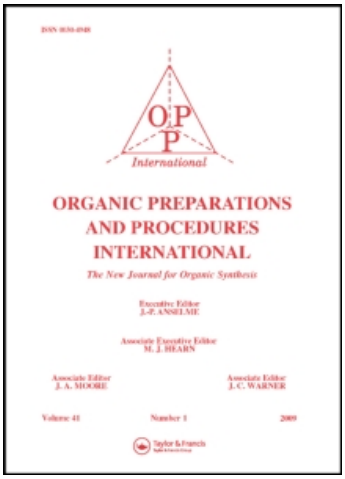

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SYNTHESIS OF INDAZOLE DERIVATIVES FROM 3, 5-DIARYL-6-ETHOXYCARBONYL-2-CYCLOHEXEN-1-ONES

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SYNTHESIS OF INDAZOLE DERIVATIVES FROM 3,5-DIARYL-6-ETHOXYCARBONYL-2-CYCLOHEXEN-1-ONES

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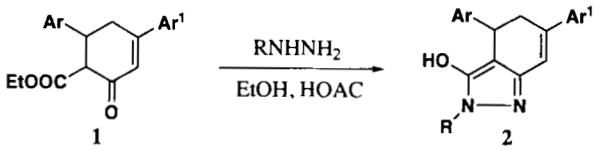
Increasing attention is being paid to the synthesis of heterocyclic compounds bearing a 1,2-diazole ring system such as indazoles because of their broad pharmacological activities. Indazole derivatives exhibit anti-inflammatory,[1] antidepressant,[2] antiarthritic,[3] antitumor[4] and analgesic[1] activities. Different pathways have been devised to generate these compounds. Most of these methods proceed from benzene derivatives on which the pyrazole moiety was attached by ring closure.[5] Other methods starting from the pyrazole ring include cycloaddition reactions[6] and Baraldi's[7] methodology of Stobbe condensation of 4-formylpyrazoles with diethyl succinate in the

presence of potassium t-butoxide. Jain *et al.*[8] reported the synthesis of indazole derivatives by addition of hydrazine hydrate to cyclohexenone or cyclohexanone derivatives. Herein, we describe the synthesis of some novel 3-hydroxyindazoles from the reaction of hydrazine hydrate or phenylhydrazine with cyclohexenone derivatives.



1 2

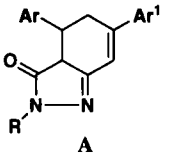
a) R = H, Ar = Ar^1 = C_6H_5; b) R = H, Ar = C_6H_5, Ar^1 = 4-Cl-C_6H_4; c) R = H, Ar = 4-Me-C_6H_4, Ar^1 = C_6H_5; d) R = H, Ar = 4-MeC_6H_4, Ar^1 = 4-Cl-C_6H_4; e) R = H, Ar = 4-Br-C_6H_4, Ar^1 = C_6H_5; f) R = H, Ar = 4-Br-C_6H_4, Ar^1 = 4-Cl-C_6H_4; g) R = H, Ar = 4-NO_2-C_6H_4, Ar^1 = C_6H_5; h) R = H, Ar = 4-NO_2-C_6H_4, Ar^1 = 4-Cl-C_6H_4; i) R = Ar = Ar^1 = C_6H_5; j) R = C_6H_5, Ar = C_6H_5, Ar^1 = 4-Cl-C_6H_4; k) R = C_6H_5, Ar = 4-Me-C_6H_4, Ar^1 = C_6H_5; l) R = C_6H_5, Ar = 4-Me-C_6H_4, Ar^1 = 4-Cl-C_6H_4; m) R = C_6H_5, Ar = 4-Br-C_6H_4, Ar^1 = C_6H_4, Ar^1 = C_6H_5; n) R = C_6H_5, Ar = 4-Br-C_6H_4, Ar^1 = 4-Cl-C_6H_4; o) R = C_6H_5, Ar = 4-NO_2-C_6H_4, Ar^1 = C_6H_5; p) R = C_6H_5, Ar = 4-NO_2-C_6H_4, Ar^1 = 4-Cl-C_6H_4

Treatment of **1a-h**[8,9] with hydrazine hydrate in the presence of ethanolic acetic acid gave the corresponding indazole derivatives **2a-h**. Jain *et al.*[8] had reported that these compounds **2a-h** can be tautomeric mixtures. In contrast, this paper established tautomers C as the sole products of the reaction by the IR and NMR data (*Table 1*).

