Synthesis of Cyclohexanone Derivatives and a Study of Enamine Reactions.

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Summary: Treatment of 2-bromomethyl cycloheptanone (3) with acetoacetic ester in the presence of sodium ethoxide furnished ethyl 1-methylcyclohexyl carbonylacetate (6) in 35% yield. A mechanism leading to the formation of the β-ketoester (6) via Favorskii rearrangement involving nucleophilic attack of a carbanion (sodio-acetoacetic ester) on the cyclopropanone intermediate (4) is suggested.

3-Methyl cyclohexanone and 2,4-dimethyl cyclohexanone (**8** and **8a**) were transformed into enamines (**9** and **9a**), which were further acylated with ethyl chloroformate by Stork's et al method [11]. Reduction of enamine (**10**) by lithium aluminum hydride afforded the syrup 3,5-dimethyl-1-cyclohexenyl-1-carboxaldehyde (**12**) in 15% yield and 3,5-dimethyl-1-cyclohexenyl-1-carbinol (**13**) in 23% yield. Similarly, the product (**11**) on reduction followed by column chromatography afforded three derivatives (**14**), (**15**) and (**16**) in low yield.

Introduction

The Favorskii rearrangement [1] is a useful synthetic tool for ring contraction and for the preparation of acids, ester and amides by the reaction of α-haloketones with hydroxides, alkoxides or amines. The currently accepted mechanism [1] of this reaction involving the attack of a nucleophile ($^-$OH, RO$^-$ or NR$_3$) on the cyclopropanone intermediate (1) suggested that it might be possible to carry out the reaction under conditions that would permit the nucleophilic attack of a carbanion on (1) so as to form the ketonic products (2) (Scheme-A).

Lithium aluminum hydride (LAH) reduces exclusively the ester group of ethyl 2-(1-pyrrolidinyl)-1-cyclohexenyl 1-carboxylate giving the corresponding derivatives [2,3]. The orientation of the double bond in the enamine ester is mainly due to the least substituted carbon atom (C-2 and C-3) of (9) and (10). In the ester group at the side chain, the orientation of the double bond changes to the most substituted carbon (C-1 and C-2), owing to the introduced conjugation between the ester group and the enamine function. Enamines [4] are known to exhibit ambident reactivity towards electrophiles [5] as well to nucleophiles [6- 9].

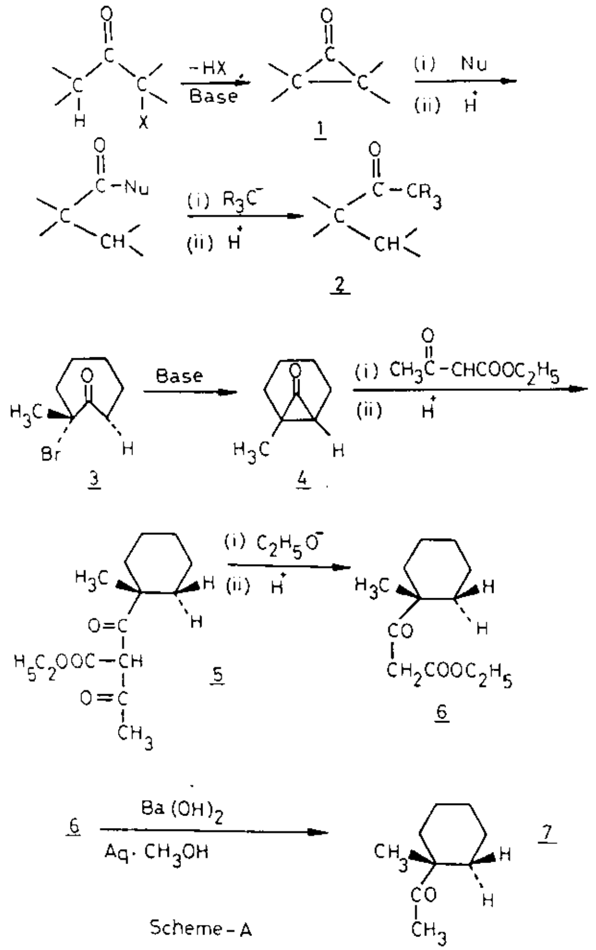
Results and Discussion

The present paper reports the successful application of the Favorskii rearrangement using sodio-acetoacetic ester as the carbanion and 2-bromo-2-methyl cycloheptanone (3) as the α-haloketone.

