ChemInform Abstract: Synthesis of Functionalized Dihydrothiophenes from Doubly Activated Cyclopropanes Using Tetrathiomolybdate as the Sulfur Transfer Reagent.

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Synthesis of Functionalized Dihydrothiophenes from Doubly Activated Cyclopropanes Using Tetrathiomolybdate as the Sulfur Transfer Reagent

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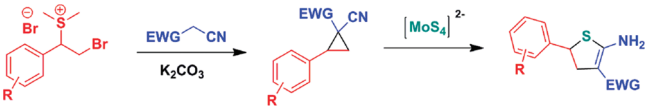
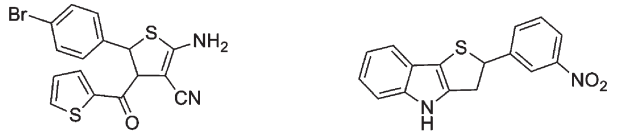


A number of doubly activated cyclopropanes were synthesized starting from various substituted bromosulfonium bromides in good yield. Regioselective ring-opening of cyclopropanes with tetrathiomolybdate as the sulfur transfer reagent gave dihydrothiophenes in excellent yield.

Dihydrothiophenes[1] and their derivatives are key components present in many natural products, bioactive compounds, and synthetic intermediates (Figure 1).[2] They contain a reactive double bond and a sulfur atom that accounts for many of their interesting ring-opening reactions. In particular, 2-amino-4,5-dihydrothiophenes have great synthetic value as they are used as starting materials for the synthesis of partially hydrogenated thieno[2,3-*b*]pyridines[3] and pyrimidines.[4]



(i) 4,5-dihydrothiophene-3-carbonitrile (Antibacterial and antifungal agent)

(ii) Thieno indoles (antimycobaterial agent)

FIGURE 1. Structures of pharmacologically important thioesters.

Although a large number of publications have appeared on the synthesis and study of thiophenes,[5] there are fewer reports on the chemistry of dihydrothiophenes and their derivatives. Dotsenko et al. has shown that 2-amino-4,5-dihydrothiophenes can be synthesized by base-catalyzed condensation of phenacyl thiocyanate with substituted thioamides.[6] They are also synthesized by a three-component condensation reaction involving aldehydes, cyanothioacetamide, and pyridinium or sulfonium ylides.[7]

More recently, Yan and co-workers have reported the synthesis of 2-amino-4,5-dihydrothiophenes through a domino reaction involving 1,3-thiazolidinedione, malononitrile, and aromatic aldehydes.[8] In general, most of the methods used for the synthesis of 2-amino-4,5-dihydrothiophenes involve multiple steps and suffer from lower yields.

Doubly activated cyclopropanes[9] are known to be valuable synthetic intermediates for the synthesis of a wide variety of 1,3 bifunctionalized molecules. Thus, we conceived a simple protocol for the synthesis of 2-amino-4,5-dihydrothiophenes starting from doubly activated cyclopropanes using benzyltriethylammonium tetrathiomolybdate, **1**,[10] as the sulfur transfer reagent. Doubly activated cyclopropanes are generally synthesized by the reaction of an alkene with a diazo compound[11] or an iodonium ylide[12] and a transition metal catalyst (mostly rhodium or copper complexes). Development of hypervalent iodine(III) reagents[12] as synthetic equivalents of diazo compounds have also been reported.[13]

However, there is no general method for the synthesis of all the doubly activated cyclopropanes using a single protocol. Since we were interested in studying the ring-opening of a variety of doubly activated cyclopropanes, we decided to modify the work reported by Chow involving the use of substituted bromosulfonium bromides[14] as precursors for the synthesis of doubly activated cyclopropanes (Scheme 1).

Accordingly, we synthesized the bromosulfonium bromides **2a**−**e** from the corresponding styrenes (Table 1). Reaction of bromosulfonium bromide **2a** with various active methylene compounds **3a**−**h** led to the corresponding doubly activated cyclopropanes **4**−**11**, respectively, in good to excellent yields. The results of this study are summarized in Table 2.

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(12) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327 and references cited therein.

