Construction of Highly Functionalized Thiophene and Benzo[*b*]thiophene Derivatives *via* a Sequence of Propargyl–Allenyl Isomerization/Cyclization/Demethylation

Dianpeng Chen, Gangdong Xing, Xueyuan Chen, Jinzhong Yao, Hongwei Zhou

PII: S0040-4039(16)31328-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.10.025
Reference: TETL 48195

To appear in: *Tetrahedron Letters*

Received Date: 14 July 2016
Revised Date: 29 September 2016
Accepted Date: 8 October 2016

Please cite this article as: Chen, D., Xing, G., Chen, X., Yao, J., Zhou, H., Construction of Highly Functionalized Thiophene and Benzo[*b*]thiophene Derivatives *via* a Sequence of Propargyl–Allenyl Isomerization/Cyclization/Demethylation, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.10.025

Construction of Highly Functionalized Thiophene and Benzo[*b*]thiophene Derivatives *via* a Sequence of Propargyl–Allenyl Isomerization/Cyclization/Demethylation

Dianpeng Chen, [a,b] Gangdong Xing, [b] Xueyuan Chen, [a] Jinzhong Yao, [a,*] and Hongwei Zhou [a,b,*]

[a] College of Biological, Chemical Sciences and Engineering, Jiaxing University, Jiaxing 314001, People's Rupublic of China

[b] Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310028, People's Republic of China

Fax: (+86) 573-83643264; E-mail: zhouhw@zju.edu.cn

Abstract

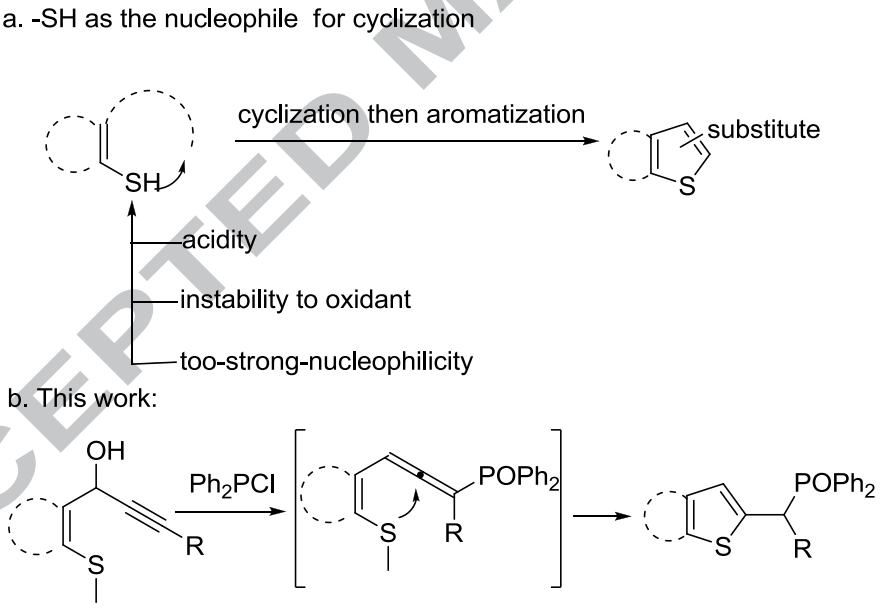
An efficient one-pot protocol for the synthesis of functionalized thiophene and benzo[*b*]thiophene derivatives was developed *via* a sequence of propargyl–allenyl isomerization/cyclization/demethylation. As a result of the readily accessible starting materials, simple operation, and mild conditions, this reaction should have potential utility in organic synthesis.

Keywords:

Substituted thiophenes are arguably the most important aromatic heterocyclic compounds due to their extensive applications in pharmacology,[1] material science,[2] and organic synthesis.[3] Thus, the preparation of polyfunctionalized thiophenes (benzothiophenes) has been of interest for the organic community over the past decades. The classical protocols to thiophene derivatives are mainly based on cyclization reactions or on direct functionalization to thiophene ring.[4] For the

construction of polysubstituted thiophenes *via* cyclization strategies, using mercapto group as the nucleophile might encounter difficulty because of its acidity, instability to oxidant and too-strong-nucleophilicity, which makes the design of substrates challenging (Scheme 1a). Replacement of the mercapto group by a relatively stable methylthio group might be a feasible solution.[5] Based on this idea and our undertanding of organosulfur chemistry [6] and propargyl-allenyl isomerization,[7] herein we wish to report the realization of an efficient access to thiophene and benzo[*b*]thiophene derivatives *via* an intramolecular nucleophilic attack of sulfur to the *in situ* generated electron-deficient allene moiety (Scheme 1b).

