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Synthesis of 1*H*-Indol-3-ylpyrazole Derivatives from 1,3,5-Triketones and Arylhydrazines: One-Pot Construction of Pyrazole and Indole Rings

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The reaction of 1,3,5-triketones and arylhydrazines provided indolylpyrazole derivatives in a one-pot reaction in good to moderate yields. Both the pyrazole and indole rings were constructed simultaneously with phenylhydrazine, $RCOCH_2CO$- moiety for the pyrazole and the remaining -CH_2COR part for the indole ring.

Key Words : Indolylpyrazole, 1,3,5-Triketones, Fischer indole synthesis

Introduction

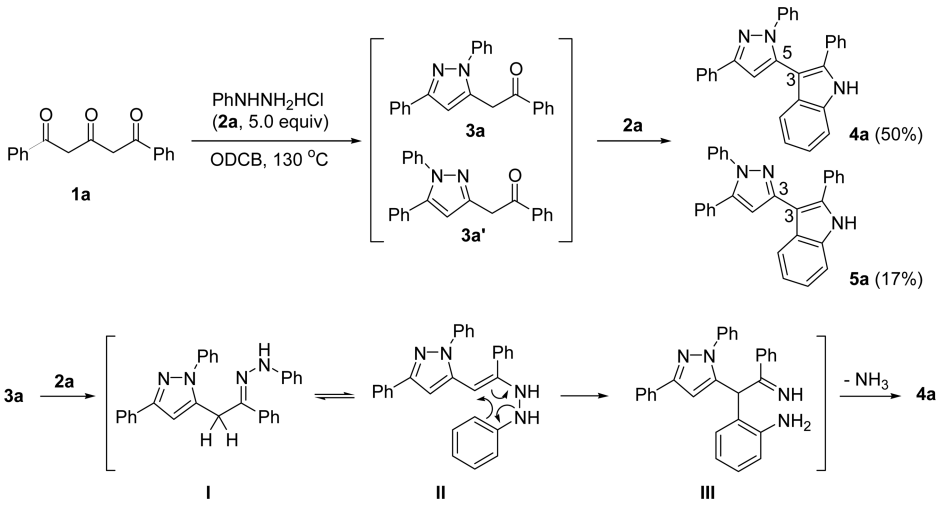
The synthesis of indolylpyrazole derivatives has been examined extensively due to their potential biological activities.[1-3] The synthesis was carried out most frequently *via* the transition metal-catalyzed coupling reaction between indoles and pyrazoles.[2] However, this approach required one pre-activated reaction partner such as bromopyrazole or bromoindole.[2] Other method involving the use of 4-pyranones as starting materials has also been reported.[3]

Results and Discussion

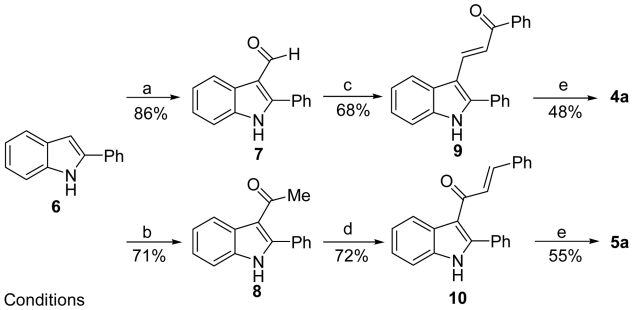
During our recent studies on the synthesis of 2,3-dihydro-4*H*-pyran-4-ones from 1,5-dicarbonyl compounds,[4] we presumed that the 1,3,5-triketone moiety of 1,5-diphenyl-1,3,5-pentanetrione (**1a**) could be used for the simultaneous construction of both pyrazole and indole rings in the reaction with phenylhydrazine, $PhCOCH_2CO$- moiety for the pyrazole and the remaining -CH_2COPh part for the indole ring, as shown in Scheme 1.

