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A CLEAN SYNTHESIS OF 3,3-BIS(5-AMINO-1*H*-PYRAZOL-4-YL)-INDOLIN-2-ONE DERIVATIVES

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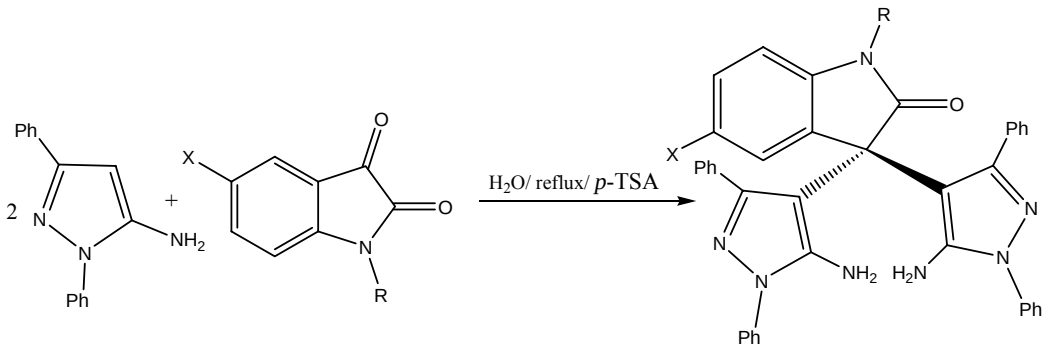
Abstract – A clean and efficient method has been reported for the condensation of 1,3-diphenyl-1*H*-pyrazol-5-amine with isatines in aqueous media to afford the corresponding 3,3-bis(5-amino-1*H*-pyrazol-4-yl)indolin-2-one derivatives in good yields.

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles.[1] Therefore, it is not surprising that research in the field of synthesis of heterocyclic compounds has received special attention.

Isatine and derivatives have proved to be versatile starting materials for the synthesis of heterocyclic, and non-cyclic, natural products, and analogues, as well as for the synthesis of potentially important compounds with biological activities.[2] Oxindoles are well known amongst these compounds. Oxindoles are useful as antibacterial, antiflammatory, and laxatives.[3] Furthermore, this heterocycle compounds were recently isolated from plant. For example, the marine alkaloid convolutamydine A, isolated from the marine bryozoan *Amathia convolute* was found to show potent activity in the differentiation of HL-60 human promyelocytic leukenie cell.[4] Therefore, a number of methods have been reported for the synthesis of oxindole derivatives.[5]

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds,[6] among them such prominent drug molecules as Celecoxib, Pyrazofurine, and many others. Recently, they have also emerged as potential atypical antipsychotics.[7]

Considering the above reports and in continuation of our previous works on synthesis of heterocyclic compounds,[8] we wish to report an efficient, and clean method for the preparation of 3,3-bis(5-amino-1,3-diphenyl-1*H*-pyrazol-4-yl)indolin-2-one derivatives (**3**) in aqueous media (**Scheme 1**).



1 **2a-g** **3a-g**

Scheme 1

To achieve suitable conditions for above transformation, we tested the reaction of 1,3-diphenyl-1*H*-pyrazol-5-amine (**1**) and isatine (**2a**) as a simple model substrate in different solvents in the presence of *p*-TSA as an inexpensive and available catalyst at reflux conditions. The results are shown in Table 1. It was found that water was a solvent of choice for the reaction and the desired product obtained in good yield in water. In organic solvent the product obtained in low to moderate yield. In the absence of solvent, the reaction was very slow and the yield of product was 50% at 100 ^{o}C after 8 h (entry 7).

Table 1. Solvent effect on the reaction[a]

Entry	Solvent	Yield (%)	Time (h)
1	EtOH (reflux)	53	6
2	MeOH (reflux)	57	6
3	$CHCl_3$ (reflux)	trace	6
4	MeCN (reflux)	45	6
5	H_2O (reflux)	75	4
6	toluene (reflux)	trace	10
7	—[b]	50	8

[a] 1,3-diphenyl-1*H*-pyrazol-5-amine (2 mmol), isatine (1 mmol), *p*-TSA (0.1 mmol). [b] The reaction was run under solvent-free conditions at 100 ^{o}C.

