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Short Communication

# Ultrasound promoted synthesis of thioesters from 2-mercaptobenzoxa(thia)zoles

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ABSTRACT

An ultrasound-enhanced method has been developed for the synthesis of a variety of thioesters from benzoyl chlorides and 2-mercaptobenzoxa(thia)zoles. Applying this methodology, 14 compounds were synthesized in excellent yields.



## 1. Introduction

Thiocarboxylic acid esters (thioesters) have been employed in a wide range of organic transformations. For example, they have been used as building blocks for heterocyclic compounds, as intermediates in the synthesis of ketones and aldehydes, as precursors of acyl radicals and anions and in asymmetric aldol reactions [1]. The use of thioesters as protecting groups for thiols has also been reported [2]. This functional group has application as an acyl donor in the resolution of secondary alcohol catalysed by lipase [3] and as cephalosporin derivatives [4]. Thioesters also play an important role in the development of thiol drugs, especially in masking the undesired odor and taste of the native thiol.

In a spite of the growing interest in new transformation methods for these compounds, preparative methods available are still based on conventional methodology. The typical procedures for the preparation of thioester are the condensation of the thiols with the parent carboxylic acid, acid chloride or acid anhydrides that requires reflux conditions and longer reaction times. Recently, the synthesis of thioesters using a combination of amines (*N*-metilimidazole and TMEDA) has been reported [5]. Other synthesis of thioesters include: carbonylation of thiols or thioethers [6,7], hydration of thioacetylenes [8] Tishchenko-type reactions [9] and iodoarenes condensation with thiols or thiocarboxylic acids [10]. Thioesters also have been synthesized using a solid support involving CsF-Celite [11], ethyl (dimethylaminopropyl)carbodiimide (EDAC) [12] and microwave-assisted fly-ash-support [13].

The chemical application of ultrasound (sonochemistry) has become an exciting field of research during the last few years. Ultrasound has been utilized to accelerate a number of synthetically useful reactions. Examples include the Biginelli-type reaction, Suzuki cross-coupling in ionic liquid, organometallic reactions, metal-catalyzed hydrogenation, phase transfer, polymer synthesis, reactions in aqueous solution and heterocyclic synthesis [14–16].

Recently, we published the formation of sulfur-containing heterocycles such as the thiazolidinones from mercaptoacetic acid [17]. In our research program also there is an interest in improving the methodologies for the preparation of sulfur derivatives compounds using alternative methods [18]. The aim of this study is the systematic synthesis of thioesters from 2-mercaptobenzoxa(thia)zoles and benzoyl chlorides using both ultrasonic irradiation method and a more conventional thermal method.

## 2. Results and discussion

First of all, we studied the conventional method for the synthesis of thioesters. The reaction carried out with one equivalent (1:1:1 of mercaptobenzooxazole **1**, benzoyl chloride **3a** and pyridine) did not show the formation of the desired thioester **4a**, and the starting material (mercaptobenzoxazole **1**) was recovered. A relative molar ratio of 1:2:2 proved to provide the optimum yields. Thus, a variety of benzoyl chlorides **3a–g** were coupled with 2-mercaptobenzoxazol **1** or 2-mercaptobenzothiazol **2** in the presence of pyridine to form the corresponding thioesters **4a–g** and **5a–g** according to Scheme 1. The reactions were carried out in refluxing THF for 24 h. In general, the desire products were isolated in good yields after purification (chromatography column).