Thus, we examined the reaction of **1a** and phenylhydrazine hydrochloride (**2a**, 5.0 equiv) in ODCB (130 °C, 5 h). To our delight, a desired 5-(indol-3-yl)pyrazole derivative **4a** was obtained in moderate yield (50%)[5] along with 3-(indol-3-yl)pyrazole **5a** (17%). The combined yield of **4a**/**5a** decreased when the reaction was performed with lesser amount of **2a**. Compounds **4a** and **5a** could be formed *via* the formation of regioisomeric pyrazoles **3a**/**3a'** and a subsequent Fischer indole synthesis process. The typical mechanism for the formation of indole ring is also shown in Scheme 1. However, we could not separate the corresponding intermediates **3a** and **3a'**.[6]

In order to confirm the structure of **4a** and **5a** unequivocally, we carried out the synthesis of these compounds from 2-phenylindole (**6**) although the synthesis required three-steps, as shown in Scheme 2. The formylation of **6** was carried out with $POCl_3$ and DMF to produce **7** in good yield (86%) according to the known method.[7] Aldol condensation of **7** with acetophenone afforded α,β-enone **9** in good yield (68%).[8] The reaction of this enone **9** and phenylhydrazine in ODCB (130 °C, 6 h) produced **4a** in moderate yield (48%),



Scheme 1



Scheme 2

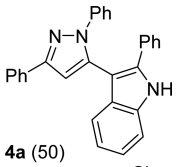
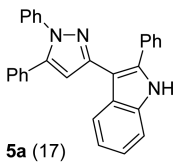
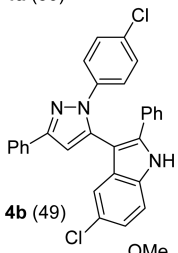
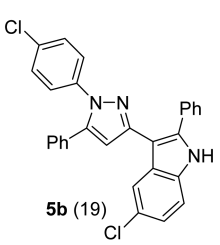
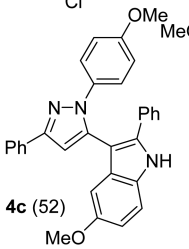
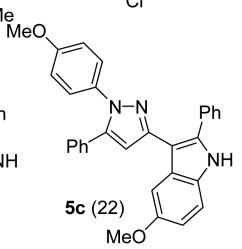
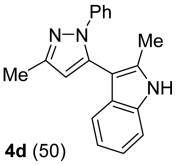
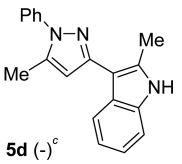
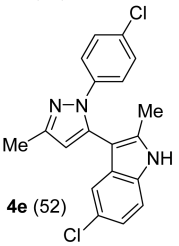
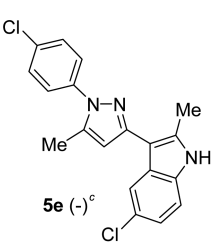
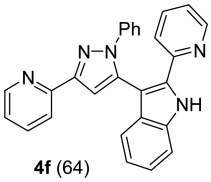
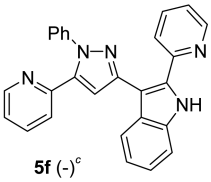
presumably *via* an aerobic oxidation of the intermediate pyrazoline derivative. Similarly, 3-acetylindole **8** was prepared by the acetylation of **6** with $POCl_3$ and DMA.[7] A sequential aldol reaction with benzaldehyde to make **10**,[8] and the following reaction with phenylhydrazine afforded **5a** in 55% yield.

Encouraged by the successful result we synthesized various indolylpyrazoles **4b-e**, **5b**, and **5c**, as shown in Table 1. The reaction of **1a** and 4-chlorophenylhydrazine hydrochloride (**2b**) afforded **4b** (49%) and **5b** (19%), as shown in entry 2. Similarly, the reaction with 4-methoxyphenylhydrazine hydrochloride (**2c**) gave **4c** (52%) and **5c** (22%) in good combined yields (entry 3). The reactions with 2,4,6-heptanetrione (**1b**) also afforded the corresponding products **4d** and **4e** in moderate yields (entries 4 and 5). However, isolation of the corresponding minor products **5d** and **5e** failed in these cases, although the formations of these compounds were observed on TLC at the right position in a small amount. Similarly, the reaction of 1,5-di(2-pyridyl)-1,3,5-pentanetrione (**1c**) and **2a** (entry 6) afforded **4f** in good yield (64%).[9]