To study the generality of this process, several examples illustrating this method for the synthesis of polyfunctionalized 3,3-bis(5-amino-1*H*-pyrazol-4-yl)indolin-2-one (**3**) were studied. The results are summarized in Table 2. Varying the substituents on the isatine did not detrimentally affect the yields. The condensation reaction proceeded smoothly under reflux in water to give the corresponding products (**3**) in good yields.

Finally, it should be mentioned when reactions were carried out in the absence of catalyst for long period of time (15-17 h) and under reflux in water the yields of products were low (<30%).

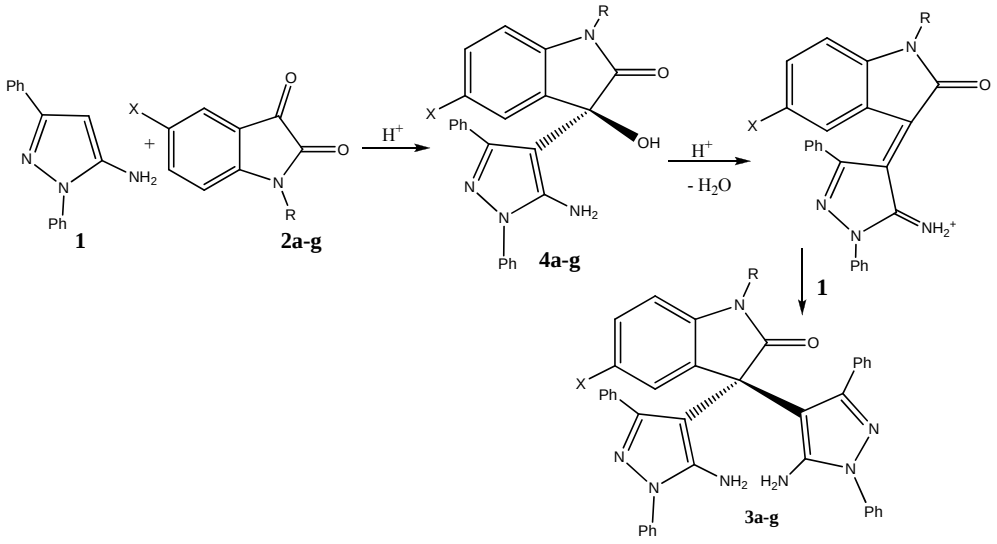
Compound (**3**) apparently result from the initial addition of 1,3-diphenyl-1*H*-pyrazol-5-amine (**1**) to the isatines (**2**) to yield intermediate (**4**), which after dehydration reacted further with another molecule of

1,3-diphenyl-1*H*-pyrazol-5-amine (**1**) to afford the corresponding 3,3-bis(5-amino-1*H*-pyrazol-4-yl)indolin-2-one (**3**) (**Scheme 2**).

Table 2. Synthesis of 3,3-bis(5-amino-1*H*-pyrazol-4-yl)indolin-2-one **3a-g**

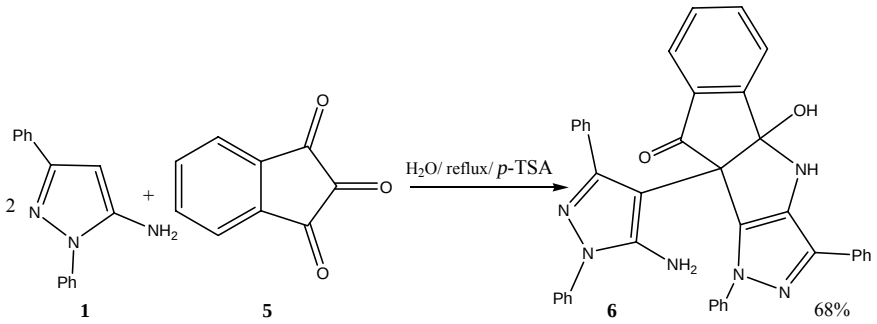
Product **3**	Compound **2**	R	X	Time (h)	Yield (%)
a	isatine (**2a**)	H	H	4	75
b	*N*-methylisatine (**2b**)	Me	H	8	70
c	*N*-ethylisatine (**2c**)	Et	H	6	72
d	*N*-benzylisatine (**2d**)	$PhCH_2$	H	7	80
e	5-bromoisatine (**2e**)	H	Br	6	82
f	5-bromo-*N*-methylisatine (**2f**)	Me	Br	5	80
g	5-nitroisatine (**2g**)	H	NO_2	4	83