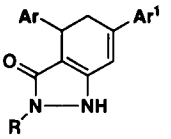
Table 1: Yields, mps and Elemental Analyses of Compounds **2a-p**

Cmpd	Yield (%)	mp (°C)	Elemental Analysis (Found) C	H	N
2a	77	215-217	79.14 (79.23)	5.59 (5.50)	9.72 (9.78)
2b	72	123-125	70.69 (70.50)	4.68 (4.60)	8.68 (8.80)
2c	75	158-160	79.44 (79.60)	6.00 (5.90)	9.27 (9.19)
2d	72	120-121	71.32 (71.18)	5.09 (5.27)	8.32 (8.40)
2e	70	146-148	62.14 (62.00)	4.12 (4.28)	7.63 (7.50)
2f	71	141-143	56.81 (56.93)	3.51 (3.66)	6.97 (6.80)
2g	65	157-158	68.45 (68.41)	4.54 (4.61)	12.61 (12.76)
2h	66	167-168	62.04 (62.19)	3.84 (3.74)	11.43 (11.60)
2i	82	170-173	82.39 (82.20)	5.53 (5.62)	7.69 (7.57)
2j	70	167-168	75.27 (75.21)	4.80 (4.95)	7.02 (7.14)
2k	80	182-184	82.51 (82.48)	5.86 (5.90)	7.40 (7.48)
2l	75	186-188	75.63 (75.52)	5.13 (5.04)	6.79 (6.70)
2m	71	213-215	67.73 (67.90)	4.32 (4.40)	6.32 (6.18)
2n	72	167-168	62.84 (62.69)	3.80 (3.92)	5.86 (5.96)
2o	77	150-151	73.33 (73.25)	4.68 (4.61)	10.26 (10.38)
2p	75	161-162	67.64 (67.49)	4.09 (4.20)	9.47 (9.34)

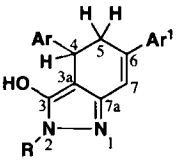
The absence of carbonyl bands in the IR spectra of the products ruled out lactam structures A and B. The ^1H NMR spectra exhibited three protons in the sp^3 shift range (H_{5a}, H_{5b} and H_4) and two protons that exchanged with D_2O at δ 10.5-11 assigned to OH and NH. On the other hand, the ^{13}C NMR spectra of these compounds showed one signal at δ 98-99. This signal can be attributed to a sp^2-hybridized carbon atom (C_{3a}) that is shifted to high field (*Table 2*).



A



B



C

The tautomer C was assigned as the sole component of these derivatives because of the effects of the NH and OH groups on the chemical shift of C_{3a}. These effects[10] can shield C_{3a} to the high field region with regard to the corresponding pyrazole structures. In order to confirm further the structure of the product, assignments of the ^1H and ^{13}C signals were carried out by H-H COSY and C-H COSY measurements. In the H-H COSY assignment, cross peaks were found between H_{5b} and H_7, and also between H_{5a}/H_{5b} and H_4. C-H COSY confirmed the chemical shifts of the carbon atoms. Similar results were obtained on the preparation of compounds **2i-p**.

