Organic LETTERS

Letter

pubs.acs.org/OrgLett

A Simple and Efficient Synthesis of Substituted 2,2′-Bithiophene and 2,2′:5′,2″-Terthiophene

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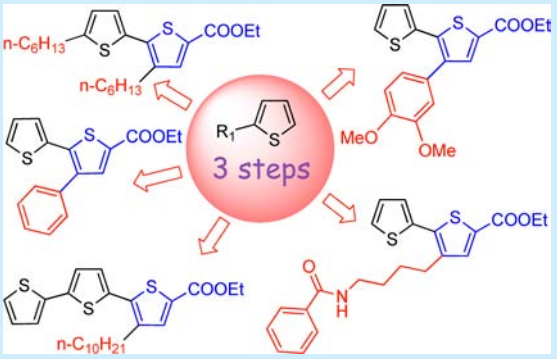
Supporting Information

ABSTRACT: A simple and efficient approach is developed for the synthesis of substituted 2,2′-bithiophene- and 2,2′:5′,2″-terthiophene-5-carboxylic acids and esters which is based on thiophene ring closure in the Fiesselmann reaction. Using this method, derivatives containing a long alkyl chain with or without an end functional group or an aryl substituent can be conveniently prepared.



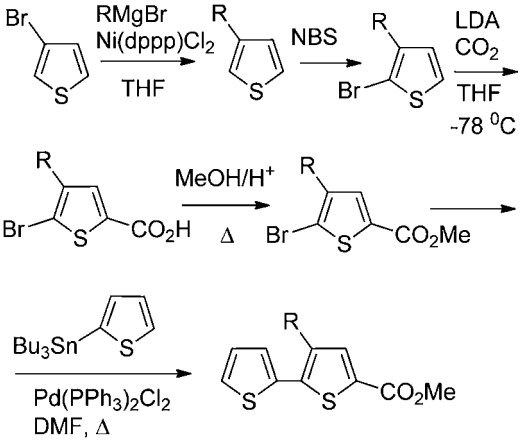
Functionalized bi- and terthiophenes are important building blocks for the synthesis of fluorescent markers for biological applications[1] and π-conjugated oligomers and polymers which are used in organic electronics as active layers in various devices such as organic light-emitting diodes, optical switches, solar cells, field effect transistors, etc.[2] They are also precursors to biologically active compounds.[3]

There are two general strategies for the synthesis of bi- and terthiophenes and similar conjugated compounds: the "building blocks" approach and the "ring closure" approach. In the first one, oxidative coupling or transition metal catalyzed cross-coupling reactions,[4] such as Stille,[4b,c] Suzuki,[4b,d−f] etc., are used for the thiophene−thiophene bond formation. Despite the fact that the "building blocks" approach is more popular, it is limited by the number of commercially available building blocks. Their low diversity and limited availability lead to decreasing efficiency of this approach. For example, a palladium-catalyzed Stille reaction was employed for the cross-coupling of 5-bromo-4-alkylthiophene-2-carboxylate ester with an appropriate thiophene organostannane to generate 3-alkyl-2,2′-bithiophene-5-carboxylate ester.[5] In this case, methyl 5-bromo-4-alkylthiophene-2-carboxylates are used as building blocks.

The known method for the preparation of these compounds starting from thiophene includes the synthesis of 3-bromothiophene[6a] (two steps), 3-alkylthiophene, and 2-bromo-3-alkylthiophem[5a,6b] and then carboxylation and etherification[5a] (Scheme 1). The last steps of this synthesis require the use of toxic reagents (organostannans, palladium catalysts) at low temperatures.

An alternative strategy for the synthesis of bi- and terthiophenes, proposed here, is based on the thiophene ring closure reaction using reagents, which contain additional conjugated aromatic rings as substituents.[4a,7]

Scheme 1. Synthesis of 3-Alkyl(aryl)-2,2′-bithiophene-5-carboxylate Starting from Thiophene by the "Building Blocks" Approach



In this paper we present this approach in which the Fiesselmann[8] reaction of ring closure is exploited in the synthesis of 3,5-substituted 2,2′-bithiophene- and 3-substituted 2,2′:5′,2″-terthiophene-5-carboxylic acids and esters.

