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# An efficient synthesis of pyrazolo[3,4-*b*]pyridine-4-spiroindolinones by a three-component reaction of 5-aminopyrazoles, isatin, and cyclic β-diketones

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ABSTRACT

Novel pyrazolopyridine-spiroindolinones were prepared by the three-component reaction of 5-aminopyrazoles, isatin, and cyclic β-diketones in aqueous media and catalyzed by *p*-TSA. This protocol provides a simple one-step procedure with the advantages of easy work-up, mild reaction conditions and environmentally benign.



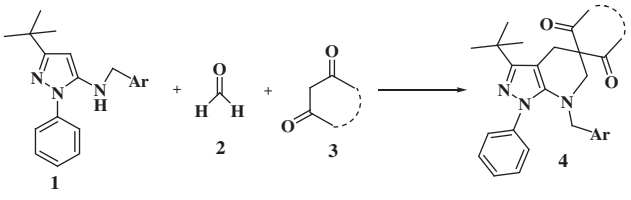
Compounds with spiro skeletons not only constitute subunits in numerous alkaloids, but are also templates for drug discovery and have been used as scaffolds for combinatorial libraries.[1] Synthesis of some spiro-derivatives has been performed by conventional methods and procedures based on three-component one-pot approaches.[2]

Isatin is a privileged lead molecule for designing potential bioactive agents, and its derivatives have been shown to possess a broad spectrum of bioactivity, as many of which have been assessed as anti-HIV,[3] anti-viral,[4] anti-tumor,[5] anti-fungal,[6] and anti-convulsants[7] agents. These interesting properties have prompted many efforts toward the synthesis and pharmacological screening of isatin derivatives.

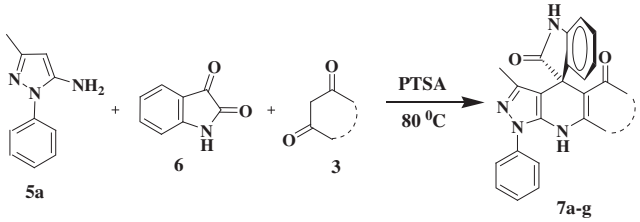
In our interest in the development of synthetic strategies to obtain functionalized heterocycles,[8] we have concentrated much of our recent efforts in the preparation of such bioactive nitrogen-containing heterocycles, and have already reported simple and efficient procedures to reach interesting molecules such as pyrazolo[3,4-*b*]pyridines with biological properties.[9]

Recently, we have described the three-component reaction between 5-(4-R-benzylamino)pyrazoles **1**, paraformaldehyde **2**, and cyclic β-diketones **3** by conventional heating or by microwave irradiation to obtain pyrazolo[3,4-*b*]pyridine-5-spirocycloalkanedione (Scheme 1).[2e]

As part of our program on the synthesis of spiro-heterocyclic compounds and the development of newselective and environmentally friendly methodologies for the preparation of these compounds, herein we report a three-component reaction between 5-amino-3-methyl-1-phenylpyrazole **5a**, β-diketones **3** and isatin **6** in aqueous media and catalytic *p*-TSA, leading to the formation of several pyrazolopyridine-spiroindolinone derivatives **7a–g** (Scheme 2, Table 1).[10]




**Scheme 1.**




**Scheme 2.**

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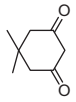
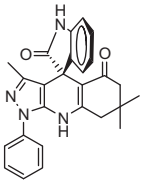
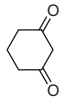
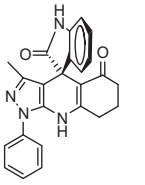
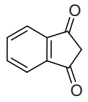
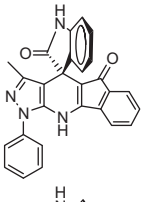
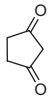
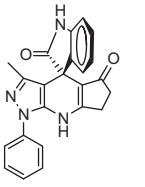
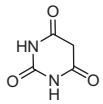
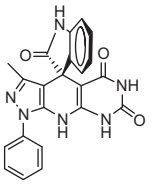
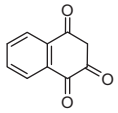
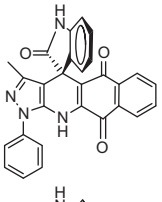
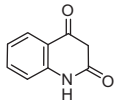
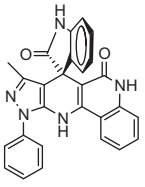
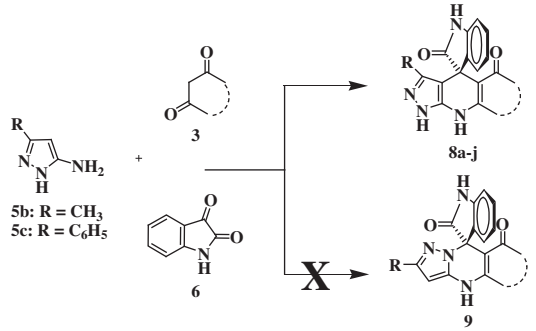
**Table 1**
Pyrazolopyridine-spiroindolinone derivatives **7a**–**g**