Table 2. Spectroscopic Data of Compounds **2a-p**

Cmpd	IR (Cm^{-1})	^{1}HNMR (δ)	^{13}CNMR (δ)
2a	3288 (OH), 1590 (C=N)	2.9 (dd, J = 16.8, 3.2 Hz, 1H, H_{5a}), 3.1 (ddd, J = 16.8, 8.4, 2.4 Hz, 1H, H_{5b}), 4.2 (dd, J = 8.4, 3.2 Hz, 1H, 6.7 (d, J = 2.4 Hz, 1H, H_7) H_4), 7.1-7.2 (m, 6H), 7.3 (m, 2H), 7.4 (m, 2H), 11 (br, 2H)	34.6, 36.4, 98.7 C_{3a}, 113.6, 125.1, 125.8, 126.9, 127.3, 127.9, 128.4, 136.5, 140.5, 141.6, 145.4, 156.3
2b	3400 (OH), 1590 (C=N)	2.8 (dd, J = 16.6, 3.2 Hz, 1H, H_{5a}), 3.1 (ddd, J = 16.6, 8.4, 2.4 Hz, 1H, H_{5b}), 4.2 (dd, J = 8.4, 3.2 Hz, 1H, H_4), 6.7 (d, J = 2.4 Hz, 1H, H_7) 7.1-7.2 (m, 5H), 7.3 (m, 2H), 7.4 (m, 2H), 11 (br, 2H)	34.5, 36.4, 98.5 C_{3a}, 113.8, 125.4, 126.0, 126.8, 127.1, 127.8, 128.0, 135.5, 141.0, 141.5, 145.5, 156.2
2c	3395 (OH), 1598 (C=N)	2.1 (s, 3H), 2.9 (dd, J = 16.7, 3.1 Hz, 1H, H_{5a}), 3.1 (ddd, J = 16.7, 8.1, 1.7 Hz, 1H, H_{5b}), 4.1 (dd, J = 8.1, 3.1 Hz, 1H, H_4), 6.7 (d, J = 1.7 Hz, 1H, H_7) 7.0 (m, 4H), 7.2 (m, 1H), 7.3 (m, 2H), 7.4 (d, J = 7.7 Hz, 2H), 10.5 (br, 2H)	20.5, 33.8, 36.4, 98.4 C_{3a}, 113.2, 125.1, 126.8, 127.5, 128.5, 128.6, 134.8, 136.3, 140.2, 142.2, 145.3, 156.2

Table 2. Continued...

Cmpd	IR (Cm^{-1})	^{1}HNMR (δ)	^{13}CNMR (δ)
2d	3375 (OH), 1588 (C=N)	2.2 (s, 3H), 2.8 (dd, J = 16.7, 3.1 Hz, 1H, H_{5a}), 3.1 (ddd, J = 16.7, 8.4, 1.9 Hz, 1H, H_{5b}), 4.1 (dd, J = 8.4, 3.1 Hz, 1H, H_4), 6.8 (d, J = 1.9 Hz, 1H, H_7) 7.0 (m, 4H), 7.4 (d, J = 8.5 Hz, 2H), 7.5 (d, J = 8.5 Hz, 2H), 10.5 (br, 2H)	20.5, 33.8, 36.2, 98.0 C_{3a}, 114.0, 126.7, 126.8, 127.5, 128.5, 128.6, 131.8, 134.8, 139.0, 142.1, 145.6, 156.1
2e	3390 (OH), 1603 (C=N)	2.9 (dd, J = 16.8, 3.0 Hz, 1H, H_{5a}), 3.1 (ddd, J = 16.8, 8.3, 2.1 Hz, 1H, H_{5b}), 4.2 (dd, J = 8.3, 3.0 Hz, 1H, H_4), 6.8 (d, J = 2.1 Hz, 1H, H_7) 7.2-7.4 (m, 5H), 7.5-7.6 (m, 4H), 10.5 (br, 2H)	33.9, 36.1, 98.5 C_{3a}, 115.0 126.3, 126.8, 127.0, 128.1, 128.5, 132.8, 134.4, 138.5, 141.1, 146.9, 156.2
