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Note

A novel access to dispirocyclohexanoneindano pyrrolidines

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Synthesis of a series of novel dispirocyclohexanoneindano pyrrolidines has been described. The cycloaddition reaction of azomethine ylide generated from ninhydrin and sarcosine with bisarylidenecyclohexanones was found to be highly region-selective.

Keywords: Azomethine ylide, cycloaddition, spiropyrrolidine, dipolarophile, regioselective

The construction of five membered heterocycles has effectively been achieved by 1,3-dipolar cycloaddition methodology[1]. Stereocontrolled synthesis of natural products has been achieved efficiently by this strategy since generation of 1,3-dipoles is often associated with high regio- and stereoselectivities[2-5]. Compounds with pyrrolidine core are very useful in treating many diseases like rheumatoid arthritis, asthma and allergies[6] and also possess anti-influenzea virus[7] and anticonvulsant activities[8]. Of the many 1,3 dipoles present, the azomethine ylide represents one of the most reactive and versatile classes of 1,3 dipoles and is readily trapped by a range of dipolarophiles forming substituted pyrrolidines[9]. The spiro ring system is frequently encountered in many pharmacologically important alkaloids. Synthetic spiropyrrolidine derivatives have activity against the aldose reductase enzyme, which controls influenza[10]. Molecules containing spiroindane have been shown to be pharmacologically important[11].

It has been well established that cycloalkanone derivatives possess substantial antifertility activity in rodents[12] and have important pharmacological properties[13]. In this article, in continuation of our efforts in the synthesis pyrrolidine based heterocycles[14] and encouraged by the recent papers[15] we present an efficient synthesis of dispirocyclohexanoneindano pyrrolidines.

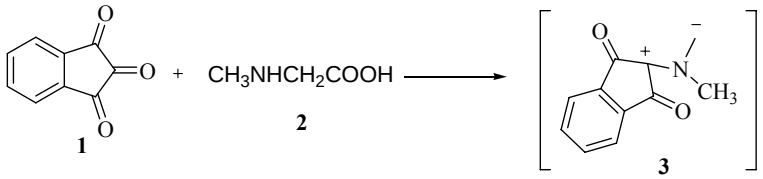
Results and Discussion

It is aimed to synthesize complex spiroheterocycles having cycloalkanone spiroindane and pyrrolidine moieties through [3+2] azomethine ylide cycloaddition methodology. Azomethine ylides are prepared by several methods from easily available starting materials. Among the methods, the decarboxylation route offers a general method in which an aldehyde or a ketone is reacted with α-amino acids[16]. For the synthetic studies we have generated a non-stabilized *anti*- dipole **3** *in situ* by the decarboxylative condensation reaction of a 1,2,3-triketone, ninhydrin **1** with sarcosine **2** (**Scheme I**).

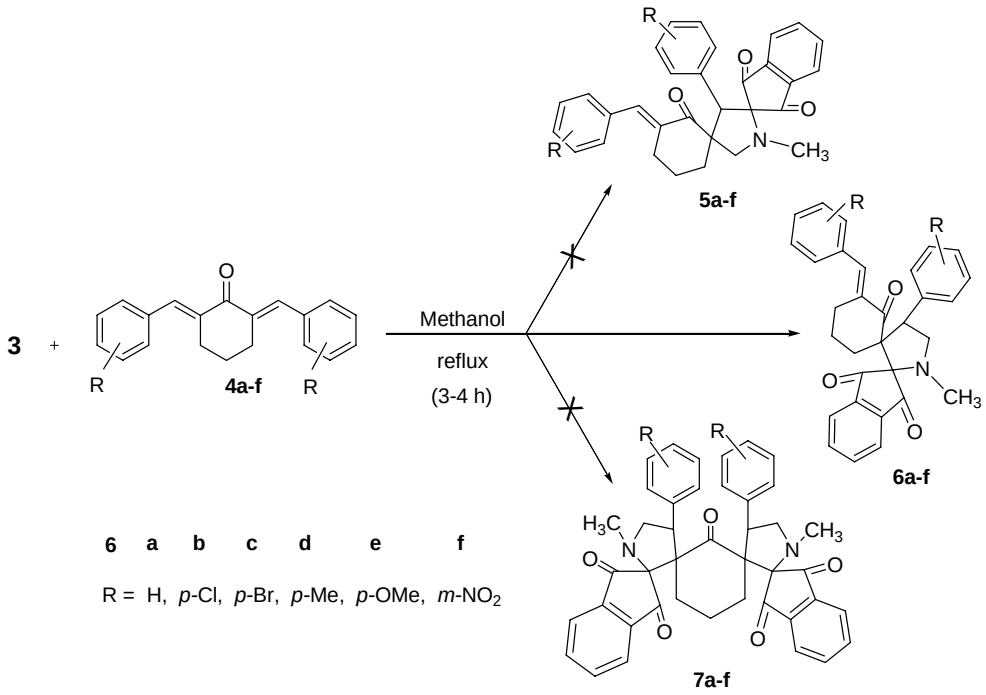
In an one pot reaction, the reaction of 2,6-bisarylidene cyclohexanones **4a-f** with the azomethine ylide **3** generated *in situ*, by the reaction of two equivalents of each of ninhydrin and sarcosine in refluxing aqueous methanol yielded a series of cycloadducts **6a-f** in good yields (**Scheme II, Table I**) as single product as evidence by TLC analysis. The formation of bis cycloadducts, **7a-f** was primarily ruled out from the mass spectrum while the other regioisomers **5a-f** were ruled out on the basis of spectral data and single crystal X-ray diffraction analysis.

