CYCLOHEXANONE DERIVATIVES : SYNTHONS FOR SUBSTITUTED QUINOLINES

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Abstract: Substituted quinolines **4, 5,** and **9** were reported from o-allyl ethers of cyclohexanone derivatives by [2,3] sigmatropic rearrangement followed by cyclization. All the new compounds were characterized by IR and ^{1}H NMR spectra.

Introduction

The chemistry of diaryl cyclohexenones has evoked considerable interest because of their utility as building blocks for the development of various fused and spiroheterocycles.[1-4] In order to explore their synthetic utility it is considered to exploit the α-keto methylene functionality once again for the synthesis of quinoline derivatives. The latter forms one of the basic units in many natural products apart from their usage as herbicides and medicinals. Although many methods are reported for their syntheses,[5,6] the thermal rearrangement of o-allyl ethers of ketoximes also led to quinoline derivatives.

Results & Discussion

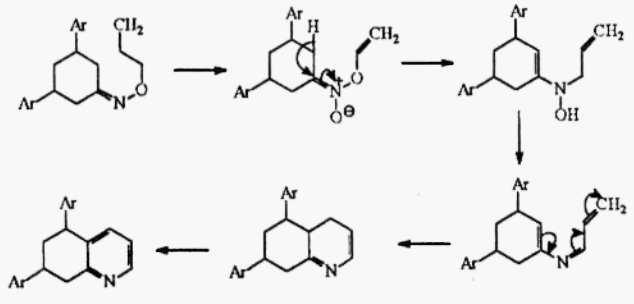
The present work constitutes the development of quinoline derivatives from diarylcyclohexenones (**1**) and diarylcyclohexanones (**6**). To accomplish this, the oxime derivatives of **1** and **6** were prepared by the reaction of **1** and **6** with hydroxylamine hydrochloride in the presence of TEA in alcohol. The IR spectra of **2** and **7** showed absorption bands in the regions 1590-1596 (C=N) and 3500-3548 (OH). Apart from this **2** displayed a band around 1625-1640 cm^{-1} (C=C). The o-allyl ethers of ketoximes **3** and **8** were obtained by refluxing **2** and **7** with allyl bromide in the presence of sodium hydroxide in methanol (Table 1).

Table 1 : Physical data of the Compounds **2- 5 & 7-9**

Compd. No.	M.P. (°C)	Yield (%)	Compd. No.	M.P. (°C)	Yield (%)
2a	175-176	70	**7a**	183-184	77
2b	162-163	72	**7b**	197-198	79
2c	169-170	80	**7c**	186-187	81
3a	149-150	67	**8a**	162-163	68
3b	142-143	66	**8b**	176-177	66
3c	137-138	69	**8c**	158-159	65
4a	124-125	70	**9a**	118-119	68
4b	137-138	62	**9b**	127-128	65
4c	129-130	65	**9c**	135-136	69
5a	147-148	78			
5b	152-153	75			
5c	165-166	76			

* The elemental analyses were obtained for 4, 5 & 9 : C ± 0.23, H ± 0.07 N ± 0.21

The absence of absorption band around 3500 and the presence of bands in the region 1152-1165 (C-O) and 1645-1652 cm^{-1} (C=C) in their IR spectra indicated their formation. In the ^1H NMR spectra of these compounds a doublet and two multiplets were observed in the regions δ 3.88-3.94 (CH_2), 4.98-5.10 (CH_2=CH-) and 5.84-6.03 (CH_2=CH-) characteristic of allylic protons. The 5,6-dihydro-5,7-diarylquinoline (**4**) and 5,6,7,8-tetrahydro-5,7-diarylquinoline (**9**) were prepared by heating **3** and **8** in an inert atmosphere at 200°C for 2-3 days (Scheme, Table 1). The formation of quinoline derivatives suggested the intermediacy of nitrone by [2,3] sigmatropic rearrangement followed by internal cyclization as per the mechanism shown below.



The IR spectra of **4** and **9** showed absorption bands around 1605-1610 and 1545-1558 cm^{-1} for C=C and C=N of pyrimidine ring. However, **4** displayed an absorption band around 1620-1625 cm^{-1} (C=C). The ^1H NMR spectra of **4** and **9** showed a double doublet at δ 6.78-6.84 (*J*=4.8-5.9, 8.0-8.2 Hz) which was assigned to C_3-H and two doublets at 8.16-8.19 (*J*=4.8-5.0 Hz) and 7.88-7,93 (*J*=8.0-8.2 Hz) were due to C_2-H and C_4-H. The other triplet, doublet and singlet at δ 3.50-3.54, 2,94-2,98 and 5.28-5.32 accounts for C_5-H, C_6-H and C_8-H. However **9** exhibited a triplet, two multiplets and a doublet at 3.44 - 3.49, 2.81-2.87, 3.29-3.34, 2,95-3.02 which were attributed to C_5-H, C_6-H, C_7-H and C_8-H, respectively. Attempts were made to dehydrogenate **4** and **9** with DDQ. Thus when **4** was heated with DDQ in benzene, gets aromatized to 5,7-diarylquinoline (**5**), while **9** could not respond for this reaction. The IR spectra of **5** showed absorption bands almost in the same region as in **4**. In the ^1H NMR spectra of **5** the absence of signals corresponding to methine and methylene protons at C-5, C-6 and C-8 confirms the formation of **5** (Table 2). In conclusion, we report the synthesis of substituted quinolines **4, 5** and **9** from cyclohexenone derivatives adopting simple, novel and facile methodology.

