Novel synthesis of substituted cyclopropane acetic acid ethyl esters from cyclopropyl alkyl ketones

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The cyclopropane acetic acid ethyl esters have been conveniently prepared in one step from cyclopropyl alkyl ketones by reacting with lead (IV) acetate in triethyl orthoformate in the presence of 70% perchloric acid. In all these reactions triethyl orthoformate is used as the solvent.

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Organic structures containing small rings have received and are still receiving increasing attention. Cyclopropane derivatives in particular, have played important roles both in theoretical as well as synthetic studies. Several methods for the preparation of cyclopropane and its derivatives have been developed. The unique electronic properties of the cyclopropyl group in conjunction with its inherent ring strain make it a valuable entity in composite functionalities which are indispensable for efficient organic synthesis. Among such functionalized cyclopropane rings are cyclopropane acetic acid esters which have recently become easily accessible. Some of the reported methods available in the literature are: (i) Simon-Smith cycloadditions to 3-butenoates, (ii) cyclopropanation of 3-butenoic acids with diazo-methane catalysed by lead (IV) acetate, (iii) reaction of transition metal carbonyl complexes and olefin to produce the substituted acetic acid ester with Danishefsky’s diene in benzene, and (iv) reaction of ketene silyl acetalts and allyl acetates in the presence of Pd(0) phosphine complexes to yield allylated products and cyclopropane derivatives. In the majority of these reactions cyclopropanation is the last step.

Results and Discussion

Previously, we have illustrated the successful use of lead (IV) acetate in combination with Lewis acids to effect a 1, 2-carbonyl transposition in acetophenones and acyclic \( \alpha, \beta \)-unsaturated ketones and a ring contraction in cyclic \( \alpha, \beta \)-unsaturated ketones and related systems. As a final test to the effectiveness of this reagent combination, we inserted a cyclopropyl group between the carbonyl and the aryl substituent to see whether the cyclopropyl ring in the cyclopropyl alkyl ketone will also facilitate a 1, 2-carbonyl shift.

In this paper, we report the results obtained from the reactions of several substituted cyclopropyl methyl ketones leading to the synthesis of substituted cyclopropane acetic acid ethyl esters via a lead (IV) acetate-perchloric acid assisted 1, 2-carbonyl transposition of the corresponding cyclopropyl alkyl ketones in triethyl orthoformate (Scheme I).

For our investigation we have chosen ketones prepared by cyclopropanation of benzylidene acetones with trimethylloxosulfonium iodide in 50% aqueous sodium hydroxide in dichloromethane with tetrabutylammonium iodide as the phase transfer catalyst. Previously, it was found that the use of BF\(_3\).Et\(_2\)O as the Lewis acid in tandem with lead (IV) acetate in benzene-methanol system gave excellent results of the expected products. In the present investigation these reaction conditions failed and most of the starting material was recovered. Presumably boron...
trifluoride etherate is not strong enough to enolize the ketone for the subsequent attack by lead (IV) acetate (Scheme II). However, when boron trifluoride etherate was replaced by perchloric acid and the reaction carried out in triethyl orthoformate the reaction proceeded at room temperature to give the product 2 in moderate to good yields. The structure of the pure product was confirmed by IR, $^1$H NMR and $^{13}$C NMR and mixed melting point. The probable mechanism is shown in Scheme II. Evidently, the elimination of lead (II) acetate from the intermediate 4 is made possible by neighboring group participation of the adjacent cyclopropane ring, thereby generating a carbocation 5 which is stabilized by the aromatic ring and which subsequently rearranges to the more stable product 2. The product 2a was further hydrolysed to the corresponding acid by refluxing with 2N NaOH for 3 hr. The recrystallised acid (mp 45-46°C) gave IR and $^1$H NMR spectral data comparable to those reported in the literature.5

In order to ascertain whether the presence of the aromatic ring is a prerequisite for the successful rearrangement, this procedure was extended to other cyclopropyl ketones which do not have an aromatic ring as one of the substituents. We found that the unsubstituted cyclopropyl methyl ketone 6a yielded only trace quantities of the expected products (from TLC analysis). However, 2, 2-dimethylcyclopropane-acetic acid ethyl ester 7b was obtained in comparable yields (Scheme III). These results agree with the observation that aryl or alkyl substituents at the 2-positions of the cyclopropyl ketone stabilize the carbocation presumed to be involved thereby enhancing the yields of the rearranged products.