The structure and the regiochemistry of all cycloadducts, 1-*N*-methyl-spiro[2.2']-indane,1′›3′-dione-spiro[3.2″]-6″-arylidenecyclohexanone-4-aryl pyrrolidines **6a-f** were unambiguously established by their spectroscopic and elemental analyses data. For example in the IR spectrum of compound **6c** the carbonyl groups of indane-1,3-dione exhibited two absorption bands at 1740 and 1704 cm^{-1}. The band at 1675 cm^{-1} indicated the formation of monocycloaddition product.

The ^1H NMR spectrum of compound **6c** showed sharp singlet at δ 2.36 due to *N*-methyl protons and a cluster of multiplets for six cyclohexyl protons. The two *N*-mehylene and the benzylic proton have appeared as triplets at δ 3.54, 3.78 and 4.89 respectively with the coupling constant of 9 Hz. Had the other regioisomeric cycloadduct **5c** formed, the benzylic proton would have been observed as a singlet. A singlet at δ 6.50 confirms the presence of olefinic proton on the benzylidene moiety. The twelve



Scheme I



Scheme II

Table I — Cycloaddition of ylide **3** generated from ninhydrin **1** and sarcosine **2** towards arylidene cyclohexanones **4a-f**

Entry	Product	R	Yield (%)	m.p. (°C)	Reaction Time (hr)
1	**6a**	H	60	137-39′	3.5
2	**6b**	*p*-Cl	60	153-55	3.5
3	**6c**	*p*-Br	70	163-65	3
4	**6d**	*p*-Me	62	152-54	4
5	**6e**	*p*-OMe	62	150-52	4
6	**6f**	*m*-NO_2	64	167-69	3

aromatic protons appeared between δ 6.88 and 7.99 as a multiplet. In the ^{13}C NMR spectrum of cycloadduct **6c**, the spiroquaternary carbons at C2 and C3 showed peaks at δ 82.93 and 66.93 respectively. The remaining carbons resonated at the appropriate δ values. The mass spectrum of **6c** exhibited the molecular ion peak at *m/z* 619.02 (M^+). The region-chemistry of the cycloadduct **6c** was further supported by its X-ray crystal structure (**Figure 1**)[17]. In the molecular structure of **6c**, the pyrrolidine ring adopts a twisted conformation while the five-membered ring in the indanedione group adopts a slight envelope conformation.

Conclusion

It is concluded that a series of dispiroindano-cyclohexanone pyrrolidines have been synthesized in good yields by azomethine ylide cycloaddition reaction. In a one-pot reaction the azomethine ylide generated from ninhydrin and sarcosine has been regioselectively trapped by various substituted bis-benzylidene cyclohexanones.

Experimental Section

IR spectra were recorded on a SHIMADZU IR-8300 series FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL 400 MHz

