Synthesis of Spiro Pyrrolidines From the Addition of Schiff Bases to α-Arylidene Cyclohexanones

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Received **Accepted**
15/04/2007 **17/07/2007**

الخلاصة

تم تحضير سلسلة من الفا–ارايليدين هكسانون حلقي (1–4) بواسطة تكاثف كليزن–شميدت، بينما تم تحضير سلسلة اخرى من N–ارايليدين بنزايل امين (قواعد شف 5–10) بالاضافة المولية المتكافئة. ان الاضافة الحلقة الانيونية 3،1 لقواعد شف على الفا–ارايليدين هكسانون حلقي تحت ظروف قاعدية انتج البايروليدينات المقابلة نوع سبايرو (11–23). لقد تم دعم تراكيب النواتج بواسطة البيانات الطيفية المتاحة والصفات الفيزياوية، كما تم استخدام البيانات النظرية لدعم الميكانيكية المقترحة.

ABSTRACT

A series of α-arylidene cyclohexanones (1-4) had been prepared via Claisen-Schmidt condensation, while other series of N-arylidene benzylamines (Schiff bases 5-10) had also been synthesized by equimolar addition. The 1,3-anionic cycloaddition of Schiff bases to α-arylidene cyclohexanones under basic conditions afforded the corresponding spiro pyrrolidines (11-23). The structures of the products are supported by valid spectral data and physical properties. Theoretical data had been used to support the suggested mechanism.

INTRODUCTION

Substituted chiral, nonracemic pyrrolidines are common structural motifs found in many natural and unnatural products that possess interesting and important biological activities, and a great deal of effects has been devoted toward the development of asymmetric methods for their synthesis[1,2]. The pyrrolidine ring is found in many natural compounds and may be fused to other rings in a variety of ways as in cocaine, lepadiformine, and (-) – coccinine[3].

We have been interested in developing a pyrrolidine synthesis that would be general enough to use for waking diverse-pyrolidine-containing compounds such as mentioned above[4].

Prior to our work, the anionic cycloaddition of 2-azaallyllithiums, a specific type of 2-azaallyl anion, with alkenes was limited to anions bearing two or more aryl groups, chemistry pioneered by Kauffmann[5]. The cyclic system of pyrrolidine is found in many important medicines

which considered as a natural products[6], and it is known that pyrrolidine and its derivatives possess a biological activity. Some substituted pyrrolidines are anti-depressant, anti-psychotic, and analgesic[7], some of which are anti-arythritic and anti-smoking[8], while others are anti-cancer, anti-microbial and anti-hypertensive[9].

Pyrrolidine dithiocarbamate (PDTC) is used as anti-viral agent against virus causes influenza by quenching the gene responsible for this virus[10].

EXPERIMENTAL

I. Instrumentation

1. Boiling points were determined by using an inverted capillary in a Thiele tube using paraffin colourless oil.
2. Melting points were determined by Electrothermal 9000 Digital-series 1998 apparatus (uncorrected).
3. Ultraviolet spectra were obtained using SPECORD 200 UV-Visible double beam Analytikjenta spectrophotometer.
4. Fourier-Transform Infrared (FT-IR) spectra were recorded by using Thermo-Nicolte Fourier-Transform Infrared (FT-IR) spectrophotometer.
5. The theoretical calculations were computed using semi-empirical AM1 module in the CS ChemOffice molecular modeling package. The data obtained from the minimized geometry were used for the theoretical calculations.

H.F = heat of formation

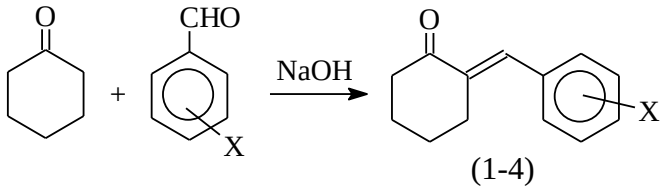
S.E = steric energy

II. Synthesis

1. Preparation of α-arylidene cyclohexanone (1-4)

General procedure[11]

