Heteroatom Chemistry
Volume 13, Number 4, 2002

Three-Component 1,3-Dipolar Cycloaddition Reactions in Synthesis of Spiro[pyrrolidine-2,3′-oxindoline] Derivatives

Abdel-Aziz S. El-Ahl

Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt

Received 1 December 2000; revised 6 September 2001

ABSTRACT: *Regio- and stereospecific syntheses of several spiro[pyrrolidine2,3′-oxindole] derivatives by cycloaddition trapping of azomethine ylides generated in situ, via decarboxylative condensation of isatin with α-amino acids or by reaction of secondary amines with isatin, are reported. 2,6-Dibenzylidenecyclohexanone, 2-arylidene-1-tetralone, and arylidenemalononitrile derivatives have been efficiently used as trapping dipolarophiles. The regio- and stereochemistry of the additions are controlled by both frontier orbital and steric interactions.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:324–329, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10038

INTRODUCTION

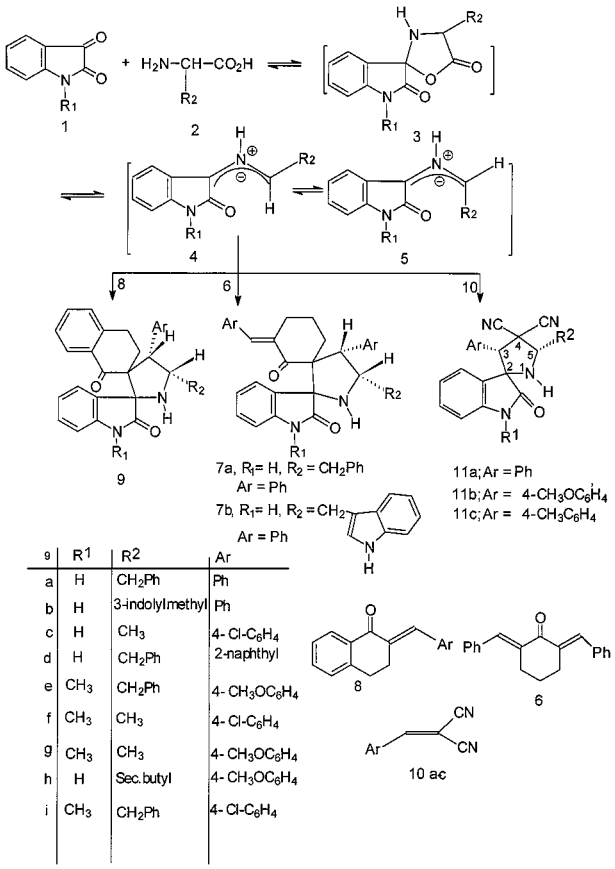
Functionalized pyrrolidine, pyrrolizidine, and oxindole alkaloids constitute classes of compounds with significant biological activity, and the spiro[pyrrolidine/oxindole] ring system is a structural feature found in a wide variety of oxindole alkaloids [1,2]. Besides, several oxindole derivatives are known to possess antibacterial, antiprotozoal, and anti-inflammatory activities [3]. Also, spiro oxindoles have been reported to behave as aldose reductase [2], poliovirus, and rhinovirus 3C-proteinase inhibitors [4]. Sequential transformations enable the facile syntheses of complex target molecules from simple building blocks in a single preparative step [5]. Their value is amplified if they also create multiple stereogenic centers [6]. Moreover, the utilization of a domino sequence often leads to the reduction of the amount of solvent, eluant, and undesired by-products, thereby contributing to the protection of the environment. The synthesis of such ring systems via multicomponent reactions, involving trapping of azomethine ylides by different dipolarophiles, have attracted the attention of several research groups, since three or more building blocks can be combined in one step to yield complex organic compounds [7]. In the last decade, several methods have been developed for the generation of azomethine ylides involving oxazolines [8], desilylation of N-(silylmethyl)imines [9] and related precursors [10], 1,2-prototropy in activated imines [11] and related metal-ion-catalyzed processes [12], and dehydrogenation of tertiary amines [13]. Also, the reactions of carbonyl compounds with primary and secondary, acyclic and cyclic, α-amino acids, with concomitant decarboxylation, have been reported to give azomethine ylides via an intermediate oxazolidin-5-one [14–16]. Careful studies of the stereochemistry of the azomethine ylides generated in this way have demonstrated that these processes occur stereospecifically, or with high stereoselectivity. The stereospecificity of azomethine ylide formation from carbonyl compounds and α-amino acids is a strong evidence for the intervention of an oxazolidin-5-one that generates the azomethine ylide via a stereospecific 1,3-dipolar cycloreversion. The stereochemical outcome of the cycloreversion step generating the azomethine ylide is dependent on the structure of both the amino acid and the