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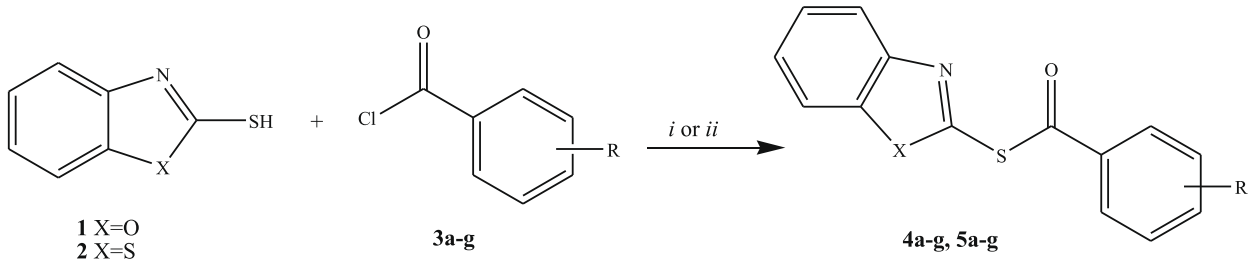


**Scheme 1.**

**Table 1**
Yields and selected physical properties of the compounds **4a–g** and **5a–g.**

| Compounds | X | R | Mp (°C)[a] | Yields (%)[b] | | GC–MS *m/z* (%) |
|---|---|---|---|---|---|---|
| | | | | US | Conventional | |
| **4a**[c] | O | H | 85–86 (83–85)[c] | 96 | 72 (90)[c] | 255 (5) [M], 195 (25), 105 (100), 77 (45), 43 (20) |
| **4b** | O | 4-$CH_3$ | 110–111 | 88 | 78 | 269 (5) [M], 209 (2), 119 (100), 91 (40), 65 (12) |
| **4c** | O | 2-$OCH_3$ | 103–105 | 91 | 83 | 284 (12) [M], 253 (16) 135(100), 77 (24), 40 (65) |
| **4d** | O | 4-$OCH_3$ | 85–88 | 94 | 77 | 285(2) [M], 258 (2), 135 (100), 107 (10), 92 (8), 77 (13) |
| **4e** | O | 2-F | 115–116 | 81 | 60 | 273 (5) [M], 213 (2), 123 (100), 95 (27), 75 (12), 43 (18) |
| **4f** | O | 3-F | 59–61 | 90 | 82 | 273 (5) [M], 213 (2), 123 (100), 95 (27), 75 (12), 43 (18) |
| **4g**[d] | O | 4-$NO_2$ | 122–125 (oil)[d] | 96 | 87 (80)[d] | 300 (10) [M], 167 (5), 150 (100), 104 (30), 76 (25) |
| **5a**[e,f,g] | S | H | 130–132 (129–131)[e] | 98 | 71 (95)[e] (86)[f] | 271 (5) [M], 197 (5), 149 (8), 105 (100), 77 (45), 43 (70) |
| **5b**[g] | S | 4-$CH_3$ | 120–121 | 86 | 82 | 285 (2) [M], 167 (2), 119 (100), 108 (2), 91 (35), 65 (12) |
| **5c** | S | 2-$OCH_3$ | 75–77 | 89 | 72 | 301(2) [M], 273 (18), 135 (100), 92 (10), 77 (29) |
| **5d**[g] | S | 4-$OCH_3$ | 62–63 | 92 | 76 | 301(2) [M], 273 (2), 135 (100), 107(8), 92 (8), 77 (15) |
| **5e** | S | 2-F | 120–121 | 84 | 71 | 289 (4) [M], 261 (2), 123 (100), 95 (25), 75 (10) |
| **5f** | S | 3-F | 129–132 | 93 | 67 | 289 (5) [M], 123 (100), 95 (43), 40 (90) |
| **5g**[g] | S | 4-$NO_2$ | 176–179 | 98 | 89 | 316 (5) [M], 167 (10), 150 (100), 120 (20), 104 (25), 76 (20) |

[a] Melting points are uncorrected.
[b] Yields of isolated compounds.
[c] Literature data [20].
[d] Literature data [11].
[e] Literature data [21].
[f] Literature yield from microwave method [13].
[g] Literature data [19].

To improve our studies, the synthesis of the same compounds **4a–g** and **5a–g** were obtained using ultrasound irradiation at room temperature for short reaction times. The mixture of benzoyl chlorides **3a–g** and pyridine in THF were reacted with 2-mercaptobenzoxa(thia)zoles **1**,**2**, leading to the corresponding thioesters **4a–g** e **5a–g** after 5 min in excellent yields (Scheme 1). The ultrasonic method was simpler and the products were isolated without further purification.