When we extended this reaction to ninhydrin (**5**), product of 9a-(5-amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-4a-hydroxy-1,3-diphenyl-1,4,4a,9a-tetrahydro-9*H*-indeno[2',1':4,5]pyrrolo[3,2-c]pyrazol-9-one (**6**) was generated in 68% yield after 7 h (**Scheme 3**). To the best of our knowledge, this paper is the first report in the synthesis of 9a-(5-amino1*H*-pyrazol-4-yl)-4a-hydroxy-tetrahydro-9*H*-indeno[2',1':4,5]pyrrolo[3,2-c]-pyrazol-9-one (**6**).



Scheme 2

When we extended this reaction to ninhydrin (**5**), product of 9a-(5-amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-4a-hydroxy-1,3-diphenyl-1,4,4a,9a-tetrahydro-9*H*-indeno[2',1':4,5]pyrrolo[3,2-c]pyrazol-9-one (**6**) was generated in 68% yield after 7 h (**Scheme 3**). To the best of our knowledge, this paper is the first report in the synthesis of 9a-(5-amino1*H*-pyrazol-4-yl)-4a-hydroxy-tetrahydro-9*H*-indeno[2',1':4,5]pyrrolo[3,2-*c*]-pyrazol-9-one (**6**).



Scheme 3

In summary, we have described a clean, efficient and simple method for the preparation of 3,3-bis(5-amino-1,3-diphenyl-1*H*-pyrazol-4-yl)indolin-2-one derivatives (**3**) in condensation reaction of 1,3-diphenyl-1*H*-pyrazol-5-amine (**1**) and isatines (**2**) under reflux in water. Furthermore, a novel synthesis of 9a-(5-amino1*H*-pyrazol-4-yl)-4a-hydroxy-tetrahydro-9*H*-indeno[2',1':4,5]pyrrolo[3,2-*c*]pyrazol-9-one (**6**) was reported.

ACKNOWLEDGMENT

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EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on FT-IR 102MB BOMEM apparatus. ^{1}H NMR and ^{13}C NMR spectra were determined on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of 3,3-bis(5-amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-indolin-2-one (3a-g): A mixture of 1,3-diphenyl-1*H*-pyrazol-5-amine (2 mmol), isatines (1 mmol) and *p*-TSA (0.1 mmol) in water (5 mL) was stirred at reflux for appropriate time according to Table 1. After completion of reaction (monitored by TLC) the reaction mixture was filtered and the precipitate washed with water (15 mL) and then recrystallized from EtOH/ H_2O (1:2) to afford the pure product (**3**).

Spectral data for products:

3a: White powder, mp180 ^{o}C (decomp.); IR (KBr) (ν_{max}, cm^{-1}): 3404, 3315, 1710, 1605; MS (m/z, %): 599 (M^+, 35), 554 (38), 402 (100), 77 (50); ^{1}H NMR (DMSO-d_6) δ_H: 4.51 (2H, s, NH_2), 4.91 (2H, s, NH_2), 6.39-7.52 (24H, m, H-Ar.), 10.48 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 50.2, 98.5, 98.9, 109.8, 121.9, 123.8, 124.2, 126.3, 127.1, 127.2, 127.4, 128.6, 128.9, 129.1, 129.4, 129.5, 132.5, 135.3, 135.4, 138.8, 139.0, 141.3, 145.6, 145.7, 150.7, 150.8, 179.4. *Anal*. Calcd for $C_{38}H_{29}N_7O$: C, 76.11; H, 4.87; N, 16.35%. Found: C, 76.16; H, 4.83; N, 16.28%.

