Tetrahedron Letters 54 (2013) 147–150

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Attempted Simmon–Smith reaction on β-alkylthio-α,β-unsaturated ketones: a regiospecific synthesis of 2,4-disubstituted thiophenes

Toreshettahally R. Swaroop [a], Rangaswamy Roopashree [a], Hiriyakkanavar Ila [b], Kanchugarakoppal S. Rangappa [a,*]

[a] Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India
[b] New Chemistry Unit, JNCASR, Jakkur, Bangalore 560 064, India

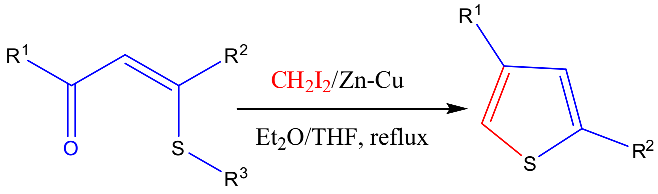
ARTICLE INFO

Article history:
Received 15 September 2012
Revised 22 October 2012
Accepted 25 October 2012
Available online 9 November 2012

Keywords:
β-Alkylthio-α,β-unsaturated ketones
Simmon–Smith reaction
2,4-Disubstituted thiophene
Regiospecific

ABSTRACT

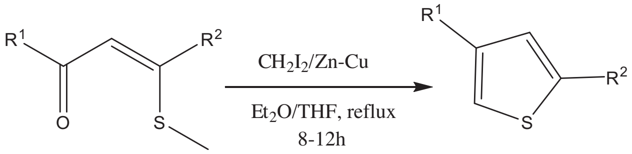
A new regiospecific route to 2,4-disubstituted thiophenes has been developed through Simmon–Smith reaction on β-methylthio-α,β-unsaturated ketones. Extension of the reaction to β-ethyl/benzylthio-α,β-unsaturated ketones also gave the corresponding 2,4-disubstituted thiophenes in a regiospecific manner. A probable mechanism involving a carbenoid methylene insertion to divalent sulfur followed by intramolecular aldol condensation has been suggested.



R^1, R^2=Alkyl/Aryl/Heteroaryl and R^3=Methyl/Ethyl/Benzyl

Thiophene represents an important class of heterocyclic compounds because of their presence in natural products,[1] pharmaceuticals,[2] organic conductors,[3] light emitting devices,[4] and semiconductors.[5] As a result, there is a continuing interest in the development of efficient and versatile methods for the synthesis of thiophene derivatives. In general, construction of thiophene ring from appropriately substituted open chain precursors[6] has attracted the attention of chemists rather than functionalization of the pre-constructed thiophene nucleus[7] since the former route provides more flexible substitution patterns.

In particular, synthesis of 2,4-disubstituted thiophenes from open chain precursors involves one pot reaction of mono substituted acetylene and sulfur,[8a] thermolysis of bis(alkylthio)allenes,[8b] and reaction of Lawesson's reagent with β-formyl ketones.[8c] However, these methods suffer from formation of regioisomeric and undesirable side products. Also, functionalization of the pre-constructed thiophene involves palladium catalyzed coupling of aryl bromides with 3-substituted thiophenes,[9a] oxidative coupling of boronic acids with 2-substituted thiophenes,[9b] double coupling of 2,4-dibromothiophenes with boronic acids and borates,[9c] α-metallation of 3-substituted thiophenes followed by reaction