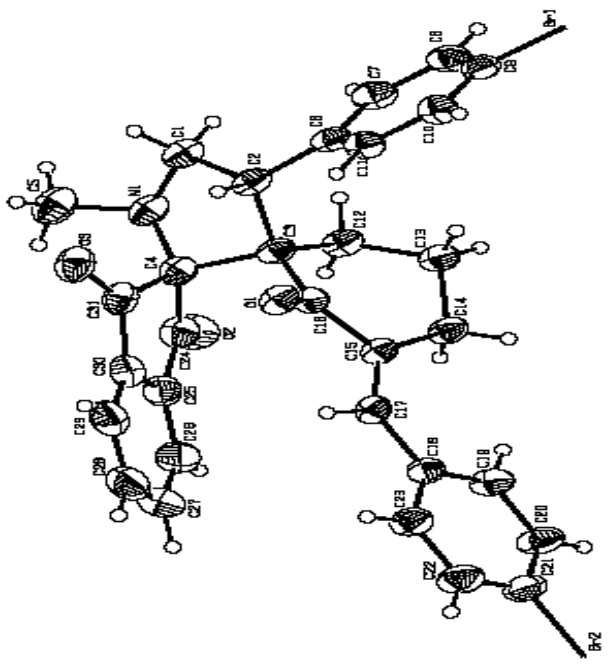


Figure 1 — Ortep diagram of **6c**

and Bruker 300 MHz instruments in $CDCl_3$ solvent with TMS as a standard. Mass spectra were recorded by JEOL-DX303 HF mass spectrometer. Elemental analyses were carried out by Perkin-Elmer CHNS 2400 instrument. Single crystal X-Ray diffraction analysis was performed using Bruker SMART APEX diffractometer. Column chromatography was performed on silica gel (ACME, 100-200 mesh). Routine monitoring of the reaction was made using TLC developed on glass plates coated with silica gel-G (ACME) of 25 mm thickness.

General procedure for the synthesis of cycloadducts 5a-h

A mixture of ninhydrin **1** (0.178 g, 1 mmole), sarcosine **2** (0.089 g, 1 mmole) and 2,6-bis-arylidenecyclohexanones **4a-f** (1 mmole) in methanol (20 mL) was refluxed until the disappearance of starting materials as shown by the TLC analysis (R_f = 0.2-0.3). The reaction-mixture was then concentrated *in vacuo* and extracted with water (50 mL) and dichloromethane (50 mL). The organic layer was washed with brine solution, dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography with hexane-ethyl acetate (9:1) [v/v]mixture to get compounds **6a-f** in good yields.

1-*N*-methyl-spiro[2.2′]-indane-1′,3′-dione-spiro-[3.2″]-6″-benzylidenecyclohexanone-4-phenylpyrrolidine, 5a

Yellow coloured solid, 60% (0.276 g); m.p.137-39°C; IR (KBr): 1736, 1705 and 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.90-2.64 (m, 6H, cyclohexyl), 2.39 (s, 3H, *N*-Me), 3.55 (t, 1H, *J* = 9 Hz), 3.85 (t, 1H, *J* = 9 Hz), 4.93 (t, 1H, benzyl, *J* = 9 Hz), 6.62 (s, 1H), 7.02-8.02 (m, 14H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.96, 26.24, 28.20, 28.41, 35.80, 51.68, 55.37, 67.32, 83.09, 122.63, 122.81, 127.26, 128.34, 128.53, 128.70, 129.37, 130.31, 131.10, 135.08, 136.43, 136.52, 136.93, 137.66, 141.31, 141.72, 199.62, 200.13, 202.06; EI-MS (70 eV): *m/z* 461.1 (M^+). Anal. Calcd for $C_{31}H_{27}NO_3$: C, 80.67; H, 5.90; N, 3.03. Found: C, 80.58; H, 6.01; N, 3.14%.

1-*N*-methyl-spiro[2.2′]-indane,1′,3′-dione-spiro[3.2″]-6″-(*p*-chloro) benzylidenecyclohexanone-4-(*p*-chloro)phenylpyrrolidine, 5b

Yellow coloured solid, 60% (0. 318 g); m.p. 153-55°C; IR (KBr): 1740, 1705 and 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.95-2.70 (m, 6H, cyclohexyl), 2.39 (s, 3H, *N*-Me), 3.50 (t, 1H, *J* = 9 Hz), 3.80 (t, 1H, *J* = 9 Hz), 4.92 (t, 1H, benzyl, *J* = 9 Hz), 6.58 (s, 1H), 7.00-8.00 (m, 12H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.96, 26.39, 28.29, 35.80, 50.59, 55.48, 66.95, 82.95, 122.64, 122.90, 128.43 128.61, 130.31, 130.67, 133.15, 133.39, 134.86, 135.23, 135.39, 135.56, 136.61, 137.90, 141.36, 141.48, 199.43, 200.15, 201.68; EI-MS (70 eV): *m/z* 531.12 (M^+). Anal. Calcd for $C_{31}H_{25}NO_3Cl_2$: C, 70.19; H, 4.75; N, 2.64. Found: C, 70.11; H, 4.65; N, 2.84%.

1-*N*-methyl-spiro[2.2′]-indane,1′,3′-dione-spiro[3.2″]-6″-(*p*-bromo) benzylidenecyclohexanone-4-(*p*-bromo)phenylpyrrolidine, 5c

Yellow coloured solid, 70% (0.433 g); m.p. 163-65°C; IR (KBr): 1740, 1704 and 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.85-2.62 (m, 6H, cyclohexyl), 2.36 (s, 3H, *N*-Me), 3.54 (t, 1H, *J* = 9 Hz), 3.78 (t, 1H, *J* = 9 Hz), 4.89 (t, 1H, benzyl, *J* = 9 Hz), 6.50 (s, 1H), 6.88-7.99 (m, 12H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.98, 26.46, 28.30, 35.81, 50.63, 55.48, 66.93, 82.93, 121.31, 122.65, 122.92, 123.22, 131.08, 131.41, 131.52, 131.60, 131.79, 133.86, 135.29, 135.33, 136.16, 136.62, 138.05, 141.41, 141.51, 199.40, 199.98, 201.62; EI-MS (70 eV): *m/z* 619.02 (M^+). Anal. Calcd for

$C_1H_{25}NO_3Br_2$: C, 60.12; H, 4.07; N, 2.26. Found: C, 60.23; H, 3.96; N, 2.37%.