The α-bromoketone (3) was prepared by N-bromosuccinimide bromination of 2-methyl cycloheptanone. Treatment of (3) with acetoacetic ester in presence of sodium ethoxide in boiling ethanol furnished the β-ketoester (6) as the main product. The β-ketoester was isolated by a combination of fractional distillation and preparative thin layer chromatography.

Formation of the β-ketoester (6) might reasonably be explained as follows: The cyclopropanone intermediate (4) obtained by the attack of a base ($C_2H_5O^-$ or CH_3COCH-$COOC_2H_5$) on the bromoketone (3), reacts with CH_3CO-$CHCOOC_2H_5$) to form $\beta,\beta-$diketoester (5). Subsequent cleavage of (5) by the attack of ethoxide ions leads to the formation of β-ketoester (6). Structural assignment was made on the basis of elemental analysis, infrared and proton magnetic resonance spectral analysis and by the conversion of (6) into known compound, 1-methyl-1-acetyl cyclohexanone (7) (Scheme-A).

The enamines of 3-methyl cyclohexanone and 2,4-dimethyl cyclohexanone [10] (8 & 8a) were obtained by reacting with secondary amine (pyrrolidine) [11]. Acylation of pyrrolidinyl cyclohexanone derivatives (9 and 9a) with ethyl chlorofor-



Scheme-A

mate in 1:1 ratio gave poor yield of the compound (10 and 11). Therefore the ratio was changed to two moles of the enamine (9), as a result the yield of compound (10) was raised to 24-30%. The low yield of the compounds (10 and 11) can however, be accounted for by the hard and soft base principle [12]. The chloroformate is classified as the hard acid and the beta-carbon compound (9) as th soft base. The main reaction is expected to be acylation of N (a hard base) to give unstable enamine salt (10a) which converted back to (9) by simple acidic hydrolysis (Scheme-B).

The compounds were characterized by the ^1H NMR spectral analysis. The proton resonance of the vinylic carbon could easily be identified using the additivity rules [13]. The infrared absorption data of the given compound (10) at 1660-70 cm^{-1} (C=O) and 1590 cm^{-1} for (C=C); the C=O group absorption is lower about 1600 cm^{-1} compared to simple unsaturated ester [14].