1a-l **2a-l**

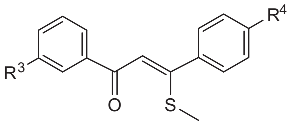
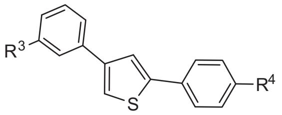
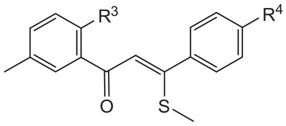
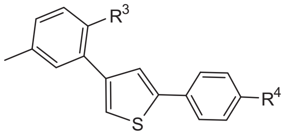
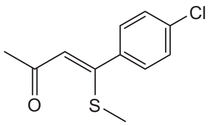
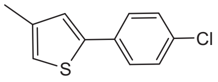
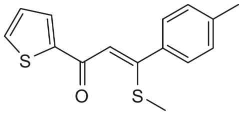
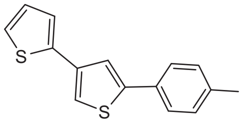
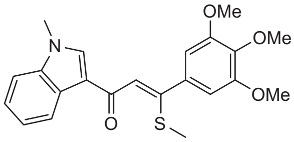
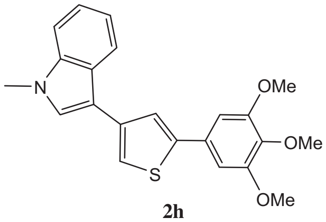
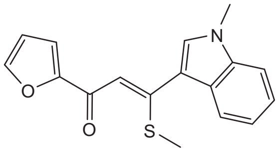
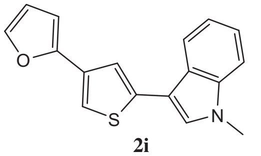
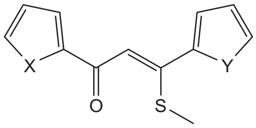
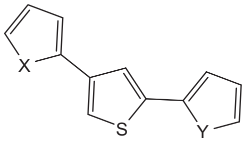
Scheme 1. Synthesis of 2,4-disubstituted thiophenes.

---

[*] Corresponding author. Tel.: +91 821 2419661; fax: +91 821 2500846.
E-mail addresses: rangappaks@gmail.com, rangappaks@chemistry.uni-mysore.ac.in (K.S. Rangappa).

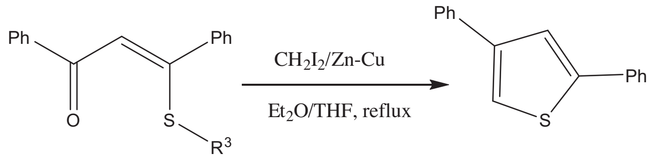
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.110

Table 1
Reaction scope of β-methylthio-α,β-unsaturated ketones **1a–l**

Entry	1	2	Yield (%)
			
1	R^3 = H, R^4 = H **1a**	**2a**	67
2	R^3 = Br, R^4 = OMe **1b**	**2b**	65
3	R^3 = OMe, R^4 = H **1c**	**2c**	61
			
4	R^3 = Me, R^4 = OMe **1d**	**2d**	60
5	R^3 = H, R^4 = Cl **1e**	**2e**	64
6	 **1f**	 **2f**	70
7	 **1g**	 **2g**	58
8	 **1h**	 **2h**	55
9	 **1i**	 **2i**	53
			
10	X = S, Y = S **1j**	**2j**	57
11	X = O, Y = S **1k**	**2k**	52
12	X = O, Y = NMe **1l**	**2l**	56

with electrophilic reagents,[9d] and Negishi cross coupling at β-position of 2-substituted thiophenes.[9e] However, a few of these methods often gave either mixture of regioisomers or suffer from lack of diverse combination of groups on thiophene ring. Consequently, despite the existence of numerous methods for the synthesis of thiophene derivatives, the development of new efficient protocol is a subject of great importance.

