Synthesis of Phenylthiomethyl Compounds from Trichloromethyl Derivatives

Moisés Romero-Ortega,*[a] Aydeé Fuentes,[a] Carlos González,[a] David Morales,[a] Raymundo Cruz[b]

[a] Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México, Paseo Colón/Paseo Tollocan s/n Toluca, Estado de México, C.P. 50000, México

[b] Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, México, D.F.

Fax +1(72)173890; E-mail: cgr@coatepec.uaemex.mx

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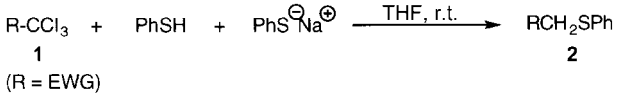
Abstract: A new method for the conversion of trichloromethyl compounds into the corresponding phenylthiomethyl derivatives by reaction with sodium thiophenolate in the presence of thiophenol is described. This transformation proceeds at room temperature in high yield and has been applied to a variety of trichloromethyl compounds.

Key words: trichloromethyl compounds, thiophenol, sodium thiophenolate, phenylthiomethyl derivatives, nucleophilic substitution

We recently reported[1] that 2-trichloromethylpyrimidines substituted with one or two alkoxycarbonyl groups were rapidly and quantitatively converted into the corresponding 2-phenylthiomethylpyrimidines by sodium thiophenolate in the presence of thiophenol at room temperature.[2] This reaction was demonstrated to be an ionic process proceeding via an intermediate 1,1-bis(phenyl-thio)methyl compound which was the major product in the absence of thiophenol. The synthetic importance of phenylthiomethyl compounds and the derived sulfoxides and sulfones,[3–5] especially in carbon–carbon bond forming reactions, prompted us to examine the possibility of effecting this conversion with other trichloromethyl compounds, many of which are readily available.

We have now found that the reaction of a variety of trichloromethyl compounds **1** with a 1:1 sodium thiophenolate/thiophenol mixture (3 equiv) produced the expected phenylthiomethyl derivatives **2**, usually in excellent yields (Scheme, Table 1).



Scheme

Several aspects of the data given in the Table deserve comment. Firstly, the reaction is successful in those cases where the substituent attached to the trichloromethyl group is strongly carbanion stabilizing (e.g., Entries **a–d**, **f–i**), but fails when such a group is absent (Entry **k**) or when it is only moderately carbanion stabilizing (Entries **j, l**) even under more vigorous conditions. This is expected provided that the reaction proceeds via at least two carbanionic intermediates.[1] In this regard it is informative to note that the reaction of 2-trichloromethylimidazole **(1e)** is very slow and stops at the 1,1-bis(phenylthio)methyl stage (Entry **e**). Lastly, the reactions are highly chemoselective as illustrated by the results with ethyl trichloroacetate (Entry **a**), trichloroacetonitrile (Entry **b**) and 1-(2-chloroethyl)-2-trichloroacetylpyrrole (Entry **d**). In each case, the phenylthiomethyl derivative was the major or exclusive product, with no significant ester cleavage, phenylthioimidate formation, or side chain chloride displacement, respectively, being observed.

Except for our own recently disclosed study,[1] the process described herein has not previously been reported. The reaction of trichloromethyl compounds with thiolates has been described,[6–8] but the products were thio ortho esters or 1,1-bis(alkylthio)methyl compounds, the latter being analogous to our result with 2-trichloromethylimidazole **(1e)**.

In conclusion, trichloromethyl compounds bearing a substituent which is highly carbanion stabilizing, are efficiently converted into phenylthiomethyl derivatives with 3 equivalents of an equimolar thiophenol/sodium thiophenolate mixture at room temperature. This process is expected to be particularly useful in those instances where the halomethyl compounds, the usual precursors of phenylthiomethyl compounds, are not readily available, or unavailable by other routes.[9–10]

The trichloromethyl compounds **1a–c** and **1j–l** are commercially available, whereas **1e–g** and **1i** were easily synthesized in good yields by literature methods.[11,12] Compound **1h** was prepared by a new method developed by us, which will be published elsewhere.

Melting points are uncorrected and were measured on a mel-temp II apparatus. ^{1}H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer using $CDCl_3$ as solvent and are reported in δ from internal TMS. IR spectra were recorded on a Nicolet FT-SX spectrophotometer and mass spectra on a Jeol JMS-Ax 505 HA mass spectrometer. Analytical TLC plates and silica gel 60 (230–400 mesh) were purchased from Merck. THF was distilled from sodium benzophenone ketyl prior to use. The reactions were conducted under N_2 atmosphere.

