A New Zn/$TiCl_4$/$LiAlH_4$ Mediated Approach to 2-Aryl- or 2-Alkyl-Substituted Benzothiophenes via Intramolecular Cyclization

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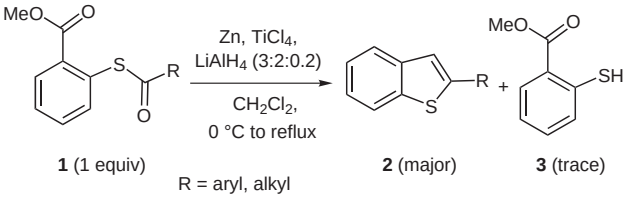
Abstract: Methyl 2-(substituted benzoylthio)benzoates undergo intramolecular ring cyclizations in the presence of Zn/$TiCl_4$/$LiAlH_4$ to give the corresponding 2-aryl- or alkylsubstituted benzothiophenes in good yields.

Key words: intramolecular cyclization reaction, Zn–$TiCl_4$–$LiAlH_4$, benzothiophenes, ester, thioester



Scheme 1

Benzothiophenes are of interest because of their frequent occurrence in nature and their wide-range of biological and physiological effects.[1] Thus the 2-substituted benzothiophene moiety is present in various active drugs such as zileuton, a potent and selective inhibitor of 5-lipoxygenase,[2] and raloxifene, which is used to treat osteoporosis (Figure 1).[3]

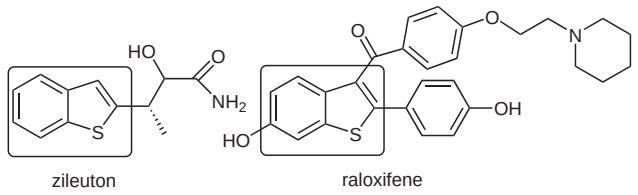


Figure 1

Although several methods for the construction of these benzothiophenes are known,[4] in light of the broad array of biological activities, the development of new, efficient and more viable routes to these compounds with diverse functionalities would be of great relevance to both synthetic and medicinal chemists. Herein, we report the first synthetic method for synthesis of benzothiophenes through the intramolecular cyclization reaction of thioesters with esters (Scheme 1).

The overall process involves a modified McMurry-type cyclization of methyl 2-(substituted benzoylthio)benzoates **1**. The McMurry reaction has previously been used for intramolecular cross-coupling reactions between esters, amides, aldehydes and ketones through reductive carbonyl coupling.[5] Thus diverse molecules such as diols, substituted alkenes, indoles and benzofurans have been synthesized quite smoothly using this route. However, the synthesis of benzothiophenes using McMurry reactions has not been reported.

Initial attempts to synthesize benzothiophene **2** by the intramolecular cyclization of a thioester with a ketone, ester or aldehyde under general McMurry conditions (Zn/$TiCl_4$/substrate, 4: 2: 1) were not successful. In the case of normal McMurry coupling reactions, an excess amount of graphite, C_8K, Zn or $LiAlH_4$ with $TiCl_3$ or $TiCl_4$ has been used to generate the low-valent titanium (LVT). When we applied the same methodology to these substrates we observed that the only recoverable product was **3**. This is probably due to the cleavage of the C–S bond of **1** by the excess amount of reductants used. Therefore, we expected that a deficiency of Zn does not generate enough LVT, which is required to form the C2–C3 bond of benzothiophene **2**. Therefore, we tried to optimize the amount of reductants needed for the intramolecular cyclization of thioesters and esters. The results are shown in Table 1.

When two equivalents of $TiCl_4$ and four equivalents of Zn were used without $LiAlH_4$, the reaction afforded a small amount of coupling product **2a** (15%), **3** as the major product (75%) and traces of unreacted starting material (5%) (Table 1, entry 1). Meanwhile, treatment of **1a** with one equivalent of $TiCl_4$ and four equivalents of Zn using reflux conditions for two hours in CH_2Cl_2 afforded less than 5% of 2-phenylbenzothiophene **2a** and 85% of starting material (Table 1, entry 2). Decreasing the amount of Zn and adding 0.5 equivalent of $LiAlH_4$ resulted in a clear enhancement of the coupling product **2a**, and the formation of the thioester deprotected product **3** was inhibited significantly (Table 1, entries 3 and 4). From these results, it was decided that the yield of coupling product strongly depends on the amount of Zn. Therefore, we decided to

