AN EFFICIENT SYNTHESIS OF 6,8-DIARYLCARBAZOLES VIA FISCHER INDOLE CYCLIZATIONS.

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Abstract: 6,8- Diaryl - 6,7-dihydrocarbazole (4), 6,8- diaryl - 6,7,8,9, - terahydrocarbazole (7), 6,8- diaryl carbazole (8) were obtained from the Fischer indole cyclization of 6 - carbethoxy- 3,5- diarylcyclohex- 2-en- 1-one (1).

Introduction

The versatility of 6- carbethoxy-3,5-diphenylcyclohexenone as an effective synthon in the synthesis of benzoisoxazoles/ benzopyrazoles[1], benzoselenadiazoles/ thiadiazoles[2] and spiro cyclohexanes[3] has been recently reported from our group. In the present communication yet another application of the former in the synthesis of carbazole derivatives, which are the constituents of several natural products has been reported[4,5].

Results and discussion

The 6-carbethoxy-3,5-diarylcyclohexenone (1) was obtained by the Knoevenagel reaction of ethyl acetoacetate with 1,3-diarylprop-2-en-1-one in presence of sodium ethoxide[6]. The subsequent hydrolysis and decarboxylation of 1 led to the formation of 3,5-diarylcyclohex -2-en-1-one (2). The latter on treatment with phenylhydrazine afforded its phenylhydrazone (3) which on indolization with acetic acid furnished 6,8-diaryl-6,7-dihydrocarbazole (4). On the other hand 2 on selective reduction with H_2/Pd at 40 psi gave 3,5-diarylcyclohexanone (5). The phenyl hydrazone of 5 (6) on similar type of cyclization with AcOH in the presence of few drops of conc. H_2SO_4 resulted 6,8- diaryl - 6,7,8,9-tetrahydrocarbazole (7). (Scheme - 1 & Table -1).

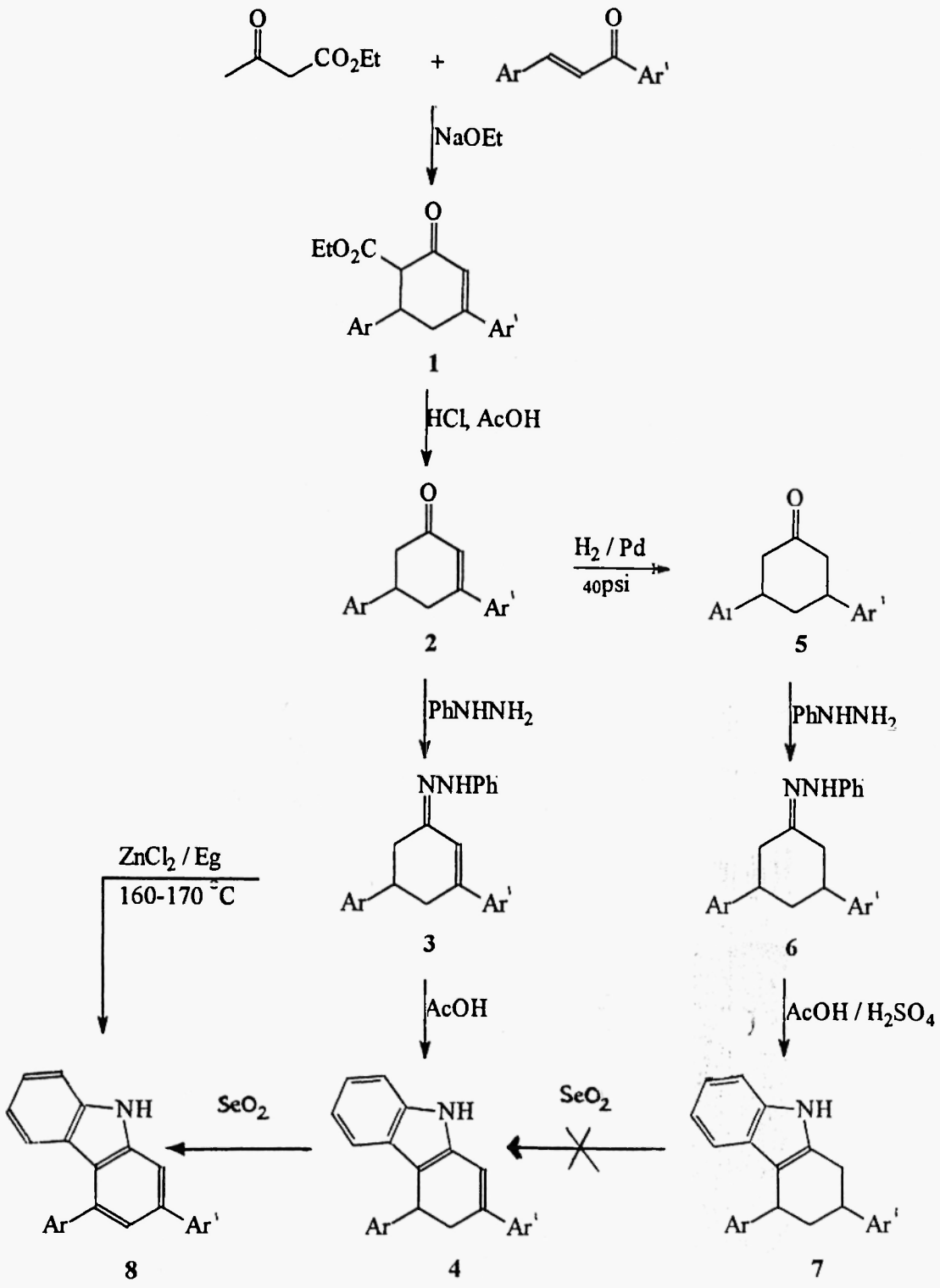
Several consequences were observed during this indolization reaction. Earlier, we have reported γ-carboline from phenylhydrazone of 4-piperidine with polyphosphoric acid [7]. When the same conditions were adopted for **3** and **6**, the reaction did not proceed and the expected products **4** and **7** were not obtained. On the other hand when indolization of **3** and **6** was carried out with zinc chloride at an elevated temperature, the 6,8-diarylcarbazole (**8**) was obtained by spontaneous dehydrogenation in poor yields only from **3**. Apart from this, **8** was also obtained from the dehydrogenation of **4** with SeO_2 (Scheme - 1), but on similar reaction, **7** remains intact without the formation of **4** or **8**.