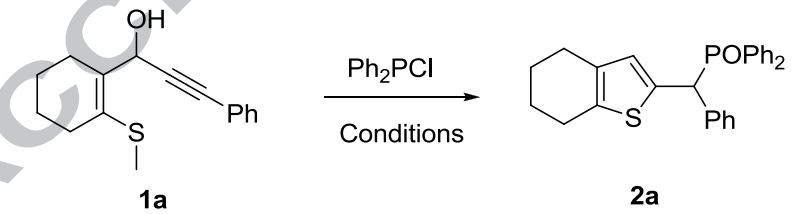
Scheme 1. Proposal of addition of methyl sulfide to *in situ* generated allene



As a first attempt, we chose 1-(2-(methylthio)cyclohex-1-enyl)-3-phenylprop-2-yn-1-ol (**1a**) as the substrate, which could be readily obtained by treatment of 2-(methylthio)cyclohex-1-enecarbaldehyde with (phenylethynyl)lithium at -78 ^{o}C. Initial studies focused on the propargyl–allenyl isomerization and cyclization of **1a** in the presence of chlorodiphenyl phosphine and triethylamine in THF at room temperature. Fortunately, the desired product diphenyl(phenyl(4,5,6,7-

tetrahydrobenzo[b]thiophen-2-yl)methyl)phosphine oxide (**2a**) was obtained in 12% yield (Table 1, entry 1). Then we began to optimize the reaction with different conditions. Replacing triethylamine by *N*,*N*-diisopropylethylamine (DIPEA) gave similar yields and the stronger organic bases such as DBU and DBN gave an unidentified mixture (Table 1, entries 2–4). Subsequent screening of other common solvents, such as, dichloroethane, 1,4-dioxane, acetonitrile and DMF did not improve the yield except toluene (Table 1, entries 5–9). Besides that, the temperature was found to influence the reactivity (Table 1, entries 9-11). Raising the temperature to 100 ^{o}C improved the yield significantly. For further optimization, we examined several triethylamine-compatible Lewis acids to promote the reactions (Table 1, entries 12-14), and $Ga(OTf)_3$ was demonstrated to be effective, affording the desired product **2a** in 85% yield (entry 12).[8] Based on these optimization studies, we confirmed that **1a** (0.5 mmol), Ph_2PCl (0.6 mmol), $Ga(OTf)_3$ (0.025mmol) and TEA (1.5mmol) in 5 mL toluene stirring at 100 ^{o}C offered the best conditions for this reaction (Table 1, entry 12).

Table 1. Optimization of the Reaction Conditions [a]



1a **2a**

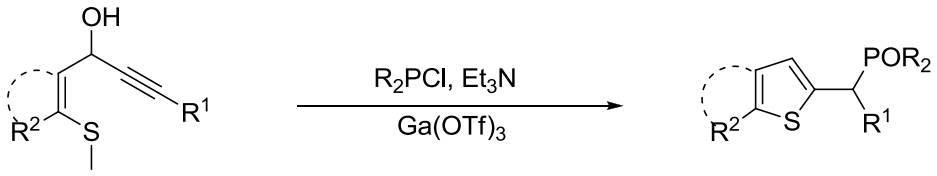
Entry	Additive	Base	Solvent	T(^{o}C)	Yield(%)
1	-	TEA	THF	r.t.	12
2	-	DIPEA	THF	r.t.	10
3	-	DBU	THF	r.t.	trace
4	-	DBN	THF	r.t.	trace
5	-	TEA	DCE	r.t.	6

6	-	TEA	1,4-dioxane	r.t.	8
7	-	TEA	MeCN	r.t.	NR
8	-	TEA	DMF	r.t.	NR
9	-	TEA	toluene	r.t.	18
10	-	TEA	toluene	60	16
11	-	TEA	toluene	100	32
12	**$Ga(OTf)_3$**	**TEA**	**toluene**	**100**	**85**
13	$Zn(OTf)_2$	TEA	toluene	100	77
14	AgOTf	TEA	toluene	100	81

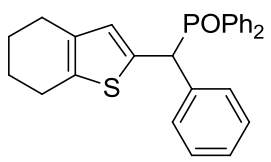
[a] Conditions: **1a** (0.5 mmol), Ph_2PCl (0.6 mmol), $Ga(OTf)_3$ (0.025mmol) and TEA (1.5mmol) in 5 mL toluene were stirred at 100 ^oC under nitrogen.

