

PbCl₂/Ga Bimetal Redox System-mediated Carbon–Carbon Bond Formation Reactions between Carbonyl Compounds and Ethyl Trichloroacetate and Iodoacetoneitrile

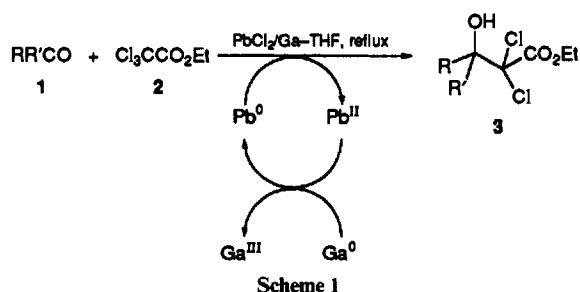
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In the presence of lead dichloride and a metallic gallium bimetal redox system, carbonyl compounds reacted with ethyl trichloroacetate and iodoacetoneitrile to afford ethyl β-substituted α,α-dichloropropionates and β-hydroxy nitriles, respectively, in moderate to excellent yields.

Although, recently, there has been considerable interest in the synthetic application of bimetal redox systems,^{1–8} gallium has received little attention compared with zinc and aluminium in this connection. Although there have been reports to the effect that Mg–HgCl₂ promotes the reaction of ethyl trichloroacetate with aldehydes to produce a non-halogenated β-hydroxy ester,¹ and that reductive addition of polyhalogenoalkanes to carbonyl compounds has been successfully achieved, the reaction of ethyl trichloroacetate with carbonyl compounds gives only a low yield of mixed products.⁵ It has also been reported the electroreduction of Cl₃CCO₂Me, Cl₂CHCO₂Me with aldehydes yields methyl β-substituted α,α-dichloropropionate (9–47%) and methyl β-substituted α-chloropropionate (32–73%).⁹



A related group of compounds the β-hydroxy nitriles are important because they can undergo a variety of transformations.¹⁰ Of the many methods for generating nitrile anions,¹¹ the Reformatsky-type reaction between bromoacetoneitrile and carbonyl compounds in the presence of zinc represents one of the most useful methods for the preparation of β-hydroxy nitriles.¹² Although, under standard conditions these are obtained only in moderate yield.¹³ Although slightly better yields are obtained with the pre-formed organozinc intermediate¹⁴ or by the use of other metals,¹⁵ the procedure is not simple. Herein, we report a novel synthesis of ethyl β-substituted α,α-dichloropropionate and β-hydroxy nitriles with the advantages of easy availability of the PbCl₂/Ga bimetal redox system, simplicity of procedure, and moderate to excellent yields of product.

Reductive Addition of Ethyl Trichloroacetate to Carbonyl Compounds in a PbCl₂/Ga Bimetal Redox System.—The reductive addition of ethyl trichloroacetate to the aldehyde **1a** (R = 4-ClC₆H₄, R' = H) was performed as follows (Scheme 1). A mixture of **1a** and **2** (ethyl trichloroacetate) (1:2) in refluxing THF was treated with lead dichloride and gallium in slight excess (1.2 equiv.) for 6 h to afford the coupling product **3a** in 72% yield. As shown in Table 1, satisfactory results were

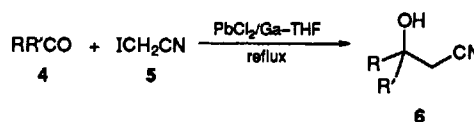


Table 1 Effect of metal salts in the reductive addition of Cl₃CCO₂Et to aldehyde **1a**^a

Entry	Metal salts	Amount of salts (mmol)	Time (h)	Yield (%) ^b
1	PbCl ₂	0.2	10	60.4
2	PbCl ₂	0.5	6	72
3	PbCl ₂	0.5	10	—(90) ^{c,d}
4	None	0	10	—(95) ^d
5	SnCl ₂	1	10	48
6	SnCl ₂	1	10	—(85) ^{c,d}
7	ZnCl ₂	1	10	—(92) ^d