The structure of carbazoles **4**, **7** and **8** was delineated by their spectral parameters (Table- 2). The usual weak NH absorption band around 3300 cm^{-1} was observed in their IR spectra. In the ^{1}H NMR spectra of **4** two sets of signals, a doublet around 2.30 - 2.35 and a triplet around 3.44 -3.47 were observed for C_7-H and C_6-H. However, **7** showed two multiplets, a triplet and a doublet at 2.25-2.35, 3.05-3.55, 3.47 -3.55 and 2.45-2.60 ppm for C_7-H, C_8-H, C_6-H and C_9-H respectively but **8** showed signals only around 6.85-8.01 ppm for aromatic protons.

The preliminary semiquantitative antimicrobial activity of the compounds **4**, **7** and **8** showed that they are active against the strains of bacteria (*Staphylococcus aureus, Bacillus subtilis* (gram+ve), *Escherichia coli* and *Klebsiella pneumoniae* (gram-ve)) and fungi *(Curvularia lunata, Fusarium solani, Aspergillus niger, Cunninghemella elegans)*[4,5]. Further studies are in progress.

Experimental :

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by thin layer chromatography (Silica gel - G, hexane : ethyl acetate 3:1). IR spectra were recorded using Perkin Elmer 993 Infrared spectrophotometer (ν, cm^{-1}) as KBr discs and ^{1}HNMR spectra were recorded in $CDCl_3$ using 200 MHz Bruker Spectrospin instrument with TMS as an internal standard (chemical shifts in ppm). The elemental analyses were obtained from microanalytical laboratory, University of Pune, Pune, India. The 6-carbethoxy-3,5- diarylcyclohex-2-en-1-one (**1a-c**), 3,5-diarylcyclohex-2-en-1-one (**2a-c**), 3,5-diarylcyclohexanone (**5a-c**), were prepared according to the literature procedures[6].


CO2Et
Ar
Ar'
NaOEt
EtO2C
1
HCl, AcOH
2
H2 / Pd
40psi
5
PhNHNH2
NNHPh
3
6
ZnCl2 / Eg
160-170 °C
AcOH
AcOH / H2SO4
NH
SeO2
SeO2
8
4
7

Scheme 1

Table 1: Physical Data of Compounds **4, 7** and **8**.

Compd No.	Ar	Ar'	Yield (%)	M.P (° C)	Mol. Formula (Mol. Wt.)	Found (Calcd) %		
						C	H	N
4a	H	H	62	110-111	$C_{24}H_{19}N$ (321.42)	89.68 (89.53)	5.95 (5.81)	4.35 (4.18)
4b	H	4-OCH_3.Ph	64	92-97	$C_{25}H_{21}NO$ (351.45)	85.43 (85.31)	6.02 (6.13)	3.98 (4.11)
4c	4-Cl.Ph	4-Cl.Ph	61	102-103	$C_{24}H_{17}NCl_2$ (390.31)	73.85 (73.74)	4.39 (4.48)	3.58 (3.47)
7a	H	H	60	115-117	$C_{24}H_{21}N$ (323.44)	89.12 (88.98)	6.54 (6.48)	4.33 (4.45)
7b	H	4-OCH_3.Ph	61	100-102	$C_{25}H_{23}NO$ (353.46)	84.95 (84.82)	6.55 (6.60)	3.96 (3.85)
7c	4-Cl.Ph	4-Cl.Ph	62	109-110	$C_{24}H_{19}NCl_2$ (392.33)	73.47 (73.62)	4.88 (4.81)	3.57 (3.70)
8a	H	H	60	125-127	$C_{24}H_{17}N$ (341.40)	90.25 (90.46)	5.36 (5.45)	4.38 (4.48)
8b	H	4-OCH_3.Ph	58	117-119	$C_{25}H_{19}NO$ (341.45)	85.73 (85.60)	5.50 (5.64)	4.00 (3.87)
8c	4-Cl.Ph	4-Cl.Ph	59	120-121	$C_{24}H_{15}NCl_2$ (388.30)	74.24 (74.12)	3.59 (3.52)	3.68 (3.82)

