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Michael Addition Reaction of Some 3,3-Dimethyl-2,6-diarylpiperidin-4-ones

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In this paper, Michael addition reaction is carried out by treating 3,3-dimethyl-2,6-diarylpiperidin-4-ones (**1a-c**) with methyl vinyl ketone in the presence of sodium ethoxide. The products **2a-c** and **3a-c** formed are analyzed by UV, IR, ^{1}H NMR and ^{13}C NMR spectral methods. In all the cases, the ^{1}H NMR studies confirm the *trans*- ring fusion.

Key Words: Michael addition, 3,3-Dimethyl-2,6-diaryl-piperidin-4-ones.

INTRODUCTION

Many different nucleophiles add to α,β-unsaturated carbonyl compounds and lead to Michael addition products[1-3]. Piperidones act as an excellent nucleophile and readily add to α,β-unsaturated carbonyl compounds. These piperidones synthesized by Noller and Baliah[4] have been subjected to several physico-chemical studies[5-8]. The derivatives of piperidones like oximes[9] and phenyl hydrazones[10] were prepared already and their conformation is analyzed by spectral methods. Rangarajan *et al.*[11] prepared some homopiperazin-5-ones with the help of Schmidt reaction. Baeyer-Villiger reaction with 3-methyl-2,6-diarylpiperidine-4-one was carried out with sulphuric acid by Pandiarajan *et al.*[12]. Literature survey reveals that there is no significant report on Michael addition reaction with 2,6-diarylpiperidin-4-ones. Hence, it is of great interest to undertake the title work to synthesis isoquinoline derivatives from substituted piperidones. Further, the isoquinoline ring system[13,14] is present in a group of alkaloids such as emetine, cephaeline, psychotrine which are medicinally important.

EXPERIMENTAL

^{13}C NMR spectra were recorded on a DRX 500 and AMX 400 spectra operating at 125.7 and 100.0 MHz respectively using 10 mm sample tubes. Solution for the measurement of spectra were prepared by dissolving 0.5

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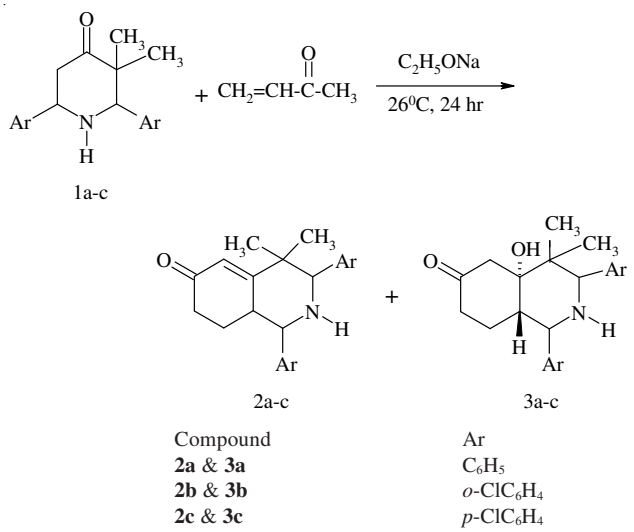
of the sample in 2.5 mL of chloroform-d containing 1 % TMS and acetone. All the chemical shift values are referenced to TMS. Proton NMR spectra were recorded on a DRX 500 NMR and AMX 400 NMR spectrometer operating at 500 and 400 MHz, respectively. Samples were prepared by dissolving about 10 mg of sample in 0.5 mL of acetone and chloroform-d containing 1 % TMS. All the chemical shifts are with reference to TMS. The C, H, N analysis was done on a Heraeus-C, H, N rapid analyzer.

Preparation of 3-substituted-2,6-diarylpiperidin-4-ones (1a-c): 2,6-Diarylpiperidones were prepared following the procedure adopted by Noller and Baliah[4]. Ammonium acetate (100 mmol), benzaldehyde (200 mmol) and appropriate ketone (200 mmol) were dissolved in 95 % alcohol (80 mL) and the solution was heated on a hot plate with gentle swirling until the colour of the mixture changed to orange. The mixture was cooled and poured into ether (100 mL) and conc. HCl (14 mL) was added. The precipitated 2,6-diarylpiperidin-4-one hydrochloride was collected by filtration and recrystallization from ethanol-ether. The hydrochloride was dispersed in acetone and conc. ammonia was added dropwise until a clear solution was obtained. The clear solution was poured into cold water and the solid precipitated was collected and crystallized from ethanol. The observed melting points are in excellent agreement with those of the reported ones.