**Experimental Section**

IR spectra were recorded on a Perkin-Elmer 983 and BOMEM DA-8 FT-IR Spectrophotometer and the frequencies are expressed in cm$^{-1}$; and $^1$H and $^{13}$C NMR spectra on Bruker ACF-300 spectrometer in CDCl$_3$ using TMS as internal standard (chemical shifts in δ, ppm). Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. All reactions were monitored by TLC on glass plates coated with silica gel (ACME’s) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution. Column chromatography was carried out using ACME’s silica gel (60-120 mesh) and hexane-ethyl acetate as the eluent.

**General procedure for the preparation of ethyl 2-aryl cyclopropyl acetate 2.** To a stirring suspension of lead (IV) acetate (10 mmoles) in triethyl orthoformate (15 mL), a solution of 2-arylcyclopropyl alkyl ketone (10 mmoles) in TEOF (10 mL) was added in one lot followed by 70% perchloric acid (2 mL). The reaction mixture was further stirred for 14-28 hr at room temperature. The solvent was distilled off under vacuum and the residue treated with chloroform. The precipitate formed was removed by filtration and the filtrate washed with water (3×50 mL) and dried (anhydrous Na$_2$SO$_4$). Removal of the solvent yielded 2 as the crude product, which was further purified by column chromatography.
Similarly, compounds 2a-j were prepared and their physical data are given in Table 1.

### Spectral and analytical data of compounds 2a-j

**Ethyl (2-phenylcyclopropyl) acetate 2a:** Colourless viscous liquid; IR (neat) 1735 cm⁻¹; ¹H NMR: δ 0.23-0.94 (m, 4H), 1.21 (t, 3H), 2.32 (m, 2H), 4.01 (q, 2H), 6.89-7.16 (m, 3H), 7.22-7.27 (m, 2H); ¹³C NMR: δ 14.4, 16.8, 17.2, 21.4, 33.1, 60.8, 128.1, 129.2, 134.3, 138.3, 140.4, 172.3; MS (EI): m/z 204 (M⁺). Anal. Calcd for C₁₃H₁₈O₃: C, 76.70; H, 7.84%.

**Ethyl 2-(2-chlorophenyl)cyclopropylacetate 2b:** Colourless viscous liquid; IR (neat) 1736 cm⁻¹; ¹H NMR: δ 0.30-0.90 (m, 4H), 1.24 (t, 3H), 2.32 (m, 2H), 4.03 (q, 2H), 6.91-7.51 (m, 4H); ¹³C NMR: δ 14.4, 16.8, 17.2, 21.4, 33.1, 60.8, 128.1, 129.2, 134.3, 138.3, 140.4, 172.3; MS (EI): m/z 238 (M⁺). Anal. Calcd for C₁₃H₁₆O₂Cl: C, 65.40; H, 6.29. Found: C, 65.53; H, 6.37%.

**Ethyl 2-(4-chlorophenyl)cyclopropylacetate 2c:** Colourless viscous liquid; IR (neat) 1736 cm⁻¹; ¹H NMR: δ 0.28-1.11 (m, 4H), 1.21 (t, 3H), 2.29 (m, 2H), 4.08 (q, 2H), 6.94-7.21 (m, 2H), 7.24-7.81 (m, 2H); ¹³C NMR: δ 14.6, 15.0, 17.1, 21.2, 32.3, 60.2, 129.8, 130.1, 137.1, 139.6, 173.4; MS (EI): m/z 238 (M⁺). Anal. Calcd for C₁₃H₁₄O₂Cl: C, 65.40; H, 6.29. Found: C, 65.47; H, 6.33%.

