Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1639

www.rsc.org/obc

PAPER

Lawesson's reagent-initiated domino reaction of aminopropenoyl cyclopropanes: synthesis of thieno[3,2-*c*]pyridinones†

Peng Huang, Rui Zhang, Yongjiu Liang and Dewen Dong*

Received 10th October 2011, Accepted 6th December 2011
DOI: 10.1039/c2ob06709a

A convenient and efficient synthesis of substituted 2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-ones has been developed and relies upon a domino reaction of dimethylaminopropenoyl cyclopropanes initiated by Lawesson's reagent. A mechanism involving regioselective thionation, ring-enlargement, and an intramolecular aza-cyclization sequence is proposed. This protocol was utilized as a one-pot route to thieno[3,2-*c*]pyridin-4(5*H*)-ones with DDQ as an oxidant.

Introduction

Thieno[3,2-*c*]pyridines and their analogues have attracted significant attention since their core structure is present in a number of synthetic organic compounds, such as cardiovascular drugs Ticlopidine and Clopidogrel, along with a broad range of pharmaceutical activities.[1] Among them, thieno[3,2-*c*]pyridin-4(5*H*)-ones are widely used as PRL phosphatase inhibitors,[2] blood-platelet aggregation inhibitors,[3] and 5-HT_3 receptor antagonists.[4] Additionally, they are versatile intermediates for the synthesis of thieno[3,2-*c*]pyridines that behave as anti-tumor, anti-inflammatory, and anti-psychotic agents.[5] The synthetic and pharmacological importance of thieno[3,2-*c*]pyridin-4(5*H*)-ones have directed considerable research activity towards the construction of the skeleton of such heterocycles.[6] The notable synthetic route is based on the thermal isomerization and cyclization of a 2-(2-isocyanatovinyl)thiophene to form the pyridinone ring as the key step.[5,7] However, most of the established synthetic approaches suffer from harsh reaction conditions, serious safety and environmental problems due to their use of thionyl chloride and sodium azide, and limited substrate scope. To match the increasing scientific and practical demands, it is of continued interest and great importance to explore simple and efficient synthetic approaches for the construction of thieno[3,2-*c*]pyridin-4(5*H*)-ones, especially those with wide applicability to achieve more elaborate and flexible substitution patterns.

On the other hand, the overwhelming importance of cyclopropane derivatives in organic synthesis has been recognized for their well-known 'unsaturated' character, which can lead to a variety of ring-opening reactions under the influence of a wide range of chemicals, *e.g.* electrophiles, nucleophiles and radicals.[8] During the course of our studies on the chemistry of cyclopropanes, we achieved efficient synthesis of substituted pyridin-2(1*H*)-ones,[9a] 1*H*-pyrazoles,[9b] isoxazoles,[9b] and spiro-fused pyrazolin-5-one *N*-oxides[10] from readily available activated cyclopropanes under Vilsmeier conditions or mediated by hypervalent iodine reagents. In our recent work, we prepared a series of dimethylaminopropenoyl cyclopropanes and developed synthesis of pyridin-2(1*H*)-ones, 2,3-dihydrofurans, and 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones.[11] In the present work, we examined the reaction behavior of such dimethylaminopropenoyl cyclopropanes toward Lawesson's reagent.[12] As a result, we developed a convenient and efficient synthesis of 2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-ones. Herein, we wish to report our preliminary results and present a plausible mechanism involving the domino reactions.

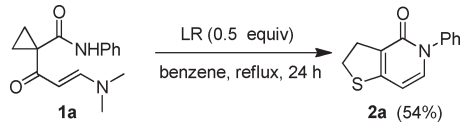
Results and discussion

The substrates, dimethylaminopropenoyl cyclopropanes **1**, were prepared according to the procedures described in our previous reports in high yields (up to 91%).[11] Thus, the reaction of 1-[3-(dimethylamino)acryloyl]-*N*-phenyl cyclopropanecarboxamide **1a** with Lawesson's reagent (LR, 0.5 equiv.) was first attempted in benzene at room temperature, however, no reaction was observed as indicated by TLC examination of the reaction mixture. When the mixture was heated to reflux for 24 h, the reaction proceeded and furnished a white solid along with small amount of intact **1a** after work-up and purification by column chromatography. The product was characterized as 5-phenyl-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one **2a** (54%) on the basis of its spectral and analytical data (Scheme 1).

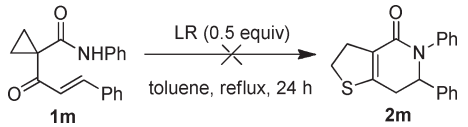
These results encouraged us to optimize the reaction conditions, including solvent, reaction temperature and the ratio of LR to **1a**. A series of experiments revealed that the reaction could proceed in other solvents, such as toluene and xylene, and

Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, China. E-mail: dwdong@ciac.jl.cn

†Electronic supplementary information (ESI) available: Experimental details, full characterization data, and copies of NMR spectra for compounds **1h–k**, **2**, and **3**. See DOI: 10.1039/c2ob06709a



Scheme 1 Reaction of **1a** with Lawesson's reagent in benzene.

