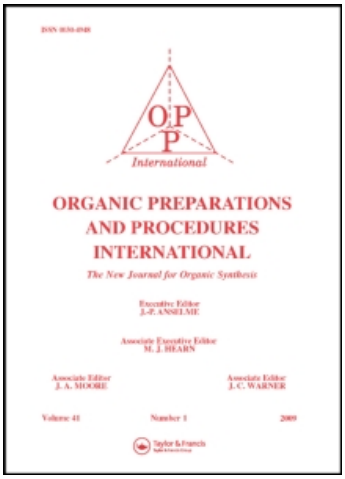


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# A CONVENIENT, ONE-POT SYNTHESIS OF THIOCARBAMATES USING *BIS*(TRICHLOROMETHYL) CARBONATE

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12. A sample of dimethyl 4,4'-diaminodiphenoate for comparison was kindly supplied by S. Strunk of Wyeth.

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## A CONVENIENT, ONE-POT SYNTHESIS OF THIOCARBAMATES USING *bis*(TRICHLOROMETHYL) CARBONATE

*Submitted by* (11/11/05)

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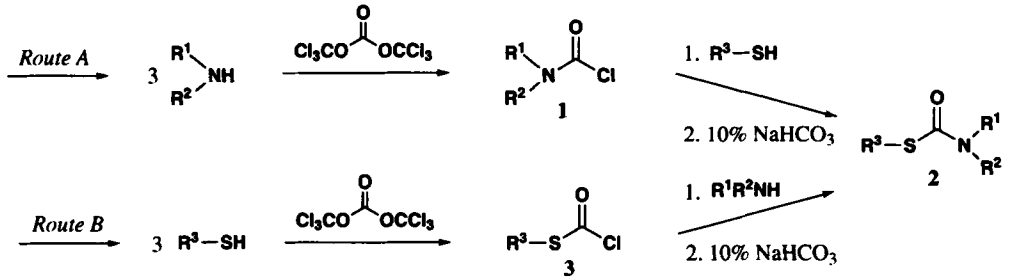
Thiocarbamates are an important class of compounds due to their biological activity[1] and have found wide applications in the chemical industry such as in the production of commodity chemicals such as herbicides,[2] pesticides,[3] bactericides[4] and antiviral agents.[5] Therefore the development of methods for the synthesis of thiocarbamates is important.

Several methods for the preparation of thiocarbamates have been reported in the literature[6] such as the reaction of amines with phosgene and thiols.[7] In addition, the direct condensation of thiols with carbamoyl chlorides[8] or isocyanates[9] has also been reported. Unfortunately, both carbamoyl chlorides and isocyanates are typically prepared from phosgene and some of them are difficult to store, as they are sensitive to water. There are a variety of other methods including (i) the reaction of carbon monoxide, amines with thiols[10] or disulfides[11] in the presence of metal catalysts, (ii) the use of sulfur[12] with amines and carbon monoxide followed by addition of alkyl halides, (iii) coupling of thiocyanates and alcohols in the presence of sulfuric acid,[13-14] (iv) the conversion of various *o*-substituted thiocarbamates *via* intramolecular rearrangement.[15] Recently, Wynne reported a synthesis of thiocarbamates from thiols[16] in which two equivalents of trichloroacetyl chloride and of amines were required. Despite of the numerous routes, most methods involve unstable reagents, multi-step procedures, harsh reaction conditions, expensive catalyst or complex materials. Base on these premises, we now report a mild and convenient one-pot procedure for the synthesis of thiocarbamates using *bis*(trichloromethyl) carbonate (BTC).

BTC is well known as an important equivalent for phosgene and has emerged as a versatile synthetic auxiliary in the preparation of various organic compounds.[17] Reactions with BTC usually proceed under relatively mild conditions and often afford good to excellent yields. The present work reports the reaction of BTC for the synthesis of thiocarbamates from thiophenols and amines.

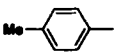
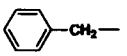
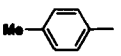
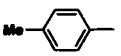
In *Scheme 1* two routes to prepare thiocarbamates were investigated. Route A involves the chlorocarbonylation of the amines with BTC followed by the addition of thiophenols. In order to avoid the formation of by-product ureas, the amines should be added to the solution of




**Scheme 1**

BTC at low temperature. However, one disadvantage of this route is that it produces amine salts in step one, which leads to difficulties in the reaction with thiophenols, giving low yields of the desired products. The experiment showed that N-substituted thiocarbamates were obtained in moderate yields by this route (*Table 1*). When secondary amines were used, only trace amount of products were detected. Hence, we preferred Route B, which involves the reaction of thiophenols with BTC to afford thiochloroformates (**3**), followed by condensation with amines. This route gave good yields of thiocarbamates.