^a Carried out with **1a** (1 mmol), Cl₃CCO₂Et (2 mmol) and Ga (1.2 mmol) in THF (4 cm³) at reflux temperature. ^b Isolated yields based on aldehyde **1a**. ^c Without Ga. ^d Aldehyde **1a** was recovered.

produced by use of a combination of lead dichloride with gallium (entries 1 and 2). The lead dichloride is indispensable, since in its absence no **3a** (entry 4) was formed. Tin dichloride could be used in place of lead dichloride when double the amount was necessary, but the yield was only 48% (entry 5). Attempted use of zinc dichloride in place of lead dichloride failed to induce reductive addition of ethyl trichloroacetate to **1a**.

We applied the PbCl₂/Ga bimetal redox system to the addition of ethyl trichloroacetate to a variety of carbonyl compounds **1**, the experimental results of which are summarized in Table 2. The reaction of ethyl trichloroacetate with aldehydes **1a–h** proceeded efficiently (entries 1–9), 1,2-addition taking place with the α,β-unsaturated aldehyde **1f**. In addition, the ketone **1i** is reactive, affording 62% of the coupling product.

Reductive Addition of Iodoacetoneitrile to Carbonyl Compounds in a PbCl₂/Ga Bimetal Redox System.—Under the same reactive conditions as for the reductive addition of ethyl trichloroacetate to carbonyl compounds, we carried out the PbCl₂/Ga bimetal redox system promoted addition of iodoacetoneitrile to carbonyl compounds, to yield β-hydroxy nitriles (see Scheme 2). The reaction gave excellent yields of product and the experimental results are summarized in Table 3. The

Table 2 Reductive addition of $\text{Cl}_3\text{CCO}_2\text{Et}$ to carbonyl compounds in a PbCl_2/Ga bimetal system

Entry	Carbonyl compound	$\text{Cl}_3\text{CCO}_2\text{Et}$ (mmol)	Time (h)	Yield (%) ^b
1	4-Chlorobenzaldehyde 1a	1	6	52
2	4-Chlorobenzaldehyde 1a	2	6	72
3	2-Bromobenzaldehyde 1b	2	7	60
4	4-Fluorobenzaldehyde 1c	2	6	80
5	Benzaldehyde 1d	2	10	61
6	4-Methylbenzaldehyde 1e	2	12	58
7	<i>trans</i> -Cinnamaldehyde 1f	2	11	67
8	Decanal 1g	2	10	75
9	Propionaldehyde 1h	2	12	67
10	Acetone 1i	2	10	62

^a Carried out with carbonyl compounds (1 mmol) and PbCl_2 (0.5 mmol) in THF (4 cm^3) at reflux temperature. ^b Isolated yield based on carbonyl compounds.

Table 3 Synthesis of β -hydroxy nitriles **6**^a

Entry	Carbonyl compound 4	Time (h)	Product yield (%) ^b
1	4-Chlorobenzaldehyde 4a	5	98
2	4-Fluorobenzaldehyde 4b	4	99
3	2-Bromobenzaldehyde 4c	4	99
4	Benzaldehyde 4d	6	92
5	4-Methylbenzaldehyde 4e	8	94
6	<i>trans</i> -Cinnamaldehyde 4f	7	70
7	Decanal 4g	8	82
8	Acetophenone 4h	8	80
9	4-Chlorobenzaldehyde 4a	5	55 ^c

^a Carried out with carbonyl compound (1 mmol), ICH_2CN (2 mmol), Ga (1.2 mmol) and PbCl_2 (0.5 mmol) in THF (4 cm^3) at reflux temperature. ^b Isolated yield based on carbonyl compound. ^c Without PbCl_2 .

reaction of aromatic aldehydes **4a–e** with iodoacetonitrile is very efficient with yields in the range 92–99%. The α,β -unsaturated aldehyde **4f** gave only 1,2-adduct whilst even the less reactive ketone **4h** produced a good yield of product. Use of metal gallium in the absence of lead dichloride gave the coupling product in only 55% yield. No reaction occurred when chloroacetonitrile replaced iodoacetonitrile under the same conditions.