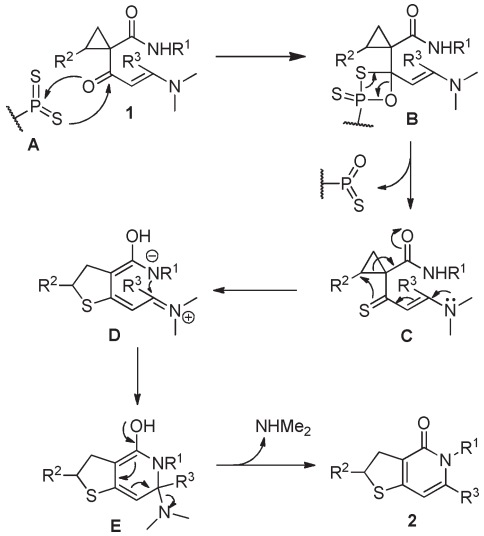


Scheme 2 Reaction of **1m** with Lawesson's reagent.

Table 1 Synthesis of 2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-ones **2**[a]

Entry	1	R^1	R^2	R^3	2	Yield (%)[b]
1	**1a**	Ph	H	H	**2a**	82
2	**1b**	2-MeC_6H_4	H	H	**2b**	80
3	**1c**	4-MeC_6H_4	H	H	**2c**	83
4	**1d**	2,4-$Me_2C_6H_3$	H	H	**2d**	84
5	**1e**	2-MeOC_6H_4	H	H	**2e**	81
6	**1f**	4-MeOC_6H_4	H	H	**2f**	87
7	**1g**	2-ClC_6H_4	H	H	**2g**	74
8	**1h**	4-ClC_6H_4	H	H	**2h**	76
9	**1i**	4-$CF_3C_6H_4$	H	H	**2i**	71
10	**1j**	Bn	H	H	**2j**	83
11	**1k**	Ph	H	Me	**2k**	68
12	**1l**	4-MeC_6H_4	Ph	H	**2l**	85

[a] Reagents and conditions: **1** (1.0 mmol), LR (0.5 mmol), toluene (dry, 10 mL), reflux, 9–11 h. [b] Isolated yields.



Scheme 3 Plausible mechanism for the domino reaction of **1** with Lawesson's reagent.

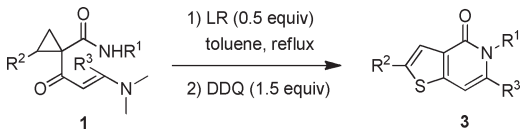
0.5 equivalents of LR was sufficient for the dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one synthesis. However, much more LR, for example more than 0.6 equivalents, would result in a complex mixture. The optimal results were obtained when **1a** was subjected to 0.5 equivalents of LR in dry toluene under reflux for 10 h, whereby the reaction exclusively afforded **2a** in 82% yield (Table 1, entry 1).

Having established the optimal conditions for the dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one synthesis, we intended to determine its scope with respect to the R^1, R^2 and R^3 groups. A series of reactions of aminopropenoyl cyclopropanes **1b–j** bearing varied aryl and alkyl amide groups were then performed with LR under the identical conditions as for **2a**. It was observed that all the reaction proceeded smoothly to afford the corresponding dihydrothieno[3,2-*c*]pyridin-4(5*H*)-ones **2** in moderate to good yields (Table 1, entries 2–10). The versatility of this dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one synthesis was further evaluated by subjecting aminopropenoyl cyclopropane **1k** and LR to the identical conditions (Table 1, entry 11). The efficiency of the cyclization proved to be suitable for aminopropenoyl cyclopropane **1l** to afford the corresponding substituted dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one **2l** in good yield (Table 1, entry 12). In this case, a single regioisomer was exclusively obtained, which indicated that the ring-opening reaction or ring-enlargement proceeded in a regioselective manner.[11a,13]

To extend the scope of this thieno[3,2-*c*]pyridinone synthesis, we prepared 1-cinnamoyl-*N*-phenylcyclopropane carboxamide **1m** and subjected it with LR to toluene under reflux. Unfortunately, the reaction formed a complex mixture, and the desired product **2m** was not even detected by means of NMR spectroscopy (Scheme 2). This result suggested that the dimethylamino group of substrate **1** is essential to the above domino reaction, in which it played dual roles as activated group for the thionation and a good leaving group for the intramolecular aza-cyclization.[14] Nevertheless, all the results demonstrated the efficiency and synthetic interest of the domino reaction with respect to a wide range of aminopropenoyl cyclopropanes **1**. We provided a facile and efficient one-pot synthesis of substituted 2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one of type **2**.

To gain an insight into the mechanism of the domino reaction, some separate experiments were conducted. No reaction was observed when **1a** was subjected to *N*,*N*-dimethyl formamide (DMF) in the absence of or in the presence of K_2CO_3 (1.5 equiv.) at 110 °C. Similarly, no reaction occurred when **1a** was treated with 1.5 equivalents of Lewis acid, such as $SnCl_4{\cdot}5H_2O$, $FeCl_3$, or $ZnCl_2$, in toluene under reflux. These results suggested that LR played a crucial role and the thionation triggered the domino reaction of **1**.[15] On the basis of all the findings, a plausible mechanism for the synthesis of **2** is presented in Scheme 3. Initially, the dissociation of LR produces phosphorus sulfide **A** in dry toluene under reflux.[16] The strong electron-donating dimethylamino group of **1** activated its conjugated carbonyl group, and makes it more liable to be thionated by **A** than the carbonyl group of amide moiety.[17] The generated oxathiaphosphetane **B** sheds off thioxophosphine oxide to afford thioketone **C**,[18] which then undergoes regioselective ring-enlargement reaction to form intermediate **D**.[13,19] Finally, intramolecular aza-cyclization of **D** along with the release of dimethylamine takes place to give dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one **2**.[14]