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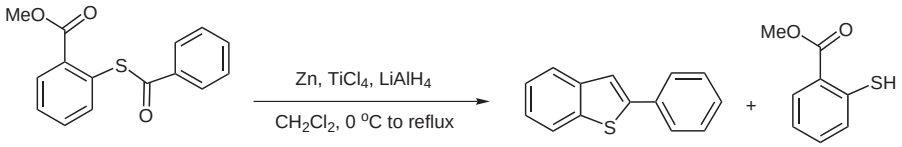
Table 1 Intramolecular Coupling Reaction of Methyl 2-(Benzoylthio)benzoate



1a **2a** **3**

Entry	Zn (equiv)	$TiCl_4$ (equiv)	$LiAlH_4$ (equiv)	Yield (%)[a]		
				2a	**3**	**1a**
1	4	2	0	15	75	5
2	4	1	0	5	0	85
3	1	1	0.5	30	10	30
4	2	2	0.5	50	20	20
5	3	2	0.5	65	30	0
6	3	2	0.2	87	<3	0
7	3	2	0.1	80	5	0

[a] Yields were calculated after purification.

use three equivalents of Zn and controlled the reaction by adding 0.5–1 equivalent of $LiAlH_4$ in order to compensate for the reduced amount of Zn in the coupling reaction of **1a**. We tried the reaction using Zn/$TiCl_4$/**1a** (3:2:1) in the presence of 0.2 equivalent of $LiAlH_4$ at reflux conditions for two hours in CH_2Cl_2 and obtained the desired benzothiophene **2a** in good yield (87%) with only trace amounts of the corresponding thiol **3** (<3%).

With established optimized reaction conditions, various methyl 2-(substituted benzoylthio)benzoates **1** were subjected to intramolecular ring cyclizations to yield 2-substituted benzothiophenes **2**. The results are summarized in Table 2.

Table 2 2-Aryl- or 2-Alkyl-Substituted Benzothiophenes Formed by an Intramolecular Cyclization Reaction[7]

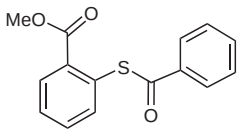
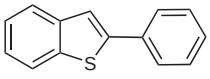
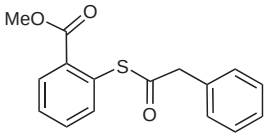
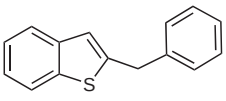
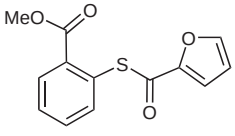
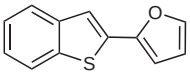
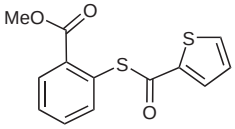
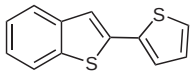
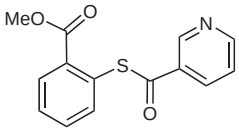
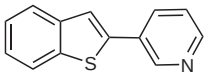
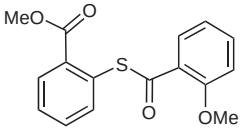
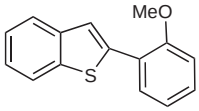
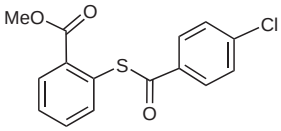
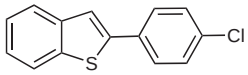
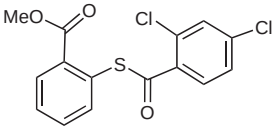
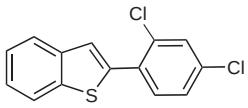
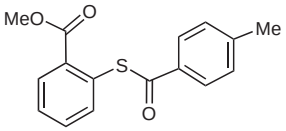
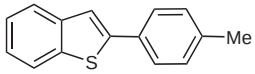
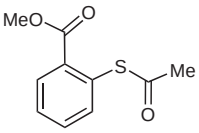
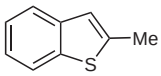
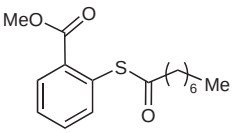
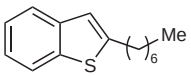
Entry	Substrate	Product	Time (h)	Yield (%)	
1	 **1a**	 **2a**	2	87[a]	35[b]
2	 **1b**	 **2b**	5	85[a]	40[b]
3	 **1c**	 **2c**	0.25	85[a]	40[b]