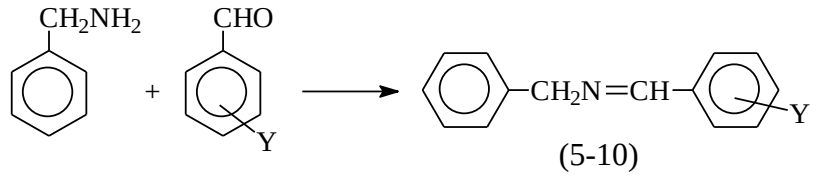
A mixture of (1.1 gm, 0.028 mole) of sodium hydroxide pellets, (10) ml of water and (6.0 ml, 0.1 mole) of ethanol was magnetically stirred in a 50 ml round-bottomed flask. A fresh distilled cyclohexanone (2.3 ml, 0.022 mole) was poured on the stirred mixture followed by the desired benzaldehyde (0.022 mole). A vigorous stirring at room temperature is continued for (3-4) hours, till the mixture become thick, then kept in a refrigerator overnight. The product was filtered by suction and washed several times with water until the filterates were neutral to litmus. The crude α-arylidene cyclohexanone is dried in air and recrystallized from ethanol, see Table-1, while the following equation illustrates the reaction:



(1-4)

2. Preparation of N-arylidene benzylamines (5-10) (Schiff bases)
General procedure[12]

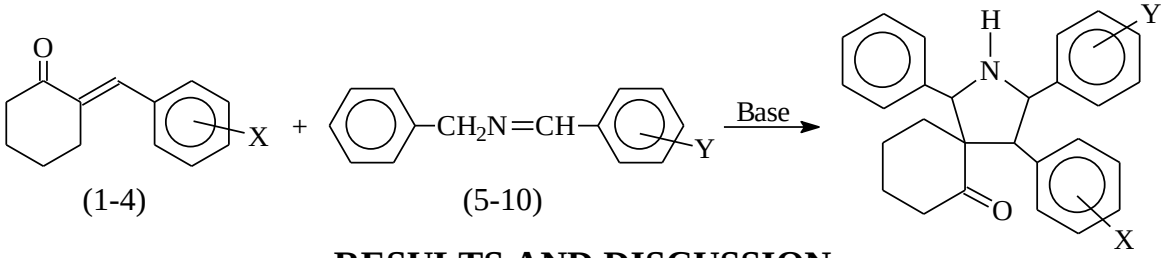
A mixture of (1.1 ml, 0.01 mole) of benzylamine and (0.01 mole) of a desired benzaldehyde is heated in a 100 ml beaker for (10 min.) at 100 °C after the addition of about (10) ml n-butanol. The precipitated Schiff base was filtered after cooling the mixture and recrystallized from ethanol, see Table-2, the following equation illustrate the formation of the Schiff bases.



(5-10)

3. 1,3-Anionic cycloaddition of N-arylidene benzylamines to α-arylidene cyclohexanone (11-23)
General procedure[13]