Table 2 One-pot synthesis of thieno[3,2-*c*]pyridin-4(5*H*)-ones **3**[a]



1 **3**

Entry	**1**	R^1	R^2	R^3	**3**	Yield (%)[b]
1	**1a**	Ph	H	H	**3a**	75
2	**1e**	2-$MeOC_6H_4$	H	H	**3e**	78
3	**1h**	4-ClC_6H_4	H	H	**3h**	73
4	**1k**	Ph	H	Me	**3k**	67
5	**1l**	4-MeC_6H_4	Ph	H	**3l**	82

[a] Reagents and conditions: **1** (1.0 mmol), LR (0.5 mmol), toluene (anhydrous, 10 mL), reflux, 9–11 h, then DDQ (1.5 mmol), reflux, 1 h. [b] Isolated yields.

Inspired by the above results, we envisaged to explore one-pot synthesis of thieno[3,2-*c*]pyridin-4(5*H*)-ones from **1**. Thus, the reaction of **1a** and LR was performed in toluene under reflux for 10 h, and then an oxidant, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), was added to the resulting mixture which was left under reflux for another hour.[20] The reaction furnished a product after work-up and purification by column chromatography. The product was characterized as 5-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one **3a** on the basis of its spectral and analytical data, and the overall yield reached 75% (Table 2, entry 1). In the same fashion, some selected aminopropenoyl cyclopropanes **1** were subjected to LR and DDQ in toluene under reflux to afford the corresponding thieno[3,2-*c*]pyridin-4(5*H*)-ones **3** in moderate to good overall yields (Table 2, entries 2–5). Therefore, we have provided a facile one-pot synthesis of substituted thieno[3,2-*c*]pyridin-4(5*H*)-ones of type **3**.

Conclusions

In summary, a facile and efficient one-pot synthesis of substituted 2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-ones **2** is developed from aminopropenoyl cyclopropanes **1** mediated by Lawesson's reagent, which involved sequential regioselective thionation, ring-enlargement, and intramolecular aza-cyclization reactions. This protocol was further utilized as a one-pot route to thieno[3,2-*c*]pyridin-4(5*H*)-ones **3** with DDQ as oxidant. The one-pot procedure is associated with readily available substrates, mild conditions, and a wide range of potential synthetic products. Further work on the utilization and extension of the scope of the methodology are currently under investigation in our laboratory.

Experimental

General methods

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 400 MHz (or 300 MHz) and 100 MHz, respectively. IR spectra (KBr) were recorded on FTIR spectrophotometer in the range of 400–4000 cm^{-1}. Elemental analyses were carried out on a Perkin-Elmer PE-2400 analyzer. Mass spectra were recorded on LDI-1700 MALDI-TOF spectrometer. Melting points were determined on a TECH X-4 micro-melting point apparatus.

Synthesis and analytical data of substrates 1

1a–g, **1l**, and **1m** are known compounds, they were readily prepared according to reported procedures.[11,13*b*,21]

***N*-(4-Chlorophenyl)-1-[3-(dimethylamino)acryloyl]cyclopropanecarboxamide (1h).** White solid, mp 186–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (dd, J_1 = 7.8, J_2 = 5.2, 2H), 1.85 (dd, J_1 = 7.8, J_2 = 5.2, 2H), 2.83 (s, 3H), 3.14 (s, 3H), 4.69 (d, J = 12, 1H), 7.23–7.28 (m, 2H), 7.56–7.60 (m, 2H), 7.75 (d, J = 12, 1H), 12.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 31.2, 37.1, 45.0, 88.0, 121.0, 127.9, 128.5, 137.3, 154.6, 169.2, 196.2. Anal. Calcd. for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57. Found: C, 61.31; H, 5.80; N, 9.68.

1-[3-(Dimethylamino)acryloyl]-*N*-(4-(trifluoromethyl)phenyl)-cyclopropanecarboxamide (1i). White solid, mp 162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (dd, J_1 = 7.8, J_2 = 5.2, 2H), 1.86 (dd, J_1 = 7.8, J_2 = 5.2, 2H), 2.83 (s, 3H), 3.14 (s, 3H), 4.68 (d, J = 12, 1H), 7.54 (d, J = 8.7, 2H), 7.73 (d, J = 8.7, 2H), 7.75 (d, J = 12, 1H), 12.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 31.4, 37.2, 45.1, 88.0, 119.5, 124.3 (q, $^1J_{CF}$ = 270) 124.9 (q, $^2J_{CF}$ = 32), 125.9 (d, $^3J_{CF}$ = 3), 141.8, 154.8, 169.8, 196.3. Anal. Calcd. for $C_{16}H_{17}F_3N_2O_2$: C, 58.89; H, 5.25; N, 8.58. Found: C, 58.68; H, 5.21; N, 8.65.