**Table 1**. Synthesis of Thiocarbamates from Amines (Route A)

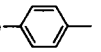
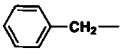
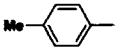
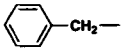
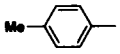
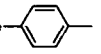
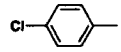
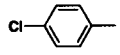
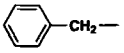
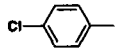
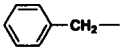
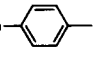
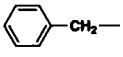
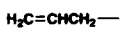
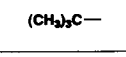
| Entry | Amines | | | Time(h) | | Product | Yield[a] |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | Step 1 | Step 2 | | (%) |
| **1** | H |  |  | 2 | 6 | **2a** | 65 |
| **2** | H |  |  | 2 | 6 | **2b** | 67 |
| **3** | H |  |  | 2 | 10 | **2e** | 57 |
| **4** | Et | Et |  | 2 | 24 | **2j** | traces |

a) Yields based on amines.

In route B, the intermediate (**3**) was formed efficiently through the reaction of one equivalent of thiophenols with a slight excess of BTC. It is observed that most of the thiophenols were consumed after stirring 0.5 h at room temperature. The amine was then added to the resulting mixture in the cold (ice-bath) and then brought to reflux to give the desired product. In comparison to reported methods for the preparation of thiocarbamates, the major advantages of the present method are its simplicity and rather mild conditions. Various substrates were tested under the optimal condition and the results are summarized in *Table 2*. As shown in *Table 2*, the

nature of the substituent on the thiophenols has no significant influence on the reaction and no by-product was detected by TLC analysis.

**Table 2.** Synthesis of Thiocarbamates from Thiophenols and Thiols (Route B)

| Entry | Amines | | | Base | Time(h) | | Product | Yield[a] |
|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | | Step 1 | Step 2 | | (%) |
| **1** | H |  |  | none | 1 | 1.25 | **2a** | 85 |
| **2** | H |  |  | none | 1 | 1 | **2b** | 88 |
| **3** | H |  |  | none | 1 | 2 | **2c** | 69 |
| **4** | H |  |  | none | 1 | 1 | **2d** | 90 |
| **5** | H |  |  | none | 1 | 1.5 | **2e** | 75 |
| **6** | H |  |  | none | 1.5 | 1.25 | **2f** | 79 |
| **7** | H |  |  | none | 1.5 | 1.25 | **2g** | 84 |
| **8** | H |  |  | none | 1.5 | 1.5 | **2h** | 71 |
| **9** | H | H |  | Py | 1 | 36 | **2i** | 0 |
| **10** | Et | Et |  | Py | 1 | 10 | **2j** | 54[b] |
| **11** | |  |  | Py | 1 | 10 | **2k** | 57[b] |
| **12** | H |  |  | none | 3 | 4 | **2l** | 70 |
| **13** | H |  |  | none | 3 | 4 | **2m** | 72 |
| **14** | H |  |  | none | 5 | 6 | **2n** | 68 |
| **15** | H |  |  | none | 5 | 6 | **2o** | 63 |

a) Yields based on thiophenols. b) Pyridine (1 equiv) and amines (2 equiv) were used.

In step two of Route B, a variety of amines were used and it was found that the nature of the amines affects the results. In the case of primary aromatic amines, the reaction proceeded efficiently giving the corresponding N-arylthiocarbamates in yields of 85-90% (*Table 2, Entries 1, 2 and 4*). When benzylamine was employed in the reaction, N-benzylthiocarbamate was obtained in 71% yield (*Table 2, Entry 8*). Secondary amines, possibly because of steric hindrance, reacted slowly with **3**, even after prolonged reaction time and the use of higher temperatures. Hence, a base catalyst was required and different bases were employed including pyridine, DMF and triethylamine. The result indicated pyridine worked the best and the prod-

ucts were prepared in 54% and 57% yields (*Table 2, Entries 10 and 11*). In an attempt to enlarge the scope of this route, benzylthiol and aliphatic thiols were examined under the same conditions and the corresponding thiocarbamates were obtained in moderate to good yields (*Table 2, Entries 12~15*).

In summary, we have developed a simple and straightforward procedure for the synthesis of thiocarbamates by using *bis*(trichloromethyl) carbonate under relatively mild conditions.

## EXPERIMENTAL SECTION

Mps are uncorrected and were obtained on an Electrothermal melting-point apparatus. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were measured on a Varian Mercur plus-400 spectrometer with tetramethylsilane (TMS) as an internal standard and $CDCl_3$ as the solvent. Mass (MS) spectra were obtained with a Finnigan Trace DSQ spectrometer. The elemental analysis was performed by Instrumental Analysis Center at Zhejiang University, Flash EA1112. All chemicals are from commercial sources. Preparative TLC was carried out on silica gel GF-254 plates.