1-*N*-methyl-spiro[2.2′]-indane,1′,3′-dione-spiro[3.2″]-6″-(*p*-methyl) benzylidenecyclohexanone-4-(*p*-methyl)phenylpyrrolidine, 5d

Yellow coloured solid, 62% (0.303 g); m.p.152-54°C; IR (KBr): 1740, 1705 and 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88-2.60 (m, 6H, cyclohexyl), 1.25 (s, 6H, Ar-Me), 2.35 (s, 3H, *N*-Me), 3.53 (t, 1H, *J* = 9 Hz), 3.85 (t, 1H, *J* = 9 Hz), 4.89 (t, 1H, benzyl, *J* = 9 Hz), 6.56 (s, 1H), 6.93-8.02 (m, 12H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.91, 21.26, 21.32, 22.90, 26.07, 28.25, 28.42, 35.77, 51.30, 55.33, 67.23, 122.55, 122.72, 128.85, 128.92, 129.02, 129.10, 130.24, 130.38, 132.24, 133.06, 133.69, 134.94, 135.35, 136.43, 136.78, 139.66, 141.66, 156.06, 160.00,198.00, 201.00, 202.00; EI-MS (70 eV): *m/z* 489.2 (M^+). Anal. Calcd for $C_{33}H_{31}NO_3$: C, 80.95; H, 6.38; N, 2.86. Found: C, 80.87; H, 6.65; N, 2.80%.

1-*N*-methyl-spiro[2.2′]-indane,1′,3′-dione-spiro[3.2″]-6″-(*p*-methoxy)benzylidenecyclohexanone-4-(*p*-methoxy)phenylpyrrolidine, 5e

Yellow coloured solid, 62% (0.323 g); m.p. 150-52°C; IR (KBr): 1745, 1704 and 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.90-2.70 (m, 6H, cyclohexyl), 2.25 (s, 6H, *O*-Me), 2.35 (s, 3H, *N*-Me), 3.50 (t, 1H, *J* = 9 Hz), 3.80 (t, 1H, *J* = 9 Hz), 4.85 (t, 1H, benzyl, *J* = 9 Hz), 6.61 (s, 1H), 6.92-8.20 (m, 12H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.96, 25.97, 28.38, 29.66, 35.82, 51.15, 55.13, 55.49, 67.33, 83.38, 113.51, 113.76, 113.86, 122.58, 122.78, 127.80, 128.79, 130.26, 132.19, 134.92, 135.53, 136.37, 136.43, 141.30, 141.78, 158.66, 160.05, 199.00, 200.10, 201.95; EI-MS (70 eV): *m/z* 521.2 (M^+). Anal. Calcd for $C_{33}H_{31}NO_5$: C, 75.99; H, 5.99; N, 2.69. Found: C, 75.78; H, 6.13; N, 2.79%.

1-*N*-methyl-spiro[2.2′]-indane,1′,3′-dione-spiro[3.2″]-6″-(*m*-nitro) benzylidenecyclohexanone-4-(*m*-nitro)-phenylpyrrolidine, 5f

Yellow coloured solid, 64% (0.352 g); m.p. 167-69°C; IR (KBr): 1740, 1705 and 1674 1550, 1347 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87-2.70 (m, 6H, cyclohexyl), 2.25 (s, 3H, *N*-Me), 3.51 (t, 1H, *J* = 9 Hz), 3.82 (t, 1H, *J* = 9 Hz), 5.00 (t, 1H, benzyl, *J* = 9 Hz), 6.65 (s, 1H), 7.22-8.19 (m, 12H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.87, 22.51, 26.96, 28.18, 29.32, 29.66, 35.76, 50.22, 55.81, 66.65, 82.10, 122.45, 122.78, 123.05, 123.28, 124.19, 124.25, 124.40, 129.31, 129.4, 134.00, 134.62, 135.49, 135.70, 135.82, 136.12, 136.41, 136.90,137.25, 137.96, 139.60, 139.75, 141.24, 141.39, 148.22, 199.29, 200.09, 202.02; EI-MS (70 eV): *m/z* 551.1 (M^+). Anal. Calcd for $C_{31}H_{25}N_3O_7$: C, 67.51; H, 4.57; N, 7.62. Found: C, 67.69; H, 4.42; N, 7.71%.

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