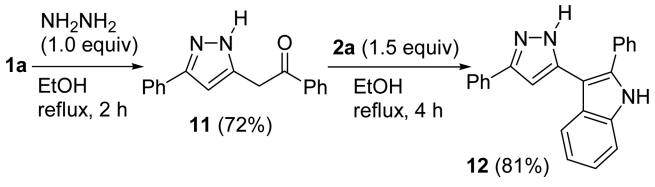
In order to make *N*-unsubstituted indolylpyrazole **12**, we examined a sequential synthesis of pyrazole **11** and a subsequent construction of indole ring, as shown in Scheme 3. Pyrazole **11** could be prepared by the reaction of **1a** and hydrazine hydrate in good yield (72%).[10] The following synthesis of indole ring was performed with phenylhydrazine hydrochloride (**2a**), and indolylpyrazole **12** was obtained in good yield (81%).

As a next entry, we examined the synthesis of pyrimidylindole derivative **14**,[11] as shown in Scheme 4. The reaction of **1a** and guanidine carbonate produced 2-aminopyrimidine derivative **13** in the presence of a catalytic amount of *p*-TsOH in ODCB in moderate yield (46%). In the reaction, a retro-aldol type side reaction lowered the yield of **13**.[12,13] With this compound **13** in our hand, the reaction with **2a** was carried out in refluxing ODCB. However, pyrimidylindole **14** was not formed at all. Instead, indolylpyrazole **4a** was formed in moderate yield (57%). The plausible reaction mechanism is proposed in Scheme 4. The intermediate **IV**, a corresponding hydrazone of **13**, could be converted to a spiro intermediate **V**. The ring-opening of **V** to **VI** and a following 1,5-H shift would generate **VII**. Addition of **2a** to **VII** and subsequent elimination of guanidine would produce **I** (*vide supra*, Scheme 1). As a last, the hydrazone **I** was

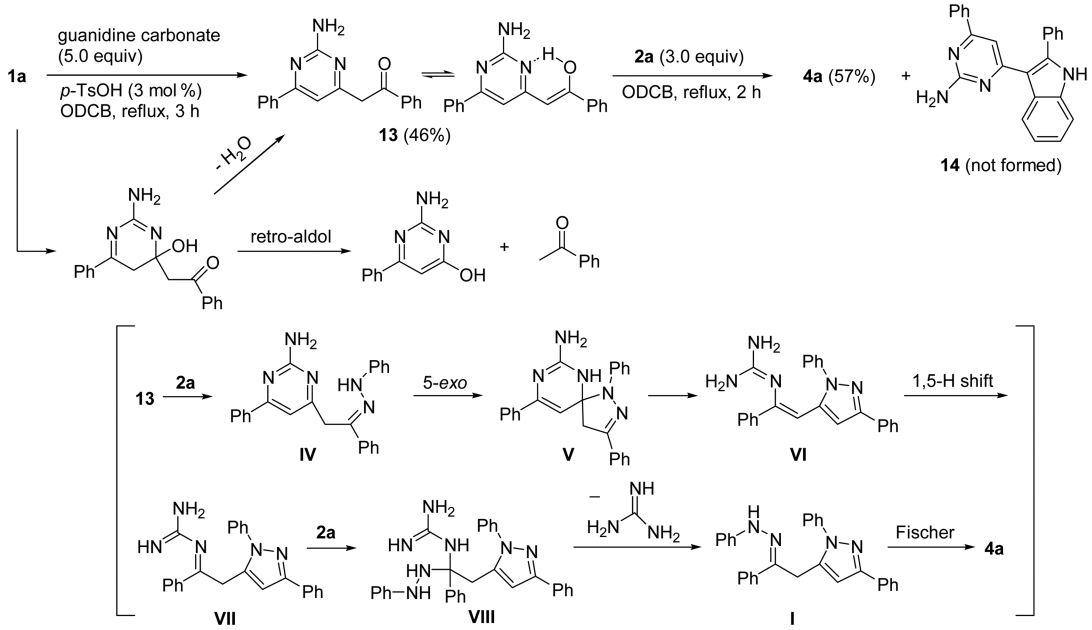
Table 1. Synthesis of indolylpyrazoles

Entry	Tri-ketone	ArNHN H_2HCl	Products (%)[a]	
1	**1a**	**2a** (Ar=Ph)	 **4a** (50)	 **5a** (17)
2	**1a**	**2b** (Ar=4-ClPh)	 **4b** (49)	 **5b** (19)
3	**1a**	**2c** (Ar=4-MeOPh)	 **4c** (52)	 **5c** (22)
4	**1b**[b]	**2a**	 **4d** (50)	 **5d** (-)[c]
5	**1b**[b]	**2b**	 **4e** (52)	 **5e** (-)[c]
6	**1c**[d]	**2a**	 **4f** (64)	 **5f** (-)[c]