2f	3380 (OH), 1593 (C=N)	2.9 (dd, J = 16.7, 3.2 Hz, 1H, H_{5a}), 3.1 (ddd, J = 16.7, 8.2, 2.0 Hz, 1H, H_{5b}), 4.1 (dd, J = 8.2, 3.2 Hz, 1H, H_4), 6.7(d, J = 2.0 Hz, 1H, H_7) 7.1-7.2 (m, 4H), 7.3-7.4 (m, 4H), 10.5 (br, 2H)	33.9, 36.2, 98.5 C_{3a}, 115.1 126.5, 126.9, 127.2, 128.1, 128.5, 131.8, 134.5, 138.0, 142.1, 146.6, 156.2
2g	3590 (OH), 1598 (C=N), 1506 (NO_2), 1342 (NO_2)	2.9 (dd, J = 16.8, 3.2 Hz, 1H, H_{5a}), 3.1 (ddd, J = 16.8, 8.4, 2.1 Hz, 1H, H_{5b}), 4.2 (dd, J = 8.4, 3.2 Hz, 1H, H_4), 6.8 (d, J = 2.1 Hz, 1H, H_7) 7.4-7.5 (m, 5H), 8.0-8.2 (m, 4H), 10.5 (br, 2H)	34.0, 36.1, 98.3 C_{3a}, 114.5, 126.5, 126.7, 127.0, 128.6, 131.6, 133.0, 135.8, 139.0, 142.5, 145.9, 156.1
2h	3440 (OH), 1598, 1511 (NO_2), 1340 (NO_2)	2.9 (dd, J = 16.6, 3.0 Hz, 1H, H_{5a}), 3.2 (ddd, J = 16.6, 8.3, 1.8 Hz, 1H, H_{5b}), 4.2 (dd, J = 8.3, 3.0 Hz, 1H, H_4), 6.8 (d, J = 1.8 Hz, 1H, H_7) 7.4-7.6 (m, 4H), 7.7-8.1 (m, 4H), 10.5 (br, 2H)	34.0, 36.1, 98.4 C_{3a}, 114.6, 126.7, 126.8, 127.0, 128.5, 129.6, 131.5, 134.8, 138.5, 142.8, 145.8, 156.1
2i	3350 (OH), 1603 (C=N)	2.9 (d, J = 16.4 Hz, 1H, H_{5a}), 3.2 (m, 1H, H_{5b}), 4.3 (m, 1H, H_4), 6.9 (s, 1H, H_7), 7.1 (m, 1H), 7.2 (m, 5H), 7.3 (m, 2H), 7.4 (m, 2H), 7.6 (m, 3H), 7.8 (d, J = 7.7 Hz, 2H), 11.2 (br, 1H)	33.2, 35.3, 97.3 C_{3a}, 117.8, 120.5, 125.0, 126.0, 126.5, 126.9, 127.5, 127.9, 128.0, 129.4, 133.1, 136.0, 138.5, 145.5, 148.0, 158.0
2j	3500 (OH), 1593 (C=N)	2.9 (d, J = 16.3 Hz, 1H, H_{5a}), 3.2 (m, 1H, H_{5b}), 4.4 (m, 1H, H_4), 6.9 (s, 1H, H_7), 7.1 (m, 1H), 7.2 (m, 5H), 7.3 (d, J = 7.8 Hz, 2H), 7.4 (m, 2H), 7.5 (d, J = 7.4 Hz, 2H), 7.8 (d, J = 7.8 Hz, 2H), 11.2 (br, 1H)	33.4, 35.5, 97.5 C_{3a}, 118.1, 120.8, 125.1, 126.0, 126.8, 126.9, 127.6, 127.8, 128.1, 128.4, 132.0, 136.5, 139.1, 145.0, 147.9, 158.0