With the optimized reaction conditions in hand, the scope of this reaction was examined (Table 2). This protocol is successful for the one-pot construction of both thiophene (**2a**-**2i**) and benzo[*b*]thiophene (**2j**-**2m**) derivatives. R^1 can be alkyl (**2i**, **2m**), alkenyl (**2h**, **2l**) or phenyl group optionally substituted with either an electron-donating group (**2b**, **2c**, **2f**, **2g**) or an electron-withdrawing group (**2d**); R^2 can be alkyl (**2a**-**2f**) or phenyl group (**2g**-**2i**).

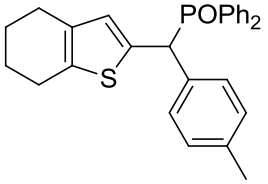
Table 2. Synthesis of thiophene and benzo[*b*]thiophene derivatives. [a]



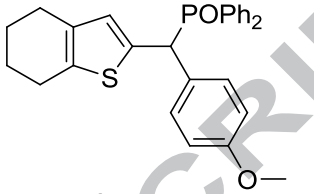
1 **2**



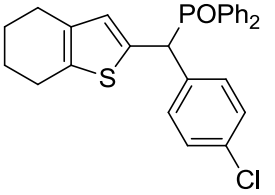
2a 85%



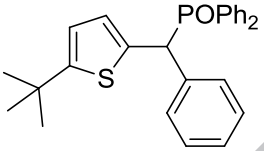
2b 78%



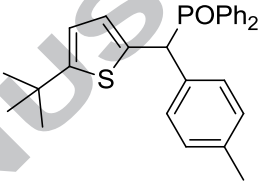
2c 67%



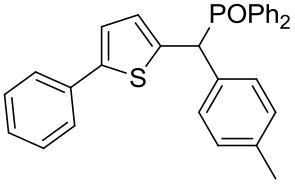
2d 73%



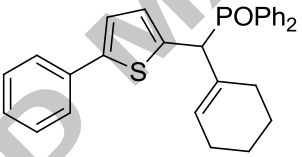
2e 68%



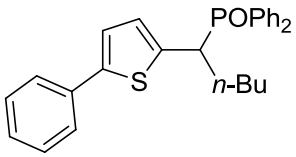
2f 61%



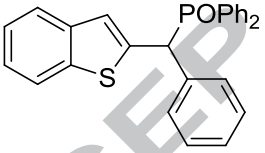
2g 78%



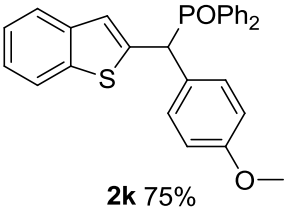
2h 74%



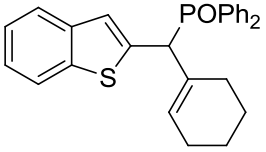
2i 72%



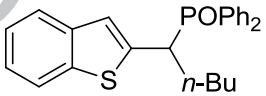
2j 85%



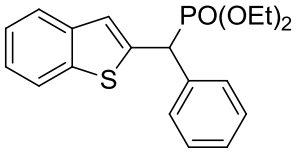
2k 75%