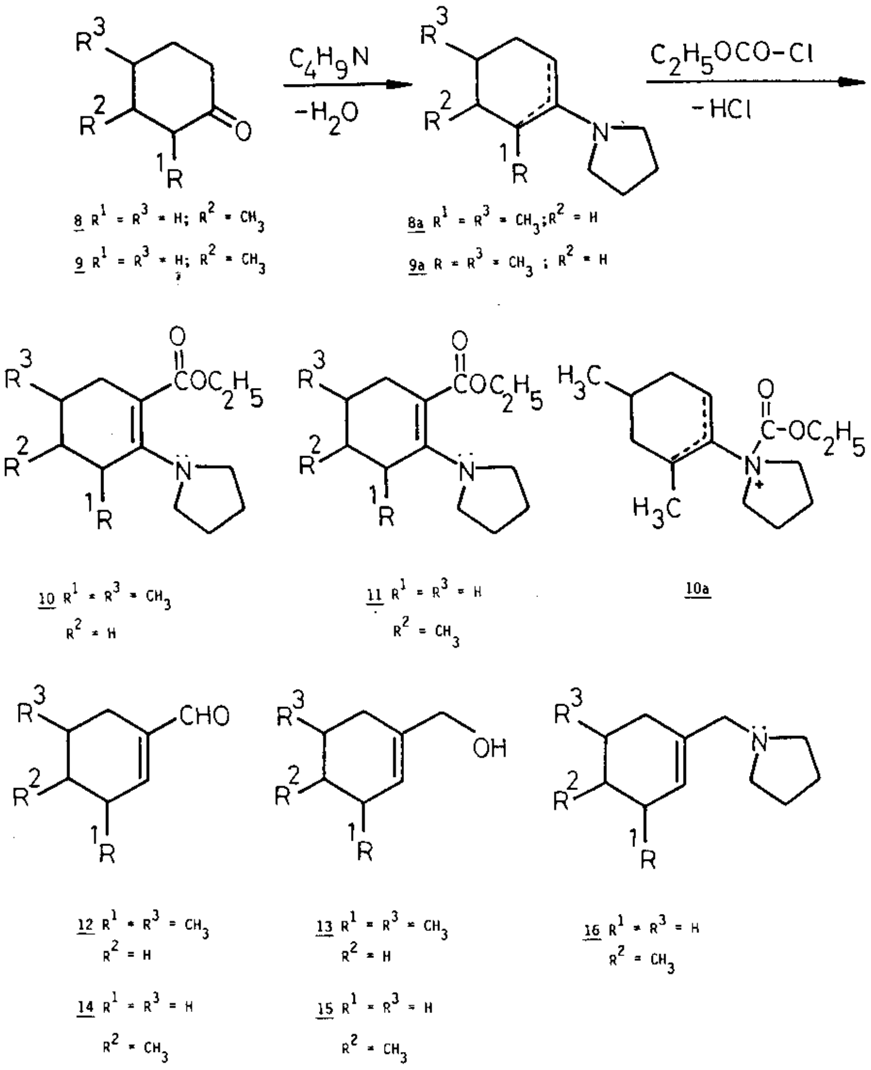
Ethyl 3,5-dimethyl-2-(1-pyrrolidinyl) cyclohexenyl-1-carboxylate (10) was reacted with lithium aluminum hydride, to give 3,5- dimethyl-1-cyclohexenyl-1-carboxaldehyde (12) and 3,5-dimethyl-1-cyclohexenyl-1-carbinol (13) in low yields. Similarly, ethyl 4- methyl-2-(1-pyrrolidinyl) cyclohexenyl-1-carboxylate (11) was treated with the reducing agent, giving 4-methyl-1-cyclohexenyl- 1-carboxaldehyde (14), 4-methyl-1-cyclohexenyl-1-carbinol (15) and 4-methyl-1-(1-cyclohexane methyl) pyrrolidine(16) in various yields.

The mechanism of the above reaction may proceed through a 1,4- addition-elimination giving ethyl-1-cyclohexenyl-1-carboxylate (a), together with the pyrrolidine salt (b). Further, reduction of (a) by the hydride ion,H^-, leads to product (13) and (15) as syrup, while the attack on (a) by the hard base, (b), gives the enamide product (c). A similar result has been reported from the reaction between piperidine crotonate and the Grignard's reagent [9]. Reduction of tertiary amide (c) to give unsaturated aldehyde (12) and (14) and the allylic amine (16) are in agreement with the literature [15]. The lithium aluminum hydride reduction seems, however, to be sensitive to the stereochemistry of the enamines, the α,β−unsaturated aldehyde formation of the investigated substrate being restricted to cyclohexene derivatives. So, this is an alternate route to obtain easily the allylic alcohol, allylic amine and unsaturated aldehyde. (Scheme- C).

The formation of α,β−unsaturated aldehyde, like 1-cyclohexenyl-1- carboxaldehyde and 4-methyl 1-cyclohexenyl-1-carboxaldehyde have been found useful for industrial purposes [16,17] and further applications have been studied with organometallic compounds [18,19].

Experimental

IR spectra were recorded on a Unicam SP 1000 spectrophotometer and refer to thin film of NaCl discs unless otherwise stated . UV spectra were obtained on a Unicam SP 1800 spectrophotometer using 95% ethanol as solvent. ^1H NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer, using $CDCl_3$ as solvent. Chemical shifts are given in δ units using tetramethylsilane as internal reference. Silica gel 60 (Merck) and Aluminium oxide 60 G (Merck) were used for column chromatography. All organic ex-