3b: White powder, mp 218 °C (decomp.); IR (KBr) (ν_{max}, cm^{-1}): 3400, 3294, 1701, 1605; MS (m/z, %): 613 (M^+, 40), 521 (30), 402 (45), 235 (100), 77 (65); ^{1}H NMR (DMSO-*d*$_6$) δ_H: 2.78 (3H, s, Me), 3.91 (2H, s, NH_2), 4.82 (2H, s, NH_2), 6.41-7.62 (24H, m, H-Ar.); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 26.1, 49.6, 97.4, 98.8, 107.5, 122.6, 124.2, 124.4, 126.5, 127.0, 127.2, 127.3, 127.4, 127.6, 127.8, 128.1, 128.7, 129.1, 129.4, 129.5, 131.5, 134.2, 134.5, 138.0, 138.4, 142.2, 144.1, 145.8, 151.3, 178.2. *Anal*. Calcd for $C_{39}H_{31}N_7O$: C, 76.33; H, 5.09; N, 15.98%. Found: C, 76.27; H, 5.03; N, 15.90%.

3c: White powder, mp 177 °C (decomp.); IR (KBr) (ν_{max}, cm^{-1}): 3447, 3310, 1705, 1603; MS (m/z, %): 627 (M^+, 51), 402 (37), 235 (100), 77 (60); ^{1}H NMR (DMSO-*d*$_6$) δ_H: 1.16 (3H, bs, Me), 3.22 (2H, bs, CH_2), 4.11 (2H, bs, NH_2), 4.64 (2H, bs, NH_2), 6.40-7.75 (24H, m, H-Ar.); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 12.6, 34.7, 49.5, 98.5, 108.9, 122.5, 123.9, 124.3, 125.9, 126.1, 127.4, 127.5, 127.7, 128.5, 128.8, 129.1, 129.6, 131.8, 134.7, 138.1, 138.4, 138.8, 141.7, 145.7, 146.3, 150.3, 150.7, 176.5. *Anal*. Calcd for $C_{40}H_{33}FN_7O$: C, 76.53; H, 5.30; N, 15.62%. Found: C, 76.59; H, 5.35; N, 15.54%.

3d: Yellow powder, mp 182 °C (decomp.); IR (KBr) (ν_{max}, cm^{-1}): 3423, 1713, 1610; MS (m/z, %): 689 (M^+, 20), 567 (48), 456 (25), 235 (45), 91 (100), 77 (40); ^{1}H NMR (DMSO-*d*$_6$) δ_H: 4.03 (2H, s,. NH_2), 4.08 and 4.68 (2H, AB system, *J*= 15.1 Hz, CH_2), 4.60 (2H, s, NH_2), 6.40-7.76 (24H, m, H-Ar.); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 43.8, 49.7, 97.9, 98.9, 108.7, 122.7, 124.3, 124.4, 124.6, 125.8, 126.2, 126.5, 127.2, 127.3, 127.4, 127.6, 127.7, 127.9, 128.0, 128.5, 128.8, 129.3, 129.4, 129.5, 129.7, 131.3, 135.8, 141.4, 144.4, 145.5, 151.3, 178.1. *Anal*. Calcd for $C_{45}H_{35}N_7O$: C, 78.35; H, 5.11; N, 14.21%. Found: C, 78.40; H, 5.17; N, 14.14%.