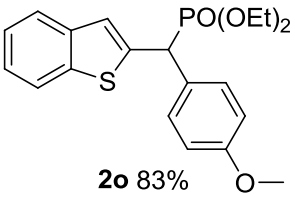
2l 79%



2m 86%



2n 78%

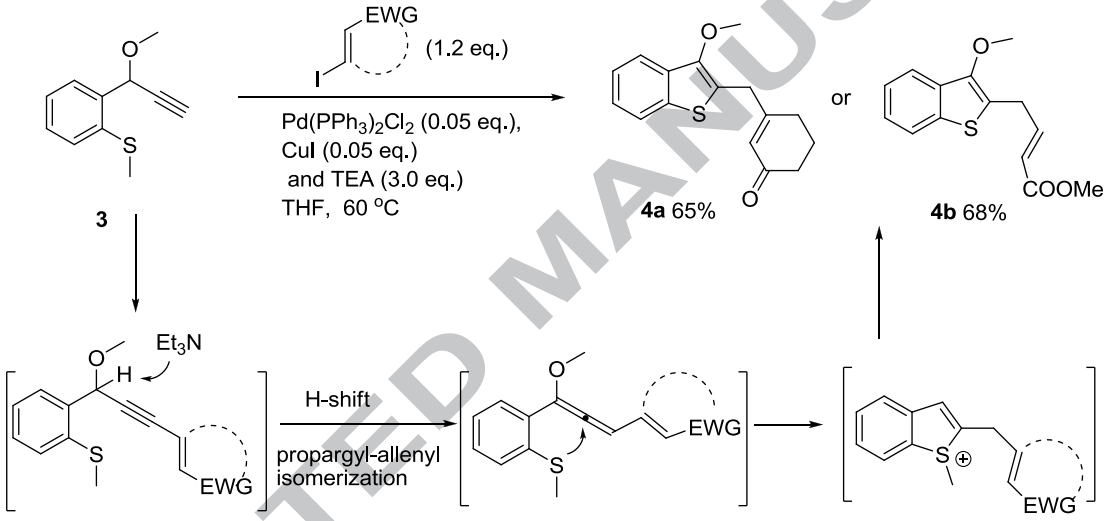


2o 83%

[a] Conditions: **1** (0.5 mmol), Ph_2PCl (0.6 mmol), $Ga(OTf)_3$ (0.025 mmol) and TEA (1.5mmol) in 5 mL toluene were stirred at 100 °C under nitrogen.

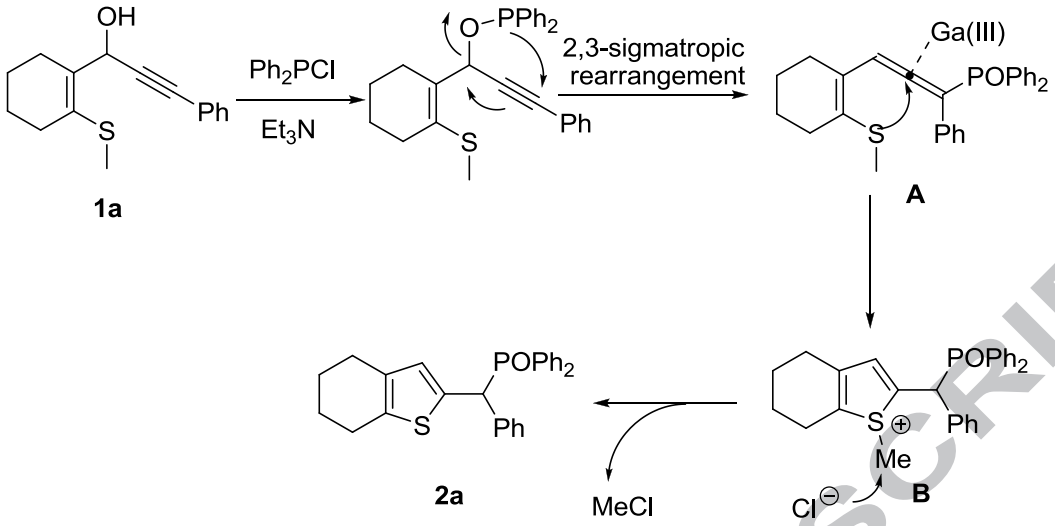
Aside the rearrangement of propargyl phosphite to allenyl phosphonate, base−assisted H−shift propargyl–allenyl isomerization is also a facile method for *in situ* generating allenes. We examined the Sonogashira coupling/propargyl–allenyl isomerization of propargyl ether with electron-deficient alkenyl iodides and obtained benzo[*b*]thiophenes **4a** and **4b**, illustrating that this benzo[*b*]thiophene formation strategy might tolerate diverse functionalization (Scheme 2).

Scheme 2. Benzo[*b*]thiophene formation *via* Sonogashira pathway.



We proposed a plausible pathway as shown in Scheme 3. First, intermediate **A** is formed *via* the propargyl phosphite/allenyl phosphonate rearrangement; then assisted with $Ga(OTf)_3$, intermediate **A** undergoes an intramolecular nucleophilic attack of methylthio group to the electron-deficient allene moiety, affording the sulfonium intermediate **B**, which experiences demethylation to give product **2a** (Scheme 3).