**Ethyl 2-(2-phenyl-1-methylcyclopropyl)acetate 2d:** Colourless viscous liquid; IR (neat) 1735 cm⁻¹; ¹H NMR: δ 0.24-0.96 (m, 3H), 1.21 (t, 3H), 1.43 (d, 3H), 2.28 (s, 2H), 4.10 (q, 2H), 6.89-7.10 (m, 3H), 7.15-7.54 (m, 2H); ¹³C NMR: δ 14.5, 17.1, 19.0, 22.1, 26.3, 32.1, 61.3, 129.4, 131.1, 133.6, 134.7, 172.3; MS (EI): m/z 218 (M⁺). Anal. Calcd for C₁₄H₁₈O₂: C, 77.06; H, 8.25. Found: C, 77.20; H, 8.33%.

**Ethyl 2-(2-chlorophenyl)-1-methylcyclopropylacetate 2e:** Colourless viscous liquid; IR (neat): 1739 cm⁻¹; ¹H NMR: δ 0.25-1.25 (m, 3H), 1.23 (t, 3H), 1.40 (d, 3H), 2.31 (s, 2H), 4.09 (q, 2H), 6.87-7.53 (m, 4H); ¹³C NMR: δ 14.8, 17.1, 19.4, 21.7, 26.3, 31.4, 61.8, 129.4, 131.2, 133.2, 136.2, 173.8; MS (EI): m/z 252 (M⁺). Anal. Calcd for C₁₄H₁₇O₂Cl: C, 66.53; H, 6.73. Found: C, 66.59; H, 6.88%.

**Ethyl 2-(4-chlorophenyl)-1-methylcyclopropylacetate 2f:** Pale yellow viscous liquid; IR (neat): 1740 cm⁻¹; ¹H NMR: δ 0.28-1.0 (m, 3H), 1.24 (t, 3H), 1.44 (d, 3H), 2.30 (s, 2H), 4.10 (q, 2H), 6.91-7.66 (m, 4H), 7.09-7.51 (m, 2H); ¹³C NMR: δ 14.6, 17.5, 19.3, 22.0, 25.8, 31.4, 60.4, 127.2, 129.4, 131.8, 173.3; MS (EI): m/z 252 (M⁺). Anal. Calcd for C₁₄H₁₇O₂Cl: C, 66.53; H, 6.73. Found: C, 66.71; H, 6.81%.

**Ethyl 2-(4-methylphenyl)cyclopropylacetate 2g:** Colourless viscous liquid; IR (neat): 1736 cm⁻¹; ¹H NMR: δ 0.28-1.10 (m, 4H), 1.10 (t, 3H), 1.41 (s, 3H), 2.25 (m, 2H), 4.08 (q, 2H), 6.88-7.01 (m, 2H), 7.09-7.51 (m, 2H); ¹³C NMR: δ 14.1, 18.7, 19.6, 25.8, 31.4, 60.4, 127.2, 129.4, 131.8, 173.3; MS (EI): m/z 218 (M⁺). Anal. Calcd for C₁₄H₁₈O₂: C, 77.06; H, 8.25. Found: C, 77.24; H, 8.46%.

**Ethyl 2-(4-methoxyphenyl)cyclopropylacetate 2h:** Pale brown viscous liquid; IR (neat): 1737 cm⁻¹; ¹H NMR: δ 0.27-1.15 (m, 4H), 1.22 (t, 3H), 2.28 (m, 2H), 3.76 (s, 3H), 4.05 (q, 2H), 6.89-7.88 (m, 4H); ¹³C NMR: δ 14.3, 15.6, 16.3, 19.3, 31.8, 52.4, 61.1, 128.6, 130.3, 136.6, 139.0, 174.3; MS (EI): m/z 234 (M⁺). Anal. Calcd for C₁₄H₂₀O₄: C, 71.79; H, 7.69. Found: C, 71.90; H, 7.60%.