***N*-Benzyl-1-[3-(dimethylamino)acryloyl]cyclopropanecarboxamide (1j).** Liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, J = 3.6, 2H), 1.67 (t, J = 3.6, 2H), 2.70 (s, 3H), 3.00 (s, 3H), 4.45 (t, J = 2.7, 2H), 4.65 (d, J = 12, 1H), 7.18–7.27 (m, 5H), 7.58 (dd, J_1 = 12, J_2 = 3.0, 1H), 9.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 31.3, 36.4, 42.9, 44.3, 88.6, 126.4, 126.9, 127.9, 138.4, 153.6, 170.5, 195.0. Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.23; H, 7.46; N, 10.37.

1-[3-(Dimethylamino)but-2-enoyl]-*N*-phenylcyclopropanecarboxamide (1k). To a well-stirred solution of 1-acetyl-*N*-phenyl cyclopropanecarboxamide (10 mmol) in benzene (25 mL) was added 1,1-dimethoxy-*N*,*N*-dimethylethanamine (15 mmol) dropwise within 5 min at room temperature. The reaction mixture was heated to reflux and stirred for 6 h, then it was slowly poured into saturated aqueous NaCl (200 mL), which was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, petroleum ether : ethyl acetate (3 : 1)) to give **1k** as a white solid (73%). White solid, mp 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (dd, J_1 = 7.5, J_2 = 5.2, 2H), 1.73 (dd, J_1 = 7.5, J_2 = 5.2, 2H), 2.54 (s, 3H), 3.01 (s, 6H), 4.78 (s, 1H), 7.04 (t, J = 7.5, 1H), 7.30 (d, J = 7.5, 2H), 7.61 (d, J = 7.5, 2H), 11.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6, 19.0, 33.5, 40.1, 89.5, 120.0, 123.3, 128.6, 138.7, 164.9, 169.6, 194.8. Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.90; H, 7.48; N, 10.20.

Synthesis and analytical data of 2

Typical procedure for the synthesis of 2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-ones 2 (with 2a as an example). To a solution of **1a** (1.0 mmol) in anhydrous toluene (10 mL) was added Lawesson's reagent (0.5 mmol) in one portion. The mixture was heated to reflux and stirred for 10 h. After **1a** was consumed as monitored by TLC, the reaction was cooled down to room temperature. The resulting mixture was then poured into saturated aqueous NaCl (50 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petroleum ether : EtOAc (2 : 1)) to give **2a** as a white solid in 82% yield.

5-Phenyl-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2a). White solid, mp 152–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29–3.37 (m, 2H), 3.42–3.49 (m, 2H), 6.24 (d, J = 6.9, 1H), 7.21 (d, J = 6.9, 1H), 7.34–7.37 (m, 2H), 7.39–7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8, 33.4, 101.9, 126.6, 126.8, 128.1, 129.0, 136.7, 140.6, 154.8, 158.3. IR (KBr, cm^{-1}) 3083, 2918, 1660, 1589, 1573, 1446, 1263, 746, 678. Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.09; H, 4.84; N, 6.11. Found: C, 68.30; H, 4.80; N, 6.06.

5-*o*-Tolyl-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2b). White solid, mp 142–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 3.30–3.36 (m, 2H), 3.44–3.49 (m, 2H), 6.24 (d, J = 6.9, 1H), 7.06 (d, J = 7.2, 1H), 7.16 (d, J = 6.9, 1H), 7.28–7.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 32.8, 33.3, 101.8, 126.9, 127.3, 128.8, 130.9, 135.2, 136.8, 139.8, 154.8, 158.1. IR (KBr, cm^{-1}) 3076, 3049, 2981, 2947, 2916, 2881, 2840, 1865, 1643, 1573, 1521, 1490, 1429, 1352, 1276, 1039, 943, 777. Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.11; H, 5.39; N, 5.76. Found: C, 69.30; H, 5.44; N, 5.70.

5-*p*-Tolyl-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2c). White solid, mp 190–191 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.28–3.34 (m, 2H), 3.42–3.48 (m, 2H), 6.22 (d, J = 7.2, 1H), 7.19 (d, J = 7.2, 1H), 7.22–7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 32.7, 33.3, 101.7, 126.2, 126.7, 129.6, 136.8, 138.0, 154.6, 158.3. IR (KBr, cm^{-1}) 3083, 3024, 2981, 2912, 2848, 1880, 1645, 1575, 1527, 1506, 1436, 1355, 1280, 1257, 1072, 939, 825. Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.11; H, 5.39; N, 5.76. Found: C, 68.93; H, 5.34; N, 5.81. MS calcd. m/z 243.1, found 244.1 [$(M + 1)^+$].

5-(2,4-Dimethylphenyl)-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2d). White solid, mp 160–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 2.35 (s, 3H), 3.28–3.33 (m, 2H), 3.35–3.47 (m, 2H), 6.21 (d, J = 6.9, 1H), 7.01–7.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 21.0, 32.8, 33.3, 101.7, 126.8, 126.9, 127.5, 131.6, 134.7, 136.9, 137.3, 138.6, 154.6, 158.3. IR (KBr, cm^{-1}) 3080, 3051, 2945, 2912, 2875, 1892, 1639, 1579, 1527, 1506, 1425, 1353, 1263, 1062, 946, 885, 823. Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44. Found: C, 70.23; H, 5.81; N, 5.40.

