Synthesis of α,α-disubstituted acetic acids using low-valent titanium

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Dihalogenocarbenes generated using low-valent titanium (LVT) undergo a one-pot cycloaddition to diaryl, aryl alkyl or dialkyl ketones to give α,α-disubstituted acetic acids such as (*R*,*S*)-2-arylpropanoic acids. TiI_4 proved most effective in this reaction for which the product yield was optimized by use of an excess of reducing agent.

Since 2-arylpropanoic acids, which may be considered as α,α-disubstituted acetic acids, are important as non-steroidal anti-inflammatory drugs (NSAIDs),[1,2] their synthesis by a variety of methods has been described.[3–5] Several of these involve reactions such as Friedel-Crafts alkylation using lactic acid derivatives,[6] asymmetric alkoxycarbonylation of aryl alkenes,[7] alkylation of chiral enolates of imides[8] and α-arylation of malonic acid derivatives,[9] whilst others are multi-stage or use expensive reagents or experimental conditions. Since such routes are industrially uneconomical, alternative, one-pot syntheses are highly prized. Here we describe such a synthesis which involves the addition of dihalogenocarbenes to methyl aryl ketones using a base such as potassium *tert*-butoxide[10,11] or low-valent titanium (LVT)[12] to generate the dihalogenocarbene.

Ti^{III} or Ti^{IV} salts and various reducing agents were used to generate the LVT in this work the scope of which is illustrated in Scheme 1.

$$R^1R^2CO \xrightarrow[:CX_2]{LVT} R^1R^2CCO_2H$$

	R^1	R^2
1	*p*-$Bu^iC_6H_4$	Me
2	Ph	Me
3	Ph	Ph
4	Me	Me
5	Et	Me
6	Pr	Me
7	6-Methoxy-2-naphthyl	Me
8	Fluoren-2-yl	Me

Scheme 1

Addition of X_2C: to C=O has not been extensively studied[13,14] and can be considered as a cyclopropanation-like procedure.[15–20] Thus, carbene generation using LVT† has been cited as the method of choice for the cyclopropanation of alkenes.[21–24]

A variety of experimental conditions were studied with methyl phenyl ketone as the reference compound (see Table 1). With $LiAlH_4$ as reducing agent it was necessary to use a molar excess (with respect to the titanium salt) in order to minimize reductive dimerization of the carbonyl compounds[25–28] ($TiCl_3$, entries 1, 2, 5; $TiCl_4$, entries 3, 6 and 10). Such a need arises because an excess of reducing agent is necessary to obtain the active species Ti^0). Similar results have been reported by McMurry *et al.*[29] for a $TiCl_3$–K system where the optimum results were obtained with $TiCl_3$–K in a 1:3 ratio. Since the oxidation state of the titanium does not affect product yields and reaction selectivity (entries 2 and 3), it may be that Ti^0 is only produced on the solid surface. If this is so, there is an excess of reducing agent on the surface titanium atoms when equimolecular ratios of $TiCl_3$–K and $TiCl_4$–K are used, and thus Ti^0 (accessible to the reagents) is produced on the surface in both cases. The product yields and reaction selectivity are little affected by the nature of the reducing agent either with the same titanium salt ($TiCl_3$; entries 7 and 8) or with titanium salts of different oxidation state ($TiCl_3$ or $TiCl_4$; entries 2 and 3, and 8 and 9). The higher selectivity for the halogenocarbene addition product obtained with TiI_4 (entry 9) compared to $TiCl_4$ (entry 10) probably reflect a greater ease of handling of one over the other (TiI_4 solid, $TiCl_4$ volatile liquid) rather than to a different reaction pathway.

In all cases, strict control of the reaction temperature ($0 > T > -5$ °C) is necessary to minimize the reductive coupling of the ketones. Further, the reaction time should be < 30 mins to avoid polymerization of the alkene.

Since use of other transition metals (Zr, Mo or Cr) rather than Ti failed to give the desired product we must conclude that only LVT can produce the dihalogenocarbene; LiAlH resulted in reduction of the carbonyl compound.