**Ethyl 2-(2, 4-dimethoxyphenyl)cyclopropylacetate 2i:** Pale brown viscous liquid; IR (neat): 1739 cm⁻¹; ¹H NMR: δ 0.30-1.11 (m, 4H), 1.21 (t, 3H), 1.41 (s, 3H), 2.30 (s, 2H), 3.75 (s, 3H), 4.09 (q, 2H); 6. 98-7.74 (m, 4H); ¹³C NMR: δ 14.0, 15.1, 17.2, 20.6, 24.2, 32.6, 55.4, 60.7, 127.8, 129.9, 136.9, 140.0, 174.8; MS (EI) : m/z 240 (M⁺). Anal. Calcd for C₁₅H₂₅O₅: C, 72.58; H, 8.06. Found: C, 72.68; H, 8.13%.

**Ethyl 2-(2,4-dimethoxyphenyl)-1-methylcyclopropylacetate 2j:** Brown viscous liquid; IR (neat): 1738 cm⁻¹; ¹H NMR: δ 0.28-1.13 (m, 4H), 1.22 (t, 3H), 2.29 (s, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 4.10 (q, 2H), 6.98-7.56 (m, 3H); ¹³C NMR: δ 14.0, 15.6, 17.8, 21.0, 31.8, 55.5, 55.8, 61.0, 128.4, 130.6, 136.2, 140.7, 174.0; MS (EI): m/z 264 (M⁺). Anal. Calcd for C₁₅H₂₉O₄: C, 68.18; H, 7.57. Found: C, 68.30; H, 7.67%.
Ethyl cyclopropylacetate 7a: Colourless viscous liquid; IR (neat): 1736 cm$^{-1}$; $^1$H NMR: $\delta$ 0.23-0.98 (m, 5H), 1.24 (t, 3H), 2.35 (m, 2H), 4.11 (q, 2H); $^{13}$C NMR: $\delta$ 15.0, 16.3, 17.2, 21.4, 30.8, 62.1, 172.3; MS (EI): m/z 120 (M$^+$). Anal. Calcd for C$_7$H$_{12}$O$_2$: C, 65.62; H, 9.37. Found: C, 65.77; H, 9.46%.

Ethyl (2, 2-dimethyl)cyclopropylacetate 7b: Colourless viscous liquid; IR (neat): 1740 cm$^{-1}$; $^1$H NMR: $\delta$ 0.23-0.88 (m, 3H), 1.11-1.21 (m, 6H), 1.25 (t, 3H), 2.29 (m, 3H), 4.20 (q, 2H); $^{13}$C NMR: $\delta$ 14.9, 15.6, 17.8, 18.6, 20.7, 21.0, 31.5, 61.8, 171.5; MS (EI): m/z 156 (M$^+$). Anal. Calcd for C$_9$H$_{16}$O$_2$: C, 69.23; H, 10.25. Found: C, 69.40; H, 10.10%.

Ethyl 2-ethylcyclopropylacetate 7c: Colourless viscous liquid; IR (neat): 1739 cm$^{-1}$; $^1$H NMR: $\delta$ 0.26-0.97 (m, 4H), 1.23 (t, 3H), 1.17 (t, 3H), 1.30 (m, 2H), 2.28 (m, 2H), 4.13 (q, 2H); $^{13}$C NMR: $\delta$ 14.1, 13.2, 16.8, 19.4, 21.8, 24.6, 30.0, 61.2, 172.1; MS (EI): m/z 156 (M$^+$). Anal. Calcd for C$_9$H$_{16}$O$_2$: C, 69.23; H, 10.25. Found: C, 69.44; H, 10.36%.

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