**General Procedure for the Synthesis of Thiocarbamates. Route A.**- The amine (2 mmol) was added to a solution of BTC (0.24 g, 0.8 mmol) in $CH_2Cl_2$ (15 mL) at 0°C and the reaction mixture was stirred for 0.5 h at same temperature, then brought to reflux for 1.5 h. The thiophenol (2.2 mmol) in $CH_2Cl_2$ (2 mL) was added directly to the mixture and the reaction was stirred until completion as indicated by TLC. The solvent was removed and the residue was diluted with ethyl acetate (20 mL) and washed with 10% $NaHCO_3$ (20 mL x 3), brine (20 mL x 3), then dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (80:20).

**Route B.**- The thiophenol or thiol (2 mmol) was added to a solution of BTC (0.24 g, 0.8 mmol) in $CH_2Cl_2$ (15 mL) at room temperature. The reaction mixture was stirred until completion as indicated by TLC, then cooled to 0-5°C. The amine (2.2 mmol) was then added slowly to the mixture which was then brought to reflux until the reaction was completed. The reaction mixture was worked up as described in Route A.

**Table 3.** Data of Thiocarbamates from Amines and Thiophenols or Thiols Using BTC

| Cmpd | mp.(°C) (*lit.*mp) | MS(EI) m/z (%) $[M+H]^+$ | IR(KBr) ($cm^{-1}$) | $^1$H NMR(δ) | $^{13}$C NMR(δ) |
|---|---|---|---|---|---|
| **2a** | 130-131.5 (129-131[21]) | 244(100) | 3270(NH) 1664(C=O) | 7.62-7.60 (2H, m, ArH), 7.46-7.43 (3H, m, ArH), 7.26-7.23 (2H, m, ArH), 7.09 (2H, d, $J$ = 8.0 Hz, ArH), 7.01 (1H, bs, NH), 2.30 (3H, s, $CH_3$) | ---- |
| **2b** | 123-124 (122-124[18]) | 230(100) | 3254(NH) 1661(C=O) | 7.63-7.60 (2H, m, ArH), 7.48-7.44 (3H, m, ArH), 7.38-7.26 (4H, m, ArH), 7.10 (1H, t, $J$ = 7.2 Hz, ArH), 7.08 (1H, bs, NH) | ---- |