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SCHEME 1. General Reaction Scheme

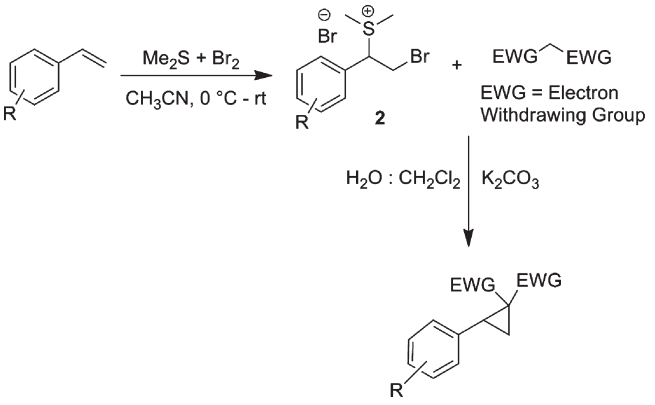

TABLE 1. Synthesis of Various Bromosulfonium Bromides

S.No	Reactant	Product	Yield (%)
1	a	2a	85
2	b	2b	80
3	c	2c	90
4	d	2d	65
5	e	2e	83

The reaction was then carried out with other substituted bromosulfonium bromides **2b**−**e** and various active methylene compounds to show the generality and synthetic utility of the reaction. The results of this study are summarized in Table 3.

After successfully synthesizing the doubly activated cyclopropanes, we then attempted the ring-opening of diester cyclopropane **4** with reagent **1** (MeOH, reflux, 5 h) to form the corresponding disulfide **20** regioselectively (1:1 diastereomeric ratio) in 70% yield (Scheme 2).[15]

The formation of product **20** from cyclopropane **4** with **1** can be visualized to take place via the initial nucleophilic attack of tetrathiomolybdate **1** to open the cyclopropane ring to form the intermediate "**X**", which then can react with

(15) The reaction does not work efficiently with ammonium tetrathiomolybdate, which is commercially available, and hence reagent **1** is used. Other sulfur transfer reagents like NaSH and Na_2S give a mixture of mono- and disulfides as products.

TABLE 2. Synthesis of Styrene-Derived Doubly Activated Cyclopropanes

S. No	Substrate	Product	E : Z [a]	Yield (%)
1	3a	4	-	62
2	3b	5	91:9	78
3	3c	6	90:10	81
4	3d	7	-	95
5	3e	8	95:5	80
6	3f	9	85:15	50
7	3g	10	80:20	60
8	3h	11	-	65

the second molecule of **4** to form intermediate **Y**. This intermediate then undergoes an internal redox process[10,16] with the formation of a disulfide bond to give product **20** and MoS_2 as the byproduct.

We then attempted the ring-opening of doubly activated cyclopropane **5** containing a cyano group with tetrathiomolybdate **1** (1.2 equiv, MeOH, 28 °C, 1 h). Interestingly, the reaction led to the formation of the dihydrothiophene derivative **21** in 88% yield. The structure of **21** was unambiguously proved by single crystal X-ray analysis (see the Supporting Information).

The formation of dihydrothiophene **21** from cyclopropane derivative **5** in the reaction with **1** may be visualized to take place initially via the formation of disulfide intermediate, which undergoes reductive cleavage with **1**[17] to form the thiolate anion that can undergo intramolecular Gewald cyclization[18] to give product **21** (Scheme 3).

When the reaction was carried out in CH_3CN as solvent, the reaction was slow and hence we were able to isolate the disulfide intermediate, which again on treatment with tetrathiomolybdate **1** gave the corresponding dihydrothiophene derivative, thereby proving the reaction mechanism.

