Iranian Journal of Organic Chemistry Vol. 3, No. 1 (2011) 585-589

Toward the synthesis of α-methylamino-α-phenyl-cycloheptanone

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Abstract: The synthesis of new derivative of α-phenyl cycloheptanone involving methyl amine in alpha position of cycloheptanone as target molecule was investigated. Some useful intermediates that are crucial in this regards have been prepared and characterized.

Keywords: α-Phenyl ketone; Imine; α-Bromo ketone; Cycloheptanone, Beckman rearrangement.

Introduction

α-Phenyl ketones are used in the synthesis of variety of molecules including biologically active and medicinal compound. Various methods for the preparation of α-phenyl ketones have been developed including conversion of aldehydes to ketones by aryldiazomethanes [1], nucleophilic acylation of o-quinone methides (an umpolung strategy for the synthesis of α-aryl ketones) [2], α-arylation of ketones by aryllead triacetates [3], α-arylation of ketones by metal complexes as an efficient catalyst [4], oxidative rearrangement of arykalkenes [5] and aminoketone rearrangement [6-11].

A search in the literature indicates that there are some reports on the synthesis of α- phenyl cycloalkanones**.** The first report of α- phenyl cycloalkanones synthesis was on the synthesis of 3-benzoyl-2-phenylcyclopentanone in 1938 [12]. Then, more papers appeared in the literature regarding enantioselective protonation of enolates with 2-sulfinyl alcohols [13]; enantioselective α-arylation of cyclohexanones [14], α-ketol rearrangement of 1-benzoylcycloalkanols [15] or α-phenyl cycloalkanones from silyl enol ethers and diphenyliodonium fluoride [16].

Different applications for such ketones have already been reported. These involve the synthesis of morphine [17] and potential hypocholesteremic agents.

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Those ketones with substituents in the ortho position have shown a statically significant reduction in serum cholesterol [18]. They also have been used to synthesize amphetamine and ketamine (2-(o-chlorophenyl)-2-(methylamino)-cyclohexanone).

Ketamine is a short-acting parenteral anesthetic agent that has been in clinical use worldwide for a long time [19]. Also, 2-methylamino-2-phenylcyclohexanone has been used for the treatment of bacterial, fungal, virus or protozoan infections as well as for immunomodulation [20].

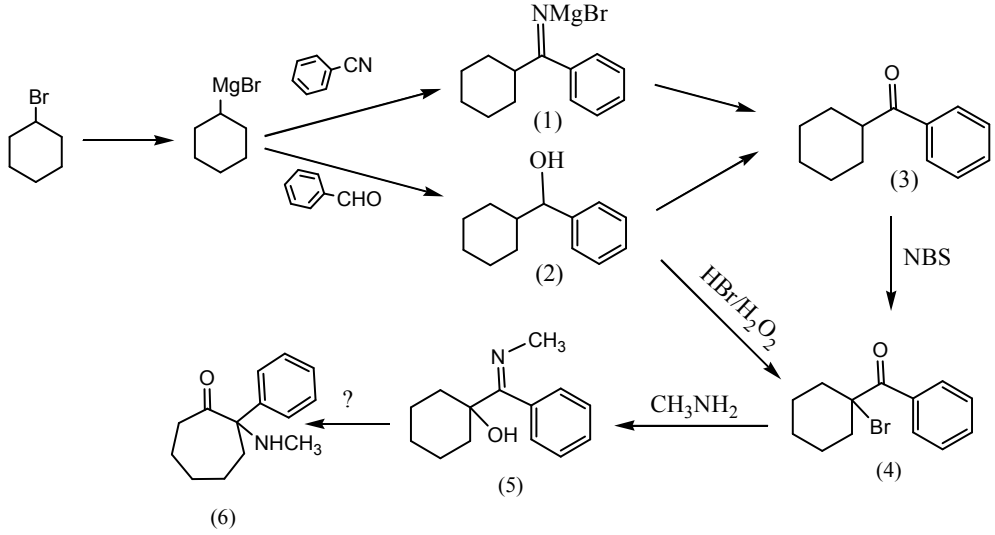
The main objective in this research has been the synthesis of new derivatives of α-phenyl cycloheptanone involving methylamine in alpha position of cycloheptanones as target molecule **6** (scheme **1**). Such ketones have been the targets to some studies followed by Calvin L. Stevens et al. using aryl-alkyl migration, ring contraction, ring expansion and rearrangement of phenyl *α*-aminoketones [6-11]. Expansion of cyclohexanones presented by C. D. Gutche [21], oxidative rearrangement of arykalkenes [5] and Aminoketone rearrangement [6-11] are more cited cases in this regards.

