A FACILE PREPARATION OF β-ALKY-β-PHENYLTHIO-α,β-UNSATURATED CARBONYL COMPOUNDS IN A SYNTHESIS OF ALKYL SUBSTITUTED THIOPHENE-2-CARBOXYLIC ESTERS

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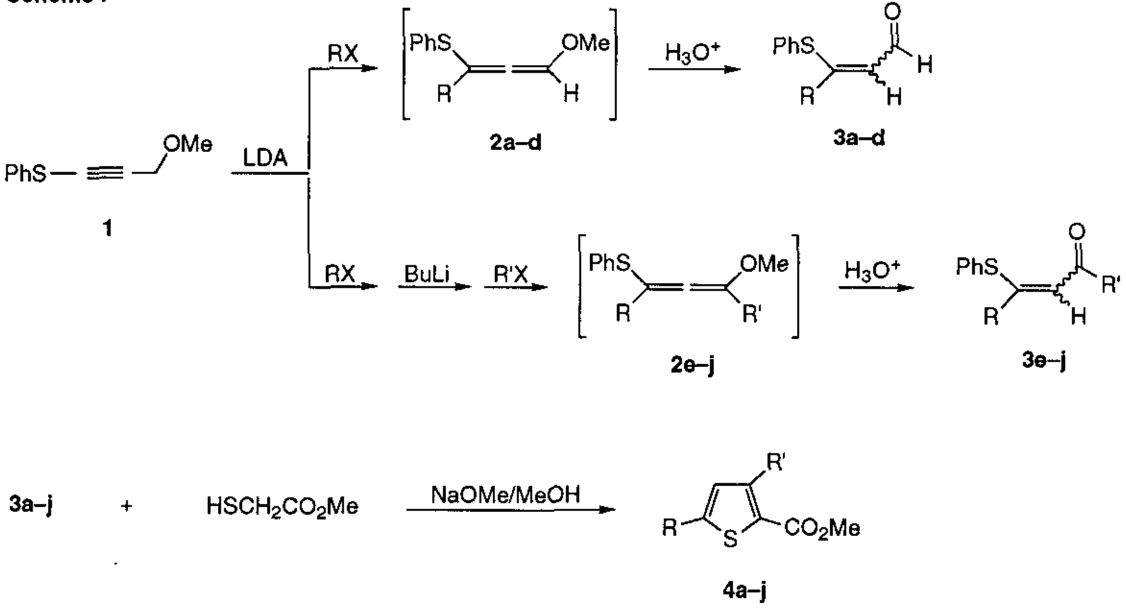
Abstract– A facile two-step or three-step one-flask procedure for a synthesis of β-alkyl-β-phenylthio-α,β-unsaturated carbonyl compounds (**3a–j**) from readily prepared 3-methoxy-1-phenylthio-1-propyne (**1**) is described. Condensation of **3a–j** with methyl thioglycolate readily affords a number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

β-Thiosubstituted α,β-unsaturated enones (vinylogous thiol esters), besides their use as a blocking group,[1] have been shown to be of interest as multifunctional synthons in organic synthesis.[2–3] 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,[4] α-pyrone,[5] pyrazole,[6] and pyrimidine[6] syntheses have been reported in the literature. As a part of our interest in studing the synthetic utility of 3-methoxy-1-phenylthio-1-propyne (**1**),[7] we now report a facile procedure for synthesizing a group of β-alkyl-β-phenylthio-α,β-unsaturated carbonyl compounds[8] which, in turn, react with the methyl thioglycolate affording 3-alkyl- and 3,5-dialkylthiophene-2-carboxylic methyl esters in good yields (Scheme I).[9]

The synthesis of β-alkyl-β-phenylthio-α,β-unsaturated aldehydes (**3a–c**) and ketones (**3d–h**) was performed by a sequence of alkylation and hydrolysis from **1**[10] which was readily prepared by phenylsulfenylation of methyl propargyl ether.[7] 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**).[10–11] 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 β-alkyl-β-phenylthio-α,β-unsaturated aldehydes (**3b–d**) were also produced by this facile two-step one-flask procedure (Table 1).