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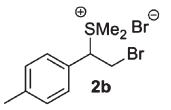
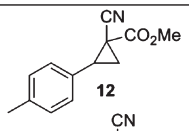
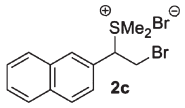
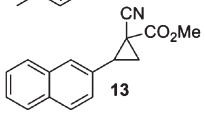
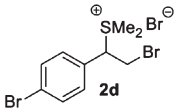
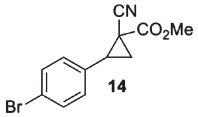
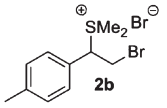
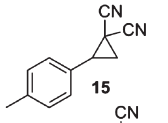
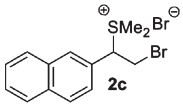
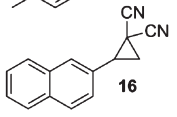
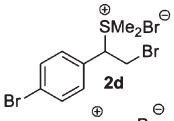
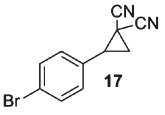
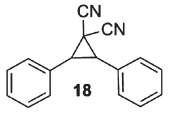
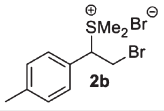
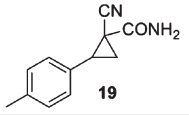
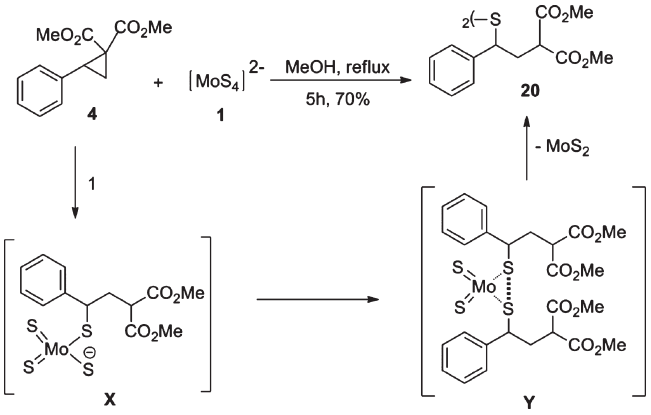
TABLE 3. Synthesis of Various Doubly Activated Cyclopropanes

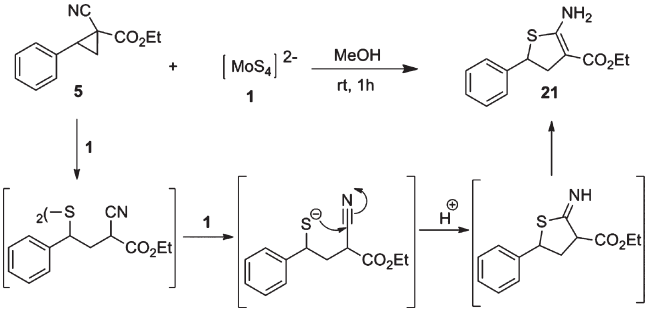
S. No	Substrate	Product	E : Z [a]	Yield (%)
1	 **2b**	 **12**	94:6	85
2	 **2c**	 **13**	87:13	70
3	 **2d**	 **14**	88:12	75
4	 **2b**	 **15**	-	95
5	 **2c**	 **16**	-	60
6	 **2d**	 **17**	-	76
7	 **2e**	 **18**	58: 42	25
8	 **2b**	 **19**	95:5	85

SCHEME 2. Synthesis of Disulfide 20 from Cyclopropane 4



To test the generality of this reaction a number of doubly activated cyclopropane derivatives substituted with a cyano group were treated with tetrathiomolybdate **1** (MeOH, 28 °C, 10 min-2 h) to give the corresponding dihydrothiophenes in very good yields (Table 4). In the absence of a phenyl group at the 2-position (compound **22**) the reaction was slower (2 h) and gave moderate yield of the corresponding dihydrothiophene **32**.

SCHEME 3. Synthesis of Dihydrothiophene 21



Substituted 2-aminothiophenes are also important synthetic intermediates in organic synthesis as they find broad applications[18,19] in pharmaceuticals, dyes, and agrochemicals. Thus, compound **23** on treatment with DDQ gave the corresponding 2-amino thiophene derivative **33** in 71% yield (Scheme 4).

Cyclopropane derivative **8** on treatment with reagent **1** gave the corresponding dihydrothiophene derivative **34** in 75% yield, which on further treatment with ethyl chloroformate and NaOMe gave compound **35**, a potential precursor of HIV-1 reverse transcriptase inhibitor,[2d,20] (HEPT analogue) in 70% yield (Scheme 5).

In conclusion, we have presented an alternative protocol for the synthesis of doubly activated cyclopropanes from a single intermediate. Also we have demonstrated the synthetic utility of benzyltriethylammonium tetrathiomolybdate **1** toward the synthesis of 2-amino-4,5-dihydrothiophenes from doubly activated cyclopropane derivatives in excellent yield under mild reaction conditions without any Lewis acid activation. Additionally we have presented a simple route for the synthesis of 2-amino thiophene **33** and a potential HIV-1 RT inhibitor, **35** (HEPT analogue).