We did not observed any influence of the benzoyl substituent group on formation of thioesters in both methods. The results are summarized in Table 1. Some of the compounds have not been previously reported, with the exceptions of compounds **5b**, **5d** and **5g** which were synthesized only by the conventional method. However, their yields and reaction times have not been previously reported [19]. Compounds **4a** [20], **4g** [11] and **5a** [13,19,21] have also been reported in the literature.

The physical properties and NMR spectra of the compounds agree with the proposed structures, and were additionally identified by comparing their physical constants with literature data (see Tables 1 and 2) [11,13,19,20]. The unknown compounds were fully characterized by NMR and by mass spectral analyses.

## 3. Experimental

The reagents and solvents were used as obtained from commercial suppliers without further purification. NMR spectra were recorded on a Bruker DPX 400 spectrometer (400.13 MHz for $^1H$ and 100.63 MHz for $^{13}C$) at 298 K, 0.5 M in $CDCl_3$ containing TMS as internal standard. Mass spectra were obtained using an HP 5973 MSD connected to an HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless, injector, auto sampler, cross-linked HP-5 capillary column (30 m 0.32 mm of internal diameter) and helium was used as the carrier gas. Melting points were determined using open capillaries on a Tecnopon PFM II apparatus and are uncorrected. Mass spectra were registered in a SHIMADZU QP 2010 spectrometer connected to a GC-SHIMADZU 2010. The reactions were carried out with a microtip probe (3 mm) connected to a 500 W Sonics Vibra-cell ultrasonic processor operating at 20 kHz at 25% of the maximum power output. The progress of the reactions were monitored by TLC.

### 3.1. Synthesis of thioesters *4a–g* and *5a–g* by conventional method

A solution of benzoyl chlorides **3a–g** (2 mmol) in THF (5 ml) was added to a stirred mixture of 2-mercaptobenzoxazole **1** or 2-mercaptobenzothiazole **2** (1 mmol) and pyridine (2 mmol) or triethylamine (2 mmol) in THF (10 ml). The mixture was stirred for 24 h at reflux temperature. The solvent was removed, $CH_2Cl_2$ (10 ml) was added, the solution was washed with HCl 0.1 N ($2 \times 10$ ml), water (10 ml) and the organic layer was separated, dried with $MgSO_4$ to give the crude products. The products were

