated carbonyl compounds from readily available starting material (**1**) and their subsequent use in the synthesis of alkyl substituted methyl thiophene-2-carboxylate as three-carbon annulation fragments were

described. In the reaction sequence, compound (1) serves as the useful 3-, and 1,3-dianionic equivalents (5) and (6) to give enones (3a-j) which, in turn, serve as the 1,3-dicationic equivalents (7) to afford the thiophenes. The use of this strategy in other heterocyclic synthesis is the subject of current investigations, the results of which will be reported in due course.

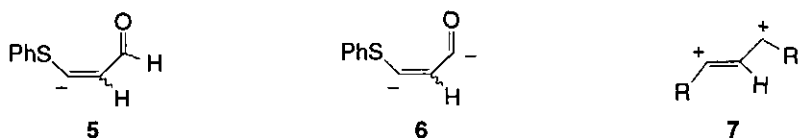


Table 1 Synthesis of  $\beta$ -alkyl- $\beta$ -phenylthio- $\alpha,\beta$ -unsaturated carbonyl compounds (3a-j) and alkyl substituted methyl thiophene-2-carboxylate (4a-j) from 3-methoxy-1-phenylthio-1-propyne (1)<sup>a</sup>

| alkyl halides                 | $\beta$ -phenylthioethylenic enones and enals (Z:E) <sup>b</sup> , % yield <sup>c</sup> | thiophene-2-carboxylic esters % yield <sup>c</sup> |
|-------------------------------|---|--|
| RX = EtI                      | 3a R = Et (9:1) <sup>d</sup> 84   | 4a R = Et, R' = H 75                               |
| RX = <i>n</i> -PrI            | 3b R = <i>n</i> -Pr (9:1) 86  | 4b R = <i>n</i> -Pr, R' = H 82                     |
| RX = <i>n</i> -BuI            | 3c R = <i>n</i> -Bu (8:1) <sup>d</sup> 90   | 4c R = <i>n</i> -Bu, R' = H 73                     |
| RX = PhCH <sub>2</sub> Br     | 3d R = PhCH <sub>2</sub> (10:1) <sup>d</sup> 81   | 4d R = PhCH <sub>2</sub> , R' = H 71               |
| RX = R'X = EtI                | 3e R = R' = Et (15:1) 71  | 4e R = R' = Et 83                                  |
| RX = R'X = <i>n</i> -PrI      | 3f R = R' = <i>n</i> -Pr (25:1) <sup>d</sup> 74   | 4f R = R' = <i>n</i> -Pr 73                        |
| RX = EtI, R'X = <i>n</i> -PrI | 3g R = Et, R' = <i>n</i> -Pr (14:1) 69  | 4g R = Et, R' = <i>n</i> -Pr 80                    |
| RX = <i>n</i> -PrI, R'X = EtI | 3h R = <i>n</i> -Pr, R' = Et (15:1) 72  | 4h R = <i>n</i> -Pr, R' = Et 70                    |
| RX = EtI, R'X = <i>n</i> -BuI | 3i R = Et, R' = <i>n</i> -B (14:1) 75   | 4i R = Et, R' = <i>n</i> -Bu 87                    |
| RX = <i>n</i> -BuI, R'X = EtI | 3j R = <i>n</i> -Bu, R' = Et (23:1) <sup>d</sup> 78                                     | 4j R = <i>n</i> -Bu, R' = Et 81                    |

<sup>a</sup>All enones and thiophenes derivatives have been fully characterized by <sup>1</sup>H nmr,<sup>11</sup> ir, and mass spectroscopies. <sup>b</sup>Z:E isomer ratios were determined by nmr peak areas of the crude hydrolysis products unless otherwise noted. <sup>c</sup>Isolated yields. <sup>d</sup>Isolated ratio of the Z- and E- isomers.