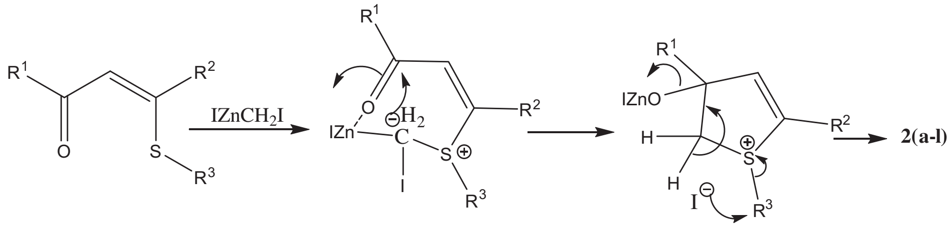
On the other hand, olefins containing various functional groups including heteroatoms undergo Simmon–Smith cyclopropanation.[10] Thus vinyl ethers, ketene *O,O*-acetals, enamines, and vinyl sulfones undergo facile cyclopropanation under these conditions.[11] In addition, Ila and co-workers have reported the unexpected formation of thiophenes from α-oxo-ketene dithioacetals[12] and



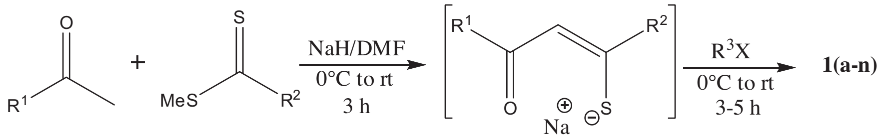
R^3=C_2H_5 **1m** **2a**

R^3=$C_6H_5CH_2$ **1n**

Scheme 2. Reaction scope of β-ethyl/benzylthio-α,β-unsaturated ketones **1m–n**.



Scheme 3. Probable mechanism for the formation of thiophenes **2**.



Scheme 4. Synthesis of β-alkylthio-α,β-unsaturated ketones **1**.

acylketene-*O*,*S*-acetals[13] under Simmon–Smith cyclopropanation conditions instead of the expected cyclopropanes or the products thereof. In continuation of this work we were interested in examining the behavior of β-alkylthio-α,β-unsaturated ketones under Simmon–Smith reaction conditions. Also, it is evident that carbenoids react preferentially on divalent sulfur in a molecule containing both a divalent sulfur and double bond.[14] In the present Letter, we wish to report a new route for the synthesis of 2,4-disubstituted thiophenes by the reaction of β-alkylthio-α,β-unsaturated ketones with Simmon–Smith reagent (Scheme 1).

The requisite Simmon–Smith reagent was prepared from methylene iodide and zinc–copper couple in the presence of catalytic amount of iodine in refluxing ether.[15] When the solution of **1a** in THF reacted with the above prepared Simmon–Smith reagent, a white solid is obtained in 67% yield which was characterized as 2,4-diphenyl thiophene **2a** (Table 1, entry 1) on the basis of spectral and analytical data. Also, no traces of cyclopropanated product could be isolated from the reaction mixture.

Similarly, other 2,4-diarylthiophenes **2b**–**e** were synthesized from respective of β-methylthio-α,β-unsaturated ketones **1b–e** in 60–65% yields (Table 1, entries 2–5). Interestingly, β-methylthio-α,β-unsaturated ketone **1f** derived from acetone also gave the corresponding 2-aryl-4-methylthiophene **2f** in good yield (Table 1, entry 6). In addition, the methodology was found to be compatible with hetero aryl and aryl substituents on **1**. Thus, β-methylthio-α,β-unsaturated ketones **1g** and **1h** furnished corresponding thiophenes in 58% and 55% yields, respectively (Table 1, entries 7 and 8). The generality of the protocol was further explored by keeping heteroaryl substituents on both sides of **1**. Thus, **1i–l** afforded respective thiophenes **2i–l** in 52–57% yields (Table 1, entries 9–12). It should be noted that, no traces of cyclopropanated products could be isolated from all the reactions which proves the regiospecificity of the reaction.

Finally, β-ethyl/benzylthio-α,β-unsaturated ketones **1m** and **1n** were next investigated in view to study the effect of different alkyl groups on sulfur atom (Scheme 2). Thus, when **1m** and **1n** were examined under the above reaction conditions, 2,4-diphenylthiophene **2a** was obtained in 60% and 53% yield in 10 and 12 h, respectively.