Experimental Section

Synthesis of Substituted Bromosulfonium Bromides. To a solution of dimethyl sulfide (2.7 mL, 35 mmol) in CH_3CN (20 mL) kept at 0 °C was added a solution of bromine (0.51 mL, 10 mmol) in CCl_4 (3 mL) to give a yellow precipitate. The corresponding styrene derivative (20 mmol) was then added and stirring was continued for 30 min at the same temperature. The solution was then brought to room temperature and diethyl ether (30 mL) was added to it to give a white precipitate that was then filtered and washed with diethyl ether to give the corresponding bromosulfonium bromide in good yield.

Bromosulfonium bromide, 2b: white solid; yield 2.72 g, 80%; mp 139.5 °C; IR (KBr) 2977, 1514, 1052, 829 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.37−7.36 (m, 4H), 5.06 (dd, J_1 = 6.3 Hz, J_2 = 8.7 Hz, 1H), 4.22−4.09 (m, 2H), 2.84 (s, 3H), 2.57 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 142.1, 130.3, 129.4, 125.6, 60.9, 29.2, 24.2, 20.4. Anal. Calcd for $C_{11}H_{16}Br_2S$: C, 38.84; H, 4.74; S, 9.43. Found: C, 38.72; H, 4.56; S, 9.69.

Synthesis of Doubly Activated Cyclopropanes from Bromosulfonium Bromides. Potassium carbonate (0.414 g, 3 mmol) was added to a solution containing the required bromosulfonium bromide (1 mmol) in CH_2Cl_2:H_2O (1:1) mixture (20 mL). The

(19) (a) Lutjens, H.; Zickgraft, A.; Figler, H.; Linden, J.; Olsson, R. A.; Scammels, P. J. *J. Med. Chem.* **2003**, *46*, 1870. (b) Nikolakopoulos, G.; Figler, H.; Linden, J.; Scammels, P. *J. Bioorg. Med. Chem.* **2006**, *14*, 2358.

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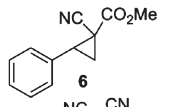
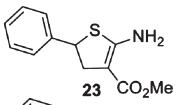
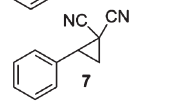
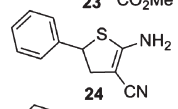
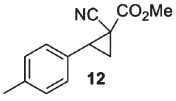
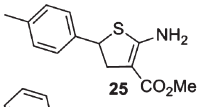
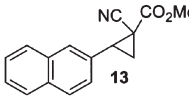
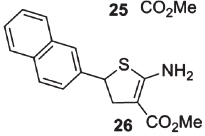
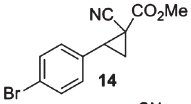
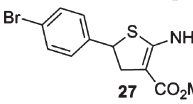
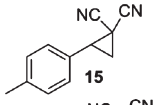
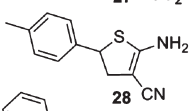
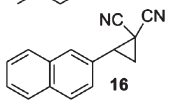
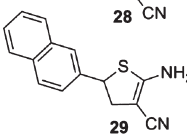
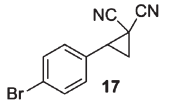
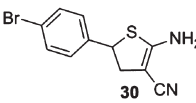
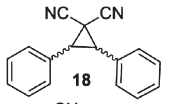
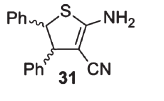
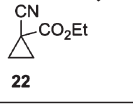
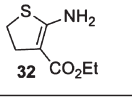
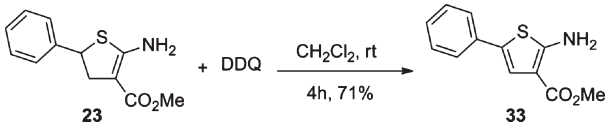
TABLE 4. Synthesis of Dihydrothiophenes

Entry	Cyclopropanes	Products	Time	Yield (%)
1	 **6**	 **23**	50 min	90
2	 **7**	 **24**	10 min	85
3	 **12**	 **25**	55 min	91
4	 **13**	 **26**	1 h	92
5	 **14**	 **27**	50 min	92
6	 **15**	 **28**	10 min	90
7	 **16**	 **29**	15 min	80
8	 **17**	 **30**	10 min	87
9	 **18**	 **31**	20 min	80
10	 **22**	 **32**	2 h	60