Scheme 3. Plausible mechanism.



In conclusion, we have developed an efficient protocol for the synthesis of functionalized thiophene and benzo[*b*]thiophene derivatives *via* a sequence of propargyl–allenyl isomerization/cyclization/demethylation in one pot. The products can be serviceable building blocks and applied widely in Wittig-type olefination.[10] This reaction demonstrates good functional group compatibility, and further studies on the synthetic application are currently ongoing.

Acknowledgements

Financial support from Natural Science Foundation of China (Nos. 21606080 and 21401078), Zhejiang Provincial Natural Science Foundation of China (No. LY14B020008) and Summit Program of Jiaxing University for Leading Talents is greatly appreciated.

Supplementary data

Supplementary data associated with this article can be found, in the online version.

Notes and reference

1. (a) Mohareb, R. M.; Abdallah, A. E. M.; Abdelaziz, M. A. *Med. Chem. Res.* **2014**, *23*, 564; (b) Sperry, J. B.; Wright, D. L. *Curr. Opin. Drug Discov. Dev.* **2005**, *8*, 723; (c) Mishra, R.; Jha, K. K.; Kumar, S.; Tomer, I. *Der Pharma Chemica* **2001**, *3*, 38.

2. (a) Abdou, M. M. *Am. J. Chem.* **2013**, *3*, 126; (b) Mishra, A.; Ma, C. Q.; Bäuerle, P. *Chem. Rev.* **2009**, *109*, 1141; (c) Ong, B. S.; Wu, Y.; Li, Y.; Liu, P.; Pan, H. *Chemistry* **2008**, *14*, 4766; (d) Osaka, I.; McCullough, R. D. *Acc. Chem. Res.* **2008**, *41*, 1202; (e) Barbarella, G.; Melucci, M.; Sotgiu, G. *Adv. Mater.* **2005**, *17*, 1581; (f) Guernion, N. J. L.; Hayes, W. *Curr. Org. Chem.* **2004**, *8*, 637; (g) Chan, H. S. O.; Ng, S. C. *Prog. Polym. Sci.* **1998**, *23*, 1167; (h) Roncali, J. *Chem. Rev.***1992**, *92*, 711.

3. (a) Mancuso, R.; Gabriele, B. *Molecules* **2014**, *19*, 15697 ; (b) Roman, G. *Mini-Rev. Org. Chem.* **2013**, *10*, 27; (c). Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109.

4. (a) Khidre, R. E.; Abdelwahab, B. F. *Turk. J. Chem.* **2013**, *37*, 685; (b) Serdyuk, O. V.; Abaev, V. T.; Butin, A. V. Nenajdenko, V. G. *Synthesis* **2011**, 2505; (c) Hameed, S.; Akhtar, T. *Curr. Org. Chem.* **2011**, *15*, 694; (d) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937; (e) Metwally, M. A.; Khalifa, M. E.; El-Hiti, G. A. *J. Sulf. Chem.* **2010**, *31*, 205; (f) Katritzky, A.R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564; (g) Erian, A. W.; Sherif, S. M.; Gaber, H. M. *Molecules* **2003**, *8*, 793; (h) Deryagina, E. N.; Voronkov, M. G. *Chem. Hetero. Compd.* **2000**, *36*, 1.

5. (a) Yamauchi, T.; Shibahara, F.; Murai, T. *Tetrahedron Lett.* **2016**, *57*, 2945; (b) Saurabh, M.; Richard, C. L. *J. Org. Chem.* **2010**, *75*, 1652; (c) Jacubert, M.; Tikad, A.; Provot, O.; Hamze, A.; Brion, J. D.; Alami, M. *Eur. J. Org. Chem.* **2010**, *23*, 4492; (d) Nakamura, I.; Sato, T.; Terada M.; Yamamoto, Y. *Org. Lett.*, **2008**, *10*, 2649; (e) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473.