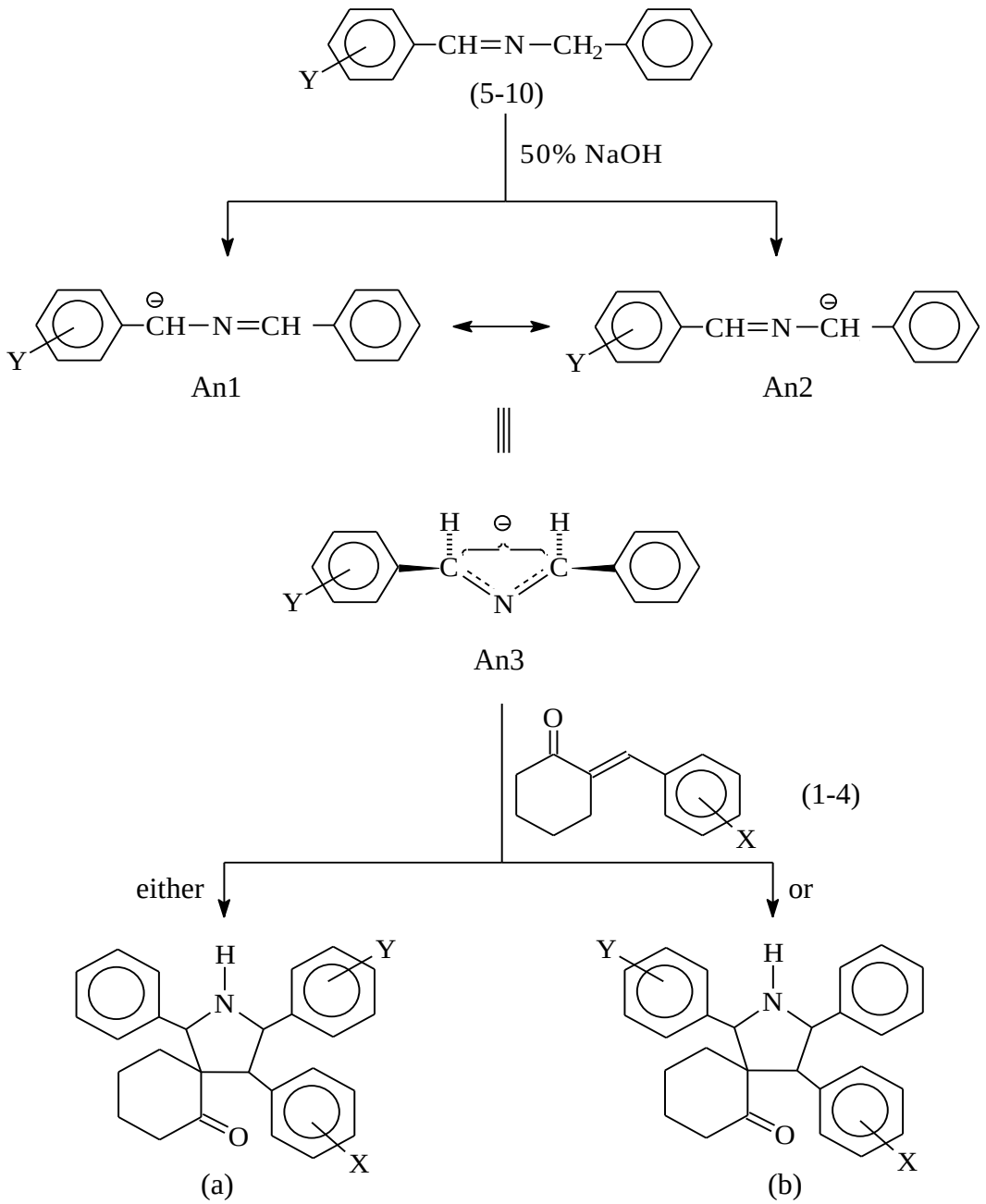
A mixture of (0.01 mole) of α-arylidene cyclohexanone and (0.01 mole) of Schiff base was stirred in the presence of (5 ml) of 50% ethanolic sodium hydroxide solution and (10 ml) of dimethyl sulfoxide, stirring at room temperature was continued for (4) hours, then the mixture was allowed to stand overnight. A (100 ml) of water was added to the mixture and separated precipitates were filtered and washed with water till the filtrate seems clear and being neutral. The solid products were dried and recrystallized from methanol-ethyl acetate, Table-3 illustrates the physical and spectral data of the spiro products which had been afforded according to the following equation:



(1-4) (5-10) (11-23)

RESULTS AND DISCUSSION

Claisen-Schimdt condensation had been used to afford the four α-arylidene cyclohexanones (1-4) to be used as a starting materials to get the spiro products after their reaction with the synthesized N-arylidene benzylamines (5-10) through 1,3-anionic cycloaddition (Scheme 1).

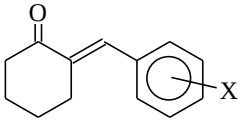


Scheme (1): 1,3-Anionic cycloaddition of Schiff bases (5-10) to α-arylidene cyclohexanone (1-4)

The UV spectra[14] for (1-4) reflect a range of (354-368) nm, that it quite correlated with the published values of these compounds[15] (n→π* bands for α,β-unsaturated ketones).

The IR spectra[16], showed a range of stretching vibrations of (1699-1653) cm^{-1} related to carbonyl group and a range of (1610-1594) cm^{-1} which concerns the carbon-nitrogen double bond, the stretching vibration at (768) cm^{-1} is for carbon-chloride bond of compound number (2), finally the vibrations at (1024) cm^{-1} and (1027) cm^{-1} are related to the ethereal C-O-C stretching of compound (3) and (4) respectively(Table-1).

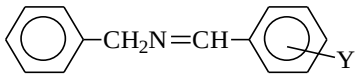
Table (1): Some physical properties and spectral data for α-arylidene cyclohexanones (1-4)



Comp. No.	Name	X	M.Wt. (g/mol)	Molecular formula	m.p. (°C)	Yield (%)	Colour	I.R (KBr) ν cm^{-1}			U.V (CH_3Cl) λ_{max} (nm)
								C=O	C=C	Others	
1	α-Benzylidene cyclohexanone	H	186	$C_{13}H_{14}O$	102-104	85	Yellow	1698	1606	-	354
2	α-(o-chlorobenzylidene) cyclohexanone	o-Cl	220	$C_{13}H_{13}OCl$	68-70	85	Yellow	1699	1610	768 C-Cl	356
3	α-(p-Methoxybenzylidene) cyclohexanone	p-OMe	216	$C_{14}H_{16}O_2$	145-147	90	Yellow	1653	1594	1024 C-O-C	368
4	α-(2,4-Dimethoxybenzylidene) cyclohexanone	2,4-DiMeO	234	$C_{15}H_{18}O_3$	150-152	90	Yellow	-	1601	1027 C-O-C	368

The other starting materials (N-arylidene benzyl amines 5-10) had been confirmed structurally according to physical and spectral data (Table-2). The UV and IR spectra were in a good agreement with the literature[14,15,17]. The UV spectra showed a range of (301-339) nm that belongs to such compounds (Schiff bases with C=N bonds).