Correspondence to: Abdel-Aziz S. El-Ahl; e-mail: sinfac@mum.mans.eun.eg.
Contract grant sponsor: Mansoura University.

carbonyl compound. The trapping of these 1,3-dipoles with dipolarophiles provides a facile entry into a wide range of heterocycles, including bridged-, fused-, and spiro-ring systems [17–20].

RESULTS AND DISCUSSION

Grigg et al. [21] has studied the formation of azomethine ylides by the condensation of 1,2-dicarbonyl compounds with amino acids or amines and their cycloaddition reactions with simple acrylate esters or maleimides. However, these studies involved only the use of simple or highly reactive dipolarophiles, such as maleimides or simple acrylate esters. In continuation of our recent studies on the syntheses of spiro oxindole derivatives via 1,3-dipolar cycloaddition reactions [22], we undertook the investigation of the reactions of azomethine ylides resulting by the reaction of isatin and amino acids with different planar electron deficient enones or unsaturated nitriles. Thus, condensation of isatin **1** with amino acids **2** could give rise to configurationally distinct azomethine ylides **4** or **5** via cycloreversions of oxazoline derivatives **3**. The transition state leading to the azomethine ylide **4** (anti-dipole) is favored over that leading to **5** (syn-dipole) because of a developing steric hindrance between the carbonyl moiety and the R_2 group (Scheme 1). Accordingly, heating isatin with phenylalanine and 2,6-dibenzylidenecyclohexanone (**6**) in aqueous ethanol afforded the cycloadduct **7a** in excellent yield as the only isolable product. Assuming that the kinetically favored dipole has the configuration **4**, we believe that **7a** arises via an endo-transition state. The formation of **7a** indicates that the reduced steric hindrance at the singly substituted azomethine ylide terminus outweighs the more favorable orbital interaction between the dipole (HOMO) of **4a** and dipolarophile (LUMO) of **6a** usually observed in these reactions [23]. The regiochemistry of **7a** was apparent from the multiplicity of the 4-H signal in its ^{1}H NMR spectrum. Thus, in **7a** this proton gives rise to a doublet ($J = 9.9$ Hz). The relative stereochemistry of 4-H and 5-H was based on the coupling constant of 4-H and 5-H ($J_{4,5} = 9.9$ Hz, indicating cis coupling); also, if 5-H (ddd, $\delta = 4.6$) is cis to the 4-aryl substituent, it should display a higher field chemical shift because of shielding by the cis-aryl group [24]. The cycloadduct **7b** was also produced in high yield by use of tryptophane as an amino acid; the cycloaddition takes place in a regio- and stereocontrolled manner. Presumably, the anti-dipole **4b** (**4**, $R_2 = 3$-indolylmethyl) is involved in the transition state, where endo-cycloaddition of the enone **6** to the W-periphery of the ylide **4b** predominates.



9	R^1	R^2	Ar
a	H	CH_2Ph	Ph
b	H	3-indolylmethyl	Ph
c	H	CH_3	4-Cl-C_6H_4
d	H	CH_2Ph	2-naphthyl
e	CH_3	CH_2Ph	4-$CH_3OC_6H_4$
f	CH_3	CH_3	4-Cl-C_6H_4
g	CH_3	CH_3	4-$CH_3OC_6H_4$
h	H	Sec.butyl	4-$CH_3OC_6H_4$
i	CH_3	CH_2Ph	4-Cl-C_6H_4