Although the reaction mechanism of the PbCl_2/Ga bimetal redox system has yet to be clarified, Scheme 1 illustrates a catalytic cycle which may be involved. In addition to the illustrated reaction process, a Pb-Ga alloy may be formed since lead(0) solvates into liquid gallium (m.p. 29.8 °C) in refluxing THF.

In conclusion, we report a convenient, novel PbCl_2/Ga bimetal redox system which promotes reactions of carbonyl compounds with ethyl trichloroacetate and with iodoacetonitrile, to yield ethyl β -substituted α,α -dichloropropionates and β -hydroxy nitriles in moderate to excellent yield. Further applications of the PbCl_2/Ga bimetal redox system are now in progress in our group.

Experimental

M.p.s and b.p.s are uncorrected. M.p.s were measured on a capillary in a Tellon tube. ¹H NMR spectra were determined in CDCl_3 on a Varian EM-360L (60 MHz) spectrometer with SiMe_4 as the internal standard. *J*-Values are given in Hz. IR spectra were recorded on a Shimadzu IR-440 instrument. Mass spectral data were obtained by electron ionization (EI) on a Finnigan 4021 spectrometer. All the reactions were

carried out under nitrogen. THF was dried and redistilled before use.

Synthesis of Ethyl β -Substituted α,α -Dichloropropionates **3. General Procedure.**—Into a mixture of PbCl_2 (139 mg, 0.5 mmol) and commercial gallium bar (83.7 mg, 1.2 mmol) in THF (4 cm^3) were added the carbonyl compound (1 mmol) and ethyl trichloroacetate (383 mg, 2 mmol). The mixture was stirred under reflux until most of **1** had been consumed, after which it was diluted with ethyl acetate. The resulting mixture was filtered through a short column of silica gel and evaporated under reduced pressure. The residue was chromatographed on a silica gel plate or column (light petroleum–ethyl acetate 5:1) to give the pure product.

Ethyl 2,2-Dichloro-3-(4-chlorophenyl)-3-hydroxypropionate **3a** (72%), δ_{H} 1.30 (3 H, t, *J* 7), 3.50 (1 H, s, br), 4.30 (2 H, q, *J* 7), 5.45 (1 H, s) and 7.33 (4 H, s); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3420vs, 1720vs, 1590m, 1490m, 1080m, 1060m and 860s.

Ethyl 3-(2-Bromophenyl)-2,2-dichloro-3-hydroxypropionate **3b** (60%), δ_{H} 1.30 (3 H, t, *J* 7), 3.36 (1 H, s, br), 4.40 (2 H, q, *J* 7), 6.16 (1 H, s) and 7.95 (4 H, m); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3495vs, 1725vs, 1595m, 1080m, 1010m, 860s and 810s; *m/z* (%) 342 (M^+ , 1), 205 (8), 187 (94), 185 (100), 171 (2), 156 (18) and 77 (52) (Found: C, 38.4; H, 3.25. $\text{C}_{11}\text{H}_{11}\text{BrCl}_2\text{O}_3$ requires C, 38.63; H, 3.24%).

Ethyl 2,2-Dichloro-3-(4-fluorophenyl)-3-hydroxypropionate **3c** (80%), δ_{H} 1.30 (3 H, t, *J* 7), 3.40 (1 H, s, br), 4.40 (2 H, q, *J* 7), 5.30 (1 H, s) and 7.25 (4 H, m); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3500vs, 1760vs, 1610m, 1180m, 1040m and 860s; *m/z* (%) 281 (M^+ , 5), 229 (12), 156 (20), 125 (100), 109 (17) and 77 (18) (Found: C, 46.9; H, 3.7. $\text{C}_{11}\text{H}_{11}\text{Cl}_2\text{FO}_3$ requires C, 47.00; H, 3.94%).