[a]Conditions: triketone (0.5 mmol), ArNHNH$_2$HCl (5.0 equiv), ODCB, 130 °C, 3-5 h. [b]**1b** is 2,4,6-heptanetrione. [c]Failed to isolate. [d]**1c** is 1,5-di(2-pyridyl)-1,3,5-pentanetrione.



Scheme 3



Scheme 4

converted to indolylpyrazole **4a**.[14]

In summary, we disclosed an efficient synthesis of indolylpyrazole derivatives from 1,3,5-triketones and arylhydrazines by simultaneous construction of both pyrazole and indole rings.

Experimental Section

Typical Procedure for the Synthesis of 4a and 5a. A mixture of **1a** (133 mg, 0.5 mmol) and **2a** (362 mg, 2.5 mmol) in ODCB (2.5 mL) was heated to 130 °C for 5 h. After the usual extractive workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 15:5:1) compound **4a**[5] was obtained as a pale yellow solid (103 mg, 50%) along with **5a** (35 mg, 17%). Other compounds were synthesized similarly, and the spectroscopic data of **4a-f**, **5a-c**, **11**,[10a] **12**,[5] and **13** are as follows.

Compound 4a:[5] 50%; pale yellow solid, mp 192-193 °C; IR (KBr) 3412, 1597, 1499, 1456, 1362 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.94-7.00 (m, 6H), 7.02-7.07 (m, 2H), 7.12-7.21 (m, 4H), 7.23-7.29 (m, 1H), 7.31-7.36 (m, 1H), 7.38-7.46 (m, 3H), 7.61 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 6.9 Hz, 2H), 8.33 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 103.27, 106.37, 111.00, 119.54, 120.86, 122.98, 124.03, 125.78, 126.42, 127.13, 127.85, 127.92, 128.11, 128.59, 128.64, 128.75, 131.65, 133.13, 135.74, 136.48, 137.71, 139.80, 151.97; ESIMS *m/z* 412 (M^++H). Anal. Calcd for $C_{29}H_{21}N_3$: C, 84.64; H, 5.14; N, 10.21. Found: C, 84.47; H, 5.33; N, 10.04.

Compound 5a: 17%; pale yellow solid, mp 116-117 °C; IR (KBr) 3416, 1595, 1499, 1456, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.29 (s, 1H), 7.10-7.38 (m, 16H), 7.62 (d, J = 7.8 Hz, 2H), 8.20 (br s, 1H), 8.20-8.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 106.91, 107.72, 110.58, 120.64, 121.63, 122.68, 124.93, 126.83, 128.01, 128.13, 128.23, 128.32, 128.55, 128.69, 128.77, 128.93, 130.84, 132.96, 135.86, 135.90, 140.28, 142.91, 147.61; ESIMS *m/z* 412 (M^++H). Anal. Calcd for $C_{29}H_{21}N_3$: C, 84.64; H, 5.14; N, 10.21. Found: C, 84.78; H, 5.42; N, 10.13.

Compound 4b: 49%; yellow solid, mp 211-212 °C; IR (KBr) 3412, 1595, 1493, 1460, 1362 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.74 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 6.91-6.94 (m, 2H), 6.96 (s, 1H), 7.10-7.21 (m, 4H), 7.27 (d, J = 8.4 Hz, 1H), 7.32-7.37 (m, 1H), 7.40-7.46 (m, 2H), 7.58 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 6.9 Hz, 2H), 8.61 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 102.43, 106.50, 112.25, 118.79, 123.50, 125.29, 125.84, 126.83, 127.14, 128.19, 128.28, 128.36, 128.69, 128.75, 129.63, 131.10, 132.29, 132.58, 134.10, 137.20, 137.90, 137.91, 152.35; ESIMS *m/z* 481 (M^++H), 483 (M^++H+2) and 485 (M^++H+4). Anal. Calcd for $C_{29}H_{19}Cl_2N_3$: C, 72.51; H, 3.99; N, 8.75. Found: C, 72.75; H, 4.11; N, 8.84.