SCHEME 1

The reactivities of some other unsaturated carbonyl systems analogous to 2,6-dibenzylidenecyclohexanone towards azomethine ylides of type **4** or **5** have been examined. It has been found that 2-arylidene-1-tetralone derivatives (**8**) react with a mixture of isatin and different primary amino acids in aqueous ethanol to give the novel cycloadducts **9a–i**, hitherto inaccessible by classical synthetic methods, in good to high yield (Scheme 1). These cycloadducts are formed via regio- and stereospecific endo-cycloadditions of **8** to azomethine ylides of type **4**. The designation of regio- and stereospecificity of the reaction is based on the multiplicity and coupling constant of 4-H in the NMR spectra of the cycloadducts **9a–i** (Table 1). To determine the scope and synthetic potential of these multicomponent reactions, which tolerate wide variations in the dipolarophile component, we have utilized trapping of azoethine ylides of type **4** or **5** with arylidenemalononitrile derivatives (**10**). When a mixture of isatin, phenylalanine, and the benzylidenemalononitrile derivative (**10a**) was heated (reflux temperature) in aqueous ethanol for 5 h, a single cycloadduct (**11a**) was obtained in 70% yield. The regiospecific formation of **11a** was apparent from the multiplicity

TABLE 1 IR and ^{1}H NMR Data of Compounds **7a,b, 9a–i, 11a–c**, and **17**

Compound No.	*IR (cm^{-1}), Selected Peaks*	*^{1}H NMR (δ)*
7a	3304, 3171, 3151, 3080, 3062, 3027, 2941, 2875, 1707, 1662, 1615, 1588, 1471, 1450, 1259, 1198	2.0 (m, 2H), 2.2 (m, 4H), 2.75 (dd, 1H, $J = 14$, 3 Hz), 2.95 (dd, 1H, $J = 14$, 8.9 Hz), 4.05 (d, 1H, $J = 9$ Hz), 4.6 (ddd, 1H, $J = 9$, 5, 3 Hz) 6.75 (q, 2H, $J = 8$ Hz), 7.1 (q, 2H, $J = 8$ Hz), 7.2 (m, 14H, ArH, NH), 7.45 (m, 3H), 8.5 (sb, 1H, NH)
7b	3370, 3229, 3103, 3051, 3010, 2937, 2918, 2876, 1728, 1668, 1611, 1486, 1466, 1449, 1419, 1351, 1326, 1251, 1175, 1153	2.3 (m, 4H), 2.85 (m, 4H), 4.25 (d, 1H, $J = 9.8$ Hz), 4.6 (ddd, 1H, $J = 9.8$, 6, 3 Hz), 6.65 (d, 1H, $J = 8$ Hz), 7.0 (m, 4H), 7.1 (m, 4H), 7.4 (m, 10H), 10.5 (s, 1H, NH, exchangeable with D_2O), 10.85 (s, 1H)
9a	3238, 3220, 3059, 3026, 2923, 2868, 1713, 1668, 1618, 1598, 1474, 1452	1.8 (sb, 1H, NH), 2.35 (m, 3H), 2.6 (m, 1H), 2.8 (dd, 1H, $J = 14$, 8 Hz), 3.0 (dd, 1H, $J = 14$, 4 Hz), 4.4 (d, 1H, $J = 9.8$ Hz), 4.52 (ddd, 1H, $J = 9.7$, 8, 3 Hz), 6.55 (m, 2H), 6.8 (m, 3H), 7.15 (m, 10H), 7.45 (m, 2H), 7.8 (d, 1H, $J = 7$ Hz), 8.25 (s, 1H, NH)