**Table 2**
Selected $^{1}H$ and $^{13}C$ NMR data of compounds **4a–g** and **5a–g.**

| Comp. | $\delta$ (ppm) for $^{1}H$ and $^{13}C$ NMR |
|---|---|
| **4a** | $^{1}H$: 8.54–7.42 (m, 9H, aryl) |
| | $^{13}C$: 171.0 (C=O); 165.7; 145.9; 143.1; 140.1; 136.7; 134.1; 128.1; 125,6; 120.9; 118.7; 111.1 |
| **4b** | $^{1}H$: 7.81–7.32 (m, 8H, aryl); 2.21 (s, 3H, Me) |
| | $^{13}C$: 176.3 (C=O); 165.4; 152.6; 148.9; 145.5; 137.2; 133.9; 128.4; 124.9; 121.6; 120.6; 114.6; 21.4 (Me) |
| **4c** | $^{1}H$: 7.96–6.88 (m, 8H, aryl); 3.93 (s, 3H, OMe) |
| | $^{13}C$: 181.3 (C=O); 171.2; 155.2; 149.6; 140.6; 136.9; 133.6; 132.4; 127.2; 126.4; 124.2; 121.3; 115.9; 111.4; 55.2 (OMe) |
| **4d** | $^{1}H$: 7.75–6.82 (m, 8H, aryl); 3.81 (s, 3H, OMe) |
| | $^{13}C$: 179.0 (C=O); 166.5; 165.2; 147.4; 136.6; 131.5; 125.2; 123.2; 114.3; 113.6; 112.2; 110.2; 53.3 (OMe) |
| **4e** | $^{1}H$: 8.22–7.05 (m, 8H, aryl) |
| | $^{13}C$: 178.7 (C=O); 165.0; 161.2; 158.2; 146.8; 134.9; 134.8; 130.8; 129.5; 126.0; 125.4; 121.9; 116.2; 110.0 |
| **4f** | $^{1}H$: 8.53–7.09 (m, 8H, aryl) |
| | $^{13}C$: 171.4 (C=O); 163.7; 163.2; 146.7; 138.8; 130.3; 127.9; 126.8; 126.1; 123.3; 121.2; 121.0; 117.4; 117.2 |
| **4g** | $^{1}H$: 8.10–7.41 (m, 8H, aryl) |
| | $^{13}C$: 181.0 (C=O); 171.2; 164.2; 152.9; 144.7; 131.2; 129.8; 128.6; 125.7; 123.8; 120.1; 110.3 |
| **5a** | [a] |
| **5b**[b] | $^{13}C$: 185.9 (C=O); 174.4; 151.4; 145.8; 139.9; 145.3; 131.6; 127.4; 126.1; 123.8; 119.9; 111.7; 21.4 (Me) |
| **5c** | $^{1}H$: 7.78–6.69 (m, 8H, aryl); 3.85 (s, 3H, OMe) |
| | $^{13}C$: 180.1 (C=O); 169.5; 158.2; 151.8; 136.5; 135.9; 131.1; 129.9; 127.6; 127.0; 126.0; 124.0; 117.3; 112.5; 55.1 (OMe) |
| **5d**[b] | $^{13}C$: 185.0 (C=O); 164.7; 151.5; 136.0; 132.7; 128.1; 126.2; 125.3; 122.8; 121.1; 114.2; 113.6; 55.5 (OMe) |
| **5e** | $^{1}H$: 8.26–7.10 (m, 8H, aryl) |
| | $^{13}C$: 191.0 (C=O); 168.7; 163.8; 161.2; 140.3; 135.4; 135.3; 132.6; 129.9; 127.1; 124.0; 121.2; 117.6; 112.3 |
| **5f** | $^{1}H$: 7.95–7.31 (m, 8H, aryl) |
| | $^{13}C$: 185.5 (C=O); 166.4; 161.2; 148.5; 140.7; 132.5; 131.2; 129.9; 127.7; 124.6; 123.7; 120.5; 119.9; 112.0 |
| **5g**[b] | $^{13}C$: 177.3 (C=O); 166.5; 158.4; 145.8; 139.3; 133.6; 128.6; 126.9; 125.1; 120.8; 119.7; 112.2 |

[a] NMR literature data [21].
[b] $^{1}H$ NMR literature data [19].

purified by column chromatography on silica gel using a mixture of chloroform:methanol (9:1) as the eluent.

### 3.2. Synthesis of thioesters *4a–g* and *5a–g* by a sonochemical method

In a 25 ml beaker, the precursor **1** or **2** (1 mmol) and benzoyl chlorides **3a–g** (2 mmol) were mixed with THF (10 ml) and pyridine (2 mmol) was added. The reaction mixtures were then sonicated by an ultrasonic probe with a frequency of 20 kHz at room temperature. The complete consumption of reagents occurred after 5 min, as monitored by TLC. The solvent was removed, $CH_2Cl_2$ (10 ml) was added, and the solution was washed with HCl 0.1 N ($2 \times 10$ ml), water (10 ml). The organic layer was separated and dried using $MgSO_4$ to give the desire products without purification.

## 4. Conclusion

In summary, ultrasound was used to promote the synthesis of 14 compounds in excellent yields in short reaction times. This procedure can be used as a replacement for conventional thermal synthetic methodology, allowing rapid access to a wide range of thioesters and reducing the reaction times and by-products. Even though the conventional thermal method also showed good yields, the reaction times needed were significantly longer (24 h rate than 5 min).

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