Phenylthiomethyl 2 Derivatives from Trichloromethyl Compounds 1; General Procedure

Thiophenol (6.6 equiv) was added to a suspension of NaH (3.3 equiv, washed free of mineral oil with anhyd hexane from a 50% suspension of NaH in mineral oil) in anhyd THF (1–3 mL/mmol of the trichloromethyl compound **1**) under a nitrogen atmosphere. After ca 10 min, the appropriate trichloromethyl derivative **1** (1 equiv) was added and the mixture was stirred at r.t. for the time given in the Table. The mixture was then quenched with sat. aq NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The organic phase was washed with H_2O, dried (Na_2SO_4) and the solvent was evaporated

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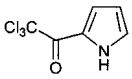
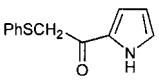
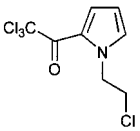
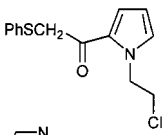
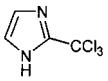
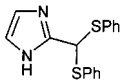
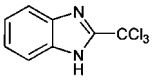
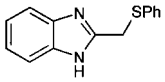
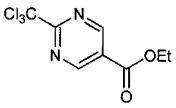
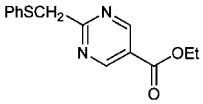
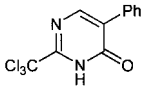
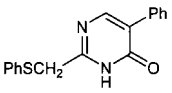
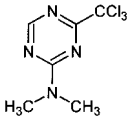
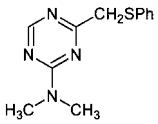
Table 1 Reduction of Trichloromethyl Compounds with Sodium Thiophenolate/Thiophenol

Entry	Substrate (**1**)	Product (**2**)	Reaction Time (min)	Ratio of hexane/ EtOAc for column chromatography	Yield (%)
a	CCl_3CO_2Et	$PhSCH_2CO_2Et$	10	80:20	98
b	CCl_3CN	$PhSCH_2CN$	5	75:25	75
c			5	80:20	~100
d			5	80:20	~100
e			720	80:20	40
f			5	90:10	71
g			10	90:10	98
h			5	95:5	80
i			60	80:20	91
j	$PhCCl_3$	–[a]			
k	$CHCl_3$	–[a]			
l	CF_3CCl_3	–[a]			

[a] No reaction.

Table 2 Physical Properties and Spectral Data of Reduction Derivatives **2** of Trichloromethyl Compounds **1**

Product[a]	mp (°C)	IR ($CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (70 eV) *m*/*z* (%)
2a	oil	1736, 1286, 1030	1.22 (t, *J* = 7.2, 3 H), 3.61 (s, 2 H), 4.17 (q, *J* = 7.2, 9 H), 7.21–7.45 (m, 5 H)	196 (M^+, 90), 123 (100)
2b	oil	2245, 1581, 1479, 1438	3.57 (s, 2 H), 7.31–7.40 (m, 3 H), 7.52–7.59 (m, 2 H)	149 (M^+, 48), 109 (100)
2c	79–80	3222, 1646, 1390, 1102	4.08 (s, 2 H), 6.25–6.30 (m, 1 H), 6.88–6.93 (m, 1 H), 7.01–7.06 (m, 1 H), 7.19–7.32 (m, 3 H), 7.38–7.43 (m, 2 H), 9.55 (br, 1 H)	217 (M^+, 58), 94 (100)
2d	oil	1642, 1467, 1409	3.75 (t, *J* = 5.6, 2 H), 4.12 (s, 2 H), 4.57 (t, *J* = 5.6, 2 H), 6.16–6.19 (m, 1 H), 6.97–7.04 (m, 2 H), 7.20–7.43 (m, 5 H)	279 (M^+), (40), 281 (M^+ + 2) (15), 156 (100), 158 (36)
2e	oil	3432, 1445, 1104	5.73 (s, 1 H), 6.95 (s, 2 H), 7.24–7.36 (m, 10H), 9.12 (br, 1 H)	298 (M^+, 20), 297 (100)
2f	138–139	3399, 3054, 1434, 1274	4.40 (s, 2 H), 7.15–7.33 (m, 9 H), 7.76–7.59 (br, 3 H)	240 (M^+, 65), 131 (100)

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Table 2 (continued)

Product[a]	mp (°C)	IR ($CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (70 eV) *m*/*z* (%)
2g	58–59	1728, 1586, 1555, 1295	1.41 (t, *J* = 7, 3 H), 4.42 (q, *J* = 7, 2 H), 4.42 (s, 2 H), 7.19–7.33 (m, 3 H), 7.37–7.41 (m, 2 H), 9.20 (s, 2 H)	274 (M^+, 100)
2h	203	3419, 3058, 1643, 1510, 1490	4.04 (s, 2 H), 7.25–7.46 (m, 8 H), 7.61–7.70 (m, 2 H, 7.99 (s, 1 H), 12.33 (br, 1 H)	294 (M^+, 100)
2i	oil	1588, 1507, 1408	3.11 (s, 3 H), 3.16 (s, 3 H), 7.11–7.32 (m, 3 H), 7.40–7.49 (m, 2 H), 8.49 (s, 1 H)	246 (M^+, 100)

[a] Satisfactory microanalyses were obtained: C ± 0.37, H ± 0.18, N ± 0.32, S ± 0.28.

in vacuo. The product was obtained from the residue by column chromatography on silica gel using hexane/EtOAc mixtures as the eluent (Tables 1 and 2).

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