6. (a) Zhou, H.; Xing, Y.; Yao, J.; Lu, Y. *J. Org. Chem.* **2011**, *76*, 4582; (b) Zhou, H.; Xing, Y.; Liu, L.; Hong, J. *Adv. Synth. Catal.* **2011**, *353*, 3146; (c) Zhou, H.; Xie, Y.; Ren, L.; Su, R. *Org. Lett.* **2010**, *12*, 356; (d) Zhou, H.; Zhu, D.; Xie, Y.; Huang, H.; Wang, K. *J. Org. Chem.* **2010**, *75*, 2706; (e) Zhou, H.; Xing, Y.; Yao, J.; Chen, J. *Org. Lett.* **2010**, *12*, 3674; (f) Zhou, H.; Zhu, D.; Xing, Y.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 2127; (g) Zhou, H.; Xie, Y.; Ren, L.; Wang, K. *Adv. Synth. Catal.* **2009**, *351*, 1289.

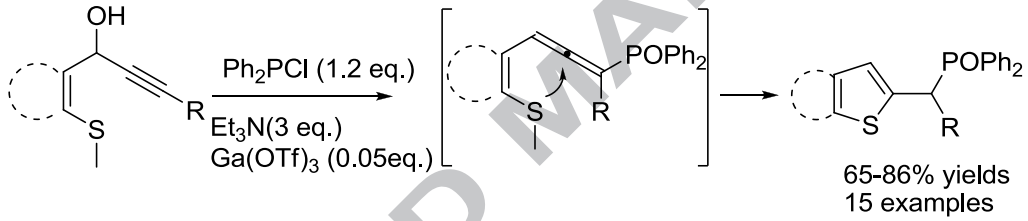
7. (a) Liu, L.; Wang, J.; Zhou, H. *J. Org. Chem*. **2015**, *80*, 4749; (b) Chen, D.; Xing, G.; Zhou, H. *Org. Chem. Front.* **2015**, *2*, 947; (c) Liu, L.; Chen, D.; Zhou, H. *Adv. Synth. Catal*. **2015**, *357*, 389; (d) Zhao, G.; Zhang, Q.; Zhou, H. *J. Org. Chem*. **2014**, *79*, 10867; (e) Zhao, G.; Zhang, Q.; Zhou, H. *Adv. Synth. Catal*. **2013**, *355*, 3492; (f) Zhou, H.; Liu, L.; Xu, S. *J. Org. Chem*. **2012**, *77*, 9418.

8. For reviews of bifunctional catalysis of cooperative Lewis acid/base systems, please see: (a) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res*. **2008**, *41*, 655; (b) Murahashi, S. C.; Takaya, H. *Acc. Chem. Res*. **2000**, *33*, 225.

9. (a) Braun, R. U.; Ansorge, M.; Müller, T. J. J. *Chem.—Eur. J*. **2006**, *12*, 9081; (b) D'Souza, D. M.; Kiel, A.; Herten, D. P.; Müller, T. J. J. *Chem.—Eur. J.* **2008**, *14*, 529; (c) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2000**, *2*, 4181; (d) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153.

10. (a) Gu, Y.; Tian, S. *Top. Curr. Chem.* **2012**, *327*, 197; (b) Takeda, T. *Modern Carbonyl Olefination*; Wiley-VCH: Weinheim, 2004.

Graphical abstract

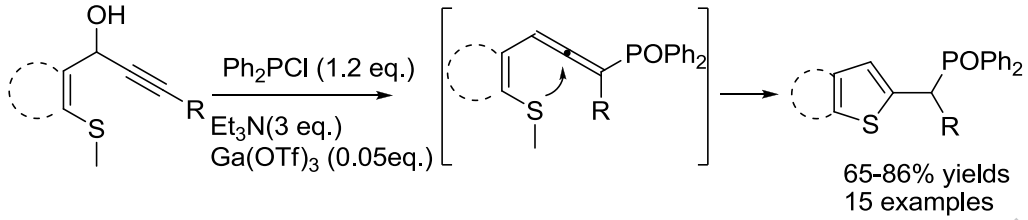


Abstract

An efficient one-pot protocol for the synthesis of functionalized thiophene and benzo[*b*]thiophene derivatives was developed *via* a sequence of propargyl–allenyl isomerization/cyclization/demethylation. As a result of the readily accessible starting materials, simple operation, and mild conditions, this reaction should have potential utility in organic synthesis.

Key words: thiophene; benzo[*b*]thiophene; propargyl–allenyl isomerization; cyclization; demethylation

Graphical abstract



Highlights

- Good functional group compatibility.
- Stable and available starting materials.
- The products can be serviceable building blocks.