5-(2-Methoxyphenyl)-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2e). White solid, mp 173–174 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.18 (t, J = 8.0, 2H), 3.43 (t, J = 8.0, 2H), 3.80 (s, 3H), 6.19 (d, J = 7.2, 1H), 7.02 (d, J = 7.8, 2H), 7.03 (d, J = 7.2, 1H), 7.23 (dd, J_1 = 7.8, J_2 = 1.5, 1H), 7.38 (t, J = 7.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.7, 33.3, 55.7, 101.3, 112.0, 120.6, 126.6, 128.6, 129.1, 129.9, 137.6, 154.2, 154.5, 158.2. IR (KBr, cm^{-1}) 3080, 3064, 2937, 2920, 2881, 2831, 1855, 1643, 1575, 1523, 1500, 1458, 1434, 1352, 1284, 1022, 757. Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.60; H, 5.09; N, 5.43.

5-(4-Methoxyphenyl)-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2f). White solid, mp 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28–3.34 (m, 2H), 3.41–3.47 (m, 2H), 3.84 (s, 3H), 6.21 (d, J = 6.9, 1H), 6.94–6.99 (m, 2H), 7.18 (d, J = 6.9, 1H), 7.23–7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9, 33.4, 55.5, 101.8, 114.3, 126.8, 127.6, 133.5, 137.1, 154.6, 158.6, 159.2. IR (KBr, cm^{-1}) 3047, 2914, 1637, 1575, 1527, 1490, 1076, 761, 700. Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.63; H, 5.02; N, 5.46.

5-(2-Chlorophenyl)-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2g). White solid, mp 184–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.26–3.37 (m, 2H), 3.40–3.49 (m, 2H), 6.26 (d, J = 7.2, 1H), 7.04 (d, J = 7.2, 1H), 7.35–7.40 (m, 3H), 7.54 (dd, J_1 = 6.0, J_2 = 3.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8, 33.2, 102.0, 126.8, 127.6, 129.3, 130.0, 130.3, 131.8, 136.5, 138.0, 155.3, 157.8. IR (KBr, cm^{-1}) 1639, 1587, 1571, 1525, 1492, 1438, 1182, 958, 756, 701. Anal. Calcd. for $C_{13}H_{10}ClNOS$: C, 59.20; H, 3.82; N, 5.31. Found: C, 59.38; H, 3.79; N, 5.35.

5-(4-Chlorophenyl)-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2h). White solid, mp 216–217 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.32 (t, J = 8.1, 2H), 3.46 (t, J = 8.1, 2H), 6.25 (d, J = 7.2, 1H), 7.17 (d, J = 7.2, 1H), 7.31 (d, J = 8.7, 2H), 7.44 (d, J = 8.7, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9, 33.4, 102.3, 126.8, 127.9, 129.3, 134.1, 136.3, 139.0, 155.2, 158.1. IR (KBr, cm^{-1}) 3083, 3045, 2948, 2887, 2846, 1880, 1643, 1598, 1575, 1525, 1488, 1434, 1355, 1282, 1016, 945, 840. Anal. Calcd. for $C_{13}H_{10}ClNOS$: C, 59.20; H, 3.82; N, 5.31. Found: C, 59.39; H, 3.78; N, 5.36.

5-[4-(Trifluoromethyl)phenyl]-2,3-dihydrothieno[3,2-*c*] pyridin-4(5*H*)-one (2i). White solid, mp 212–213 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29–3.35 (m, 2H), 3.44–3.50 (m, 2H), 6.28 (d, J = 7.2, 1H), 7.18 (d, J = 7.2, 1H), 7.51 (d, J = 8.1, 2H), 7.74 (d, J = 8.1, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9, 33.4, 102.7, 123.6 (q, $^1J_{CF}$ = 270), 126.3 (d, $^3J_{CF}$ = 3), 127.0, 127.1, 130.4 (q, $^2J_{CF}$ = 33), 136.0, 143.5, 155.6, 158.0. IR (KBr, cm^{-1}) 3085, 1654, 1598, 1571, 1490, 1018, 838, 771, 700. Anal. Calcd. for $C_{14}H_{10}F_3NOS$: C, 56.56; H, 3.39; N, 4.71. Found: C, 56.75; H, 3.37; N, 4.75. MS calcd. m/z 297.1, found 298.1 [$(M + 1)^+$].

5-Benzyl-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2j). White solid, mp 88–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.27–3.31 (m, 2H), 3.38–3.44 (m, 2H), 5.10 (s, 2H), 6.14 (d, J = 7.2, 1H), 7.13 (d, J = 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8, 33.4, 51.4, 102.1, 126.6, 127.9, 128.0, 128.8, 136.0, 136.6, 154.3, 158.7. IR (KBr, cm^{-1}) 3055, 2935, 1639, 1589, 1575, 1529, 1421, 1261, 724, 694. Anal.

Calcd. for $C_{14}H_{13}NOS$: C, 69.11; H, 5.39; N, 5.76. Found: C, 68.90; H, 5.44; N, 5.81.

6-Methyl-5-phenyl-2,3-dihydrothieno[3,2-c]pyridin-4(5H)-one (2k). White solid, mp 179–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92 (s, 3H), 3.28 (t, J = 8.1, 2H), 3.41 (t, J = 8.1, 2H), 6.13 (s, 1H), 7.17 (d, J = 6.9, 2H), 7.40–7.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 32.7, 33.3, 101.9, 123.7, 128.0, 128.5, 129.5, 138.7, 145.0, 154.6, 159.7. IR (KBr, cm^{-1}) 3068, 3039, 2948, 2916, 2879, 1890, 1633, 1581, 1542, 1485, 1450, 1396, 1271, 1064, 1018, 912, 854, 761, 700. Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.11; H, 5.39; N, 5.76. Found: C, 69.42; H, 5.45; N, 5.72.