Compound 5b: 19%; yellow solid, mp 120-121 °C; IR (KBr) 3418, 1566, 1495, 1464, 1356 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.32 (s, 1H), 7.13-7.24 (m, 5H), 7.28-7.33 (m, 6H), 7.37-7.41 (m, 3H), 7.58-7.61 (m, 2H), 8.21 (d, J = 2.1 Hz, 1H), 8.43 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 105.96, 107.88, 111.79, 120.73, 123.02, 126.05, 126.34, 128.48, 128.55, 128.62, 128.65, 128.72, 128.76, 128.83, 128.98, 130.15, 132.22, 132.75, 134.23, 137.46, 138.33, 143.40, 147.37; ESIMS *m/z* 481 (M^++H), 483 (M^++H+2) and 485 (M^++H+4).

Compound 4c: 52%; yellow solid, mp 237-239 °C; IR (KBr) 3393, 1595, 1510, 1485, 1462, 1248 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) d 3.67 (s, 3H), 3.79 (s, 3H), 6.51 (d, J = 9.0 Hz, 2H), 6.85 (dd, J = 8.7 and 2.1 Hz, 1H), 6.89 (s, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 2.1 Hz, 1H), 7.18 (app s, 5H), 7.30-7.35 (m, 2H), 7.41-7.45 (m, 2H), 7.96 (d, J = 7.2 Hz, 2H), 10.28 (br s, 1H); ^{13}C NMR ($CDCl_3$ +DMSO-d_6, 75 MHz) δ 55.09, 55.48, 100.11, 102.19, 105.49,

111.99, 112.64, 113.09, 125.01, 125.37, 127.08, 127.24, 127.45, 128.06, 128.34, 128.92, 130.98, 131.97, 133.20, 137.01, 138.09, 151.21, 154.37, 157.66 (one carbon is overlapped); ESIMS *m/z* 472 (M^++H). Anal. Calcd for $C_{31}H_{25}N_3O_2$: C, 78.96; H, 5.34; N, 8.91. Found: C, 79.15; H, 5.39; N, 8.74.

Compound 5c: 22%; yellow solid, mp 198-200 °C; IR (KBr) 3408, 1597, 1614, 1454, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 3H), 3.87 (s, 3H), 6.33 (s, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.87 (dd, *J* = 8.7 and 2.4 Hz, 1H), 7.18-7.40 (m, 11H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 2.4 Hz, 1H), 8.25 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.40, 55.92, 103.35, 106.79, 107.08, 111.35, 112.77, 113.86, 126.30, 127.88, 128.07, 128.28, 128.49, 128.67, 128.70, 128.78, 130.84, 131.13, 133.02, 133.65, 136.58, 142.83, 147.35, 154.77, 158.35; ESIMS *m/z* 472 (M^++H).

Compound 4d: 50%; white solid, mp 183-184 °C; IR (KBr) 3391, 1599, 1501, 1458, 1366 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (s, 3H), 2.43 (s, 3H), 6.32 (s, 1H), 7.02-7.07 (m, 1H), 7.09-7.21 (m, 4H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 1H), 8.26 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.21, 13.73, 103.77, 108.94, 110.28, 118.88, 120.15, 121.68, 123.63, 126.26, 127.91, 128.65, 133.65, 135.17, 137.26, 140.64, 149.56; ESIMS *m/z* 288 (M^++H). Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.48; H, 6.19; N, 14.47.

Compound 4e: 52%; white solid, mp 178-179 °C; IR (KBr) 3410, 1595, 1497, 1464, 1414, 1364 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.96 (s, 3H), 2.42 (s, 3H), 6.31 (s, 1H), 7.09 (dd, *J* = 8.7 and 1.8 Hz, 1H), 7.14-7.22 (m, 5H), 7.32 (d, *J* = 1.8 Hz, 1H), 8.41 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.27, 13.65, 103.23, 109.42, 111.43, 118.19, 122.13, 124.72, 126.11, 128.85, 128.93, 132.04, 133.52, 135.22, 136.64, 138.96, 150.03; ESIMS *m/z* 357 (M^++H), 359 (M^++H+2), 361 (M^++H+4). Anal. Calcd for $C_{19}H_{15}Cl_2N_3$: C, 64.06; H, 4.24; N, 11.80. Found: C, 64.31; H, 4.15; N, 11.92.