Preparation of 4,4-dimethyl-1,3-diaryl-1,2,3,4,6,7,8,10-octahydroisoquinolin-6-one (2a-c) and 9-hydroxy-4,4-dimethyl-1,3-diaryldecahydroisoquinolin-6-one (3a-c): A solution of sodium ethoxide is prepared from 2 g of freshly cut sodium and 60 mL of absolute ethanol in a round-bottomed flask. Then 0.01 mol of 3,3-dimethyl-2,6-diarylpiperidin-4-ones in absolute ethanol is added and the contents are stirred for 1 h at room temperature. Then 0.01 mol of methyl vinyl ketone is added. The stirring is continued for overnight. To the reaction mixture, 100 mL of chloroform is added followed by ice water and shake well. The chloroform layer is separated and extracted with brine solution. Then the chloroform layer is dried with anhydrous sodium sulphite and evaporated. The products are separated by column chromatography.

RESULTS AND DISCUSSION

When 3,3-dimethyl-2,6-diarylpiperidone (**1a-c**) is treated with methyl vinyl ketone in the presence of sodium ethoxide (**Scheme-I**), two major products, 4,4-dimethyl-1,3-diaryl-1,2,3,4,6,7,8,10-octahydroisoquinolin-6-one (**2a-c**) and 9-hydroxy-4,4-dimethyl-1,3-diaryldecahydroisoquinolin-6-one (**3a-c**) are formed. Spectral analysis shows that the one with higher R_f value is an α,β-unsaturated ketone and the other with lower R_f value is a bicyclic alcohol.



Compound	Ar
2a & **3a**	C_6H_5
2b & **3b**	*o*-ClC_6H_4
2c & **3c**	*p*-ClC_6H_4

Scheme-I

The UV spectrum of compound **2a** shows a λ_{max} around 275 nm, which is characteristic of an α,β-unsaturated ketone. The IR spectrum shows strong carbonyl absorption at 1686 cm^{-1} that is characteristic of a cyclic α,β-unsaturated ketone stretching frequency. The ^{13}C NMR chemical shifts of the compound **2a** are assigned by comparing[12] the chemical shifts of compound **1a**. The signal at 60.2 ppm is assigned to C-1 and the signal at 67.5 ppm is due to C-3. The ring fusion slightly shields the benzylic carbons C-2 and C-6 in piperidone **1a**. The signal for C-4 is shielded by 9 ppm as compared to the piperidone, which is in accordance with the expected decrease in electronegativity when carbonyl is converted to alkenes. Due to the deshielding mechanism of carbon-carbon double bond, the C-5 and C-9 appear at 133.4 and 152.5 ppm, respectively. The ^{13}C chemical shifts are assigned similarly for other compounds **2b** and **2c** and are listed in Table-1.

The ^{1}H NMR data helps us to predict the type of ring fusion. The doublet at 3.82 ppm is due to the coupling of benzylic proton with adjacent proton H-8. The observed coupling constant value is 10.72 Hz, which is typical of diaxial coupling and this, could happen only when the ring fusion is trans. The ^{1}H NMR chemical shifts are assigned for the products by comparing[12] with that of the parent compound **1a-c**. Similarly, the chemical shifts are assigned to other compounds **2b** and **2c**. The ^{1}H NMR data are listed in Table-2.

The second compound 9-hydroxy-4,4-dimethyl-1,3-diphenyldecahydro isoquinolin-6-one (**3a**) isolated from the addition reaction is having a lower R_f value. The IR spectrum of the compound shows two characteristic absorptions at 3450 and 1712 cm^{-1}. The former peak is due to -OH group and the latter

TABLE-1
^{13}C NMR CHEMICAL SHIFTS (ppm) OF THE
COMPOUNDS **2a-2c** AND **3a-3c**

Carbon	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**
C-1	60.2	60.4	60.6	63.5	63.0	63.1
C-3	67.5	67.0	66.5	57.3	56.3	56.2
C-4	40.2	40.3	40.4	39.4	39.4	56.2
C-5	133.0	132.4	132.9	43.4	43.0	43.16
C-6	196.2	195.2	195.3	210.15	210.62	213.2
C-7	43.3	43.20	43.1	42.7	42.2	43.3
C-8	33.5	33.0	33.0	31.8	32.2	33.12
C-9	152.5	151.6	151.9	81.4	84.0	84.1
C-10	33.2	34.20	34.71	32.9	32.2	32.84
Gem	20.1	20.2	20.3	20.1	20.2	20.9
dimethyl	21.2	21.0	21.1	21.1	21.2	21.7
Aromatic	126-128.32	127-129	127.12-128.60	127.30-128.40	128.33-129.32	128.42-129.60