Results and discussion

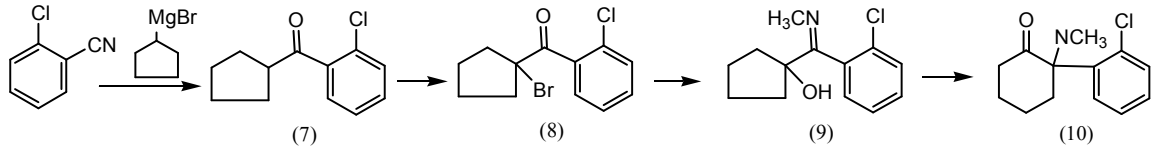
The target molecule **6** was tried to be prepared in a four-step synthetic method shown in Scheme **1**. The synthetic rout has originally taken from the ketamine synthesis with some major modifications using bromocyclohexanone as starting material. In the

ketamine synthesis, bromocyclopentanone is used instead as shown in Scheme **2**. The synthetic method for ketamine reported by Stevens et al. has several drawbacks including low yield and long reaction time for ketone **7** and using benzene. Here, efforts have been made to improve the reaction condition to increase the yield of ketone **3** in a shorter period of time. Also, bromoketone **4** was directly synthesized from the corresponding alcohol **2** in one step in high yield.

As shown in Scheme **1**, our initial experiment focused on the synthesis of iminium salt **1** from bromocyclohexane and benzonitrile followed by acidification to get ketone **3** in quantitative yield. The reaction was performed in the presence of $CuBr.Me_2S$ in 1h. This reaction was also performed in the absence of Cu catalyst under the similar reaction condition as reported for the preparation of ketone **7** (Scheme **2**) and 30% yield was obtained after 48h. The keton **3** was then brominated with NBS to get α-bromoketone **4**. α-Bromoketone **4** was also prepared in 95% yield from alcohole **2** in one step oxidation-bromination reaction at 70 °C for 4h. In this new operationally simple and safe procedure, an aqueous H_2O_2–HBr mixture was applied in the presence of LiCl. Alcohol to a-bromoketone transformation by a 4-step addition of H_2O_2–HBr mixture at room temperature using H_2O as solvent has been recently reported by A. Podgorsek et al. [22]. They have obtained 83-97% yields for different alcohols over the 10-48h. They have obtained a mixture of ketones and bromoketones. It is of interest to note that the same procedure was applied to the alcohol **2** and a mixture of ketone **3** and bromoketon **4** was obtained in 1:1 mole ratio (resulted from 1H NMR integration). For the synthesis of alcohole **2** the known procedure of nucleophilic addition of Grignard reagent to aldehyde in diethyl ether was used.



Scheme 1. Synthetic pathway designed for the preparation of 2-methylamino-2-phenyl-cycloheptanone (**6**)



Scheme 2. Synthetic pathway for the preparation of 2-methylamino-2-(*O*-phenyl)-cyclohexanone (Ketamine)

The condensation reaction of bromoketone **4** with methyl amine was initiated at -40 °C for 4h and followed at RT for 1h to get α-hydroxyimine **5** in 85% yield. It is of interest to note that this reaction becomes complicated if initiated at higher temperature. We have found out that under such condition other reactions such as elimination of HBr, nucleophilic reaction with H_2O and hydrolysis of imine functional group take place

and, therefore, the corresponding α, β-unsaturated compound and α-hydroxyketone are generated.
The last step was the Beckman rearrangement of α-hydroxyimine **5** to reach 2-methylamino-2-phenyl-cycloheptanone as target molecule. This thermal reaction reported by Stevens et al. for the synthesis of ketamine from α-hydroxyimine **9** appeared promising but found not applicable to the current case. The thermal treatment was refluxing α-hydroxyimine **5** in decaline for 4 and 8h. Therefore, different reaction conditions for the Beckman rearrangement of α-hydroxyimine **6** to the target molecule **6** were tried as given in Table **1**.