Scheme-B

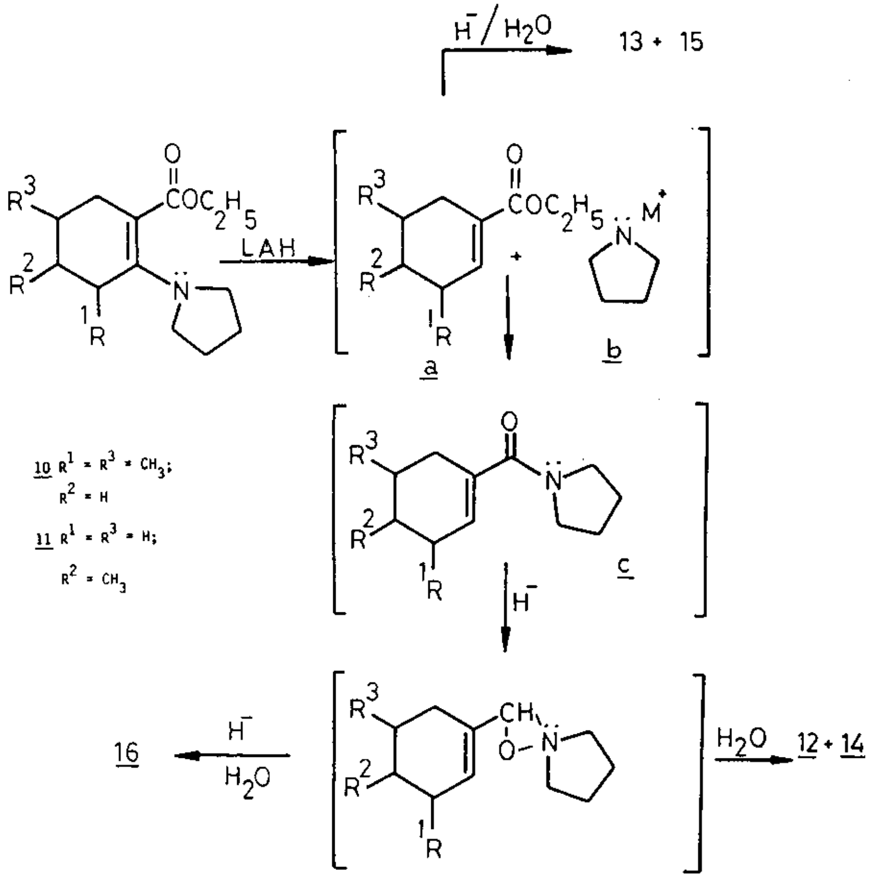
tracts were dried over anhydrous $MgSO_4$. M.p.s and b.ps are uncorrected.

2-Bromo-2-methyl cycloheptanone (3)

2-Methyl cycloheptanone (1) (1.26 g, 0.010 mole), N-bromosuccinimide (1.74 g, 0.010 mole), benzoyl peroxide (20 mg) and carbon tetrachloride (20 ml) were heated under reflux until all the solid material come to the top of the liquid surface (1.5 hrs). Workup by washing with water, drying and concentration gave 2.05 g (quantitative yield) of the bromoketone (3) as an oil, b.p. 64-68 C°/0.38 mm. IR: ν_{max} 1705 cm^{-1} (C=O). ^{1}H-NMR: δ 1.67 (3H, s, CH_3). (Found: C, 47.06; H, 6.25; Br, 38.90% Calcd. for $C_8H_{13}OBr$ requires C, 46.84; H, 6.39; Br, 38.3%).

Ethyl-1-methyl cyclohexyl carbonylacetate (6)

Ethyl acetoacetate (2.60 g, 0.02 mole) was added to a sodium ethoxide solution prepared by dissolving sodium (0.46 g) in ethanol (20 ml). After stirring at room temperature for 5 minutes, 2-bromo-2-methylcycloheptanone (2.05 g, 0.01 mole) was added. The mixture was refluxed for 3 hrs. The solvent was removed and water (30 ml) was added. Extraction with ether, drying and concentration gave an oil (2.91 g). Purification by fractional distillation followed by preparative t.l.c. furnished ethyl 1-methyl cyclohexyl carbonylacetate (6) (0.75 g) 35% yield as a colourless oil b.p. 100C°/0.8 mm. UV: λ_{max} 250 nm (ε, 3380). IR: ν_{max} 1745, 1703, 1642 and 1610 cm^{-1}. ^{1}H NMR : δ 4.15 (2H, q, $COOCH_2CH_3$); 3.49 (2H, s, $CO.CH_2COOC_2H_5$),



Scheme-C

1.22 (3H, t, $COOCH_2CH_3$).1.10 (3H, s, quaternary CH_3 group). (Found: C, 67.85; H, 9.21% Calcd. for $C_{12}H_{20}O_3$ requires C, 67.89; H, 9.50%).