9b	3261, 3234, 3061, 3027, 2950, 2924, 2870, 1715, 1668, 1619, 1598, 1489, 1474, 1452	1.9 (sb, 1h, NH), 2.4 (m, 3H), 2.6 (m, 1H), 2.9 (dd, 1H, $J = 14$, 5 Hz), 2.97 (dd, 1H, $J = 14$, 2.7 Hz), 4.4 (d, 1H, $J = 10.8$ Hz), 4.65 (ddd, 1H, $J = 10$, 5, 2.7 Hz), 6.5 (d, 1H, $J =$ 7.50 Hz), 6.6 (t, 1H, $J = 7.5$ Hz), 6.85 (m, 2H), 7.15 (m, 10H), 7.45 (m, 2H), 7.8 (s, 1H, NH), 7.9 (d, 1H, $J = 8$ Hz)
9c	3262, 3065, 3028, 2959, 2926, 2869, 1715, 1663, 1620, 1598, 1488, 1475, 1454, 1329, 1285	1.29 (d, 3H, $J = 6$ Hz), 1.95 (sb, 1H, NH), 2.52 (m, 4H), 4.15 (d, 1H, $J = 9.7$ Hz), 4.35 (m, 1H), 6.6 (t, 2H), 6.8 (d, 1H), 6.95 (q, 2H), 7.15 (m, 4H), 7.40 (m, 2H), 7.9 (d, 1H, $J = 8$ Hz), 8.3 (s, 1H, NH)
9d	3265, 3246, 3164, 3112, 3057, 2951, 2923, 2854, 1720, 1665, 1620, 1598, 1452, 1325	1.7 (m, 2H), 1.85 (sb, 1H, NH), 2.0 (m, 2H), 2.6 (dd, 1H, $J = 14$, 6 Hz), 2.75 (dd, 1H, $J = 14$, 3 Hz), 4.2 (d, 1H, $J = 9$ Hz), 4.5 (ddd, 1H, $J = 11$, 6, 2.9 Hz), 6.2 (m, 2H), 6.4 (m, 2H), 6.8 (m, 12H), 7.45 (m, 4H), 8.2 (s, 1H, NH)
9e	3265, 3057, 3027, 2923, 2833, 1703, 1673, 1604, 1510, 1495, 1468, 1455	2.05 (bs, 1H, NH), 2.34 (m, 4H, CH_2—CH_2), 2.87 (dd, 1H, $J_1 = 14$ Hz, $J_2 = 6$ Hz), 3.12 (dd,1H, $J = 14$, 4 Hz), 3.15 (s, 3H, CH_3), 3.79 (s, 3H, OMe), 4.35 (d, 1H, $J = 10$ Hz), 4.75 (ddd, 1H, $J_1 = 3$ Hz, $J_2 = 10$ Hz, $J_3 = 6$ Hz), 6.49–7.26 (m, 14H), 7.47 (d, 2H, $J = 8$ Hz), 7.82 (d, 1H, $J = 8$ Hz)
9f	3272, 3055, 2957, 2920, 2866, 1709, 1655, 1607, 1492,1470, 1370, 1347, 1309, 1277	1.3 (d, 3H, $J = 7$ Hz), 2.1 (bs, 1H, NH), 2.33 (m, 4H, CH_2—CH_2), 3.19 (s, 3H, —NCH_3), 4.17 (d, 1H, $J = 10$ Hz), 4.43 (m, 1H), 6.58–6.83 (m, 3H, ArH), 6.93–7.23 (m, 4H, ArH), 7.26–7.3 (d, 2H, $J = 8$ Hz), 7.46–7.5 (d, 2H, $J = 8$ Hz), 7.88–7.92 (dd, 1h, $J_1 = 2$ Hz, $J_2 = 10$ Hz)
9g	3270, 3055, 2963, 2924, 2869, 2838, 1707, 1656, 1607, 1512, 1495, 1470, 1456, 1370, 1350, 1308	1.3 (d, 3H, CH_3, $J = 8$ Hz), 2.1 (bs, 1H, NH), 2.35 (m, 4H, CH_2—CH_2), 3.22 (s, 3H, N—CH_3), 3.79 (s, 3H, —OCH_3), 4.15 (d, 1H, $J = 10$ Hz), 4.43 (m, 1H), 6.57–6.79 (m, 2H), 6.85 (d, 2H, $J = 8$ Hz), 6.96–7.27 (m, 5H), 7.45 (d, 2H, $J = 8$ Hz), 7.88 (d, 1H, $J = 8$ Hz)
9h	3282, 3255, 3065, 3028, 2956, 2931, 2871, 2839, 1715, 1663, 1617, 1603, 1512, 1471, 1328, 1302	0.85 (m, 5H), 1.75 (m, 1H), 2.4 (m, 4H), 3.75 (s, 3H, OCH_3), 4.1 (d, 1H, $J = 8.5$ Hz), 4.4 (m, 1H), 6.6 (m, 2H), 6.75 (m, 3H), 6.9 (m, 2H), 7.15 (m, 2H), 7.4 (m, 2H), 7.9 (d, 1H), 8.0 (s, 1H, NH)