Table 2 2-Aryl- or 2-Alkyl-Substituted Benzothiophenes Formed by an Intramolecular Cyclization Reaction[7] (continued)

Entry	Substrate	Product	Time (h)	Yield (%)	
4	 **1d**	 **2d**	0.5	85[a]	40[b]
5	 **1e**	 **2e**	1	60[a]	30[b]
6	 **1f**	 **2f**	2	80[a]	30[b]
7	 **1g**	 **2g**	0.25	80[a]	40[b]
8	 **1h**	 **2h**	0.5	80[a]	35[b]
9	 **1i**	 **2i**	0.5	75[a]	30[b]
10	 **1j**	 **2j**	1	70[a]	30[b]
11	 **1k**	 **2k**	4	65[a]	26[b]

[a] The yield using our method ($Zn/TiCl_4/LiAlH_4$/substrate, 3:2:0.2:1).
[b] The yield using McMurry conditions ($Zn/TiCl_4$/substrate, 4:2:1).

Phenyl-, benzyl-, furan-, and thiophene-substituted substrates **1a**–**d** were reacted using the optimized conditions yielding the corresponding benzothiophenes **2a**,[6] **2b**, **2c**,[4f] and **2d** in 85–87% yield. However, methyl 2-(3-pyridylthio)benzoate (**1e**) gave **2e** in only 60% yield. Substrates **1f**–**h** containing *o*-methoxyphenyl, *p*-chlorophenyl and *o*,*p*-dichlorophenyl were treated under the same conditions to obtain **2f**, **2g** and **2h** in 80% yields, and *p*-methylphenyl derivative **1i** gave **2i**[6] in 75% yield. The preceding benzothiophene approach was extended to 2-

alkyl-substituted benzothiophenes. Thus, methyl 2-(acetylthio)benzoate (**1j**) and methyl 2-(heptylthio)benzoate (**1k**) cyclized intramolecularly to give **2j**[4f] and **2k**[4f] in 70% and 65% yields respectively. According to the results obtained, substitution of the aromatic ring did not significantly affect the product yield but it was slightly lower in the case of molecules with electron-donating groups (Table 2, entries 6, 9, 10 and 11). All of these reactions proceeded via an intramolecular carbon–carbon bond formation reaction between two carbonyl groups.

The reaction seems to proceed via an initial reduction of two carbonyl groups to form the pinacolate[6,8,9,10] followed by elimination as in the usual McMurry reaction. It seems that by reducing the stoichiometric amount of Zn, its activity is partially reduced which in turn controls the overall reaction by sustaining the thioester group until the C2–C3 bond in the benzothiophene is formed from the two carbonyl groups in substrate **1**.

We found that the ratio of Zn and $TiCl_4$ was pivotal to the McMurry reaction of methyl (2-substituted benzoylthio)benzoates **1** and that the addition of $LiAlH_4$ improves the yield of the desired benzothiophenes **2**.

In summary, we have established the first synthetic methodology for the preparation of 2-substituted benzothiophenes using a modified McMurry reaction. The present method provides a simple and facile process for the direct synthesis of 2-substituted benzothiophenes from methyl 2-(substituted aroylthio)benzoates or methyl 2-(substituted acylthio)benzoates.

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References and Notes

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(7) A mixture of Zn dust (3.0 mmol) and $LiAlH_4$ (0.2 mmol) in CH_2Cl_2 (30 mL) was stirred for 30 min at 0 °C. To the reaction mixture $TiCl_4$ (2.0 mmol) was added dropwise and the temperature was brought slowly to r.t.. The reaction mixture was suspended for 1 h at r.t. and substrate **1** (**1a–k,** 1.0 mmol) was added slowly. The reaction mixture was heated at reflux with stirring for 30 min to 2 h and allowed to cool to r.t. It was then passed through a short silica gel column using EtOAc as eluent to eliminate inorganic salts. The filtrate was evaporated, and the residue was purified by flash column chromatography using *n*-hexane–EtOAc (5:1) as eluent to afford pure **2a–k**.

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