Table 2: Spectroscopic data of compounds **4, 5 & 9**

Compd. No.	^1H NMR ($CDCl_3$) δ, ppm
4a	2.96 (d, 2H, C_6-H), 3.50 (t, 1H, C_5-H), 5.30 (s, 1H, C_8-H), 6.80 (dd, 1H, *J*=5.0, 8.1 Hz, C_3-H), 7.90 (d, 1H, *J*=8.1 Hz, C_4-H), 8.19 (d, 1H, *J*=5.0 Hz, C_2-H)
4b	2.94 (d, 2H, C_6-H), 3.51 (t, 1H, C_5-H), 3.84 (s, 6H, Ar-OCH_3), 5.28 (s, 1H, C_8-H), 6.82 (dd, 1H, *J*=4.8, 8.1 Hz, C_3-H), 7.93 (d, 1H, *J*=8.1 Hz, C_4-H), 8.18 (d, 1H, *J*=4.8 Hz, C_2-H).
5a	6.91 (dd, 1H, *J*=4.9, 8.0 Hz, C_3-H), 7.35 (s, 1H, C_6-H), 7.74 (s, 1H, C_8-H), 7.89 (d, 1H, *J*=8.0 Hz, C_4-H), 8.32 (d, 1H, *J*=4.9 Hz, C_2-H)
5c	6.94 (dd, 1H, *J*=4.9, 8.1 Hz, C_3-H), 7.42 (s, 1H, C_6-H), 7.84 (s, 1H, C_8-H), 7.88 (d, 1H, *J*=8.1 Hz, C_4-H), 8.29 (d, 1H, *J*=4.9 Hz, C_2-H)
9a	2.84-2.87 (m, 2H, C_6-H), 2.95 (d, 2H, C_8-H), 3.29-3.33 (m, 1H, C_7-H), 3.49 (t, 1H, C_5-H), 6.78 (dd, 1H, *J*=4.9, 8.2 Hz, C_3-H), 7.89 (d, 1H, *J*=8.2 Hz, C_4-H), 8.19 (d, 1H, *J*=4.9 Hz, C_2-H)
9c	2.81-2.85 (m, 2H, C_6-H), 3.02 (d, 2H, C_8-H), 3.31-3.34 (m, 1H, C_7-H), 3.44 (t, 1H, C_5-H), 6.84 (dd, 1H, *J*=4.8, 8.0 Hz, C_3-H), 7.88 (d, 1H, *J*=8.0 Hz, C_4-H), 8.16 (d, 1H, *J*=4.8 Hz, C_2-H)

Experimental

Melting points were determined in open capillaries on Tempo Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by thin layer chromatography (silica gel-G, BDH), pet. ether (40-60°C): ethyl acetate (3:1) as eluents). The IR spectra were recorded on a Perkin-Elmer Infrared spectrometer (ν_{max} in cm^{-1}) model 337 in KBr pellets. The ^1H NMR spectra were recorded in $CDCl_3$ 200 MHz on Bruker spectrospin and Varian EM-360 spectrometers with TMS as an internal standard (Chemical shifts in δ ppm). Microanalyses were performed by Microanalytical laboratory, University of Pune, Pune, India.

3,5-Diaryl-2-cyclohexenone (**1**) and 3,5-diarylcyclohexanone (**6**) were prepared according to literature procedures.[7,8]

Preparation of Oxime of 3,5-diaryl-2-cyclohexenone (2a-c) / 3,5-diaryl-cyclohexanone (7a-c).

A solution of 3,5-diarylcyclohexenone (**2**) / 3,5-diarylcyclohexanone (**6**) (0.01 mol), hydroxylamine hydrochloride (0.69 g, 0.012 mol) and a catalytic amount of triethylamine in ethanol was refluxed on a water bath for 1-2 hrs. The contents were concentrated and cooled. The product separated was filtered and dried. It was recrystallized from ethanol to get pure **2/7.**

Preparation of O-allyl ether of 3,5-diaryl-2-cyclohexenone oxime (3a-c)/ 3,5-diarylcyclo-hexanone oxime (8 a-c).