(Continued)

TABLE 1 Continued

Compound No.	*IR (cm^{-1}), Selected Peaks*	*^1H NMR (δ)*
9i	3271, 3205, 2923, 1702, 1675, 1606, 1487, 1470, 1348, 1287, 1229	1.85 (sb, 1H, NH), 2.35 (m, 4H), 2.85 (dd, 1H, $J = 13.5, 8$ Hz), 2.95 (dd, 1H, 13.2, 3 Hz), 3.1 (s, 3H), 4.35 (d, 1H, $J = 9.9$ Hz), 4.6 (ddd, $J = 9.5, 6, 4$ Hz), 6.5 (d, 1H, $J = 7.2$ Hz), 6.65 (t, 1H, $J = 8$ Hz), 6.75 (d, 1H, $J = 8$ Hz), 6.95 (t, 1H, $J = 8$ Hz), 7.15 (m, 9H), 7.45 (m, 2H), 7.85 (d, 1H, $J = 8$ Hz)
11a	3321, 3274, 3086, 3060, 2952, 2924, 2857, 2218, 1719, 1620, 1471, 1332, 1191	1.85 (sb, 1H, NH), 2.75 (dd, 1H, $J = 9.5$, 19 Hz), 3.16 (dd, 1H, $J = 6$, 19 Hz), 3.82 (dd, 1H, $J = 6, 9.6$ Hz), 6.32 (s, 1H), 6.74 (m, 2H), 7.11 (m, 3H), 7.3 (m, 6H), 7.44 (sb, 1H, NH), 7.74 (m, 2H), 8.21 (d, 1H)
11b	3341, 3225, 3083, 3061, 3030, 2956, 2936, 2220, 1719, 1615, 1513, 1469, 1398, 1329, 1301, 1281	1.85 (sb, 1H, NH), 2.15 (dd, 1H, J=17.5, 12.5 Hz), 2.55 (dd, 1H, J=17.5, 7.5), 3.15 (dd, 1H, J=11.5, 7 Hz), 3.55 (s, 3H, OCH_3), 6.05 (s, 1H), 6.45 (d, 1H, J=8 Hz), 6.65 (d, 2H, J=8 Hz), 6.78 (d, 2H, $J = 8$ Hz), 6.9 (q, 3H, $J = 8$ Hz), 7.1 (m, 3H), 7.15 (sb, 1H, NH), 7.47 (d, 2H, $J = 8$ Hz), 7.75 (d, 1H, $J = 8$ Hz)
11c	3337, 3273, 3061, 3030, 2925, 2860, 2220, 1714, 1617, 1470, 1394, 1331, 1303, 1200, 1107	1.78 (sb, 1H, NH), 2.39 (s, 3H, CH_3), 2.72 (dd, 1H, $J = 10, 17$ Hz), 3.14 (dd, 1H, $J = 6$, 17 Hz), 3.77 (dd, 1H, $J = 6, 10$ Hz), 6.25 (s, 1H), 6.7 (m, 3H), 7.09 (d, 2H), 7.24 (m, 5H), 7.46 (sb, 1H, NH), 7.53 (d, 2H) 7.86 (d, 1H, $J = 7.2$ Hz)
17	3157, 3090, 2941, 2889, 2845, 2220, 1685, 1615, 1558, 1467, 1439, 1410, 1365, 1331, 1250, 1207, 1156, 1129,1110, 970	1.77 (m, 6H, $3 \times CH_2$), 3.66 (s, 1H), 3.69 (m, 4H, $2 \times CH_2$), 6.88 (d, 1H, $J = 8$ Hz, ArH), 7.02 (t, 1H, ArH), 7.14 (t, 1H, ArH), 7.88 (d, 1H, ArH), 8.92 (sb, 1H, NH)

of 3-H, which displayed a singlet in its ^{1}H NMR spectrum at δ 4.65. The presence of two strongly conjugative electronegative cyano groups reduces the energy gap between the dipole HOMO and the dipolarophile LUMO; therefore, **11a** is thought to be formed via the more favorable frontier orbital interaction between the HOMO of the kinetically favored dipole **4** and dipolarophile LUMO. The malononitrile derivatives **10b,c** afforded the cycloadducts **11b,c** in comparable yields. The relative stereochemistry was based on the chemical shift of the methoxy group in **11b**, which displayed a high field chemical shift ($\delta = 3.55$) because of the shielding effect of the benzene ring of the *cis*-benzyl group. The shielding effect of a *cis*-vicinal or a *cis*-β-phenyl substituent on the protons resonance or methyl group resonance in methoxycarbonyl groups attached to pyrrolidine rings is well established [25].