1-Methyl-1-acetyl cyclohexanone (7)

Ethyl 1-methyl cyclohexyl carbonylacetate (6) (63 mg) was refluxed with barium hydroxide hydrated (120 mg) methanol (1 ml) and water (1.5 ml) for 16 hrs. Workup by the addition of water, extraction with ether, followed by drying and concentration of the ethanol extracts gave 31 mg. of 1-methyl-1-acetyl cyclohexanone as a colourless oil, b.p. 62-65 C°/1.3 mm. IR: ν_{max} 1700 cm^{-1}. ^1H NMR: δ 2.10 (3H, s, $COCH_3$); 1.08 (3H, s, quaternary CH_3 group). (Found: C, 77.12; H, 11.41% Calcd. for $C_9H_{16}O$: requires C, 77.08; H, 11.50%). 2,4-Dinitrophenyl hydrazone derivative had m.p. 130-132° (lit. [20] m.p. 134 C°).

The synthesis of the starting compounds, 3-methyl cyclohexanone (8) and 2,4-dimethyl cyclohexanone (8a) was carried out according to the lit. [10] and then pyrrolidine enamines (9 and 9a) were prepared by the method of G. Stork *et. al.*, [11].

3-Methyl cyclohexanone (8) (5.62 g, 0.05 mole) and pyrrolidine (3.55 g, 0.05 mole) together with a catalytic amount of *p*-toluene sulfonic acid (30 mg) were dissolved in benzene (100 ml) and refluxed for 16 hrs. using Dean-stork's apparatus for water separation. The solvent was evaporated and the enaminone (9) was purified by fractional distillation under vacuum at 102-104 C°/3 mm, giving 4.11 g (69% yield) as colourless liquid. IR: ν_{max} 1445, 1140-20, 1890-60 cm^{-1}. (Found: C, 79.48; H, 11.50; N, 8.45% Calcd. for $C_{11}H_{19}N$ required C, 79.94; H, 11.57; N, 8.47%).

Under similar procedure pyrrolidine enamine of 2,4-dimethyl cyclohexanone (9a) was prepared boiling at 113-118 C°/5 mm as a light yellow syrup in 51% yield. The infrared spectrum is in confirmity with the structure.

Ethyl 3,5-dimethyl-2(1-pyrrolidinyl)-cyclohexenyl-1-carboxylate (10)

Compound (9a) (33.22 g, 0.18 mole) and ethyl chloroformate (11.0 g, 0.012 mole) in dry toluene (150 ml) were stirred under nitrogen atmosphere. After 2 hrs. stirring it was heated under refluxing for 12 hrs. The solution was cooled and filtered with suction. The precipitates of enamine hydrochloride were washed with dry ether. The combined filtrate and washing were returned into flask dried ($MgSO_4$) evaporated and then distilled under vaccuo to give 17.5 g (53% yield) b.p. 127-132 C°/11 mm. IR: ν_{max} 1665, 1455, 1440-25, 1680-70 cm^{-1}. (Found: C, 71.51; H, 10.21; N, 5.45% Calcd. for $C_{15}H_{25}NO_2$ requires C, 71.67; H, 10.02; N, 5.56%).

Ethyl 4-methyl-2(1-pyrrolidinyl)-cyclohexenyl-1- carboxylate(11)

To compound (9) (29.70 g, 0.18 mole) and ethyl chloroformate (11.0 g, 0.012 mole) were mixed in dry toluene (150 ml). After stirring and refluxing for 12 hrs. It was worked up to give 18.23 g (63% of the required compound, boiling at 112-118 C°/7-8 mm. IR: ν_{max} 1665, 1145, 1430-25, 1680-75 cm^{-1}. (Found: C, 70.63; H, 9.70; N, 5.58% Calcd. for $C_{14}H_{23}NO_2$ requires C, 70.84; H, 9.76; N, 5.89%).