Compound 4f: 64%; pale yellow solid, mp 100-102 °C; IR (KBr) 3430, 1594, 1494, 1459, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.02-7.09 (m, 4H), 7.13 (ddd, *J* = 8.1, 6.9 and 1.2 Hz, 1H), 7.19-7.30 (m, 5H), 7.31-7.38 (m, 2H), 7.47 (td, *J* = 7.8 and 1.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.79 (td, *J* = 7.8 and 1.8 Hz, 1H), 8.19 (dt, *J* = 7.8 and 1.2 Hz, 1H), 8.41-8.47 (m, 1H), 8.67-8.73 (m, 1H), 10.16 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 104.14, 108.43, 111.42, 119.98, 120.34, 120.77, 121.26, 122.31, 122.72, 123.74, 123.85, 126.99, 128.40, 129.45, 134.32, 135.33, 136.63, 136.64, 137.79, 139.81, 148.85, 149.20, 149.53, 152.15, 152.62; ESIMS *m/z* 414 (M^++H). Anal. Calcd for $C_{27}H_{19}N_5$: C, 78.43; H, 4.63; N, 16.94. Found: C, 78.62; H, 4.89; N, 16.68.

Compound 11:[10a] 72%; white solid, mp 151-152 °C; IR (KBr) 3333, 1674, 1578, 1462, 1449, 1339 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) δ 4.38 (s, 2H), 6.47 (s, 1H), 7.24-7.29 (m, 1H), 7.33-7.39 (m, 2H), 7.43-7.49 (m, 2H), 7.54-7.59 (m, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 8.05 (d, *J* = 7.2 Hz, 2H), 12.45 (br s, 1H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz) δ 37.44, 102.40, 125.35, 127.70, 127.72, 128.50, 128.52, 128.57, 131.23, 133.24, 136.16, 196.30 (one carbon is overlapped); ESIMS *m/z* 263 (M^++H).

Compound 12:[5] 81%; white solid, mp 285-286 °C; IR (KBr) 3397, 1599, 1489, 1456, 1329 cm^{-1}; ^1H NMR ($CDCl_3$ +DMSO-d_6, 300 MHz) δ 6.70 (s, 1H), 7.13-7.24 (m, 2H), 7.26-7.43 (m, 7H), 7.54-7.56 (m, 2H), 7.77-7.80 (m, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 10.00 (br s, 2H); ^{13}C NMR ($CDCl_3$ +DMSO-d_6, 75 MHz) δ 102.01, 103.27, 111.23, 119.55, 120.66, 122.78, 125.55, 127.72, 127.84, 128.21, 128.32, 128.59, 128.85, 132.04, 132.70, 135.67, 135.98, 139.99, 150.60; ESIMS *m/z* 336 (M^++H).

Compound 13: 46%; yellow solid, mp 111-112 °C; IR (KBr) 3484, 3390, 3319, 1685, 1637, 1602, 1578, 1493, 1449, 1372 cm^{-1}; [keto form] ^1H NMR ($CDCl_3$, 300 MHz) δ 4.32 (s, 2H), 5.26 (br s, 2H), 7.04 (s, 1H), 7.40-7.49 (m, 6H), 7.94-7.99 (m, 2H), 8.05 (d, *J* = 7.2 Hz, 2H); [enol form] ^1H NMR ($CDCl_3$, 300 MHz) δ 5.26 (br s, 2H), 6.01 (s, 1H), 6.78 (s, 1H), 7.40-7.49 (m, 5H), 7.55-7.60 (m, 1H), 7.81-7.86 (m, 2H), 7.94-7.99 (m, 2H), 15.06 (br s, 1H); [keto+ enol form] ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.90, 93.55, 104.15, 107.84, 125.86, 126.99, 127.12, 128.40, 128.67 (2C), 128.75, 130.10, 130.42, 130.52, 133.48, 136.00, 136.35, 137.15, 137.40, 159.07, 163.36, 164.60, 164.80, 165.16, 165.87, 169.01, 195.82 (one carbon is overlapped); ESIMS *m/z* 290 (M^++H).

