

A Facile and Efficient Route to the Synthesis of Ethyl 3-Oxo-Cyclohexene-1-Carboxylate as a Valuable Synthetic Intermediate

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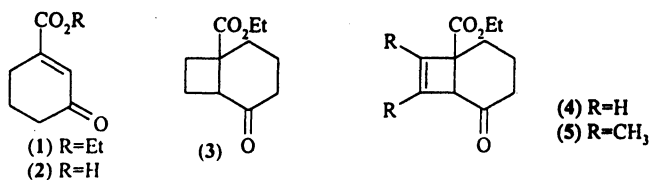
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Cyclohexanol-1-ethylcarboxylate was prepared from readily available cyclohexanone cyanohydrin in 85.5% and treated with thionyl chloride (SOCl_2) in the presence of pyridine under argon atmosphere to provide ethyl cyclohexene-1-carboxylate in 80% yield. This product was conveniently transformed to ethyl 3-oxo-cyclohexene-1-carboxylate in a moderate yield (52%).

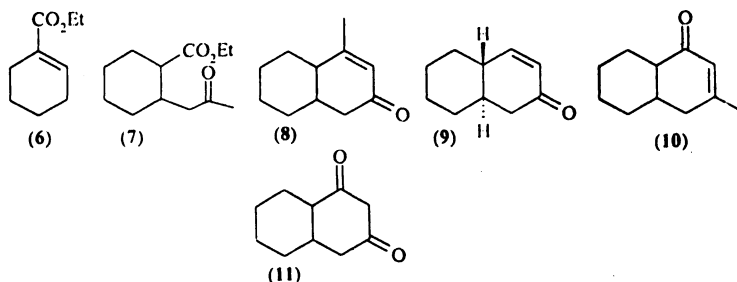
Key Words: Synthesis, Ethyl 3-oxo-cyclohexene-1-carboxylate, Synthetic, Intermediate.

INTRODUCTION

Ethyl 3-oxo-cyclohexene-1-carboxylate (1) as a synthetic intermediate has attracted a great deal of attention and the photochemical cycloaddition reaction of this compound with ethylene, acetylene and 2-butyne for the synthesis of adducts 3-5 have been studied.¹



Ethyl cyclohexene-1-carboxylate (6), the precursor to 1, in this research, is also an important intermediate and has been used in conjunction with Gilman reagent to prepare the keto ester 7,² a type of structure which provides opportunity for the development of annulation processes as much compared with Robinson annulation technique.³ This process has been successfully employed in the synthesis of α , β -unsaturated ketones (8–10) and β -diketone (11) with fused rings.² Stereospecific free radical hydrostannation of methyl ester of 6 has also been studied.⁴



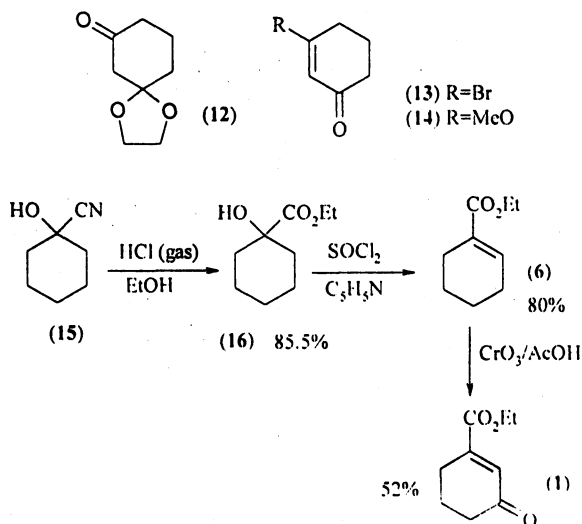
RESULTS AND DISCUSSION

Following our continued studies in the synthesis of norbornene monoester skeletons^{5,6} we explored the synthesis of ethyl 3-oxo-cyclohexene-1-carboxylate **1**, as a dienophile, which could be used for the synthesis of norbornene structures in Diels-Alder methodology.

Previous preparations of 3-oxo-cyclohexene-1-carboxylic acid (**2**) using addition of hydrogen cyanide to the ketal (**12**) of dihydroresorcinol, followed by hydrolysis and dehydration to **2**,⁷ due to low overall yield and method starting from either 3-bromocyclohex-2-en-1-one (**13**), prepared from 1,3-cyclohexenedione due to diketal formation at protection stage, double bond isomerization and severe reaction conditions were not satisfactory. Methods employing 3-methoxycyclohexenone (**14**)¹ through a Micheal type addition-elimination reaction with diethylaluminium cyanide⁸ followed by protection and hydrolysis due to using expensive starting material longer reaction scheme was not impressive. Ethyl cyclohexene-1-carboxylate (**6**), the precursor of ethyl 3-oxo-1-cyclohexene-1-carboxylate and the related acid (**2**) has been prepared in a long reaction scheme (5 steps) starting from *trans*-2-chlorocyclohexanol.⁹

An improved preparation of methyl ester of (**1**) has also been reported¹⁰ in which cyclohexanecarboxylic acid is converted to methyl 1-bromocyclohexanecarboxylate by a variation of the Hell-Volhard-Zelinsky reaction and then the bromoester is dehydrated with quinoline and the resultant unsaturated ester is oxidized at an allylic position with chromium trioxide in an acetic acid with overall 49% yield.