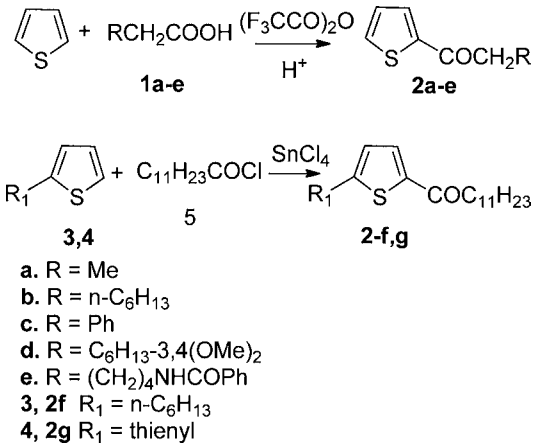
Ketones **2a−e** were obtained by the reaction of thiophene and the corresponding carboxylic acids **1a−e** in the presence of trifluoroacetic anhydride.[9]

Received: February 3, 2014
Published: March 13, 2014

dx.doi.org/10.1021/ol500356w | Org. Lett. 2014, 16, 1833−1835

2-Hexylthiophene, bithiophene, and lauric acid chloroanhydride in the presence of $SnCl_4$ were used for the synthesis of (5-hexyl-2-thienyl)dodecan-1-one **2f** and 1-(2,2′-bithien-5-yl)dodecan-1-one **2g** (Scheme 2). The yields of **2a–g** were in the range of 67–88%.

Scheme 2. Synthesis of Thienyl Ketones 2a–f



Thienyl ketones **2a–g** were converted to acrylaldehydes **6a–g** *via* the Vilsmeier–Haack–Arnold reaction with phosphorus oxychloride in dimethylformamide. Products were purified by column chromatography and identified by elemental analysis and spectroscopic means (NMR and FTIR). Compounds **6a–g** were obtained as mixtures of *Z*- and *E*-isomers with the total yields ranging from 67% to 87% (see Scheme 3 and Table 1).

Scheme 3. Chloroformylation of Thienyl Ketones 2a–g

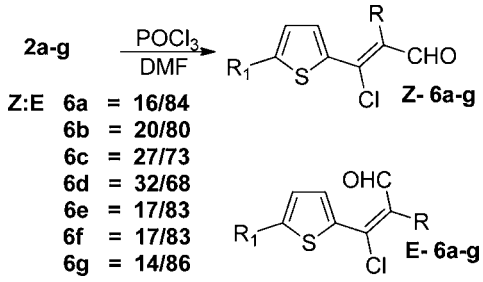


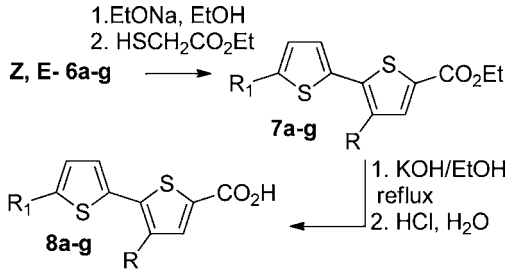
Table 1. Yields of Products 2, 6–8

entry	product	R	R_1	2	*Z,E*-6	7	8
1	a	Me	H	84	67	84	80
2	b	*n*-C_6H_{13}	H	87	75	80	93
3	c	Ph	H	88	87	83	79
4	d	$C_6H_3(OMe)_2$	H	45	78	76	78
5	e	$(CH_2)_4NHCOPh$	H	69	70	55	70
6	f	*n*-$C_{10}H_{21}$	*n*-C_6H_{13}	67	71	82	88
7	g	*n*-$C_{10}H_{21}$	thienyl	71	67	93	83