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References and Notes

1. For the biological activities of some indolylpyrazole derivatives, see: (a) Zhang, D.; Wang, G.; Zhao, G.; Xu, W.; Huo, L. *Eur. J. Med. Chem*. **2011**, *46*, 5868-5877. (b) Pierce, L. T.; Cahill, M. M.; McCarthy, F. O. *Tetrahedron* **2011**, *67*, 4601-4611. (c) Diana, P.; Carbone, A.; Barraja, P.; Kelter, G.; Fiebig, H.-H.; Cirrincione, G. *Bioorg. Med. Chem*. **2010**, *18*, 4524-4529. (d) Zhang, N.; Ayral-Kaloustian, S.; Anderson, J. T.; Nguyen, T.; Das, S.; Venkatesan, A. M.; Brooijmans, N.; Lucas, J.; Yu, K.; Hollander, I.; Mallon, R. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 3526-3529. (e) Velankar, A. D.; Quintini, G.; Prabhu, A.; Weber, A.; Hunaeus, G.; Voland, B.; Wuest, M.; Orjeda, C.; Harel, D.; Varghese, S.; Gore, V.; Patil, M.; Gayke, D.; Herdemann, M.; Heit, I.; Zaliani, A. *Bioorg. Med. Chem*. **2010**, *18*, 4547-4559. (f) Diana, P.; Carbone, A.; Barraja, P.; Martorana, A.; Gia, O.; DallaVia, L.; Cirrincione, G. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6134-6137. (g) Sivaprasad, G.; Perumal, P. T.; Prabavathy, V. R.; Mathivanan, N. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 6302-6305. (h) Reddy, M. V. R.; Billa, V. K.; Pallela, V. R.; Mallireddigari, M. R.; Boominathan, R.; Gabriel, J. L.; Reddy, E. P. *Bioorg. Med. Chem*. **2008**, *16*, 3907-3916.
2. For the synthesis of indolylpyrazole derivatives by a transition metal-catalyzed coupling reactions, see: (a) Khan, T. A.; Kumar, S.; Venkatesh, C.; Ila, H. *Tetrahedron* **2011**, *67*, 2961-2968. (b) Delaunay, T.; Genix, P.; Es-Sayed, M.; Vors, J.-P.; Monteiro, N.; Balme, G. *Org. Lett*. **2010**, *12*, 3328-3331. (c) Delaunay, T.; Es-Sayed, M.; Vors, J.-P.; Monteiro, N.; Balme, G. *Eur. J. Org. Chem*. **2011**, 3837-3848. (d) Bobko, M. A.; Kaura, A. C.; Evans, K. A.;

Su, D.-S. *Org. Lett*. **2012**, *14*, 3906-3908. (e) Stansfield, I.; Pompei, M.; Conte, I.; Ercolani, C.; Migliaccio, G.; Jairaj, M.; Giuliano, C.; Rowley, M.; Narjes, F. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 5143-5149. (f) Pintori, D. G.; Greaney, M. F. *J. Am. Chem. Soc*. **2011**, *133*, 1209-1211. (g) Nayak, M.; Batra, S. *Eur. J. Org. Chem*. **2012**, 3677-3683.