Table 1. Reaction conditions for the preparation of 2-methylamino-2-phenyl-cycloheptanone (**6**)

Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (h)
1	Decaline	reflux	-	4h
2	Decaline	reflux	-	8h
3	Decaline	reflux	H_2SO_4 (2)	4h
4	Decaline	reflux	$FeCl_3$ (2)	4h
5	Diphenyl ether	200	-	4h
6	Diphenyl ether	200	$FeCl_3$ (2)	4h
7	Diphenyl ether	200	$PdCl_2$ (2)	4h

As is clear from the data provided in Table **1**, two different high boiling solvents decaline and diphenyl ether were used under in the absence and presence of catalysts H_2SO_4, $FeCl_3$ and $PdCl_2$. In all the cases the starting imine **5** was recovered. In the case of H_2SO_4, formation of the related α-hydroxyketone was also noticed. The final thermal rearrangement is under investigation. Also, other routs for the preparation of the target molecule **6** are under investigation using cycloheptanone as the key starting material.

Conclusion

Phenyl cyclohexyl ketone was prepared from benzonitrile under the presence of Cu (I) catalyst in high yield in a reaction with cyclohexyl magnesium bromide. The reaction was optimized and the yield was improved. It was also prepared from benzaldehide in two steps passing via the corresponding alcohol. Then, α-bromo cyclohexyl phenyl ketone was prepared by the α-bromination of ketone with NBS. The same α-bromo cyclohexyl phenyl ketone was obtained in a single reaction from the treatment of alcohol with HBr/H_2O_2 in quantitative yield. It was found out that when the bromoketone is treated with aliphatic and aromatic amines, depending on the reaction temperature, elimination of HBr or condensation take place. Under the controlled low temperature, the ketone reacts with liquid methylamine and α-hydroxy imine derivative is prepared in 65-70% yield.

Experimental

General remarks

All the reagents were bought from Merck. IR spectra were recorded on Bruker Tensor 27 and Perkin Elmer.^{1}HNMR spectra were recorded on Bruker 250 MHz. ^{13}CNMR spectra were recorded on Bruker 62.90 MHz.

Synthesis

Cyclohexyl magnesium bromide

Cyclohexyl magnesium bromide was synthesized in THF according to the literature [23] and used immediately after preparation.

*Cyclohexyl phenyl ketone (**3**)*

To a stirred solution of benzonitrile (32 mmol) and 37 mmol, (2M in THF) of cyclohexylmagnesium bromide in toluene (40 mL) was added CuBr.Me_2S (0.37 mmol), and the mixture was heated to distill THF and then refluxed (under nitrogen) for 4h. After cooling to 25 °C, H_2O (5 mL) was cautiously added, followed by 30 mL of 15% H_2SO_4. After stirring the mixture for 5 h, 20 mL of hexane was added. The organic layer was separated, and the aqueous layer was extracted twice with 10-mL portions of diethyl ether. The combined organic phase was dried on $MgSO_4$ and concentrated by rotary evaporator to afford 6g brown oil. Following chromatography (silica gel, hexane 10:1 hexane/ethyl acetate) 5.7g (95%) of cyclohexyl phenyl ketone was obtained as white crystalline compound. mp: 52 °C, IR (KBr), *v* (cm^{-1}): 2922, 2852, 1665, 1578, 1444. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.96-7.92 (m, 2H), 7.55-7.42 (m, 3H), 3.31-3.22 (m, 1H), 1.91-1.82 (m, 4H), 1.76-1.72 (t, 2H), 1.61-1.23 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 203.9 (C), 136.4 (C), 132.7 (CH), 128.6 (CH), 128.3

(CH), 45.6 (CH), 29.4 (CH_2), 26.0 (CH_2), 25.9 (CH_2).

*Cyclohexyl phenyl ketone (**3**) from (**2**)*

For the alcohol oxidation, five times as much alcohol, MnO_2 was added in $CHCl_3$, and then it was stirred for 24 hours and worked up by diatom soil. The product was obtained as colorless crystals in 75-80% yield.