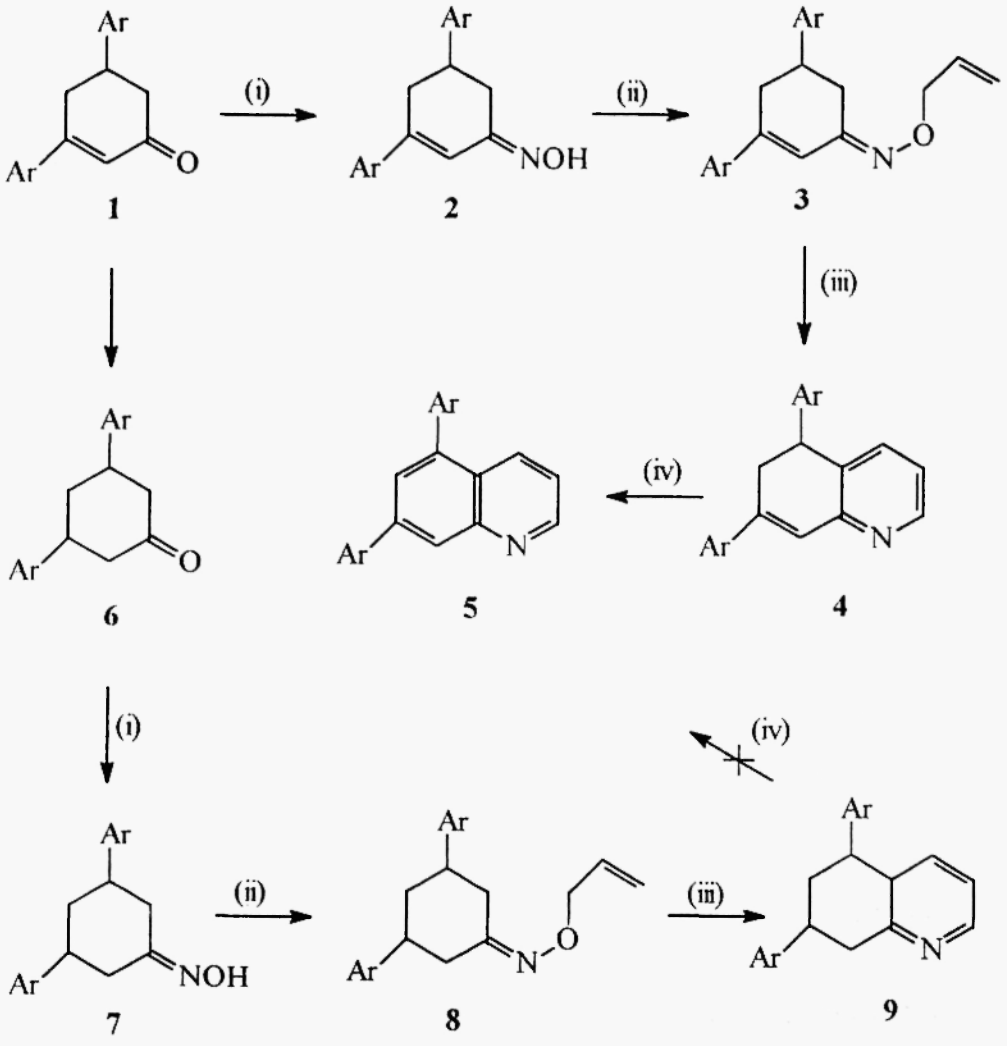
A mixture of **2/7** (0.01 mol) and allyl bromide (1.43 g, 0.02 mol) in methanol was cooled at ice-salt bath temperature. To this, a solution of sodium hydroxide (3 g) in methanol (60 ml) was added and refluxed for 3-4 hrs. The reaction mixture was cooled, the precipitated NaBr was removed by filtration and the filtrate was concentrated. The resultant viscous mass was solidified by heating with hexane and filtered through a column of silica gel to obtain pure **3/8.**

Preparation of 5,6-dihydro-5,7-diarylquinoline (4a-c) / 5,6,7,8-tetrahydro-5,7-diaryl-quinoline (9a-c).

A solution of **3/8** (0.003 mol) in dry benzene (10 ml) was taken in a pyrex sealed tube under nitrogen atmosphere and heated at 200°C in an oil bath for two days. It was cooled and opened. The contents were transfered and benzene was removed under reduced pressure. The semi-solid obtained was subjected to column chromatography to get pure **4/9**.

Preparation of 5,7-diarylquinoline (5a-c).

A 1:1.5 molar mixture of **4/9** and DDQ in dry benzene (20 ml) was heated at reflux temperature for 2 hrs under nitrogen atmosphere. The precipitated DDQ-H_2 was filtered off



(i) NH_2OH / TEA / EtOH (ii) CH_2=CH-CH_2Br / MeOH
(iii) Δ / C_6H_6 (iv) DDQ / Δ

Ar = a) Ph b) 4-OCH_3.Ph c) 4-Cl.Ph

SCHEME

and the filtrate on flash evaporation afforded crude product, which was purified by passing through a column of silica gel.

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