We have found a simple alternative route for the preparation of (**1**) from readily available cyclohexanonecyanohydrin (**15**) in a three-step reaction (Scheme-1). In this study cyclohexanonecyanohydrin was directly converted to the related ethyl



Scheme-1

ester (**16**) in the presence of dry HCl (gas) and EtOH in 85.5% yield. Treatment of this ester alcohol with SOCl_2 and pyridine gave ethyl cyclohexene-1-carboxylate (**6**) in 80% yield. Chromic anhydride/acetic acid (glacial) oxidation of **6** at allylic position furnished the desired ester **1** in 52% yield. The structure of α , β -unsaturated ketoester **1** was established by spectroscopic analysis which was consistent with those of the literature.¹

Finally we conclude that the route presented here for the preparation of ketoester **1** because of short reaction steps, cheap materials and good yields is quite promising.

EXPERIMENTAL

Melting points were measured with Electro Thermal and are uncorrected. IR spectra were determined on a Shimadzu IR-470 spectrometer. ^1H NMR spectra were recorded on a Bruker AC, FT-NMR (80 MHz) in deuteriochloroform (CDCl_3) with tetramethylsilane (TMS). Thin layer chromatography (TLC) was carried out on Merk Kieselgel 60H ASTM 35-70.

Cyclohexanol-1-ethylcarboxylate (**16**)

In a 250 mL carious tube equipped with a teflon tap cyclohexanonecyano-hydrin (24 g, 0.19 mol) and absolute ethanol (200 mL) was added. The reaction mixture was cooled in an ice bath and HCl gas was passed through the mixture for 3 h. The reaction vessel was closed and kept in a freezer at -4°C for 72 h. The reaction mixture was acidified by 6 N hydrochloric acid (220 mL) and evaporated under vacuum at 35°C in order to remove the excess of ethanol and water. The residue was extracted by ether (3×100 mL) and the ethereal solution was washed by sodium bicarbonate, dried (MgSO_4) and evaporated in a rotatory evaporator to provide cyclohexanol-1-ethylcarboxylate (27.8 g, 0.162 mol) in 85.5% yield; IR: 3465 (s), 1930 (vs), 1855 (vs), 1728 (vs), 1445 (s), 1275 (vs), 1235 (vs), 1155 (vs) and 1060 (s) cm^{-1} .

Ethyl cyclohexene-1-carboxylate (**6**)

To a magnetically stirred solution of cyclohexanol-1-ethylcarboxylate (7 g, 40.7 mmol) in pyridine (30 mL) cooled in an ice bath, under argon gas, thionyl chloride (40 mL) was added dropwise. The reaction mixture was stirred for 11 h and 20 g ice was added. The product was extracted by ether (3×50 mL) and the combined ethereal solution was dried (MgSO_4) and evaporated under vacuum and the residue was purified by column chromatography (ethyl acetate/petroleum ether, 1 : 6) to furnish ethyl cyclohexene-1-carboxylate (5 g, 32.5 mmol) in 80% yield; IR (neat): 3030 (w), 2930 (vs), 2850 (s), 1700 (vs), 1645 (m), 1450 (m), 1380 (m), 1280 (s), 1240 (vs), 1090 (vs), 925 (m) cm^{-1} ; ^1H NMR (CDCl_3): δ 6.9 (m, 1H), 4.1 (q, $J = 7$ Hz, 2H), 2.2 (m, 4H), 1.5 (m, 4H), 1.3 (t, 7 Hz, 3H) ppm.

Ethyl 3-oxo-1-cyclohexene-1-carboxylate (**1**)¹

To a magnetically stirred solution of ethyl cyclohexene-1-carboxylate (3 g, 19.5 mmol), H_2O (0.4 mL) and glacial acetic acid (21.4 mL), CrO_3 (3 g, 30 mmol)

was added gradually over 1 h. The reaction mixture was stirred at room temperature for 10 h. Ice (10 g) was added, neutralized cautiously by 30% KOH solution at temperature not exceeding 40°C by external cooling. The mixture extracted by ether (3 × 30 mL) and dried over MgSO₄. The ethereal solution was washed with saturated NaHCO₃, brine, water and evaporated in a rotatory evaporator. The residue was purified by column chromatography (ethyl acetate/petroleum ether: 1/6) to provide **1** (1.7 g, 10.1 mmol) in 52% yield; IR: 3030 (w), 1718 (s), 1685 (s), 1615 (w), 1270 (s) cm⁻¹; ¹H NMR (CDCl₃): δ 6.68 (t, J = 2 Hz, 1 H), 4.22 (q, J = 7 Hz, 2H), 2.4 (m, 4H), 2.02 (m, 2H), 1.26 (t, J = 7 Hz, 3H) ppm.

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