Table 2. Continued...

Cmpd	IR (Cm^{-1})	^{1}HNMR (δ)	^{13}CNMR (δ)
2k	3400 (OH), 1603 (C=N)	2.2 (s, 3H), 2.9 (d, J = 16.0 Hz, 1H, H_{5a}), 3.2 (dd, J = 16.0, 12 Hz, 1H, H_{5b}), 4.4 (m, 1H, H_4), 6.9 (s, 1H, H_7), 7.0 (d, J = 8.0 Hz, 2H), 7.1 (d, J = 8.0 Hz, 2H), 7.2-7.3 (m, 4H), 7.4 (m, 2H), 7.5 (d, J = 8.0 Hz, 2H), 7.8 (d, J = 8.0 Hz, 2H), 11.2 (br, 1H)	20.5, 33.0, 35.5, 97.0 C_{3a}, 117.6, 118.1, 120.0, 120.8, 125.1, 126.7, 126.9, 128.4, 128.7, 129.0, 132.0, 134.9, 139.1, 141.9, 147.9, 158.1
2l	3350 (OH), 1598 (C=N)	2.2 (s, 3H), 2.9 (d, J = 16.3 Hz, 1H, H_{5a}), 3.2 (m, 1H, H_{5b}), 4.4 (m, 1H, H_4), 6.9 (s, 1H, H_7), 7.1 (m, 4H), 7.2 (m, 1H), 7.3 (d, J = 7.9 Hz, 2H), 7.4 (m, 2H), 7.5 (d, J = 7.9 Hz, 2H), 7.8 (d, J = 8.0 Hz, 2H), 11 (br, 1H)	20.3, 33.6, 35.8, 97.5 C_{3a}, 116.0, 120.9, 125.4, 125.7, 126.8, 127.3, 128.1, 128.9, 130.1, 135.4, 138.4, 139.6, 140.4, 142.0, 148.3, 158.1
2m	3450 (OH), 1593 (C=N)	2.9 (d, J = 16.3 Hz, 1H, H_{5a}), 3.2 (m, 1H, H_{5b}), 4.4 (m, 1H, H_4), 6.9 (s, 1H, H_7), 7.2 (m, 1H), 7.3 (m, 4H), 7.4 (m, 2H), 7.5-7.6 (m, 5H), 7.8 (d, J = 7.9 Hz, 2H), 11 (br, 1H)	33.7, 35.9, 97.6 C_{3a}, 116.2, 120.5, 125.0, 125.7, 126.6, 127.5, 128.5, 128.9, 130.4, 135.4, 139.2, 139.6, 140.7, 143.0, 149.3, 158.2
2n	3350 (OH), 1600 (C=N)	2.9 (d, J = 16.3 Hz, 1H, H_{5a}), 3.2 (m, 1H, H_{5b}), 4.4 (m, 1H, H_4), 6.9 (s, 1H, H_7), 7.2 (m, 4H), 7.3 (m, 1H), 7.4 (m, 2H), 7.5-7.6 (m, 4H), 7.8 (d, J = 8.0 Hz, 2H), 11 (br, 1H)	33.7, 35.9, 97.6 C_{3a}, 116.3, 120.6, 125.4, 125.6, 126.4, 127.8, 128.3, 128.9, 131.6, 136.4, 138.4, 139.5, 140.4, 142.0, 148.5, 158.1
2o	3400 (OH), 1618 (C=N), 1511 (NO_2), 1340 (NO_2)	2.9 (d, J = 16.3 Hz, 1H, H_{5a}), 3.3 (m, 1H, H_{5b}), 4.5 (m, 1H, H_4), 6.9 (s, 1H, H_7), 7.5-7.7 (m, 5H), 7.8 (m, 2H), 7.9-8.0 (m, 5H), 8.2 (d, J = 7.9 Hz, 2H), 11 (br, 1H)	33.8, 36.1, 97.7 C_{3a}, 116.2, 120.8, 125.1, 125.8, 126.9, 127.2, 128.4, 129.9, 131.2, 135.5, 138.7, 140.1, 142.4, 144.0, 148.6, 158.2
2p	3400 (OH), 1610 (C=N), 1505 (NO_2), 1330 (NO_2)	2.9 (d, J = 16.3 Hz, 1H, H_{5a}), 3.3 (m, 1H, H_{5b}), 4.5 (m, 1H, H_4), 6.9 (s, 1H, H_7), 7.5-7.7 (m, 5H), 7.8 (m, 2H), 7.9-8.0 (m, 4H), 8.2 (d, J = 8.0 Hz, 2H), 11 (br, 1H)	33.8, 36.1, 97.7 C_{3a}, 116.4, 120.9, 125.5, 125.8, 126.8, 127.3, 128.7, 129.5, 131.5, 135.8, 139.4, 139.8, 140.5, 143.0, 148.4, 158.1

In summary, we have described a convenient method for the preparation of 4,6-diaryl-3-hydroxyindazoles from the reaction of 3,5-diaryl-6-ethoxycarbonyl-2-cyclohexen-1-ones with hydrazine hydrate or phenylhydrazine. Compared to the previous report, using a 1:2 ratio of starting materials in our procedure produces 3-hydroxyindazole tautomers which are assigned by IR and NMR spectroscopy.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus. Infrared (IR) spectra were obtained using a Magna-Nicolet IR 550 spectrometer; values are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker-Avance DRX-400 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Mass spectra were acquired on a Finnigan MAT 44S, with an ionization voltage of 70 eV. The elemental analyses (C, H, N) were obtained using a Carlo ERBA Model EA 1108 analyzer.

Typical Procedure for the Synthesis of 4,6-diphenyl-3-hydroxyindazoles.- To a mixture of compounds **1a-p** (1 mmol) and glacial acetic acid (15 mL) in ethanol (15 mL) was added hydrazine hydrate or phenylhydrazine (2 mmol). The mixture was refluxed on a water-bath for 6 hr. Then the solid was collected, washed with cold ethanol and crystallized from ethanol. Compounds **2b-2f** are white and compounds **2a, 2g-2p** are yellow.

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