2-Phenyl-5-*p*-tolyl-2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (2l). White solid, mp 140–141 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.49 (dd, J_1 = 16.8, J_2 = 7.7, 1H), 3.73 (dd, J_1 = 16.8, J_2 = 7.7, 1H), 5.15 (t, J = 9.0, 1H), 6.21 (d, J = 7.1, 1H), 7.24 (d, J = 7.1, 1H), 7.26–7.28 (m, 5H), 7.34 (t, J = 7.8, 2H), 7.44 (d, J = 7.4, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 41.6, 53.6, 101.4, 125.1, 126.1, 126.9, 127.6, 128.5, 129.5, 137.2, 137.9, 138.0, 141.5, 153.6, 158.0. IR (KBr, cm^{-1}) 3041, 2839, 1650, 1610, 1581, 1512, 1249, 1020, 831. Anal. Calcd. for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39. Found: C, 75.45; H, 5.32; N, 4.44.

Synthesis and analytical data of 3

Typical procedure for the synthesis of thieno[3,2-*c*]pyridin-4(5*H*)-ones 3 (with 3a as an example). To a solution of **1a** (1.0 mmol) in anhydrous toluene (10 mL) was added Lawesson's reagent (0.5 mmol) in one portion. The mixture was heated to reflux and stirred for 10 h. After **1a** was consumed as monitored by TLC, DDQ (1.5 mmol) was added. The reaction was stirred under reflux for a further 1 h, then cooled down to room temperature. The resulting mixture was then poured into saturated aqueous NaCl (50 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petroleum ether : EtOAc (5 : 1)) to give **3a** as a white solid in 75% yield.

5-Phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (3a). White solid, mp 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (d, J = 7.2, 1H), 7.22 (d, J = 7.2, 1H), 7.30 (d, J = 5.2, 1H), 7.40–7.50 (m, 5H), 7.69 (d, J = 5.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.8, 124.6, 125.5, 126.8, 128.1, 129.1, 131.1, 132.5, 140.9, 147.4, 158.6. IR (KBr, cm^{-1}) 3091, 3080, 3064, 2927, 2862, 1639, 1577, 1488, 1452, 1290, 1267, 1137, 956, 769, 717. Anal. Calcd. for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.93; H, 3.96; N, 6.11.

5-(2-Methoxyphenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (3e). White solid, mp 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H), 6.74 (d, J = 7.2, 1H), 7.04–7.12 (m, 3H), 7.28–7.32 (m, 2H), 7.40–7.45 (m, 1H), 7.70 (d, J = 5.1, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 101.2, 112.2, 120.7, 124.1, 125.5, 128.8, 129.5, 130.0, 131.1, 133.4, 147.5, 154.5, 158.6. IR (KBr, cm^{-1}) 3066, 3010, 2977, 2842, 1645, 1596, 1573, 1498, 1463, 1438, 1286, 1018, 956, 771. Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.11; H, 4.28; N, 5.49.

5-(4-Chlorophenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (3h). White solid, mp 184–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, J = 7.2, 1H), 7.19 (d, J = 7.2, 1H), 7.34 (d, J = 5.2, 1H), 7.36–7.39 (m, 2H), 7.46–7.48 (m, 2H), 7.69 (d, J = 5.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.2, 124.9, 125.6, 128.2, 129.4, 131.1, 132.1, 134.1, 139.3, 147.5, 158.5. IR (KBr, cm^{-1}) 3056, 2948, 1641, 1577, 1527, 1481, 1259, 946, 730. Anal. Calcd. for $C_{13}H_8ClNOS$: C, 59.66; H, 3.08; N, 5.35. Found: C, 59.90; H, 3.05; N, 5.30.

6-Methyl-5-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (3k). White solid, mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 6.64 (s, 1H), 7.20–7.24 (m, 3H), 7.44–7.47 (m, 1H), 7.50–7.54 (m, 2H), 7.61 (d, J = 5.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 101.4, 123.0, 125.3, 128.3, 128.5, 128.9, 129.5, 138.8, 140.3, 147.8, 160.0. IR (KBr, cm^{-1}) 3078, 3008, 2958, 2921, 1639, 1598, 1577, 1564, 1488, 1294, 769, 700. Anal. Calcd. for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.44; H, 4.63; N, 5.86.

2-Phenyl-5-*p*-tolylthieno[3,2-*c*]pyridin-4(5*H*)-one (3l). White solid, mp 216–217 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 6.72 (d, J = 7.2, 1H), 7.22 (d, J = 7.2, 1H), 7.31 (s, 4H), 7.35 (d, J = 7.2, 1H), 7.43 (t, J = 7.5, 2H), 7.67 (d, J = 7.5, 2H), 7.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 101.7, 120.8, 126.1, 126.6, 128.3, 129.0, 129.9, 132.2, 132.9, 133.5, 138.2, 138.4, 143.2, 146.8, 158.7. IR (KBr, cm^{-1}) 2954, 1647, 1616, 1577, 1523, 1512, 1413, 1325, 1164, 1062, 837, 754. Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.68; H, 4.76; N, 4.41. Found: C, 75.90; H, 4.80; N, 4.46.

Acknowledgements

Financial support of this research by the National Natural Science Foundation of China (20572013 and 20872136) is greatly acknowledged.