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- 8 For  $\beta$ -phenylthio- $\alpha,\beta$ -unsaturated enones derived from acetylenic and  $\beta$ -chlorovinyl ketones see (a) ref. 3c; (b) ref. 5; (c) E. N. Prilezhaeva, G. S. Vasil'ev, I. L. Mikhelashvili, and V. S. Bogdanov, *Zh. Org. Khim.*, 1971, **7**, 1349 (*Chem. Abstr.*, 1971, **75**, 129023); (d) A. E. Pohland and W. R. Benson, *Chem. Rev.*, 1966, **66**, 161; (e) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 1946, 945. They all suffered the limitations in overall yield and/or the inconvenient synthetic operations in the preparation of starting materials.
- 9 For the synthesis of thiophene-2-carboxylic esters by ring construction method, see (a) S Gronowitz, *Adv. Heterocycl. Chem.*, 1963, **1**, pp. 1-125; (b) 'Thiophene and its Derivatives,' Vol 1, ed. by S. Gronowitz, Wiley Interscience, 1985; pp. 1-214; Vol 3, pp. 588-666.
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- 11  $^1\text{H}$  Nmr spectra data (200 MHz,  $\text{CDCl}_3$ ,  $\delta$ , ppm) for some selected compounds: **2a**: 1.13 (t, 3 H,  $J = 7.2$  Hz), 2.31 (dq, 2 H,  $J = 7.2, 2.2$  Hz), 3.18 (s, 3 H), 6.65 (t, 1 H,  $J = 2.2$  Hz), 7.35 (m, 5 H); **Z-3a**: 1.05 (t, 3 H,  $J = 7.2$  Hz), 2.25 (q, 2 H,  $J = 7.2$  Hz), 6.20 (d, 1 H,  $J = 6.8$  Hz), 7.41 (m, 5 H), 10.17 (d, 1 H,  $J = 6.8$  Hz); **E-3a**: 1.38 (t, 3 H,  $J = 7.2$  Hz), 2.82 (q, 2 H,  $J = 7.2$  Hz), 5.39 (d, 1 H,  $J = 7.4$  Hz), 7.44 (m, 5 H), 9.79 (d, 1 H,  $J = 7.4$  Hz); **Z-3f**: 0.69 (t, 3 H,  $J = 7.2$  Hz), 0.97 (t, 3 H,  $J = 7.2$  Hz), 1.34 (m, 2 H), 1.67 (m, 2 H), 2.12 (t, 2 H,  $J = 7.2$  Hz), 2.48 (t, 2 H,  $J = 7.2$  Hz), 6.29 (s, 1 H), 7.31-7.56 (m, 5 H); **E-3f**: 0.85 (t, 3 H,  $J = 7.2$  Hz), 0.98 (t, 3 H,  $J = 7.2$  Hz), 0.97 (t, 3 H,  $J = 7.2$  Hz), 1.40-1.72 (m, 4 H), 2.18 (t, 2 H,  $J = 7.2$  Hz), 2.79 (t, 2 H,  $J = 7.2$  Hz), 5.57 (s, 1 H), 7.47 (m, 5 H); **Z-3j**: 0.68 (t, 3 H,  $J = 7.2$  Hz), 1.00-1.18 (m, 2 H), 1.14 (t, 3 H,  $J = 7.2$  Hz), 1.28-1.37 (m, 2 H), 2.11 (t, 2 H,  $J = 7.2$  Hz), 2.52 (q, 2 H,  $J = 7.2$  Hz), 6.29 (s, 1 H), 7.38, 7.54 (2 m, 5 H); **E-3j**: 0.90-0.99 (2 t, 6 H,  $J = 7.2$  Hz), 1.37-1.48, 1.55-1.67 (2 m, 4 H), 2.22 (q, 3 H,  $J = 7.2$  Hz), 2.82 (t, 4 H,  $J = 7.2$  Hz), 5.57 (s, 1 H), 7.48 (m, 5 H); **4d**: 3.82 (s, 3 H), 4.13 (s, 2 H), 6.78 (d, 1 H,  $J = 3.8$  Hz), 7.28 (m, 5 H), 7.62 (d, 1 H,  $J = 3.8$  Hz); **4f**: 0.96 (m, 6 H), 1.58-1.75 (m, 4 H), 2.74 (t, 2 H,  $J = 7.3$  Hz), 2.92 (t, 2 H,  $J = 7.3$  Hz), 3.82 (s, 3 H), 6.65 (s, 1 H); **4j**: 0.93 (t, 3 H,  $J = 7.2$  Hz), 1.21 (t, 3 H,  $J = 7.2$  Hz), 1.30-1.47, 1.58-1.73 (2 m, 4 H), 2.77 (t, 2 H,  $J = 7.2$  Hz), 2.96 (q, 2 H,  $J = 7.2$  Hz), 3.82 (s, 3 H), 6.68 (s, 1 H).