TABLE-2
^{1}H NMR CHEMICAL SHIFTS (ppm) OF THE
COMPOUNDS **2a-2c** AND **3a-3c**

Protons	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**
H-1	3.82	3.88	3.87	3.53	3.55	3.57
H-3	3.63	3.65	3.65	3.42	3.41	3.42
H-5	6.72	6.77	6.78	2.85	2.86	2.86
H-7	2.65-2.85	2.66-2.85	2.67-2.88	2.62	2.70	2.69
H-8	1.35-1.85	1.37-1.90	1.41-1.92	1.54	1.49	1.50
H-10	2.33-2.55	2.11-2.54	2.15-2.56	1.89	1.88	1.89
Gem	1.05	0.97	0.96	0.97	0.99	0.98
dimethyl	0.97	0.99	0.97	0.85	0.85	0.84
Aromatic	7.24-7.42	7.21-7.38	7.22-7.39	7.20-7.80	7.21-7.77	7.28-7.56
C-10	33.2	34.20	34.71	32.9	32.2	32.84
Gem	20.1	20.2	20.3	20.1	20.2	20.9
dimethyl	21.2	21.0	21.1	21.1	21.2	21.7
Aromatic	126-128.32	127-129	127.12-128.60	127.30-128.40	128.33-129.32	128.42-129.60

is due to carbonyl group without any extended conjucation. This confirms that the compound is a ketonic alcohol (**3a-c**), without unsaturation. The ^{13}C NMR shows absorption at 210.2 ppm corresponding to the carbonyl group (C-6). Owing to the deshielding effect of -OH group, the C-9 appears in downfield region. The ^{13}C NMR values are listed in the Table-1 for the products (**3a-c**). The doublet at 3.42 ppm is due to the coupling of benzylic proton with

adjacent proton H-8 (**3a**). The observed coupling constant value is 11.02 H2, which is typical of *vicinal* coupling. Hence, the ring fusion is *trans* and not *cis*. Similar justification is given for the compounds **3b** and **3c**. The ^{1}H NMR data for the products **3a-c** are listed in Table-2.

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REFERENCES

1. M.J. Weiss and C.R. Hauser, *J. Am. Chem. Soc.*, **71**, 2026 (1949).
2. E.P. Kohler and C.F.H. Allen, *J. Am. Chem. Soc.*, **46**, 1522 (1924).
3. D.B. Andrews and R. Connor, *J. Am. Chem. Soc.*, **57**, 895 (1935).
4. C.R. Noller and V. Baliah, *J. Am. Chem. Soc.*, **70**, 3853 (1948).
5. K. Selvaraj, P. Nanjappa, K. Ramalingam and K. Ramarajan, *J. Chem. Soc., Perkin Trans. II*, 49 (1983).
6. K. Ramalingam, K.D. Berlin, N. Satyamurthy and R. Sivakumar, *J. Org. Chem.*, **44**, 471 (1979).
7. M.U. Hasan, M. Arab, K. Pandiarajan, R. Sekar and D. Marko, *Magn. Res. Chem.*, **23**, 292 (1985).
8. M.K. Aroney, C.Y. Chen, R.J.W. Le Fevre and A.N. Singh, *J. Chem. Soc (B)*, 98 (1966).
9. R.T. Sabapathy Mohan, Ph.D. Thesis, Annamalai University, India, (1985).
10. K. Subramani, Ph.D. Thesis, Annamalai University, India (1999).
11. T. Rangarajan, K. Pandiarajan and Chellappa, *Indian J. Chem.*, **21B**, 778 (1982).
12. K. Pandiarajan, *Indian J. Chem.*, **30B**, 490 (1991).
13. R. Lüllmann-Rauch, R. Pods and B. von Witzendorff, *Toxicology*, **110**, 1, 27 (1996).
14. M.B. de Jesus, L. de Matos Alves Pinto, L.F. Fraceto, Y. Takahata, A.C.S. Lino, C. Jaime and E. de Paula, *J. Pharm. Biomed. Anal.*, **41**, 1428 (2006).

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