The probable mechanism of thiophene formation from β-alkylthio-α,β-unsaturated ketones **1** is as shown in Scheme 3. It might involve attack of carbenoid methylene on sulfur atom of **1** to give sulfur ylide **3**. Coordination of zinc with carbonyl oxygen lone pair might assist the intramolecular nucleophilic addition–elimination in the intermediate sulfur ylide **3**. Finally, dealkylation of the sulfonium salt **4** probably assisted by iodide ion furnishes thiophenes **2**.

The required β-alkylthio-α,β-unsaturated ketones **1a–n** were synthesized in excellent yield by Claisen type condensation of acetyl compounds **5** with dithioesters[16] **6** in the presence of excess of sodium hydride in DMF followed by in situ alkylation of enethiolate anion **7** by alkylating agents such as methyl iodide, ethylbromide, and benzyl bromide (Scheme 4).[17]

In conclusion, we have reported a new synthetically important, mechanistically interesting, regiospecific method for 2,4-disubstituted thiophenes from β-methylthio-α,β-unsaturated ketones. The regiospecificity of the reaction has been proved in the presence of various substituents. The protocol has also been proved to be extendable to β-ethyl/benzylthio-α,β-unsaturated ketones. The present method is superior over the reported methods which were associated with regio isomeric mixtures of products.[8,9] Further synthetic applications of this methodology are currently underway in our laboratory.

Acknowledgment

T.R.S. thanks CSIR, New Delhi for Junior and Senior Research Fellowship, financial support to K.S.R. through BRNS Project (Vide No. 2009/37/40/BRNS/2266 Dated 23-11-2009) and UGC Major Research Project (Vide No. 39-106/2010(SR) Dated 24-12-2010) is greatly acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.110.

References and notes

1. Koike, K.; Jia, Z.; Nikaib, T.; Liu, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197–198.
2. (a) Pinto, I. L.; Jarvest, R. L.; Serafinowska, H. T. *Tetrahedron Lett.* **2000**, *41*, 1597–1600; (b) Leuker, T. J.; Beaton, H. G.; Whiting, M.; Kete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731–7735; (c) Holmes, J. M.; Lee, G. C. M.; Wijino, M.; Weinkam, R.; Wheeler, L. A.; Garst, M. E. *J. Med. Chem.* **1994**, *37*, 1646–1651.
3. (a) Kiani, M. S.; Mitchell, G. R. *Synth. Met.* **1992**, *46*, 293–306; (b) Wolf, J. J.; Wortmann, R. *Adv. Phys. Org. Chem.* **1999**, *32*, 121–217.
4. Greenham, N. C.; Morratti, S. C.; Bradley, D. D. C.; Friend, R. H.; Holmes, A. B. *Nature (London)* **1993**, *365*, 628–629.