Reductive dimerization of the ketone can be minimized by using the dimethyl acetal of the ketone, the protecting group then being readily removed after the generation of the carbene and its addition to C=O[30–32] (see Table 2). A variety of ketones were used (see Table 3), the yields of product from which were either better or similar to those described in the literature.

The racemic nature of the obtained acid was determined by ^1H NMR using (*R*,*R*)-1,2-diphenylethane-1,2-diamine as chiral agent.[35]

Other potential dihalogenocarbene generators (CCl_4, CF_2Br_2, $CFCl_3$, $CHCl_3$ and $CHFBr_2$) were studied and the results for their reactions are shown in Table 4 using methyl phenyl ketone as the reference substrate.

These results show that only tetrahalogenomethanes can be converted into 2-phenylpropanoic acid although the product yield is unrelated to the nature of the halogeno substitutents, similar results being obtained with CCl_4, CF_2Br_2 and $CFCl_3$. This suggests that formation of X_2C: in the reaction medium is important in this synthesis, since with only partially halogenated methanes dimerization and reduction occur.

Experimental

^1H NMR spectra were taken with a Varian VXR-300 NMR spectrometer using $CDCl_3$ with Me_4Si as internal standard.

† This is the unstable species generated by the reaction between TiX_n and a reducing agent. Since it is still uncertain whether the species is Ti^0 or a mixture of Ti^0 and Ti^I, the former is used to describe LVT in the literature.

Table 1 Influence of reaction conditions[a] on the preparation of (*R,S*)-2-phenylpropanoic acid using LVT

Entry	TiX_n–reducing agent (molar ratio)	T[a]/°C	t/min	Yield (%)[b] PPA[d]	Yield (%)[b] DPB[e]	Selectivity (%)[c]
1	$TiCl_3$–$LiAlH_4$ (1:0.5)	66	60	15	40	27
2	$TiCl_3$–$LiAlH_4$ (1:1)	66	60	20	45	31
3	$TiCl_4$–$LiAlH_4$ (1:1)	66	60	18	42	30
4	$TiCl_4$–$LiAlH_4$ (1:1.5)	0	60	26	30	46
5	$TiCl_3$–Mg (1:1.5)	0	30	30	22	58
6	$TiCl_4$–$LiAlH_4$ (1:2)	−5	30	40	20	67
7	$TiCl_3$–$LiAlH_4$ (1:2.5)	0	30	45	12	79
8	$TiCl_3$–Mg (1:2.5)	0	30	52	10	84
9	TiI_4–$LiAlH_4$ (1:2.5)	0	30	67	5	93
10	$TiCl_4$–$LiAlH_4$ (1:2.5)	−5	30	56	10	85
11	TiI_4–$LiAlH_4$ (1:3)	−5	30	75	5	94
12	$TiCl_3$–Mg (1:3)	0	30	52	10	84

[a] See Experimental section. [b] Determined by ^{1}H NMR. [c] Reaction selectivity = [%PPA/(%PPA + %DPB)] × 100. [d] PPA = (*R,S*)-2-phenylpropanoic acid. [e] DPB = 2,3-diphenylbutene.

Table 2 Dependence of product yields for the reaction of acetophenone (ACP) with *p*-isobutylacetophenone (PIBACP) on whether or not the ketone function was protected as an acetal (C)

Substrate	Reaction conditions[a]	Yield of carboxylic acid (%)	Yield of olefin (%)	Selectivity[b]
ACP	$TiCl_3$–$LiAlH_4$ (1:2.5)	35	55	39
ACP (C)	$TiCl_3$–$LiAlH_4$ (1:2.5)	55	10	85
ACP	$TiCl_4$–$LiAlH_4$ (1:2.5)	42	35	54
ACP (C)	TiI_4–$LiAlH_4$ (1:3)	75	5	94
PIBACP	TiI_4–$LiAlH_4$ (1:3)	57	25	69
PIBACP (C)	TiI_4–$LiAlH_4$ (1:3)	70	5	93

[a] See Experimental section. [b] Reaction selectivity = [%acid/(%acid + %alkene)] × 100.