Notes and references

1 (*a*) M. J. Quinn and D. J. Fitzgerald, *Circulation*, 1999, **100**, 1667–1672; (*b*) P. B. Berger, *Curr. Cardiol. Rep.*, 1999, **1**, 192–198; (*c*) N.-T. Ha-Duong, S. Dijols, A.-C. Macherey, J. A. Goldstein, P. M. Dansette and D. Mansuy, *Biochemistry*, 2001, **40**, 12112–12122; (*d*) P. M. Dansette, J. Libraire, G. Bertho and D. Mansuy, *Chem. Res. Toxicol.*, 2009, **22**, 369–373; (*e*) P. M. Dansette, S. Thébault, G. Bertho and D. Mansuy, *Chem. Res. Toxicol.*, 2010, **23**, 1268–1274; (*f*) A. A. Henry, C. Yu and F. E. Romesberg, *J. Am. Chem. Soc.*, 2003, **125**, 9638–9646.
2 S. Daouti, W. Li, H. Qian, K.-S. Huang, J. Holmgren, W. Levin, L. Reik, D. L. McGady, P. Gillespie, A. Perrotta, H. Bian, J. F. Reidhaar-Olson, S. A. Bliss, A. R. Olivier, J. A. Sergi, D. Fry, W. Danho, S. Ritland, N. Fotouhi, D. Heimbrook and H. Niu, *Cancer Res.*, 2008, **68**, 1162–1169.
3 (*a*) W. Halczenko, J. J. Cook, M. A. Holahan, G. R. Sitko, M. T. Stranieri, G. Zhang, R. J. Lynch, J. J. Lynch Jr., R. J. Gould and G. D. Hartman, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2771–2776; (*b*) G. D. Hartman, W. Halczenko, J. D. Prugh, (Merck), *WO* 9426745, 1994; (*c*) J. P. Maffrand, (Parcor), *GB* 2023599, 1980.
4 J. Berger, R. D. Clark, (Syntex), *US* 5189041, 1993
5 (*a*) J. S. New, W. L. Christopher, J. P. Yevich, R. Butler, R. F. Schlemmer, Jr., C. P. Vandermaelen and J. A. Cipollina, *J. Med. Chem.*, 1989, **32**,

1147–1156; (*b*) A. O. Stewart, P. A. Bhatia, C. M. McCarty, M. V. Patel, M. A. Staeger, D. L. Arendsen, I. W. Gunawardana, L. M. Melcher, G.-D. Zhu, S. A. Boyd, D. G. Fry, B. L. Cool, L. Kifle, K. Lartey, K. C. Marsh, A. J. Kempf-Grote, P. Kilgannon, W. Wisdom, J. Meyer, W. M. Gallatin and G. F. Okasinski, *J. Med. Chem.*, 2001, **44**, 988–1002; (*c*) H. R. Heyman, R. R. Frey, P. F. Bousquet, G. A. Cunha, M. D. Moskey, A. A. Ahmed, N. B. Soni, P. A. Marcotte, L. J. Pease, K. B. Glaser, M. Yates, J. J. Bouska, D. H. Albert, C. L. Black-Schaefer, P. J. Dandliker, K. D. Stewart, P. Rafferty, S. K. Davidsen, M. R. Michaelides and M. L. Curtin, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1246–1249; (*d*) L. Abbott, P. Betschmann, A. Burchat, D. J. Calderwood, H. Davis, P. Hrnciar, G. C. Hirst, B. Li, M. Morytko, K. Mullen and B. Yang, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1167–1171; (*e*) Y. Miyazaki, M. Nakano, H. Sato, A. T. Truesdale, J. D. Stuart, E. N. Nartey, K. E. Hightower and L. Kane-Carson, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 250–254; (*f*) L. Zhao, Y. Zhang, C. Dai, T. Guzi, D. Wiswell, W. Seghezzi, D. Parry, T. Fischmann and M. A. Siddiqui, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7216–7221.

6 (*a*) W. Halczenko and G. D. Hartmann, *Synth. Commun.*, 1996, **26**, 1363–1370; (*b*) M. Farnier, S. Soth and P. Fournari, *Can. J. Chem.*, 1976, **54**, 1066–1073; (*c*) S. Mochida, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.*, 2010, **39**, 744–746.

7 (*a*) J. M. Barker, *Adv. Heterocycl. Chem.*, 1977, **21**, 65–118; (*b*) V. P. Litvinov, V. V. Dotsenko and L. G. Krivokolysko, *Adv. Heterocycl. Chem.*, 2007, **93**, 117–178.

8 (*a*) H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165–198; (*b*) F. Gnad and O. Reiser, *Chem. Rev.*, 2003, **103**, 1603–1624; (*c*) O. G. Kulinkovich,, *Chem. Rev.*, 2003, **103**, 2597–2632; (*d*) F. D. Simone and J. Waser, *Synthesis*, 2009, 3353–3374.

9 (*a*) W. Pan, D. Dong, K. Wang, J. Zhang, R. Wu, D. Xiang and Q. Liu, *Org. Lett.*, 2007, **9**, 2421–2423; (*b*) K. Wang, D. Xiang, J. Liu, W. Pan and D. Dong, *Org. Lett.*, 2008, **10**, 1691–1694.