3. For the synthesis of indolylpyrazole derivatives *via* a sequential construction of pyrazole and indole rings, see: (a) Usachev, B. I.; Obydennov, D. L.; Roschenthaler, G.-V.; Sosnovskikh, V. Y. *J. Fluorine Chem*. **2012**, *137*, 22-26. (b) Usachev, B. I.; Obydennov, D. L.; Sosnovskikh, V. Y. *J. Fluorine Chem*. **2012**, *135*, 278-284. (c) Usachev, B. I.; Obydennov, D. L.; Kodess, M. I.; Sosnovskikh, V. Y. *Tetrahedron Lett*. **2009**, *50*, 4446-4448. (d) Usachev, B. I.; Obydennov, D. L.; Kodess, M. I.; Roschenthaler, G.-V.; Sosnovskikh, V. Y. *Russ. Chem. Bull. Int. Ed*. **2009**, *58*, 1248-1252. (e) Sechi, M.; Innocenti, A.; Pala, N.; Rogolino, D.; Carcelli, M.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 5801-5806. A one-pot synthesis of indolylpyrazole from 1,5-di(*p*-tolyl)pentane-1,3,5-trione and phenylhydrazine hydrochloride was also reported; however, the paper prepared only one compound in very low yield (25%) in refluxing EtOH, see: (f) Jukic, M.; Cetina, M.; Pavlovic, G.; Rapic, V. *Struct. Chem*. **1999**, *10*, 85-90.
4. Kim, S. H.; Lee, S.; Kim, S. H.; Lim, J. W.; Kim, J. N. *Tetrahedron Lett*. **2012**, *53*, 4979-4983.
5. Dandia, A.; Rani, B.; Saha, M. *Indian J. Chem. Technol*. **1998**, *5*, 159-162.
6. The formation of pyrazole ring might occur preferentially over the indole ring.[1f,3c,3d] Thus, **3a**, **3a'**, and the corresponding hydrazones of **3a** and **3a'** could be the possible intermediates. In this respect, the reaction of **1a** with a limited amount (0.9 equiv) of phenylhydrazine hydrochloride was examined at low temperature (EtOH, 40 °C) in order to separate major intermediate(s) such as **3a** or the hydrazone of **3a**; however, so many spots were observed including **4a** and **5a**, and we failed to identify the major intermediate(s). Thus, we cannot exclude the possibility for the initial formation of an indole ring and a subsequent pyrazole formation at this stage.
7. Qu, J.; Kumar, N.; Alamgir, M.; Black, D. StC. *Tetrahedron Lett*. **2009**, *50*, 5628-5630.
8. (a) Black, D. StC.; Deb-Das, R. B.; Kumar, N. *Aust. J. Chem*. **1992**, *45*, 611-621. (b) Butin, A. V.; Uchuskin, M. G.; Pilipenko, A. S.; Serdyuk, O. V.; Trushkov, I. V. *Tetrahedron Lett*. **2011**, *52*, 5255-5258. (c) Dandia, A.; Sehgal, V.; Upreti, M. *Phosphorous, Sulfur and Silicon* **1995**, *105*, 93-99.
9. During the evaluation process one of the reviewers suggested the synthesis of indolylpyrazoles with other 1,3,5-triketones. Thus, we prepared 1,5-di(2-pyridyl)-1,3,5-pentanetrione (**1c**) according to the reported method and examined the reaction with **2a**. For the preparation of **1c**: Saadeh, H. A.; Abu Shairah, E. A.; Charef, N.; Mubarak, M. S. *J. Appl. Polym. Sci*. **2012**, *124*, 2717-2724.
10. (a) El-Kholy, I. E.-S.; Rafla, F. K.; Soliman, G. *J. Chem. Soc*. **1962**, 1857-1863. (b) Chou, S.-Y.; Chen, C.-J.; Tsai, S.-L.; Sheu, H.-S.; Lee, G.-H.; Lai, C. K. *Tetrahedron* **2009**, *65*, 1130-1139.
11. For the synthesis and biological activity of pyrimidylindole derivatives, see: (a) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080-3098. (b) Akue-Gedu, R.; Debiton, E.; Ferandin, Y.; Meijer, L.; Prudhomme, M.; Anizon, F.; Moreau, P. *Bioorg. Med. Chem*. **2009**, *17*, 4420-4424. (c) Radwan, M. A. A.; El-Sherbiny, M. *Bioorg. Med. Chem*. **2007**, *15*, 1206-1211.
12. The formation of appreciable amounts of acetophenone and 2-amino-4-hydroxy-6-phenylpyrimidine was observed on TLC.
13. Actually, the compound **13** existed as a keto/enol (2:3) tautomeric mixture in its ^{1}H NMR spectrum. For the similar keto/enol equilibration of 1-substituted-2-azinyl-1-ethanones, see: (a) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Akhmedova, R. G. *ARKIVOC* **2005** (vi) 329-338. (b) Prekupec, S.; Makuc, D.; Plavec, J.; Suman, L.; Kralj, M.; Pavelic, K.; Balzarini, J.; De Clerq, E.; Mintas, M.; Raic-Malic, S. *J. Med. Chem*. **2007**, *50*, 3037-3045.
14. The regioisomeric indolylpyrazole **5a** was not formed at all in the reaction, and the result could be a strong evidence for the suggested mechanism.