Ethyl 2,2-Dichloro-3-phenylpropionate **3d** (61%), b.p. 125 °C/0.5 mmHg, δ_{H} 1.25 (3 H, t, *J* 7), 3.60 (1 H, s, br), 4.34 (2 H, q, *J* 7), 5.34 (1 H, s) and 7.40 (5 H, s); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3420vs, 1720vs, 1590m, 1080m, 1010m and 860s; *m/z* (%) 263 (M^+ , 5), 210 (12), 156 (8), 107 (63), 91 (23), 77 (43) and 71 (100) (Found: C, 50.25; H, 4.5. $\text{C}_{11}\text{H}_{12}\text{Cl}_2\text{O}_3$ requires C, 50.21; H, 4.60%).

Ethyl 2,2-Dichloro-3-hydroxy-3-(4-methylphenyl)propionate **3e** (58%), b.p. 140 °C/0.7 mmHg, δ_{H} 1.30 (3 H, t, *J* 7), 2.25 (3 H, s), 3.60 (1 H, br), 4.20 (2 H, q, *J* 7), 5.25 (1 H, s) and 7.38 (4 H, m); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3450vs, 1717vs, 1605m, 1070m, 1010m, and 860s; *m/z* (%) 278 ($\text{M} + 1$, 0.3), 225 (2), 156 (0.6), 121 (100), 91 (21) and 77 (17) (Found: C, 52.3; H, 4.9. $\text{C}_{12}\text{H}_{14}\text{Cl}_2\text{O}_3$ requires C, 52.00; H, 5.09).

Ethyl 2,2-Dichloro-3-hydroxy-5-phenylpent-4-enoate **3f** (67%), b.p. 128 °C/0.4 mmHg, δ_{H} 1.25 (3 H, t, *J* 7), 3.40 (1 H, s, br), 4.42 (2 H, q, *J* 7), 4.80 (1 H, d), 6.15–6.90 (2 H, m) and 7.20 (5 H, s); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3450vs, 1750vs, 1660m, 1610m, 1120m, 1020m and 970m; *m/z* (%) 235 ($\text{M} - \text{HOCl}$, 7), 156 (3), 133 (27), 115 (53), 91 (33) and 71 (100) (Found: C, 54.0; H, 4.9. $\text{C}_{13}\text{H}_{14}\text{Cl}_2\text{O}_3$ requires C, 54.00; H, 4.88%).

Ethyl 2,2-Dichloro-3-hydroxydodecanoate **3g** (50%), b.p. 148 °C/0.5 mmHg, δ_{H} 0.81 (3 H, t), 1.30 (3 H, t, *J* 7), 1.70–1.30 (14 H, m), 3.50 (1 H, s, br), 4.20 (2 H, q, *J* 7) and 4.40 (3 H, t); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3480vs, 1760vs, 1590m, 1020m, 840m and 790m; *m/z* (%) 313 (M^+ , 2), 259 (2), 156 (100) and 147 (39) (Found: C, 53.6; H, 8.5. $\text{C}_{14}\text{H}_{26}\text{Cl}_2\text{O}_3$ requires C, 53.67; H, 8.37).

Ethyl 2,2-Dichloro-3-hydroxypentanoate **3h** (75%), b.p. 63 °C/0.4 mmHg (lit.,¹⁶ 75 °C/0.8 mmHg), δ_{H} 0.95 (3 H, t), 1.25 (3 H, t, *J* 7), 1.40 (2 H, m), 2.80 (1 H, s, br), 4.05 (1 H, t) and 4.40 (2 H, q, *J* 7); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3500vs, 1720s, 1600s, 1060s, 1020m and 870m.

Ethyl 2,2-Dichloro-3-hydroxy-3-methylbutyrate **3i** (62%), b.p. 53 °C/0.5 mmHg, lit.,¹⁶ 43 °C/0.2 mmHg, δ_{H} 1.30 (3 H, t, *J* 7), 1.95 (6 H, s), 3.16 (1 H, s, br) and 4.20 (2 H, q, *J* 7);

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3500vs, 1720vs, 1600m, 1070m, 1020m and 870s.