Table 2 : Spectroscopic data of compounds **4, 7** and **8**

Compd. No.	IR (KBr) cm^{-1}	^{1}HNMR ($CDCl_3$) δ ppm
4a	3315, 1620	2.35 (d, 2H, J=6.4 Hz, C_7 - H); 3.44 (t, 1H, J = 6.4 Hz, , C_6 - H); 6.98 - 7.55 (m, 16H, Ar -H, NH, C_9-H)
4b	3300, 1650	2.30 (d, 2H, J=6.0 Hz, C_7 - H); 3.47 (t, 1H, J=6.0 Hz, C_6 - H); 3.78 (s, 3H, OCH_3-Ar); 7.01 - 7.70 (m, 15 H, Ar - H, NH, C_9-H)
4c	3298, 1645	---
7a	3320, 1635	2.30 - 2.35 (m, 2H,C_7 - H); 2.60 (d, 2H, J=6.8 Hz, C_9 - H); 3.55 (t, 2H, J=4.8Hz, C_6 - H); 3.12-3.55 (m, 1H, C_8 - H); 7.00 - 7.48 (m, 15H, Ar - H, NH)
7b	3290, 1625	----
7c	3360, 1610	2.25 -2.32 (m, 2H, C_7 - H); 2.45 (d, 2H, J=5.9 Hz, , C_9 - H); 3.47 (t, 1H, J=5.4 Hz , C_6 - H), 3.05- 3.41 (m, 1H, C_8 - H); 6.96-7.54 (m, 13H, Ar-H, NH)
8a	3375, 1650	6.85 - 7.94 (m, 17H, Ar -H, NH)
8b	3368, 1625	3.82 (s, 3H, OCH_3-Ar); 7.05 - 8.01 (m, 16H, Ar - H, NH)
8c	3360, 1650	----

Preparation of 3,5-diphenylcyclohex-2-en-1-one phenylhyrdazone(3a-c) / 3,5-diphenylcyclohexanone phenylhydrazone (6a-c).

A mixture of **2/5** (0.01 mol), phenylhydrazine (0.01 mol) in ethanol (25 mL) was refluxed for 2-3 hrs on a steam bath and cooled. The seperated solid was filtered, washed with alcohol and recrystallized from ethanol to get pure **3a-c / 6a-c.**

Preparation of 6,8-diaryl-6,7-dihydrocarbazole (4a-c).

The phenylhydrazone **3a-c** (0.005 mol) in glacial acetic acid (10 mL) was heated (60-70°C) until the evolution of gas ceases. Then, the reaction mixture was cooled to room temperature and poured onto crushed ice. The separated solid was filtered and purified through a column of silica gel-G (60-120 mesh) using ethyl acetate : pet ether (60-80°C) as solvent mixture gave **4a-c**.

Preparation of 6,8-diaryl - 6,7,8,9-tetrahydrocarbazole (7a-c).

The phenylhydrazone **6** (0.005 mol) in glacial acetic acid (20 mL) and a catalytic amount of conc. H_2SO_4 were heated to 60-70°C while stirring until the solid gets dissolved completely. Heating was continued until the evolution of gas ceases. Then, the reaction mixture was cooled to room temperature and poured onto crushed ice. The separated solid was filtered and purified through a column of silica gel.

Preparation of 6,8-diarylcarbazole (8a-c).

Method A : A mixture of **3** (0.005 mol), a catalytic amount of anhydrous zinc chloride and ethylene glycol (25 mL) was heated (160-170°C) under reflux for 2 hrs. Then, the reaction mixture was cooled to room temperature and filtered to remove the unreacted zinc chloride. When the filtrate was poured onto crushed ice, a gummy substance was obtained which was purified through a column of silica gel.

Method B : A mixture of **4** (0.005 mol) in glacial acetic acid (20 mL) was stirred well at 70-80°C. To this, selenium dioxide powder (0.01 mol) was added portion-wise and heating was continued until the evolution of gas ceases. Then, the reaction mixture was cooled to room temperature and filtered to remove the deposited selenium. The filtrate was poured onto crushed ice and the crude product obtained was recrystallized from ethanol.

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