**Table 3**. Continued...

| Cmpd | mp.(°C) (*lit*.mp) | MS(EI) m/z (%) $[M+H]^+$ | IR(KBr) ($cm^{-1}$) | $^1H$ NMR(δ) | $^{13}C$ NMR(δ) |
|---|---|---|---|---|---|
| **2c** | 90-91 (90[19]) | 244(100) | 3300(NH) 1648(C=O) | 7.58-7.56 (2H, m, ArH), 7.42-7.39 (3H, m, ArH), 7.35-7.23 (5H, m, ArH), 5.36 (1H, bs, NH), 4.45 (2H, d, *J* = 5.6 Hz, $CH_2$) | ---- |
| **2d** | 129-130 (130-130.5[20]) | 244(100) | 3295(NH) 1662(C=O) | 7.49 (2H, d, *J* = 7.6 Hz, ArH), 7.36-7.25 (6H, m, ArH), 7.09 (1H, t, *J* = 7.6 Hz, ArH), 7.05 (1H, bs, NH), 2.40 (3H, s, $CH_3$) | ---- |
| **2e** | 130.2-130.7 (129-130[19]) | 258(100) | 3298(NH) 1648(C=O) | 7.45 (2H, d, *J* = 8.4 Hz, ArH), 7.33-7.20 (7H, m, ArH), 5.60 (1H, bs, NH), 4.44 (2H, d, *J* = 6.0 Hz, $CH_2$), 2.37 (3H, s, $CH_3$) | ---- |
| **2f** | 146-147 (a) | 278(100) 280(37) | 3285(NH) 1657(C=O) | 7.50 (2H, d, *J* = 8.4 Hz, ArH), 7.40 (2H, d, *J* = 8.4 Hz, ArH), 7.29-7.26 (2H, m, ArH), 7.11 (2H, d, *J* = 8.0 Hz, ArH), 7.02 (1H, bs, NH), 2.31 (3H, s, $CH_3$) | 164.8, 140.3, 135.6, 135.0, 134.2, 130.3, 129.5, 124.7, 119.7, 21.0 |
| **2g** | 158.5-160.5 (158-160[21]) | 264(90) 266(30) | 3291(NH) 1660(C=O) | 7.53-7.50 (2H, m, ArH), 7.42-7.29 (6H, m, ArH), 7.12 (1H, t, *J* = 7.6 Hz, ArH), 7.09 (1H, bs, NH) | ---- |
| **2h** | 150-151 (151-152[19]) | 278(100) 280(30) | 3302(NH) 1650(C=O) | 7.48 (2H, d, *J* = 8.4 Hz, ArH), 7.38-7.26 (7H, m, ArH) 5.63 (1H, bs, NH), 4.47 (2H, d, *J* = 5.6 Hz, $CH_2$) | ---- |
| **2j** | oil (oil[10]) | 210(100) | 1653(C=O) | 7.53-7.48 (2H, m, ArH), 7.40-7.36 (3H, m, ArH), 3.43 (4H, q, *J* = 7.2 Hz, $NCH_2$), 1.20 (6H, br, $CH_3$) | ---- |
| **2k** | 50-52 (53[22]) | 221(70) 222(47) | 1651(C=O) | 7.55-7.52 (2H, m, ArH), 7.43-7.40 (3H, m, ArH), 3.57 (4H, br, $NCH_2$), 1.70 (6H, br, $CH_2$) | ---- |
| **2l** | 92-93 (92.1-94.2[23]) | 243(60) 244(20) | 3243(NH) 1650(C=O) | 7.41-7.26 (9H, m, ArH), 7.12 (1H, t, *J* = 7.2 Hz, ArH), 7.02 (1H, bs, NH), 4.23 (2H, s, $CH_2$) | ---- |
| **2m** | 109-110 (109.1-110.3[23]) | 257(100) 258(30) | 3247(NH) 1648(C=O) | 7.37-7.23 (7H, m, ArH), 7.11 (2H, d, *J* = 8.4 Hz, ArH), 6.95 (1H, bs, NH), 4.44 (2H, s, $CH_2$), 2.31 (3H, s, $CH_3$) | ---- |
| **2n** | 67-69 (69-70[20]) | 194(70) | 3230(NH) 1622(C=O) | 7.41 (2H, d, *J* = 8.0 Hz, ArH), 7.32 (2H, t, *J* = 8.0 Hz, ArH), 7.12 (1H, t, *J* = 7.6 Hz, ArH), 7.02 (1H, bs, NH), 5.94-5.77 (1H, m, =CH), 5.31-5.12 (2H, m, $CH_2$=), 3.64 (2H, d, *J* = 6.8 Hz, $CH_2$) | ---- |
| **2o** | 140-141 (142-143[20]) | 210(60) | 3313(NH) 1689(C=O) | 7.35 (2H, d, *J* = 8.0 Hz, ArH), 7.30-7.26 (2H, m, ArH), 7.03 (1H, t, *J* = 7.2 Hz, ArH), 6.46 (1H, bs, NH), 1.52 (9H, s, $CH_3$) | ---- |

a) *Anal*. Calcd. For $C_{14}H_{12}ClNOS$: C, 60.54; H, 4.35; N, 5.04. Found: C, 60.57; H, 4.26; N, 5.09

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## AN IMPROVED SYNTHESIS OF 2-*n*-(PROPYL)-1*H*-IMIDAZOLE-4,5-DICARBOXYLIC ACID DIETHYL ESTER

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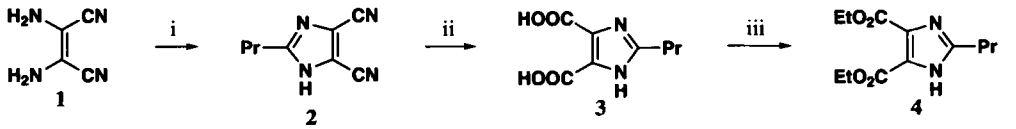
Diethyl 2-(*n*-propyl)-1*H*-imidazole-4,5-dicarboxylate (**4**) is an intermediate in the synthesis of *olmesartan*, a non-peptide angiotensin II receptor antagonist.[1-2] Yanagisawa *et al.*[3-4] reported using diaminomaleonitrile and trimethyl orthobutyrate as starting materials. Thus, diaminomaleonitrile was treated with trimethyl orthobutyrate in acetonitrile to provide the 2- (*n*-propyl)-1*H*-imidazole-4,5-dicarbonitrile (96% yield) which was then hydrolyzed under acidic conditions to afford **3** (80%). Esterification of **3** in ethanol in the presence of hydrogen chloride gave **4** in 86% yield (*Scheme 1*).




i) *n*-PrC(OMe)$_3$; MeCN, Δ, 5 h, xylene, 7 h; ii) HCl, $H_2O$, Δ, 8 h; iii) HCl (gas), EtOH, 3 h

**Scheme 1**

However, this method is not practical for large-scale preparation because diaminomaleonitrile is toxic and expensive, requiring long reaction times and tedious work-up. To overcome