Grigg and co-workers [26] described a 1,5-H shift route to azomethine ylides via the reaction of carbonyl compounds containing the moiety O=C–C=X (**A**) with unactivated primary and secondary amines. The charge in the intermediate iminium ion (**B**) facilitates a 1,5-H shift (arrows) to produce an azomethine ylide of type **C** (Scheme 2). Prompted by this work, we extended our studies to azomethine ylides generated by reactions of isatin with secondary amines. Thus, we investigated the reactions of 3,3-dipiperidino-2-oxindole (**12**) [27], which is easily obtained by the reaction of isatin with piperidine, with arylidenemalononitrile derivatives **10a–c** in acetonitrile under reflux. The reactions afforded the Michael adduct **17** in high yield, but the cycloadduct **14** was not detected in the reaction mixture. However, the Michael adduct **17** is thought to be formed by cycloreversion of the cycloadduct **14**. This cycloadduct was too labile to be isolated under the reaction conditions to give the isatylidenemalononitrile **15** and the azomethine ylide **16**. The isatylidenemalononitrile **15** underwent Michael addition with piperidine to give the Michael adduct **17** in high yield. The reaction gave the same results using different substituted arylidenemalononitrile derivatives (Scheme 2).

EXPERIMENTAL

Melting points (°C) (uncorrected) were determined using a Griffin melting point apparatus. IR spectra were recorded on a MATTSON 5000 FTIR spectrometer. NMR spectra were run on ^{1}H NMR

TABLE 2 Characterization Data of Compounds **7a, b, 9a-i, 11a-c**, and **17**

Compound No.	R_1	R_2	Ar	M.P. (°C)	Yield (%)	M^+	Analysis Calcd./Found C	H
7a	H	CH_2Ph	C_6H_5	180–182	90	525.2	82.41 82.74	6.15 5.93
7b	H	3-Indolylmethyl	C_6H_5	210	86	337.2 (M^+-226)	80.97 80.69	5.90 5.48
9a	H	CH_2Ph	C_6H_5	125	85	484	81.79 81.95	5.83 5.61
9b	H	CH_2Ph	4-Cl-C_6H_4—	135–137	82		76.36 76.59	5.24 5.47
9c	H	CH_3	4-Cl-C_6H_4—	135	86		73.21 73.05	5.24 5.49
9d	H	CH_2Ph	2-Naphthyl	120–122	70		83.12 83.38	5.66 5.95
9e	CH_3	CH_2Ph	4-$CH_3OC_6H_4$—	150	84		79.52 79.23	6.1 6.47
9f	CH_3	CH_3	4-Cl-C_6H_4—	112	89		73.60 73.34	5.51 5.73
9g	CH_3	CH_3	4-$CH_3OC_6H_4$—		82		76.97 76.65	6.24 6.03
9h	H	*sec*-Butyl	4-$CH_3OC_6H_4$—	140	86	481.3	77.47 77.14	6.71 6.98
9i	CH_3	CH_2Ph	4-Cl-C_6H_4—	200	80		76.61 76.93	5.48 5.96
11a	H	CH_2Ph	C_6H_5—	179–180	70		77.21 77.02	4.99 5.25
11b	H	CH_2Ph	4-$CH_3OC_6H_4$	188–190	74		74.64 74.93	5.10 5.45
11c	H	CH_2Ph	4-$CH_3C_6H_4$	212–214	78		77.49 77.67	5.30 5.05
17				166–168	68		68.55 68.73	5.75 5.41