Table 3 Product yields for the synthesis of α,α-disubstituted acetic acids using LVT[a]

Ketone[b]	Reaction conditions[c]	Yield carboxylic acid (%)	Yield alkene (%)	Yield alcohol (%)	Yield of unchanged starting material (%)	Literature yield of the carboxylic acid (%)
1	TiI_4–$LiAlH_4$ (1:3)	70	5	5	0	24,[33] 55,[9] 74[5]
2	TiI_4–$LiAlH_4$ (1:3)	56	10	5	12	58[5]
3	$TiCl_4$–$LiAlH_4$ (1:2.5)	60	5	10	0	—
4	TiI_4–$LiAlH_4$ (1:2.5)	38	18	12	10	—
5	TiI_4–$LiAlH_4$ (1:2.5)	40	22	10	0	—
6	$TiCl_3$–$LiAlH_4$ (1:2.5)	45	20	10	10	—
7	TiI_4–$LiAlH_4$ (1:3)	55	25	16	0	29[34]
8	TiI_4–$LiAlH_4$ (1:3)	20	20	10	35	—

[a] Determined by ^{1}H NMR. [b] As acetal. [c] See Experimental section.

Table 4 Product yields for a variety of halogenomethanes as substrate [$TiCl_4$–$LiAlH_4$ (1:2.5)]

Halogenomethane	Yield (%)[a] PPA[b]	DPE[c]	PE[d]
CCl_4	55	10	0
CF_2Br_2	50	12	0
$CFCl_3$	56	5	0
$CHCl_3$	0	26	48
$CHFBr_2$	0	39	35

[a] Determined by ^{1}H NMR. [b] PPA = 2-phenylpropanoic acid. [c] DPE = 2,3-diphenylbut-2-ene. [d] PE = 1-phenylethanol.

IR spectra were obtained using a Buck Scientific 500 spectrophotometer. Elemental analysis were carried out by the Microanalysis Service of the Universidad Complutense, using a Perkin-Elmer 2400-CHN. Elemental analysis and IR spectra were in agreement with the structure of each acid. Commercial Merck silica gel was used for column chromatography. The starting ketones were obtained from Aldrich or prepared according to the methods previously described in the literature.[36] The ketals were prepared using methanol, methyl orthoformate and the corresponding ketone.[37]

The enantiomeric purity of the acids was determined as follows.

(i) With a Chiracel OD column in a HPLC chromatograph Waters for the R^- and S^- acids **1**, **2** and **8**. The mobile phase for acid **1** was: hexane–isopropyl alcohol–formic acid (1000:10:1, v/v) R_F/cm^3 min^{-1} 1; t_R/min R 21, S 23; λ/nm 254. For acid **2**: hexane–isopropyl alcohol–trifluoroacetic acid (98:2:1, v/v) R_F/cm^3 min^{-1} 1; t_R/min R 20, S 23; λ/nm 254. For acid **8**: hexane–isopropyl alcohol–acetic acid, (97:3:1, v/v), R_F/cm^3 min^{-1} 0.4; t_R/min R 46, S 51; λ/nm 270.

(ii) By ^{1}H NMR using (*R,R*)-1,2-diphenylethane-1,2-diamine as chiral agent.[35]

Method A (using $TiCl_4$–$LiAlH_4$): general procedure

Dry THF (150 cm^3) under nitrogen in a flask was cooled to −5 °C and of $TiCl_4$ (9.5 g, 0.05 mol) was carefully added to it over 20 min. This was followed by a solution of $LiAlH_4$ (4.74 g, 0.125 mol) in THF (30 cm^3), added to the mixture over 30 min. After this the reaction mixture was cooled again to −5 °C, when the appropriate dimethyl acetal (0.005 mol) in THF (50 cm^3) was added to it followed immediately by $CFCl_3$ (6 g, 0.05 mol). The mixture was stirred at −5 °C for 30 min after which it was hydrolysed with water and extracted with diethyl ether (200 cm^3). The crude product was purified by flash chromatography.