Table (2): Some physical properties and spectral data for α-arylidene benzylamine (5-10) (Schiff bases)

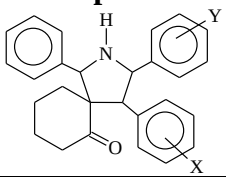


Comp. No.	Name	Y	m.p. or b.p. (°C)	Yield (%)	I.R (KBr) ν cm^{-1}			U.V (CH_3Cl) λ_{max} (nm)
					C=N	NO_2 (asy/sym)	Others	
5	N-(m-Nitrobenzylidene) benzylamine	m-NO_2	59-62	80	1670	1500 1318	-	301
6	N-(p-Nitrobenzylidene) benzylamine	p-NO_2	50-52	60	1675	1500 1340	-	338
7	N-(o-Chlorobenzylidene) benzylamine	o-Cl	139-140	85	1665	-	705 C-Cl	336
8	N-(p-Bromobenzylidene) benzylamine	p-Br	39-41	85	1668	-	700 C-Br	336
9	N-(p-Methoxybenzylidene) benzylamine	p-OMe	202-204	75	1665	-	1145 C-O-C	290
10	N-(2,4-Dimethoxybenzylidene) benzylamine	2,4-DiMeO	125-126 (liquid)	60	1645	-	1140 C-O-C	339

The afforded pyrrolidines (11-23) and their structures were supported using physical properties and valid spectral data (Table-3). The UV spectra[18] showed a rang of (324-368) nm which is related to such cycles, that is to say that the presence of three phenyl rings with some different substituents causes the absorption at such λ_{max} in addition to the carbonyl group and the pyrrolidine ring. The most effective transition is the $n \rightarrow \pi^*$ which is highly affected by the solvent.

The IR spectra manifested a range of (1679-1637) cm^{-1} attributed to the carbonyl stretching vibration[15], while a range of (3448-3443) cm^{-1} is related to NH stretching vibration[19], the other C-O-C (ethereal) vibration[20] seemed at the range of (1266-1248) cm^{-1} for asymmetric stretching and a range of (1034-1025) cm^{-1} for the symmetrical vibration, finally, the carbon-halogen stretching vibrations denoted at a range of (755-751) cm^{-1} for C-Cl and a range of (701-582) cm^{-1} for C-Br.

Table (3): Some physical properties and spectral data for the spiro pyrrolidines (11-23)