Synthesis of β -Hydroxy Nitriles 6.—3-(4-Chlorophenyl)-3-hydroxypropanenitrile **6a** (98%) oil,¹⁷ δ_{H} 2.68 (2 H, d, *J* 6), 3.70 (1 H, s, br), 4.95 (1 H, t, *J* 6) and 7.30 (4 H, s); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3500vs, 2240m and 830s.

3-Fluorophenyl-3-hydroxypropanenitrile **6b** (99%), b.p. 142 °C/0.5 mmHg (lit.,¹⁷ b.p. 150–152 °C/1 mmHg), δ_{H} 2.48 (2 H, d, *J* 6), 3.50 (1 H, s, br), 4.75 (1 H, t, *J* 6) and 6.95 (4 H, m); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3450vs, 2240m and 830s.

3-(2-Bromophenyl)-3-hydroxypropanenitrile **6c** (99%), m.p. 70–72 °C, δ_{H} 2.60 (2 H, d, *J* 6), 3.65 (1 H, s, br), 4.95 (1 H, t, *J* 6) and 7.35 (4 H, m); $\nu_{\max}(\text{KCl})/\text{cm}^{-1}$ 3450vs, 2245m and 850s; *m/z* (%): 227, 225 (M^+ , 6, 7), 208 (0.3), 187 (84), 157 (19), 91 (3) and 77 (100) (Found: C, 47.9; H, 3.54. $\text{C}_9\text{H}_8\text{BrNO}$ requires C, 47.81; H, 3.57%).

3-Hydroxy-3-phenylpropanenitrile **6d** (92%), b.p. 157–158 °C/1.0 mmHg (lit.,²⁰ b.p. 154–155 °C/1 mmHg), δ_{H} 2.50 (2 H, d, *J* 6), 3.66 (1 H, s, br), 4.90 (1 H, t, *J* 6) and 7.25 (5 H, s); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3400vs, 2240m, 1610w and 720s.

3-Hydroxy-3-(4-methylphenyl)propanenitrile¹⁸ **6e** (94%), b.p. 145 °C/0.4 mmHg, δ_{H} 2.40 (3 H, s), 2.67 (2 H, d, *J* 6), 3.48 (1 H, s, br), 5.01 (1 H, t, *J* 6) and 7.35 (4 H, m); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3450vs, 2240m and 830s.

3-Hydroxy-5-phenylpent-4-enenitrile **6f** (70%), b.p. 152 °C/0.6 mmHg (lit.,¹⁹ 143 °C/0.5 mmHg), δ_{H} 2.50 (2 H, d, *J* 6), 3.60 (1 H, s, br), 4.60 (1 H, m), 6.20–6.70 (2 H, m) and 7.30 (5 H, s); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3420vs, 2240m, 1650s and 840s.

3-Hydroxydodecanenitrile **6g** (82%), b.p. 130–132 °C/0.4 mmHg, δ_{H} 0.85 (3 H, t), 1.42 (14 H, m), 1.95 (2 H, m), 2.45 (2 H, d, *J* 6), 3.65 (1 H, m) and 4.10 (1 H, s, br); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3450vs, 3100w and 2250m; *m/z* (%): 197, 195 (M^+ , 2, 20), 179 (4), 157 (2), 85 (13) and 43 (100) (Found: C, 73.5; H, 12.0; N, 7.35. $\text{C}_{12}\text{H}_{23}\text{NO}$ requires C, 73.05; H, 11.75; N, 7.10%).

3-Hydroxy-3-phenylbutanenitrile **6h** (80%), b.p. 155–157 °C/5 mmHg (lit.,²⁰ b.p. 149–150 °C/4 mmHg), δ_{H} 1.60 (3 H, s), 2.65 (2 H, s), 3.40 (1 H, s, br) and 7.25 (5 H, s); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3450vs, 2240m and 720s.

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