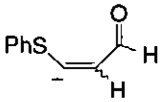
The same strategy was successfully applied on the synthesis of β-phenylthio-α,β-unsaturated ketones. Treatment of **1** in THF with LDA (1 equiv.), alkyl iodide (1 equiv.), *n*-BuLi (1 equiv.), and alkyl iodide (1.5 equiv.) sequentially followed by the hydrolysis gave the desired ketones (**3e–j**) in 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 β-alkyl substituted β-phenylthio-α,β-unsaturated carbonyl compounds from readily availabe 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, sereve 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.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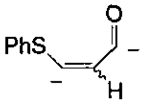
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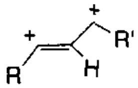
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Table 1 *Synthesis of* β-*alkyl*-β-*phenylthio*-α,β-*unsaturated* carbonyl compounds (**3a–j**) and alkyl substituted methyl thiophene-2-carboxylate (**4a–j**) from 3-methoxy-1-phenylthio-1-propyne (**1**)[a]

alkyl halides	β-phenylthioethylenic enones			thiophene-2-carboxylic esters	
	and enals	(*Z*:*E*)[b],	% yield[c]		% yield[c]
RX = EtI	**3a** R = Et	(9:1)[d]	84	**4a** R = Et, R' = H	75
RX = *n*-PrI	**3b** R = *n*-Pr	(9:1)	86	**4b** R = *n*-Pr, R' = H	82
RX = *n*-BuI	**3c** R = *n*-Bu	(8:1)[d]	90	**4c** R = *n*-Bu, R' = H	73
RX = $PhCH_2Br$	**3d** R = $PhCH_2$	(10:1)[d]	81	**4d** R = $PhCH_2$, R' = H	71
RX = R'X = EtI	**3e** R = R' = Et	(15:1)	71	**4e** R = R' = Et	83
RX = R'X = *n*-PrI	**3f** R = R' =*n*-Pr	(25:1)[d]	74	**4f** R = R' =*n*-Pr	73
RX = EtI, R'X = *n*-PrI	**3g** R = Et, R' =*n*-Pr	(14:1)	69	**4g** R = Et, R' =*n*-Pr	80
RX = *n*-PrI, R'X = EtI	**3h** R = *n*-Pr, R' = Et	(15:1)	72	**4h** R = *n*-Pr, R' = Et	70
RX = EtI, R'X = *n*-BuI	**3i** R = Et, R' = *n*-B	(14:1)	75	**4i** R = Et, R' = *n*-Bu	87
RX = *n*-BuI, R'X = EtI	**3j** R = *n*-Bu, R' = Et	(23:1)[d]	78	**4j** R = *n*-Bu, R' = Et	81

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

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REFERENCES AND NOTES

1 R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1615 and 1620.

2 (a) R. K. Dieter, *Tetrahedron*, 1986, **42**, 3029; (b) H. Junjappa, H. Ila, and C. V. Asokan, *ibid.*, 1990, **46**, 5423.

3 (a) D. Batty, D. Chrich, and S. M. Fortt, *J. Chem. Soc., Perkin Trans. I*, 1990, 2857; (b) M. Pellet and F. Huet, *Tetrahedron*, 1988, **44**, 4463; (c) S. Danishefsky, T. Harayama, and R. K. Singh, *J. Am. Chem. Soc.*, 1979, **101**, 7008; (d) T. Nishio and Y. Omote, *Synthesis*, 1980, 1013 and refereces cited therein; (e) S. Akiyama, S. Nakatsuji, and T. Hamamura, *Tetrahedron lett.*, 1979, 2809 and 2813.

4 (a) M. Watanabe, M. Tsukazaki, Y. Hirakawa, M. Iwao, and S. Furukawa, *Chem. Pharm. Bull.*, 1989, **37**, 2914; (b) T. Nishio, M. Sugawara, and Y. Omote, *J. Heterocycl. Chem.*, 1979, **16**, 815.

5 R. K. Dieter and J. R. Fishpaugh, *J. Org. Chem.*, 1988, **53**, 2031.

6 S. Apparao, R. H. Ila, and H. Junijappa, *Synthesis*, 1982, 792.

7 H. H. Tso, T. K. Hwang,and Y. J. Chen, *Bull. Inst. Chem., Academia Sinica*, 1994, **41**, 25.

8 For β-phenylthio-α,β-unsaturated enones derived from acetylenic and β-chlorovinylic 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 it's Derivatives,' Vol 1, ed. by S. Gronowitz, Wiley Interscience, 1985; pp. 1–214; Vol 3, pp. 588–666.

10 The same sequence was previously used for the synthesis of β-alkylthiovinylic aldehydes in a similar system, see R. M. Carlson, R. W, Jones, and A. S. Hatcher, *Tetrahedron Lett.*, 1975, 1741.

11 ^{1}H Nmr spectra data (200 MHz, $CDCl_3$, δ, 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).

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