The isomer ratios were determined by the integration of the signals ascribed to formyl protons in the ^1H NMR spectra of the mixtures, which appear in the spectral range from 10.3 to 10.6 to 9.6–9.9 ppm with the chemical shift of the dominant *E*-isomer (≥68%) being located upfield with respect to that of the *Z*-isomer.[10]

The mixtures of *Z*- and *E*-isomers **6a–f** were converted to the corresponding esters **7a–f** through condensation with ethyl mercaptoacetate in the presence of sodium ethoxide in ethanol under reflux with yields of 55–93%. Hydrolysis of **7a–f** in ethanol containing sodium hydroxide led to the formation of carboxylic acids **8a–f** with yields of 70–93% (Scheme 4).

Scheme 4. Synthesis of Substituted 2,2′-Bithiophene- and 2,2′:5′,2″-Terthiophene-5-carboxylic Acids and Esters



Compounds **2f**, **6a–c,f**, and **7a,b,f,g** were obtained in the form of an oil and purified by column chromatography on silica gel. The solid products **2e,g**, **6d,e,g**, **7c,d,e**, and **8a–g** were recrystallized from suitable solvents. All intermediate and final products were identified by elemental analysis, NMR, and IR.

To conclude, we have elaborated a simple and efficient method for the synthesis of substituted 2,2′-bithiophene- and 2,2′:5′,2″-terthiophene-5-carboxylic acids and esters containing an alkyl chain with or without an end functional group or an additional aryl substituent.

This method, being more versatile than those previously reported, is based on the thiophene ring closure using the Fiesselmann reaction. In particular, compounds **7** and **8** can be obtained in good yields from commercial reagents in only three and four steps, respectively.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Russian Foundation for Basic Research (12-03-98013-p_sibiria_a). The authors would like to thank Prof. Adam Pron (Warsaw University of Technology) for constructive discussions.

■ REFERENCES

(1) (a) Capobianco, M. L.; Barbarella, G.; Manetto, A. *Molecules* **2012**, *17*, 910–933.

(2) (a) Mishra, A.; Ma, C.-Q.; Bäuerle, P. *Chem. Rev.* **2009**, *109*, 1141–1276. (b) Mitschke, U.; Debaerdemaeker, T.; Bäuerle, P. *Eur. J. Org. Chem.* **2000**, *3*, 425–437. (c) Mitschke, U.; Mena Osteritz, E.; Debaerdemaeker, T.; Sokolowski, M.; Bäuerle, P. *Chem.—Eur. J.* **1998**, *4*, 2211–2224. (d) Fisyuk, A. S.; Demadrille, R.; Querner, C.; Zagorska, M.; Bleuse, J.; Pron, A. *New J. Chem.* **2005**, *25*, 707–713. (e) Levi, M. D.; Fisyuk, A. S.; Demadrille, R.; Markevich, E.; Gofer, Y.;

Aurbach, D.; Pron, A. *Chem. Commun.* **2006**, *31*, 3299−3301. (f) Pomerantz, Z.; Levi, M. D.; Salitra, G.; Demadrille, R.; Fisyuk, A.; Zaban, A.; Aurbach, D.; Pron, A. *Phys. Chem. Chem. Phys.* **2008**, *10*, 1032−1042. (g) Kotwica, K.; Kurach, E.; Louarn, G.; Kostyuchenko, A. S.; Fisyuk, A. S.; Zagorska, M.; Pron, A. *Electrochim. Acta* **2013**, *111*, 491−498.

(3) (a) Cui, M.; Li, Z.; Tang, R.; Jia, H.; Liu, B. *Eur. J. Med. Chem.* **2011**, *46*, 2908−2916. (b) Xu, W.-C.; Ashendel, C. L.; Chang, C.-J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2279−2282. (c) Ismail, M. A.; El Bialy, S. A.; Brun, R.; Wenzler, T.; Nanjunda, R.; Wilson, W. D.; Boykin, D. W. *Bioorg. Med. Chem.* **2011**, *19*, 978−984.