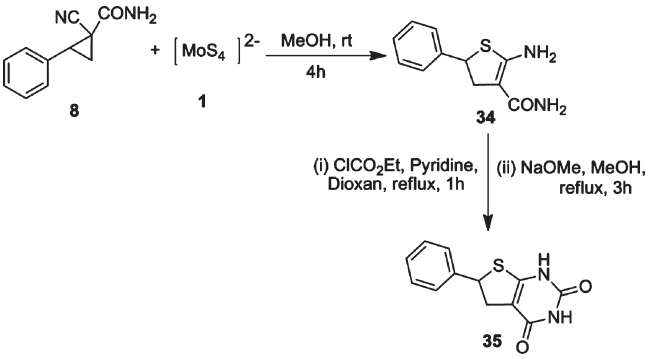
SCHEME 4. Synthesis of 2-Amino Thiophene 33



23 **33**

corresponding activate methylene compound (2 mmol) was added to it and the reaction mixture was stirred for 8 h at room temperature. The CH_2Cl_2 layer was then separated and the aqueous layer was washed three times with dichloromethane (10 mL) and added to the organic layer. The combined organic layer was dried over anhydrous sodium sulfate and then evaporated. The residue was then purified by column chromatography on silica gel to give the corresponding doubly activated cyclopropanes in moderate to good yields.

SCHEME 5. Synthesis of Potential HIV-1 RT Inhibitor 35



8 **1** **34** **35**

1,1′-(2-Phenylcyclopropane-1,1-diyl)diethanone, 11: light yellow solid; yield 0.131 g, 65%; mp 58.0 °C; IR (neat) 1683, 1356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.11 (m, 5H), 3.29 (t, J = 8.4 Hz, 1H), 2.25 (dd, J_1 = 5.4 Hz, J_2 = 7.5 Hz, 1H), 2.27 (s, 3H), 1.80 (s, 3H), 6.65 (dd, J_1 = 5.4 Hz, J_2 = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 202.0, 134.1, 128.4, 128.3, 127.4, 52.6, 35.5, 30.3, 27.5, 18.9; HR-MS m/z calcd for $C_{13}H_{14}O_2Na^+$ [M + Na^+] 225.0891, found 225.0881.

General Procedure for the Synthesis of Dihydrothiophenes. To a well-stirred solution of the corresponding cyclopropane derivative (1 mmol) in MeOH (4 mL) was added benzyltriethylammonium tetrathiomolybdate, **1** (0.731 g, 1.2 mmol). The reaction mixture was then stirred until the disappearance of the starting cyclopropane. The solvent was removed; the residue was extracted with CH_2Cl_2 (5 mL) and diethyl ether (20 mL) and filtered through a Celite pad. The residue was again extracted with CH_2Cl_2 (5 mL) followed by extraction with diethyl ether (20 mL) and filtered again through a Celite pad. The combined extract was evaporated and the residue was purified by column chromatography on silica gel to give the corresponding dihydrothiophene derivative.

Ethyl 2-amino-5-phenyl-4,5-dihydrothiophene-3-carboxylate, 21: white crystalline solid (0.219 g, 88%); mp 107.5 °C; IR (neat) 3407, 3309, 1650, 1603, 1516, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.6 Hz, 2H), 7.34−7.25 (m, 3H), 6.08 (br s, 2H), 4.86 (t, J = 8.0 Hz, 1H), 4.18−4.11 (m, 2H), 3.40 (dd, J_1 = 8.4 Hz, J_2 = 14.4 Hz, 1H), 3.15 (dd, J_1 = 7.6 Hz, J_2 = 14.4 Hz, 1H), 1.26 (t, J = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.0, 141.5, 128.6, 127.7, 127.2, 91.0, 59.0, 51.4, 41.6, 14.6; HR-MS m/z calcd for $C_{13}H_{15}NO_2SNa^+$ [M + Na^+] 272.0721, found 272.0723.

Acknowledgment. P.G. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for a Senior Research Fellowship.

Supporting Information Available: Experimental procedures, full characterization, ^1H NMR spectra, and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.