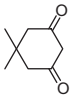
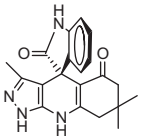
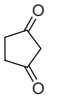
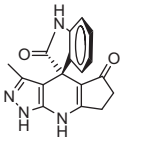
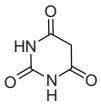
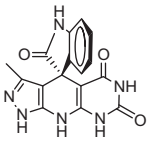
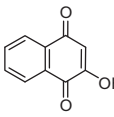
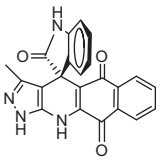
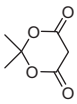
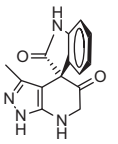
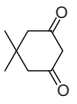
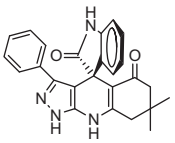
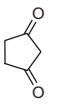
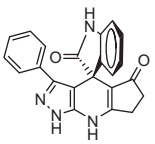
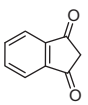
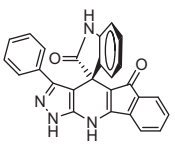
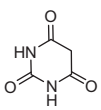
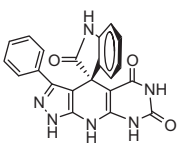
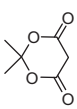
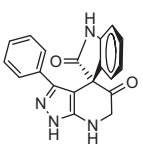
| Entry | β-Diketone | Product | Mp (°C) | Yield (%) | *m/z* |
|---|---|---|---|---|---|
| **a** |  |  | 241–243 | 75 | 424 |
| **b** |  |  | 315–318 | 78 | 396 |
| **c** |  |  | 304–305 | 45 | 430 |
| **d** |  |  | 335–337 | 72 | 382 |
| **e** |  |  | >350 | 77 | 412 |
| **f** |  |  | 304–307 | 70 | 458 |
| **g** |  |  | 298–300 | 52 | 445 |

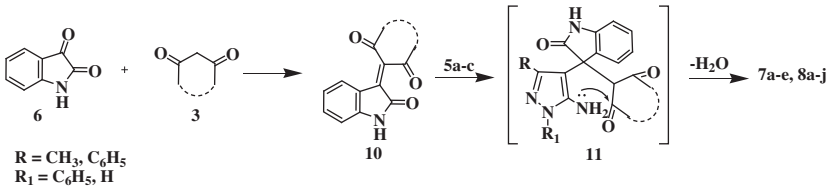



**Scheme 3.**

In order to evaluate the versatility and regiochemistry of this procedure we performed the three-component reaction, under the same reaction conditions,[10] between 5-amino-*1H*-pyrazoles **5b** and **5c**, β-diketones **3** and isatin **6**. The presence of a third nucleophilic center in the 1-*NH*-aminopyrazoles **5b**,**c**, could lead to the formation of spiro-pyrazolo[3,4-*b*]pyridines **8** or spiro-pyrazolo[1,5-*a*]pyrimidines **9** (Scheme 3).