*Cyclohexyl phenyl methanol (**2**)*

To a stirred solution of benzaldehyde (32 mmol) in 20 mL diethylether at 0 °C was added slowly 37 mmol (2M in diethylether) of cyclohexylmagnesium bromide and the mixture was stirred for 1h under nitrogen atmosphere. After cooling to 0 °C, 15 mL of H_2O was cautiously added, followed by 30 mL of 15% H_2SO_4. After stirring for 20 min at 0 °C , 20 mL of diethylether was added, the organic layer was separated, and the aqueous layer was extracted twice more with 10-mL portions of diethylether. The combined organic phase was dried on $MgSO_4$. The organic phase was concentrated by solvent removal under reduced pressure to afford pure powder product Cyclohexyl phenyl methanol in 95% yield. mp: 165 °C; IR (KBr) ν (cm^{-1}): 3326, 2916, 2848, 1491, 1136, 972, 760, 702, 678.

*Bromocyclohexyl phenyl ketone (**4**) from (**3**)*

To a mixture of cyclohexyl phenyl ketone (10 mmol) and NBS (10.5 mmol) in dry Et_2O (10 mL) was added NH_4OAc (1 mmol). After stirring at 25 °C for 10 h, the mixture was filtered and the filtrate was washed with water, dried and the solvent was evaporated. The residue was chromatographed (hexane–ethyl acetate = 10: 1) on silica gel to give corresponding bromo ketone in 70% yield.

*α-Bromocyclohexyl phenyl ketone (**4**) from (**2**)*

Cyclohexyl phenyl methanole (2, 0.02 mol, 3.8 g) was placed in flask and the flask was covered with aluminium foil. An aqueous solution of HBr (47%, 3.4 mL, 1.5 mol equiv.) and LiCl (0.8 g, 0.02 mol) was added to **2**. After stirring the mixture at room temperature for 5 min, 30% aqueous solution of H_2O_2 (8 mL, 4 mol equiv.) was added to the reaction mixture. The reaction was complete after only 3h at 70 °C and color change was noticed. The organic phase was isolated to get a 5.2 g (99%) colorless Oil. Then, the liquid product was washed twice with 5-mL portions of methanol to obtained pure solid product α-Bromo cyclohexyl phenyl ketone**.** IR (neat) ν (cm^{-1}): 2934, 2857, 1674, 1596, 1446. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.33–1.45 (1H, m), 1.48–1.60 (3H, m), 1.72-1.85 (2H, m) – 2.12-2.22 (2H, m), 2.28–2.38 (2H, m), 7.37-7.44 (2H, m), 7.48-7.55 (1H, m), 8.04-8.09 (2H, m). ^{13}C NMR (62.90 MHz, $CDCl_3$), δ: 23.5 (CH_2), 24.9 (CH_2), 38.2 (CH_2), 67.9 (C), 128.1 (2CH), 129.7 (2CH), 132.0 (CH), 135.8 (C), 197.4 (C).

*1-hydroxycyclohexyl-phenyl ketone-N-methylimine (**5**)*

In a sealed vitreous glass reactore cooled at -40 °C by Liq. N_2 vapor containing 4 mL methylamine was slowly added α-Bromocyclohexyl phenyl ketone (1 g, 3.7 mmol). After stirring for 6 h, 10 mL of hexane was added, the organic layer was separated and the organic phase was concentrated by solvent removal under reduced pressure to afford brown crystal. The crystals was washed twice more with 10-mL portions of methanol to afford shiny crystal in 85% yield. mp 118 °C (lit. 118–120), IR (KBr), ν (cm^{-1}): 3302, 1651, 1243, 988, 712 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.48-1.64(6H, m), 1.67-1.84 (4H, m), 2.95 (3H, S), 6.99- 7.03 (2H, m), 7.37-7.45 (3H, m). ^{13}C NMR (62.90 MHz, $CDCl_3$) δ: 21.6($2CH_2$), 25.2 (CH_2), 35.2 ($2CH_2$), 39.2 (CH_3), 74.5 (C), 127.1 (2CH), 128.2 (CH), 128.4 (2CH), 135.4 (C), 178.0 (C).

Acknowledgement

Partial financial support by Imam Hossein University is gratefully acknowledged.

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