Reduction of Enamine (10) with Lithium Aluminiumhydride (LAH)

To an ice cold solution of LAH (3.2 g, 0.08 mole) in anhydrous ether (100 ml) stirring under nitrogen atmosphere, was added dropwise ethyl 3,5-dimethyl-2(1-pyrolidinyl)-cyclohexenyl 1- carboxylate (10) (10.0 g, 0.04 mole) in 5-10 minutes. Stirring was continued at room temperature for 3 hrs. Then, added dropwise at zero degree 20 ml of 3% sodium hydroxide, the ice-bath was removed and stirring continued for another 15 minutes at room temperature. The mixture was filtered off and extracted twice with ether, finally dried ($MgSO_4$), concentrated to give a mixture of product (12) and (13). It was then column chromatographed using a mixture of silica-gel and alumina (Al_2O_3) 3:1 w/w, and eluted with ether-pentane (1:1 v/v). The elutes were concentrated to give 3,5-dimethyl 1-cyclohexenyl-1-carboxaldehyde (12) in 15% yield and had infrared bands at ν_{max} 1680, 1640 and 1440 cm^{-1}; ^{1}H NMR : δ 9.45 (1H, s, CHO), 6.78 (1H, t, J = 3Hz, H-C=C), 2.5-2.8 (4H, m), 1.3-1.9 (m, 3H), 1.08-1.1 (6H, t, J = 3Hz, H-C=O), 2.5- 2.8(4H, m), 1.3-1.9 (m, 3H), 1.08-1.1 (6H, d, J = 8Hz,, CH_3-CH). (Found: C, 78.81; H, 10.05% Calcd. for $C_9H_{14}O$ requires C, 78.31; H, 10.21%).

The other fractions on concentration afforded 3,5-dimethyl-1-cyclohexenyl-1-carbinol-(13) in 23% yield. IR: ν_{max} 3450 (OH) 1455, 1440-30 and 1245 cm^{-1}; ^{1}H NMR : δ 4.35 (s, OH), 6.45 (1H, t, J = 3.5 Hz, H-C=C), 2.5-2.8 (4H, m), 1.25-2.01 (3H, m), 1.02-1.07 (6H, d, J = 8.1 Hz, CH_3-CH). (Found: C 77.18; H, 11.44% Calcd. for $C_9H_{16}O$ requires C, 77.08; H, 11.50%).

Reduction of Ethyl 4-methyl-2(1-pyrrolidinyl)-cyclohexenyl- 1-carboxylate (11)

(9.2 g, 0.04 mole) with a ice-cold solution of lithium aluminiumhydride (3.2 g, 0.08 mole) in anhydrous ether (100). After workup, gave a mixture of three products which were separated on Aluminium oxide silica gel column and eluted with ether-pentane mixture.

On concentration the fractions gave the following colourless syrups: *4-Methyl-1-cyclohexenyl-1-carboxaldehyde* (14) in 28% yield as a colourless oil. IR: ν_{max} 1680, 1645, 1445 cm.$^{-1}$ ^{1}H NMR: δ 9.40 (1H, s, CHO), 6.60 (1H, s, H-C=C), 1.2-2.0 (7H, m), 1.16 (3H, d, J = 6 Hz,CH_3-CH). (Found: C, 77.27; H, 9.70% Calcd. for $C_8H_{12}O$ requires C, 77.37; H, 9.74%). *4-Methyl-1-cyclohexenyl-1-carbinol*(15) in 19% yield as liquid. IR: ν_{max} 3450, 1440-25, 1250 cm^{-1}. (Found: C, 75.89; H, 11.10% Calcd. for $C_8H_{14}O$ requires C, 76.13; H, 11.18%); and the last recovered derivatives *4-Methyl-1(cyclohexenyl methyl)-pyrrolidine*(16) in 13% yield as a liquid. IR: ν_{max} 1460, 1440-25, 1660 cm^{-1}. ^{1}H NMR: δ 5.58 (1H, s, H-C=C), 2.85 (2H, s, $-CH_2N$), 2.41 (4H, t, J = 6 Hz, $-CH_2N$), 1.5-2.4 (12H, m).

(Found: C, 80.18; H, 11.88; N, 7.70% Calcd. for $C_{12}H_{21}N$ requires C, 80.38; H, 11.80; N, 7.80%).

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