Comp. No.	Name	X	Y	m.p. (°C)	Yield (%)	Colour	I.R (KBr) ν cm^{-1}			U.V (CH_3Cl) λ_{max} (nm)
							C=O	N-H	Others	
11	Cyclohexanon-2-spiro-2`,4`-diphenyl-5`-(2,4-dimethoxy phenyl)-[3`]-pyrrolidine	H	2,4-DiMeO	148-150	40	Brown	1669	3444	1028 1262 C-O-C	368
12	Cyclohexanon-2-spiro-2`-phenyl-4`-(o-chlorophenyl)-5`-(2,4-dimethoxy phenyl)-[3`]-pyrrolidine	o-Cl	2,4-DiMeO	100-102	40	Brown	1678	3448	1034 1266 C-O-C 751 C-Cl	338
13	Cyclohexanon-2-spiro-2`,4`-diphenyl-5`-(p-nitrophenyl)-[3`]-pyrrolidine	H	p-NO_2	198-200	35	Red	1641	3445	1341 C-NO_2	360
14	Cyclohexanon-2-spiro-2`-phenyl-4`-(p-methoxy phenyl)-5`-(2,4-dimethoxy phenyl)-[3`]-pyrrolidine	p-OMe	2,4-DiMeO	220-222	40	Yellow	1676	3444	1026 1251 C-O-C	368
15	Cyclohexanon-2-spiro-2`-phenyl-4`-(p-methoxy phenyl)-5`-(m-nitrophenyl)-[3`]-pyrrolidine	p-OMe	m-NO_2	120-122	40	Dark brown	1679	3443	1027 1250 C-O-C 1347 C-NO_2	368
16	Cyclohexanon-2-spiro-2`-phenyl-4`-(2,5-dimethoxy phenyl)-5`-(2,4-dimethoxy phenyl)-[3`]-pyrrolidine	2,5-DiMeO	2,4-DiMeO	220-224	30	Yellow	1661	3448	1028 1264 C-O-C	368
17	Cyclohexanon-2-spiro-2`-phenyl-4`-(2,5-dimethoxy phenyl)-5`-(p-bromophenyl)-[3`]-pyrrolidine	2,5-DiMeO	p-Br	118-120	50	Pale yellow	1668	3443	1032 1251 C-O-C 701 C-Br	366
18	Cyclohexanon-2-spiro-2`-phenyl-4`-(p-methoxy phenyl)-5`-(b-bromophenyl)-[3`]-pyrrolidine	p-MeO	p-Br	108-110	70	yellow	1666	3443	1033 1263 C-O-C 582 C-Br	368
19	Cyclohexanon-2-spiro-2`-phenyl-4`,5`-di(p-methoxy phenyl)-[3`]-pyrrolidine	p-MeO	p-MeO	92-94	85	White	1640	3443	1034 1248 C-O-C	358
20	Cyclohexanon-2-spiro-2`-phenyl-4`-(2,5-dimethoxy phenyl)-5`-(p-methoxy phenyl)-[3`]-pyrrolidine	2,5-DiMeO	p-MeO	98-100	80	White	1641	3444	1033 1249 C-O-C	336
21	Cyclohexanon-2-spiro-2`-phenyl-4`-(o-chlorophenyl)-5`-(p-methoxy phenyl)-[3`]-pyrrolidine	o-Cl	p-MeO	90-92	80	Yellowish white	1640	3444	1033 1248 C-O-C 751 C-Cl	324
22	Cyclohexanon-2-spiro-2`-phenyl-4`-(o-chlorophenyl)-5`-(b-bromophenyl)-[3`]-pyrrolidine	o-Cl	p-Br	122-124	90	White	1637	3444	7003 C-Br 752 C-Cl	342
23	Cyclohexanon-2-spiro-2`-phenyl-4`-(p-methoxy phenyl)-5`-(o-chlorophenyl)-[3`]-pyrrolidine	p-MeO	o-Cl	152-154	30	Yellow	1657	3444	1025 1250 C-O-C 755 C-Cl	368

The 1,3-cycloaddition reaction of Schiff bases (5-10) to α-arylidene cyclohexanones (1-4) is passed through the following suggested mechanism[21] (Scheme 1).

It is obvious that the strong base (NaOH) may abstracts an acidic proton from the Schiff base to afford the anion An1 which in turn resonate to give the anion An2, both An1 and An2 can be represented by the equivalent hybrid An3.

The addition of one mole of N-arylidene cyclohexanone to An3 may lead to the production of the isomer (a) or the isomer (b). In the light of the values of the heat of formation (H.F) and the steric energy (S.E) (Table-4), it is concluded that (a) may be predominate.

Table (4): Heat of formation (H.F) and steric energy (S.E) of final products (11-23)

Comp. No.	H.F (Kcal/mole)	S.E (Kcal/mole)
11a	-26.72764	37.67815
11b	-26.05804	37.32981
12a	-27.03265	45.94420
12b	-27.00822	45.26365
13a	50.65342	37.53821
13b	49.53609	39.65823
14a	-64.74389	45.70163
14b	-65.21534	48.71519
15a	14.49786	37.95341
15b	11.49595	38.75468
16a	-97.77710	55.75074
16b	-97.79879	57.94244
17a	-20.22194	36.12594
17b	-19.68219	36.65040
18a	14.84119	29.17400
18b	14.06340	29.33428
19a	-22.79252	37.39347
19b	-27.89615	38.50438
20a	-62.09895	46.16057
20b	-62.31352	46.74833
21a	9.35865	33.20892
21b	9.73087	34.22443
22a	50.56105	25.24840
22b	50.00597	25.07982
23a	4.37232	30.00714
23b	4.49245	30.67931

Prior to this work[22], it was found that fused pyrrolidines had been prepared by the 1,3-anionic cycloaddition of a series of Schiff bases to 1,4-benzoquinone and the reaction was controlled by the type of the substituent on the Schiff base and it was found that electron-donating

groups need less energy to afford the final product compared with the electron-withdrawing groups. In the present work it is found that both α-arylidene cyclohexanones (1-4) and Schiff bases (5-10) control the rate of the reaction and H.F (-97) Kcal/mole for dimethoxy derivatives is the lowest value compared with H.F (50.561 and 50.563) Kcal/mole for the nitro derivative and the chlorobromo derivative respectively, which means that electron-donation enhances the rate and electron-withdrawal inhibits the rate of the reaction.

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