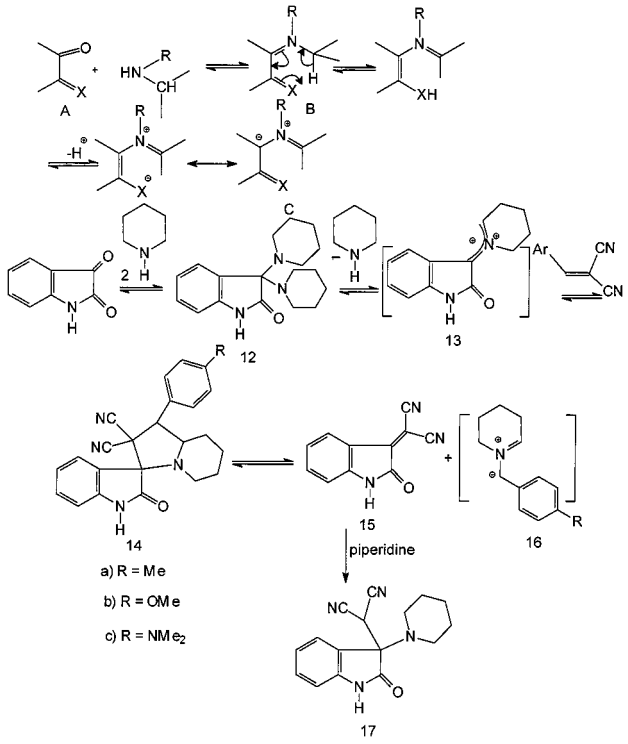
Varian-Gemini (200 MHz) and Brucker FTNMR (200 MHz) spectrometers using $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are expressed in δ relative to TMS as an internal standard. MS were recorded on a G.C. mass EX1000QP Schmadzu (Japan) mass spectrometer. The reported yields refer to pure isolated materials obtained by either crystallization or by column chromatography by use of silica gel 60 (Merck). Elemental analyses were carried out at the microanalytical unit, Faculty of Science, Cairo or Mansoura University.

General Procedure for the Reaction of Isatin, Amino Acids, and 2,6-Dibenzylidenecyclohexanone: Preparation of Dispiro[1′H-indoline-3′,2-(5-alkyl-4-arylpyrrolidine)-3,2″-(6-arylidenecyclohexanone)]-2′-one

A mixture of isatin (**1**) (0.005 mol), the appropriate amino acid (**2**) (0.005 mol), and 2,6-dibenzylidenecyclohexanone (**6**) (0.005 mol) was suspended in 40 ml (3:1) of an ethanol–water mixture. The reaction mixture was heated under reflux for 3–5 h and left to cool overnight. The precipitate that had formed was collected by filtration and recrystallized from ethanol to give **7a** or **7b** as colorless crystals (cf. Tables 1 and 2).

General Procedure for the Reaction of Isatin, Amino acids, and 2-Arylidene-1-tetralone Derivatives: Preparation of Dispiro[1′H-indoline-3′,2-(5′-alkyl-4′-arylpyrrolidine)-3,2″-(1-tetralone)]-2′-one

A mixture of isatin (**1**) (0.005 mol), the appropriate amino acid (**2**) (0.005 mol) and 2-arylidene-1-tetralone (**8**) (0.005 mol) was suspended in 40 ml (3:1) of an ethanol–water mixture .The reaction mixture was heated under reflux for 2–6 h. The solvent was distilled off under reduced pressure and the residue was chromatographed using a mixture of silica, 60–80 „ac (the boiling fraction 60–80 „ac of Pet. ether) and ethyl acetate in the ratio of 2:1, 1:1, 3:1, 4:1, 2:1, 2:1, 3:1, 2:1, and 1:1 mixture for **9a, 9b, 9c, 9d, 9e, 9f, 9g, 9h**, and **9i** respectively.



SCHEME 2

General Procedure for the Reaction of Isatin, Amino Acids, and Arylidenemalononitrile Derivatives: Preparation of 3-aryl-5-benzyl-spiro[pyrrolidine-2,3′-indoline]-4,4-dicarbonitrile-2′-ones

A mixture of isatin (**1**) (0.005 mol), the appropriate amino acid (**2**) (0.005 mol), and the arylidenemalononitrile derivatives **6a–c** (0.005 mol) was suspended in 40 ml (3:1) of an ethanol–water mixture. The reaction mixture was heated under reflux for 4–6 h. The solvent was distilled off under reduced pressure and the residue was triturated with hot methanol, filtered, and recrystallized from ethanol to give compounds **11a–c** (cf. Tables 1 and 2).