10 K. Wang, X. Fu, J. Liu, Y. Liang and D. Dong, *Org. Lett.*, 2009, **11**, 1015–1018.

11 (*a*) R. Zhang, Y. Liang, G. Zhou, K. Wang and D. Dong, *J. Org. Chem.*, 2008, **73**, 8089–8092; (*b*) R. Zhang, Y. Zhou, Y. Liang, Z. Jiang and D. Dong, *Synthesis*, 2009, 2497–2500.

12 For the utilization of Lawesson's reagent, see: (*a*) D. Brillon, *Sulfur Rep.*, 1992, **12**, 297–338; (*b*) T. Ozturk, E. Ertas and O. Mert, *Chem. Rev.*, 2007, **107**, 5210–5278; (*c*) M. Jesberger, T. P. Davis and L. Barner, *Synthesis*, 2003, 1929–1958; (*d*) M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061–5087; (*e*) D. Brayton, F. E. Jacobsen, S. M. Cohen and P. J. Farmer, *Chem. Commun.*, 2006, 206–208; (*f*) Z. Kaleta, G. Tárkányi, Á. Gömöry, F. Kálmán, T. Nagy and T. Soós, *Org. Lett.*, 2006, **8**, 1093–1095; (*g*) J. F. Sanz-Cervera, R. Blasco, J. Piera, M. Cynamon, I. Ibáñez, M. Murguía and S. Fustero, *J. Org. Chem.*, 2009, **74**, 8988–8996.

13 (*a*) P. Gopinath and S. Chandrasekaran, *J. Org. Chem.*, 2011, **76**, 700–703; (*b*) Z. Zhang, Q. Zhang, S. Sun, T. Xiong and Q. Liu, *Angew. Chem., Int. Ed.*, 2007, **46**, 1726–1729.

14 (*a*) R. Zhang, D. Zhang, Y. Guo, G. Zhou, Z. Jiang and D. Dong, *J. Org. Chem.*, 2008, **73**, 9504–9507; (*b*) R. Zhang, D. Zhang, Y. Liang, G. Zhou and D. Dong, *J. Org. Chem.*, 2011, **76**, 2880–2883; (*c*) Y. Li, W. Li, R. Zhang, Y. Zhou and D. Dong, *Synthesis*, 2008, 3411–3414; (*d*) J. Liu, X. Fu, Y. Zhou, G. Zhou, Y. Liang and D. Dong, *Aust. J. Chem.*, 2010, **63**, 1267–1271.

15 For domino reactions initiated by thionation, see: (*a*) S. E. Clayton, C. D. Gabbutt, J. D. Hepworth and B. M. Heron, *Tetrahedron*, 1993, **49**, 939–946; (*b*) A. Riu, A. Harrison-Marchand, J. Maddaluno, M. Gulea, H. Albadri and S. Masson, *Eur. J. Org. Chem.*, 2007, 4948–4952; (*c*) C. D. Gabbutt, J. D. Hepworth, B. M. Heron and J.-L. Thomas, *Chem. Commun.*, 1999, 541–542; (*d*) C. D. Gabbutt, J. D. Hepworth and B. M. Heron, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2603–2608; (*e*) M. G. Barthakur, A. Chetia and R. C. Boruah, *Tetrahedron Lett.*, 2006, **47**, 4925–4927.

16 (*a*) F. Peyrane, J.-L. Fourrey and P. Clivio, *Chem. Commun.*, 2003, 736–737; (*b*) J. A. Seijas, M. P. Vázquez-Tato and J. Crecente-Campo, *Tetrahedron*, 2010, **66**, 8210–8213.

17 For selected thionation of carboxyl groups with Lawesson's reagent, see: (*a*) M. Ori and T. Nishio, *Heterocycles*, 2000, **52**, 111–116; (*b*) L. Wang and O. Phanstiel, *J. Org. Chem.*, 2000, **65**, 1442–1447; (*c*) O. E. Jensen, S.-D. Lawesson, R. Bardi, A. M. Piazzesi and C. Toniolo, *Tetrahedron*, 1985, **41**, 5595–5506.

18 (*a*) A. Ishii, R. Yamashita, M. Saito and J. Nakayama, *J. Org. Chem.*, 2003, **68**, 1555–1558; (*b*) E. Miserazzi, M. A. Spotti, R. Profeta, S. Spada, A. Nalin, E. Moro and D. Andreotti, *Tetrahedron Lett.*, 2011, **52**, 448–452.

19 J. B. Rasmussen, R. Shabana and S.-O. Lawesson, *Tetrahedron*, 1981, **37**, 197–202.

20 For the transformation of dihydrothiophenes to thiophenes, see: (*a*) K. Yamagata, M. Takaki, K. Ohkubo and M. Yamazaki, *Liebigs Ann. Chem.*, 1993, 1263–1267; (*b*) K. Yamagata, Y. Tomioka, M. Yamazaki, T. Matsuda and K. Noda, *Chem. Pharm. Bull.*, 1982, **30**, 4396–4401; (*c*) E. Nagashima, K. Suzuki and M. Sekiya, *Chem. Pharm. Bull.*, 1982, **30**, 4384–4395; (*d*) P. A. Rosy, W. Hoffmann and N. Müller, *J. Org. Chem.*, 1980, **45**, 617–620.

21 F. Liang, S. Lin and Y. Wei, *J. Am. Chem. Soc.*, 2011, **133**, 1781–1783.