3e: White powder, mp 203 °C (decomp.); IR (KBr) (ν_{max}, cm^{-1}): 3423, 3314, 1700, 1598; MS (m/z, %): 677 (M^+, 30), 634 (42), 235 (100), 77 (85); ^{1}H NMR (DMSO-*d*$_6$) δ_H: 4.62 (2H, s, NH_2), 5.07 (2H, s, NH_2), 6.72-7.55 (23H, m, H-Ar.), 10.61 (1H, s, NH); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 50.4, 97.7, 98.2, 111.7, 114.0, 123.8, 124.2, 127.1, 127.4, 127.6, 127.8, 128.7, 128.9, 129.5, 129.6, 131.4, 134.5, 135.1, 135.2, 138.8, 139.0, 140.7, 145.8, 146.0, 150.6, 150.7, 179.3. *Anal*. Calcd for $C_{38}H_{28}BrN_7O$: C, 67.26; H, 4.16; N, 14.45%. Found: C, 67.31; H, 4.11; N, 14.52%.

3f: White powder, mp 215 °C (decomp.); IR (KBr) (ν_{max}, cm^{-1}): 3423, 3314, 1709, 1602; MS (m/z, %): 691 (M^+, 30), 634 (40), 235 (60), 77 (100); ^{1}H NMR (DMSO-*d*$_6$) δ_H: 2.74 (3H, s, Me), 4.55 (2H, s, NH_2), 5.26 (2H, s, NH_2), 6.73-7.63 (23H, m, H-Ar.); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 26.6, 49.7, 96.6, 98.3, 110.7, 114.8, 123.8, 124.3, 127.1, 127.6, 127.9, 128.7, 128.9, 129.1, 129.6, 129.7, 131.5, 133.9, 134.9, 135.1, 138.8, 139.1, 142.1, 145.7, 146.6, 150.6, 151.6, 176.9. *Anal*. Calcd for $C_{39}H_{30}BrN_7O$: C, 67.63; H, 4.37; N, 14.16%. Found: C, 67.69; H, 4.31; N, 14.22%.

3g: White powder, mp 228 °C (decomp.); IR (KBr) (ν_{max}, cm^{-1}): 3429, 1713, 1605; MS (m/z, %): 644 (M^+, 34), 597 (65), 235 (100), 77 (90); ^{1}H NMR (DMSO-*d*$_6$) δ_H: 4.56 (2H, s, NH_2), 5.11 (2H, s, NH_2), 6.74-7.92 (23H, m, H-Ar.), 11.14 (1H, s, NH); ^{13}C NMR (DMSO-*d*$_6$) δ_C: 50.2, 97.1, 97.3, 110.0, 123.6,

123.9, 124.3, 125.9, 127.1, 127.3, 127.6, 127.8, 128.5, 128.8, 128.9, 129.5, 129.6, 132.7, 134.9, 135.2, 138.6, 138.8, 142.3, 146.2, 147.7, 150.4, 150.6, 180.0. *Anal*. Calcd for $C_{38}H_{28}N_8O_3$: C, 70.80; H, 4.38; N, 17.38%. Found: C, 70.75; H, 4.32; N, 17.46%.

Synthesis of 9a-(5-amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-4a-hydroxy-1,3-diphenyl-1,4,4a,9a-tetrahydro-9*H*-indeno[2',1':4,5]pyrrolo[3,2-*c*]pyrazol-9-one (**6**): A mixture of 1,3-diphenyl-1*H*-pyrazol-5-amine (2 mmol), ninhydrine (1 mmol), and *p*-TSA (0.1 mmol) in water (5 mL) was stirred at reflux for 7 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered and the precipitate washed with water (15 mL) and then recrystallized from MeOH/H_2O (1:2) to afford the pure product **6.** White powder (68%), mp 162 ^oC (decomp.); IR (KBr) (ν_{max}, cm^{-1}): 3417, 3324, 1696, 1609; MS (m/z, %): 612 (M^+, 40), 594 (54), 364 (100), 262 (87), 77 (85); ^1H NMR (DMSO-d_6) δ_H: 7.00 (2H, bs, NH_2), 7.12-8.00 (24H, m, H-Ar.), 10.33 (1H, s, OH), 12.44 (1H, s, NH). *Anal*. Calcd for $C_{39}H_{28}N_6O_2$: C, 76.45; H, 4.61; N, 13.72. Found: C, 76.50; H, 4.55; N, 13.78.

Due to very low solubility of the product (**6**), we can not report the ^{13}C NMR data for this product.

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