Reaction of 3,3-Dipiperidino-2-oxindole with Arylidenemalononitrile Derivatives

A suspension of 3,3-dipiperidino-2-oxindoline (**12**) [27] (5 mmol) and each arylidenemalononitrile derivative (**6**) in 30 ml of dry acetonitrile was refluxed for 3–4 h. The reaction mixture was cooled and acetonitrile distilled under reduced pressure. The oily residue that had formed was chromatographed (silica, pet. ether:ethyl acetate 1:1) to give **17**.

REFERENCES

[1] Molineux, R. J. In Alkaloids: Chemical and Biological Perspective; Pelletier, S. W. (Ed.); Wiley: New York, 1987; Ch. 1.
[2] Fujimori, S. Jap Pat Appl 88-2912; Chem Abstr 1990, 112, 98409.
[3] (a) Pajouhesh, H.; Parsons, R.; Popp, F. D. J Pharm Sci 1983, 72, 318–321; (b) Popp, F. D. J Heterocycl Chem 1984, 21, 1367–1368.
[4] Skiles, J. W.; MeNeil, D. Tetrahedron Lett 1990, 31, 7277–7280.
[5] (a) Bunce, R. A. Tetrahedron 1995, 51, 13103–13159; (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. Chem Rev 1995, 95, 195–206.
[6] Vender, P. A. (Ed.). Frontiers in Organic Synthesis, Chem Rev 1996, 96, 1–600.
[7] Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Acc Chem Res 1996, 29, 123–131.
[8] Vedejs, E.; Grissom, J. J Am Chem Soc 1988, 110, 3238–3246.
[9] Padwa, A.; Eisenbarth, P.; Venkatramanan, M. K.; Wong, G. S. K. J Org Chem 1987, 52, 2427–2432.
[10] Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, K. Bull Chem Soc Jpn 1986, 59, 2537–2545.
[11] Grigg, R. Chem Soc Rev 1987, 16, 89–121.
[12] Tsuge, O.; Kanemasa, S.; Yoshioka, M. J Org Chem 1988, 53, 1384–1391.
[13] Grigg, R.; Heaney, F. J Chem Soc, Perkin Trans 1 1989, 198–200.
[14] Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. J Chem Soc, Chem Commun 1984, 182–183.
[15] Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. J Chem Soc, Chem Commun 1987, 49–51.
[16] Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. J Chem Soc, Perkin Trans 1 1988, 2703–2713.
[17] Grigg, R.; Gunaratne, H. Q. N.; Kemp, J. J Chem Soc, Perkin Trans 1 1984, 41–46.
[18] Grigg, R.; Basanagoudar, L. D.; Kennedy, D. A.; Malone, J. F.; Thianpatanagul, S. Tetrahedron Lett 1982, 23, 2803–2806.
[19] Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V.; Thianpatanagul, S.; Tute, S. M. Tetrahedron Lett 1983, 24, 4363–4366.
[20] Armstrrong, P.; Grigg, R.; Jordan, M.; Malone, J. F. Tetrahedron 1985, 41, 3547–3558.
[21] Grigg, R.; Henderson, D.; Hudson, A. J. Tetrahedron Lett 1989, 30, 2841–2844.
[22] El-Ahl, A. S. Pol J Chem 1996, 70, 27–31.
[23] Barr, D. A.; Grigg, R.; Gunaratne, H. Q. N.; Kemp, J.; McMeekin, P.; Sridharan, V. Tetrahedron 1988, 44, 557–570.
[24] Grigg, R.; Kemp, J.; Malone, J. F.; Rajviroongit, S.; Tangthongkum, A. Tetrahedron 1988, 44, 5361–5374.
[25] Grigg, R.; Kemp, J.; Warnock, W. J. J Chem Soc, Perkin Trans 1 1987, 2275–2284.
[26] Ardill, H.; Dorrity, M. J. R.; Grigg, R.; Leon-Ling, M.-S.; Malone, J. F.; Sridharan, V.; Thianpatanagul, S. Tetrahedron 1990, 46, 6433–6448.
[27] Johnson, A.W.; McCaldin, D. J. J Chem Soc 1957, 3470–3477; Chem Abstr 1958, 52, 4639a.