(4) (a) Gronowitz, S.; Hörnfeldt, A.-B. *Thiophenes (Best Synthetic Methods)*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier: 2004; pp 745−943. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (c) Stas, S.; Sergeyev, S.; Geerts, Y. *Tetrahedron* **2010**, *66*, 1837−1845. (d) Price, S.; Bordogna, W.; Braganza, R.; Bull, R. J.; Dyke, H. J.; Gardan, S.; Gill, M.; Harris, N. V.; Heald, R. A.; van den Heuvel, M.; Lockey, P. M.; Lloyd, J.; Molina, A. G.; Roach, A. G.; Roussel, F.; Sutton, J. M.; White, A. B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 363−369. (e) Zambianchi, M.; Di Maria, F.; Cazzato, A.; Gigli, G.; Piacenza, M.; Della Sala, F.; Barbarella, G. *J. Am. Chem. Soc.* **2009**, *131*, 10892−10900. (f) Molin, M. D.; Matile, S. *Org. Biomol. Chem.* **2013**, *11*, 1952−1957.

(5) (a) Zhang, Y.; Chunchang, Z.; Yang, J.; Kapiamba, M.; Haze, O.; Rothberg, L. J.; Ng, M. K. *J. Org. Chem.* **2006**, *77*, 9475−9483. (b) Jaafari, A.; Ouzeau, V.; Ely, M.; Rodriguez, F.; Chane-ching, K.; Yassar, A.; Aaron, J. J. *Synth. Met.* **2004**, *147*, 183−189.

(6) (a) *Organic Syntheses*; Wiley & Sons: New York, 1964; Vol. *44*, pp 9−11. (b) Ng, M.-K.; Wang, L.; Yu, L. *Chem. Mater.* **2000**, *12*, 2988−2991. (c) Zhao, C.; Zhang, Y.; Wang, C.; Rothberg, L. J.; Ng, M.-K. *Org. Lett.* **2006**, *8*, 1585−1588.

(7) (a) Herbivo, C.; Comel, A.; Kirsch, G.; Manuela, M.; Raposo, M. *Tetrahedron.* **2009**, *65*, 2079−2086. (b) Raposo, M. M. M.; Ferreira, A.; Amaro, M. F. P.; Belsley, M.; Moura, J. C. V. P. *Dyes Pigm.* **2009**, *83*, 59−65. (c) Wynberga, H.; Metselaara, J. *Synth. Commun.* **1984**, *1*, 1−9.

(8) (a) Li, J. J. Fiesselmann thiophene synthesis. In *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, 4th ed.; Springer: Dordrecht, Heidelberg, London, New York, 2009; pp 225−226. (b) Bezboruah, P.; Gogoi, P.; Gogoi, J.; Boruah, R. C. *Synthesis* **2013**, *45*, 1341−1348.

(9) (a) Gally, C. *Synthesis* **1979**, 303−304. (b) Sundby, E.; Andersen, M. M.; Hoff, B. H.; Anthonsen, T. *ARKIVOC* **2001**, *(x)*, 76−84. (c) Adak, L.; Bhadra, S.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 3811−3814. (d) Baumgartner, M. T.; Gallego, M. H.; Pierini, A. B. *J. Org. Chem.* **1998**, *63*, 6394−6397. (e) Dorofeenko, G. N.; Sadekova, E. Y.; Kuznetsov, E. V. *Preparative Chemistry of Pyrylium Salts*; Rostov University: Rostov, Russia, 1972; p 110.

(10) Minkin, V. I.; Sadekov, I. D.; Rivkin, B. B.; Zakharov, A. V.; Nivorozhkin, V. L.; Kompan, O. E.; Struchkov, Yu. T. *J. Organomet. Chem.* **1997**, *536*−*537*, 233−248.

dx.doi.org/10.1021/ol500356w | *Org. Lett.* 2014, 16, 1833−1835