Method B (using TiI_4–$LiAlH_4$): general procedure

Dry THF (150 cm^3) in a flask was cooled to −5 °C and TiI_4 (27.8 g, 0.05 mol) was added to it followed by a solution of $LiAlH_4$ (4.74 g, 0.125 mol) in THF (30 cm^3), added to the mixture over 30 min. The appropriate dimethyl acetal (0.05 mol) in $CFCl_3$ (10 cm^3, 0.14 mol) was then added to the mixture, after which the latter was stirred at −5 °C for 30 min. After the mixture had been hydrolysed with water it was extracted with diethyl ether (200 cm^3). The crude product was purified by flash chromatography, except for the aliphatic acids **5** and **6** the high adsorptivity of which made chromatography impracticable.[38] These were purified by distillation *in vacuo*.

Method C (using $TiCl_3$–Mg): general procedure

Mg^0 (3.6 g, 0.15 mol) was added to a stirred slurry of $TiCl_3$ (7.7 g, 0.05 mol) in dry THF (150 cm^3) at room temperature under an inert atmosphere. After being refluxed for 30 min the black mixture was cooled to room temperature and the appropriate dimethyl acetal (0.05 mol) added to it followed immediately by $CFCl_3$ (6 g, 0.05 mol). After 1 h under reflux the reaction mixture was cooled to room temperature and hydrolysed with water. The mixture was then filtered under vacuum and concentrated to dryness to give the crude product. This was purified by flash chromatography.

(*R*,*S*)-2-(4-Isobutylphenyl)propanoic acid 1. Mp 76 °C (hexane) [lit.,[39] mp 75–77 °C (hexane)]; $\delta_H(CDCl_3)$ 10.5 (1 H, s), 8.4–6.7 (4 H, m), 3.6 (1 H, q), 2.4 (2 H, d), 1.8 (1 H, m), 1.4 (3 H, d) and 0.8 (6 H, d).

(*R*,*S*)-2-Phenylpropanoic acid 2. Bp 152 °C/16 mmHg (lit.,[40] bp 150 °C/16 mmHg); $\delta_H(CDCl_3)$: 10.9 (1 H, s), 7.3–6.8 (4 H, m), 3.5 (1 H, q) and 1.3 (3 H, d).

Diphenylacetic acid 3. Mp (hexane) 150 °C [lit.,[41] mp 147–149 °C (hexane)]; $\delta_H(CDCl_3)$ 7.4–7.2 (10 H, m) and 5.1 (1 H, s).

2-Methylpropanoic acid 4. Bp 152 °C (lit.,[42] 153–154 °C); $\delta_H(CDCl_3)$ 2.6 (1 H, m) and 1.2 (6 H, d).

2-Methylbutanoic acid 5. Bp 176 °C (lit.,[43] 174–176 °C); $\delta_H(CDCl_3)$ 2.4 (1 H, m), 1.7 (1 H, m), 1.5 (1 H, m), 1.2 (3 H, d) and 0.9 (3 H, t).

2-Methylpentanoic acid 6. Bp 198 °C (lit.,[44] 196–197 °C); $\delta_H(CDCl_3)$ 2.5 (1 H, m), 1.7 (1 H, m), 1.4 (1 H + 2 H, m), 1.2 (3 H, d) and 0.9 (3 H, t).

(*R*,*S*)-2-(Fluoren-2-yl)propanoic acid 7. Mp (acetonitrile) 181 °C [lit.,[45] 183–184 °C (acetonitrile)]; $\delta_H(CDCl_3)$ 7.8–7.2 (7 H, m), 3.9 (2 H, s), 3.7 (1 H, q) and 1.5 (3 H, d).

(*R*,*S*)-2-(6-methoxy-2-naphthyl)propanoic acid 8. Mp (acetone–hexane) 154 °C [lit.,[34] 152–154 °C (acetone–hexane)]; $\delta_H(CDCl_3)$ 11.0 (1 H, s), 7.8–6.9 (6 H, m), 3.9 (3 H, s), 3.7 (1 H, q) and 1.5 (3 H, d).

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