**Table 2**
Pyrazolopyridine-spiroindolinone derivatives **8a**–**j**

| Entry | Pyrazole | β-Diketone | Product | Mp °C | Yield (%) | *m/z* |
|---|---|---|---|---|---|---|
| **a** | **5b** |  |  | 320–322 | 78 | 348 |
| **b** | **5b** |  |  | >350 | 65 | 306 |
| **c** | **5b** |  |  | >350 | 96 | 336 |
| **d** | **5b** |  |  | 333–335 | 75 | 382 |
| **e** | **5b** |  |  | 323–325 | 67 | 268 |
| **f** | **5c** |  |  | >350 | 60 | 410 |
| **g** | **5c** |  |  | >350 | 68 | 368 |
| **h** | **5c** |  |  | 318–320 | 49 | 416 |
| **i** | **5c** |  |  | >350 | 92 | 398 |
| **j** | **5c** |  |  | >350 | 75 | 330 |




**Scheme 4.**

The reaction showed a high regioselectivity. In all cases only a sole regioisomer **8** was obtained and in good yields (60–96%) (only one product, pyrazolo[3,4-*b*]pyridine-spiroindolinones **8a–j**) (Table 2). We consider that the formation of the pyrazolepyridine isomer **8** is due to the higher nucleophilicity of the C-4 over the N-1 in the aminopyrazole **5b**,**c**. This orientation has been observed by us in the reaction of N*H*-5-aminopyrazoles with dimedone and other carbonyl compounds.[8e,f]

The structures of all new compounds were determined on the basis of their analytical techniques, 1D and 2D NMR, and MS, spectroscopic data which agree with the proposed structures.

A possible mechanism for the established three-component reaction is outlined in Scheme 4. We consider that the β-diketone iniatilly reacts with isatin to give the condensation product **10**, which undergoes a Michel-type addition of 5-aminopyrazole **5a–c** followed by the cyclocondensation of the intermediate adduct **11** to give the corresponding products **7a–g** and **8a–j**.

In summary, the described three component synthesis in aqueous media is a simple, practical, environmentally friendly and very regioselective method for the preparation of some novel heterocyclic compound containing spiropyrazolopyridine system, with the advantages of easy work-up and mild reaction conditions. The biological and fluorescent properties of the new compounds obtained in this research are under investigation.

## Acknowledgements

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## References and notes

1. (a) Kuster, G. J. T.; van Berkom, L. W. A.; Kalmoua, M.; van Loevezijn, A.; Sliedregt, L. A. J. M.; van Steen, B. J.; Kruse, C. G.; Rutjes, F. P. J. T.; Scheeren, H. W. J. *Comb. Chem.* **2006**, *8*, 85–94; (b) Macleod, C.; Martinez-Teipel, B. I.; Barker, W. M.; Dolle, R. E. J. *Comb. Chem.* **2006**, *8*, 132–140; (c) Lang, G.; Pinkert, A.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2005**, *68*, 1796–1798; (d) Maier, C. A.; Wuensch, B. *J. Med. Chem.* **2002**, *45*, 438–448.
2. (a) Rahimizadeh, M.; Shiri, A.; Bakavoli, M. *Chin. Chem. Lett.* **2007**, *18*, 689–693; (b) Rolandsgard, M.; Baldawi, S.; Sirbu, D.; Bjørnstad, V.; Rømming, C.; Undheim, K. *Tetrahedron* **2005**, *61*, 4129–4140; (c) Arya, K.; Dandia, A. *J. Fluorine Chem.* **2007**, *128*, 224–231; (d) Marti, C.; Carrei, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219; (e) Quiroga, J.; Cruz, S.; Trilleras, J.; Pantoja, D.; Abonia, R.; Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2010**, *51*, 4717–4719; (f) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2006**, *47*, 27–30; (g) Rad-Moghadam, K.; Youseftabar-Miri, L. *Synlett* **2010**, 1969–1973.
3. Ratan Bal, T.; Anand, B.; Yogeeswari, P.; Sriram, Dh. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4451–4455.
4. Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109–2112.
5. Tripathy, R.; Reiboldt, A.; Messina, P. A.; Iqbal, M.; Singh, J.; Bacon, E. R.; Angeles, T. S.; Yang, S. X.; Albom, M. S.; Robinson, C.; Chang, H.; Ruggeri, B. A.; Mallamo, J. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2158–2162.
6. Amal Raj, A.; Raghunathan, R.; Sridevikumaria, M. R.; Raman, N. *Bioorg. Med. Chem.* **2003**, *11*, 407–419.
7. