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[3+3] Annulation of donor–acceptor cyclopropanes with mercaptoacetaldehyde: application to the synthesis of tetrasubstituted thiophenes†

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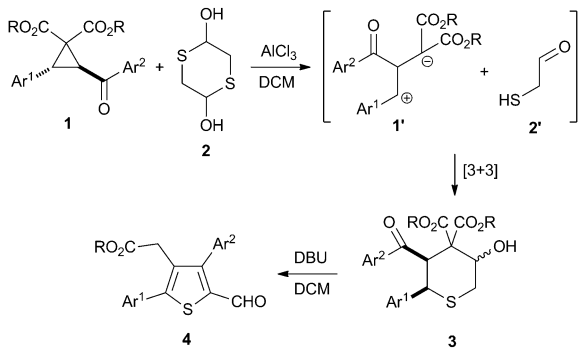
A conceptually new method for synthesis of tetrasubstituted thiophenes in two steps from *trans*-2-aroyl-3-aryl-cyclopropane-1,1-dicarboxylates and 1,4-dithiane-2,5-diol has been developed. It involves $AlCl_3$-mediated [3+3] annulation of the cyclopropane-derived 1,3-zwitterionic intermediates with *in situ* generated mercaptoacetaldehyde, followed by DBU-induced rearrangement of the resulting tetrahydrothiopyranols. The target thiophenes are produced in 55–82% yields.

The thiophene ring is encountered in a notable number of pharmaceuticals[1] such as *articaine*, *cymbalta*, *plavix*, *raltitrexed* and *zyprexa* and also in natural products[2] such as *echinothiophene*, *urothione* and *xanthopappins A–C*. Further, thiophene-based materials find widespread applications in organic electronics as semiconductors, field effect transistors, light emitting diodes, molecular wires, photovoltaic materials, and nonlinear optical materials, *etc.*[3] The importance of thiophene derivatives has driven the development of numerous methods for the synthesis of thiophenes with diverse substitution patterns.[4] To complement these reports, we herein report a *de novo* synthesis of tetrasubstituted thiophenes from tetrahydrothiopyranols, which are in turn prepared by [3+3] annulation of activated donor–acceptor (D–A) cyclopropanes with *in situ* generated mercaptoacetaldehyde (Scheme 1).

D–A cyclopropanes are valuable building blocks in organic synthesis[5] and upon treatment with Lewis acids, they readily undergo ring-opening to form 1,3-zwitterions, which participate in several [3+*n*] (*n* = 2, 3, 4) annulation reactions with apt partners giving an assortment of carbo- and heterocycles. As compared with [3+2] annulations of D–A cyclopropanes, only a small number of [3+3] and [3+4] annulations are known. Especially, for *trans*-2-aroyl-3-aryl-cyclopropane-1,1-dicarboxylates **1**, only a few [3+2] annulations (with aldehydes,[6] nitriles[7] and isocyanates[8]) have been reported and no higher order annulation has been known to date.



Scheme 1 Synthesis of tetrahydrothiopyranols and thiophenes.

1,4-Dithiane-2,5-diol (**2**) is also a versatile synthetic precursor and releases mercaptoacetaldehyde *in situ* upon treatment with tertiary amines[9] or certain organocatalysts.[10] The phenomenon has been exploited in many [3+2] annulations for accessing a variety of tetra- and dihydrothiophenes and thiophenes.[9,10] However, only recently, its first ever-known [3+3] annulation with azomethineimine has been reported.[11]

We envisaged that the [3+3] annulation of *trans*-2-aroyl-3-aryl-cyclopropane-1,1-dicarboxylates **1**, with *in situ* prepared mercaptoacetaldehyde (**2′**), would not only represent the previously unknown partnership in D–A cyclopropane chemistry, but also furnish useful tetrahydrothiopyranol derivatives **3**. Pleasingly, when **1a** was reacted with **2** in the presence of $AlCl_3$ (1 equiv.) in DCM at room temperature, a chromatographically homogeneous, diastereomeric mixture of **3a** and **3a′** (dr 9 : 1) was obtained in 74% isolated yield (Scheme 2). Our attempts to improve the yield of the mixture or prepare one of the diastereomers exclusively by varying the Lewis acid or its loading and also changing the solvent or reaction temperature did not materialize. However, we were able to separate the major diastereomer **3a** in the pure form (60% yield) from the mixture by crystallization. It may be noted that the separation of this diastereomeric mixture into individual components is quite unnecessary

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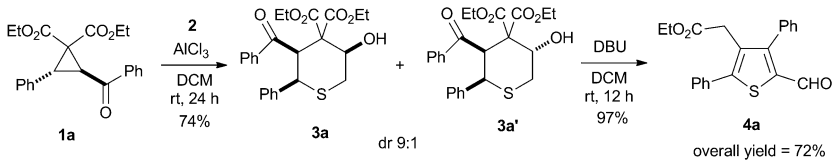
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all products, including copies of ^{1}H and ^{13}C NMR spectra and X-ray structural information of **3m** and **4d** (CIF). CCDC 981071 and 981072. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00565a



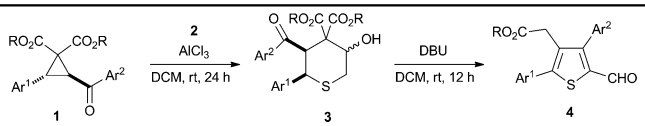
Scheme 2 Formation of a diastereomeric mixture of tetrahydrothiopyranols and their conversion into a thiophene.

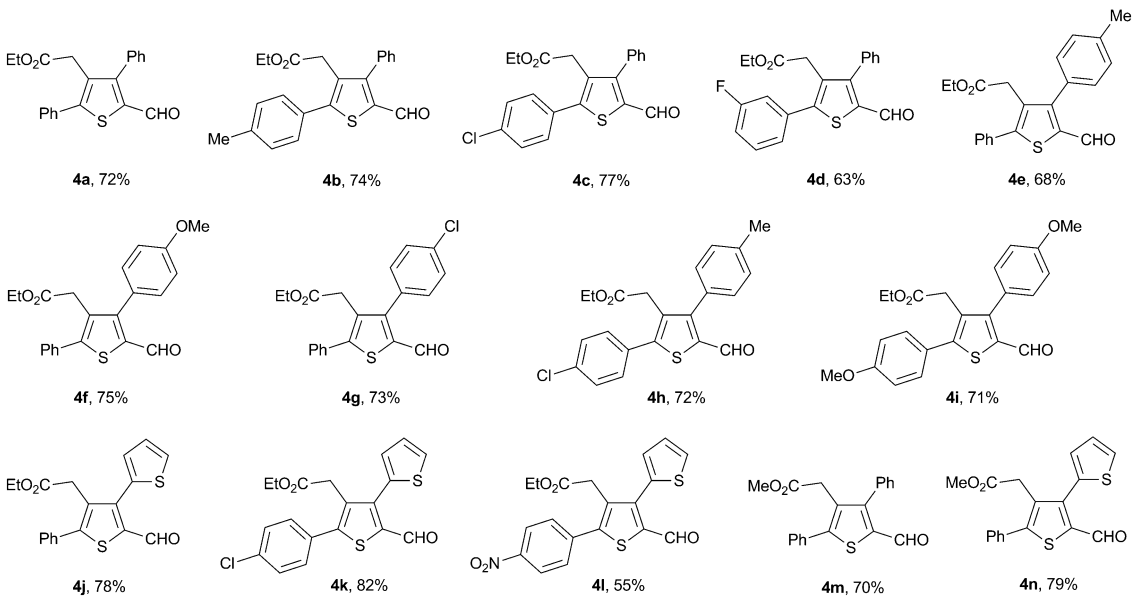
because both diastereomers are equally suitable for further conversion into a thiophene and, moreover, the stereochemical information would be lost in the final product. Thus, when the diastereomeric mixture of **3a** and **3a′** was treated with DBU in DCM, the target thiophene **4a** was produced in 97% yield (overall yield = 72%; pure **3a** also gave **4a** in identical yield). We also attempted to develop one-pot synthesis of **4a** from **1a** by coupling both the steps, but it resulted in a complicated mixture. Thus, the removal of the Lewis acid by at least filtering through Celite after the first step is mandatory before proceeding to the second step.

Next, we examined the scope of the two-step transformation for various 2-aroyl-3-aryl-cyclopropane-1,1-dicarboxylates (Table 1). The placement of different electron releasing and halogen substituents on the two aromatic rings Ar^1 and Ar^2 was well tolerated and the respective thiophenes **4a–4i** were produced in good overall yields. However, when the nitro substituent was present on Ar^1 (*p*-nitrophenyl), the reaction was sluggish and no isolable amount of tetrahydrothiopyranol could be obtained even after 5 days. On the other hand, the nitro substituent on Ar^2 (*p*-nitrophenyl) produced a complicated mixture, from which no traces of thiophene could be isolated. Next, we focused our attention on replacing Ar^1 and Ar^2 with heteroaromatic rings. We envisaged that when either or both of Ar^1 and Ar^2 are thienyl, it would lead to di- and trithiophenes. Unfortunately, when Ar^1 was 2-thienyl, it produced a complicated mixture. However, when Ar^2 was 2-thienyl, we obtained the expected dithiophenes **4j–l**. Surprisingly, dithiophene **4l** which has *p*-nitrophenyl as Ar^1 was also accessible, albeit in low yield. Methyl esters of the starting cyclopropanes were also equally compatible in the reaction as exemplified by the formation of thiophene **4m** and dithiophene **4n** from the respective precursors. In the majority of reactions, the intermediate tetrahydrothiopyranols were obtained as mixtures of diastereomers with 2,3,5-*cis*-isomers being predominant. We did not attempt to separate or purify the diastereomers and proceeded to the next step after removing the Lewis acid by passing through Celite. Nevertheless, in certain cases, we obtained tetrahydrothiopyranols [**3a** (Ar^1 = Ar^2 = Ph, R = Et), **3k** (Ar^1 = 4-ClC_6H_4, Ar^2 = 2-thienyl, R = Et) and **3m** (Ar^1 = Ar^2 = Ph, R = Me)] as single diastereomers by repeated crystallization of the corresponding mixtures. The structures of tetrahydrothiopyranol **3m** and thiophene **4d** were unambiguously confirmed by X-ray crystallographic studies (Fig. 1).[12]

We propose the following mechanism for the overall transformation of *trans*-cyclopropanediesters **1** into thiophenes **4** (Scheme 3). The Lewis acid coordinates with the malonyl unit of **1**, which results in C1–C3 bond cleavage to form the intimate ion-pair **A**.[6–8,13]

Table 1 Scope of the two-step thiophene synthesis[a,b]





[a] Reaction conditions: the reaction was conducted with **1** (0.5 mmol) and **2** (2.5 mmol) in the presence of $AlCl_3$ (0.5 mmol) in DCM (5 mL) at rt for 24 h and then crude **3** was treated with DBU (1 mmol) in DCM (5 mL) at rt for 12 h. [b] Isolated overall yield.

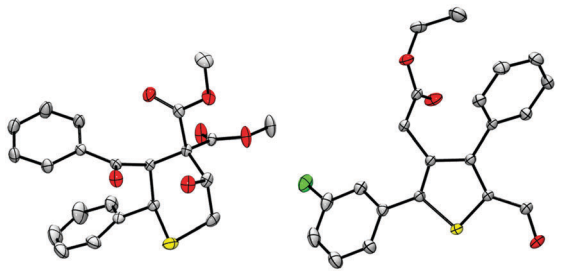
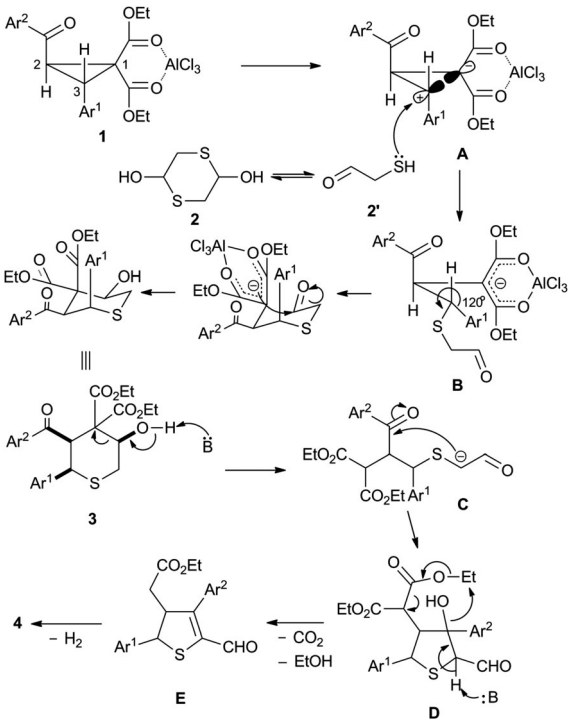


Fig. 1 X-ray structures of **3m** (left) and **4d** (right).



Scheme 3 Plausible reaction mechanism for formation of thiophenes **4**.

Mercaptoacetaldehyde (**2′**) generated *in situ* from **2** attacks C3 of **A** in a S_N2 fashion to give **B**, which undergoes a 120° rotation to bring the malonate anion closer to the aldehyde carbonyl group. The ensuing nucleophilic attack of the malonate anion on carbonyl gives the cyclized product **3** in which the hydroxyl group is in the equatorial position (the attack on the opposite face of the carbonyl would give the minor diastereomer **3′** in which the hydroxyl group is in an unfavourable axial position). In the second step, the base (DBU) removes the hydroxyl proton of **3** (+**3′**) which leads to ring-opening followed by the formation of a carbanion as shown in **C**. The anion attacks the ketone carbonyl group to give tetrahydrothiophene **D**. Base-assisted elimination of CO_2 and ethanol from **D** gives dihydrothiophene **E**, which upon aromatization affords thiophene **4**.

In summary, we have developed a new two-step procedure for the synthesis of tetrasubstituted thiophenes from D–A cyclopropanes and 1,4-dithiane-2,5-diol. The first step involves $AlCl_3$-mediated [3+3] annulation of the cyclopropane-derived zwitterionic intermediates with *in situ* generated mercaptoacetaldehyde to afford tetrahydrothiopyranols, and the second step involves DBU-mediated rearrangement of tetrahydrothiopyranols into thiophenes. This method is operationally simple and requires only cheap and readily available starting materials. We are currently exploring the synthesis of thiophene-based advanced materials using the methodology for molecular electronics study.

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Notes and references

1 (*a*) L. Wang, C. Cherian, S. K. Desmoulin, L. Polin, Y. Deng, J. Wu, Z. Hou, K. White, J. Kushner, L. H. Matherly and A. Gangjee, *J. Med. Chem.*, 2010, **53**, 1306; (*b*) C. J. O' Connor, M. D. Roydhouse, A. M. Przybyl, M. D. Wall and J. M. Southern, *J. Org. Chem.*, 2010, **75**, 2534; (*c*) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2013, DOI: 10.1021/jm401375q.

2 (*a*) E. C. Taylor and L. A. Reiter, *J. Am. Chem. Soc.*, 1989, **111**, 285; (*b*) K. Koike, Z. Jia, T. Nikaido, Y. Liu, Y. Zhao and D. Guo, *Org. Lett.*, 1999, **1**, 197; (*c*) Y. Tian, X. Wei and H. Xu, *J. Nat. Prod.*, 2006, **69**, 1241.

3 (*a*) J. M. Tour, *Acc. Chem. Res.*, 2000, **33**, 791; (*b*) J.-M. Raimundo, P. Blanchard, I. L. Rak, R. Hierle, L. Michauxa and J. Roncali, *Chem. Commun.*, 2000, 1597; (*c*) H. E. Katz, Z. Bao and S. L. Gilat, *Acc. Chem. Res.*, 2001, **34**, 359; (*d*) A.-L. Ding, J. Pei, Y.-H. Lai and W. Huang, *J. Mater. Chem.*, 2001, **11**, 3082; (*e*) S. Allard, M. Forster, B. Souharce, H. Thiem and U. Scherf, *Angew. Chem., Int. Ed.*, 2008, **47**, 4070; (*f*) A. Mishra, C.-Q. Ma and P. Bauerle, *Chem. Rev.*, 2009, **109**, 1141; (*g*) W. Wu, Y. Liu and D. Zhu, *Chem. Soc. Rev.*, 2010, **39**, 1489; (*h*) A. Mishra and P. Bauerle, *Angew. Chem., Int. Ed.*, 2012, **51**, 2020; (*i*) Y. Chen, X. Wan and G. Long, *Acc. Chem. Res.*, 2013, **46**, 2645.

4 For recent reports, see: (*a*) Y. Zhang, M. Bian, W. Yao, J. Gu and C. Ma, *Chem. Commun.*, 2009, 4729; (*b*) W. You, X. Yan, Q. Liao and C. Xi, *Org. Lett.*, 2010, **12**, 3930; (*c*) G. C. Nandi, S. Samai and M. S. Singh, *J. Org. Chem.*, 2011, **76**, 8009; (*d*) M. Teiber and T. J. J. Muller, *Chem. Commun.*, 2012, 2080; (*e*) B. Gabriele, R. Mancuso, G. Salerno and R. C. Larock, *J. Org. Chem.*, 2012, **77**, 7640; (*f*) B. Gabriele, R. Mancuso, L. Veltri, V. Maltese and G. Salerno, *J. Org. Chem.*, 2012, **77**, 9905; (*g*) C. R. Reddy, R. R. Valleti and M. D. Reddy, *J. Org. Chem.*, 2013, **78**, 6495; (*h*) L.-R. Wen, T. He, M.-C. Lan and M. Li, *J. Org. Chem.*, 2013, **78**, 10617; (*i*) H. Jullien, B. Quiclet-Sire, T. Tetart and S. Z. Zard, *Org. Lett.*, 2014, **16**, 302.

5 For reviews, see: (*a*) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; (*b*) M. Yu and B. L. Pagenkopf, *Tetrahedron*, 2005, **61**, 321; (*c*) C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051; (*d*) F. De Simone and J. Waser, *Synthesis*, 2009, 3353; (*e*) M. Y. Melnikov, E. M. Budynina, O. A. Ivanova and I. V. Trushkov, *Mendeleev Commun.*, 2011, **21**, 293; (*f*) P. Tang and Y. Qin, *Synthesis*, 2012, 2969–2984; (*g*) M. A. Cavitt, L. H. Phun and S. France, *Chem. Soc. Rev.*, 2014, **43**, 804.

6 (*a*) G. Yang, Y. Shen, K. Li, Y. Sun and Y. Hua, *J. Org. Chem.*, 2011, **76**, 229; (*b*) G. Yang, Y. Sun, Y. Shen, Z. Chai, S. Zhou, J. Chu and J. Chai, *J. Org. Chem.*, 2013, **78**, 5393.

7 G. Sathishkannan and K. Srinivasan, *Org. Lett.*, 2011, **13**, 6002.

8 Y. Sun, G. Yang, Z. Chai, X. Mu and J. Chai, *Org. Biomol. Chem.*, 2013, **11**, 7859.

9 (*a*) A. Barco, N. Baricordi, S. Benetti, C. D. Risib and G. P. Pollini, *Tetrahedron Lett.*, 2006, **47**, 8087; (*b*) Y. Dong, D. Navarathne, A. Bolduc, N. McGregor and W. G. Skene, *J. Org. Chem.*, 2012, **77**, 5429; (*c*) N. Baricordi, S. Benetti, V. Bertolasi, C. D. Risi, G. P. Pollini, F. Zamberlan and V. Zanirato, *Tetrahedron*, 2012, **68**, 208; (*d*) C. Xu, J. Du, L. Ma, G. Li, M. Tao and W. Zhang, *Tetrahedron*, 2013, **69**, 4749.

10 (*a*) J. Tang, D. Q. Xu, A. B. Xia, Y. F. Wang, J. R. Jiang, S. P. Luo and Z. Y. Xu, *Adv. Synth. Catal.*, 2010, **352**, 2121; (*b*) J.-B. Ling, Y. Su, H.-L. Zhu, G.-Y. Wang and P.-F. Xu, *Org. Lett.*, 2012, **14**, 1090; (*c*) S.-W. Duan, Y. Li, Y.-Y. Liu, Y.-Q. Zou, D.-Q. Shi and W.-J. Xiao, *Chem. Commun.*, 2012, 5160; (*d*) Y. Su, J.-B. Ling, S. Zhang and P.-F. Xu, *J. Org. Chem.*, 2013, **78**, 11053.

11 X. Fang, J. Li, H.-Y. Tao and C.-J. Wang, *Org. Lett.*, 2013, **15**, 5554.

12 CCDC 981071 for compound **3m** and CCDC 981072 for compound **4d**. See the ESI† for details.

13 P. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li and J. S. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 8642.