5. (a) Morrison, J. J.; Murray, M. M.; Li, X. C.; Holmes, A. B.; Morrati, S. C.; Friend, R. H.; Sirringhaus, H. *Synth. Met.* **1999**, *102*, 987–988; (b) Li, X. C.; Sirringhaus, H.; Garrier, F.; Holmes, A. B.; Morrati, S. C.; Feeder, N.; Clegg, W.; Teat, S. J.; Friend, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 2206–2207.
6. (a) Koji, S.; Satoshi, K. *Synthesis* **1982**, *12*, 1056–1058; (b) Hideo, K.; Keiichi, N.; Kazuhiko, Y.; Hiroo, I. *Synthesis* **1996**, *10*, 1193–1195; (c) Annabelle, H. P.; Frutos, H.; Bernd, H.; Jean, G. *Synlett* **2003**, 63–66; (d) Zhang, H.; Yang, G.; Chen, J.; Chen, Z. *Synthesis* **2004**, *18*, 3055–3059.
7. (a) Shevchenko, N. E.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2003**, *8*, 1191–1200; (b) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074–5075.
8. (a) Darabi, H. R.; Aghapoor, K.; Mohsenzadeh, F. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 2483–2489; (b) Shimizu, T.; Sakamaki, K.; Kamigata, N. *Tetrahedron Lett.* **1997**, *38*, 8529–8532; (c) Ramila, A.; Joaquin, P.; Camacho, E. *Heterocycles* **1997**, *45*, 2425–2430.
9. (a) Dong, J. J.; Roy, D.; Roy, R. J.; Ionita, M.; Doucet, H. *Synthesis* **2011**, *21*, 3530–3548; (b) Kirchberg, S.; Tani, S.; Ureda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387–2391; (c) Steven, C. D. R.; Adam, W. D.; Christopher, L. J. *Synthesis* **2009**, *1*, 138–142; (d) Huo, L.; Hou, J.; Zhang, S.; Chen, H.-Y.; Yang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 1500–1503; (e) Mokoto, M.; Andrzej, R. *Synlett* **2004**, 177–181.
10. Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 40–46. Chapt. 1.
11. (a) Wenkert, E.; Mueller, R. A.; Reardon, E. J.; Sethe, S. S.; Scharf, D. J.; Tosi, G. *J Am. Chem. Soc.* **1970**, *92*, 7428–7436; (b) Kuelhne, M. E.; King, J. C. *J. Org. Chem.* **1973**, *38*, 304–311; (c) Nishimura, J.; Furukawa, J.; Kawabata, N.; Kitayama, M. *Tetrahedron* **1971**, *27*, 1799–1806; (d) Conia, J. M.; Girard, C. *Tetrahedron Lett.* **1973**, *14*, 2767–2770; (e) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27–31.
12. (a) Thomas, A.; Singh, G.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1989**, *30*, 3093–3096; (b) Bhat, L.; Thomas, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1992**, *48*, 10377–10388.
13. Bhat, L.; Ila, H.; Junjappa, H. *Synthesis* **1993**, *10*, 959–960.
14. Cohen, T.; Kosarych, Z. *J. Org. Chem.* **1982**, *47*, 4005–4008.
15. General procedure for the synthesis of 2,4-disubstituted thiophenes (**2a–l**): To a well stirred suspension of Zn–Cu couple (2 g, 15 mmol) in dry ether (20 mL) under a nitrogen atmosphere, a small crystal of iodine and diiodomethane (3.35 g, 12.5 mmol) were added and the reaction mixture was refluxed for 1 h. A solution of β-alkylthio-α,β-unsaturated ketone **1** (5 mmol) in dry THF (20 mL) was added to the reaction mixture which was further refluxed with stirring for 8–12 h (monitored by TLC). The solvent was removed under reduced pressure and the residue was diluted with EtOAc (100 mL) and water (150 mL). The extract was filtered to remove unreacted Zn–Cu couple and the residue was washed with EtOAc (25 mL). The EtOAc layer was separated and washed with brine (50 mL), then dried over anhydrous Na_2SO_4 and concentrated to give crude products which were purified by column chromatography over silica gel using hexane as eluent.
16. Ramadas, S. R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, *8*, 605–622. and references cited therein.
17. To a suspension of sodium hydride (12.5 mmol) in DMF (10 mL), a solution of acetyl compound **5** (5 mmol) and dithioester **6** (5 mmol) in DMF (15 mL) was added at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The alkylating agent (methyl iodide or ethyl bromide or benzyl bromide) was added at 0 °C to the reaction mixture which is further stirred at room temperature for 3–5 h (monitored by TLC). Crushed ice was then added to quench the excess of sodium hydride and the reaction mixture was diluted with water (50 mL). The reaction was extracted with EtOAc (50 mL × 3), washed with water (50 mL × 2) and brine (50 mL), dried over anhydrous Na_2SO_4 and then concentrated to give crude products which were purified by column chromatography over silica gel using hexane–EtOAc (8:2) mixture as eluent.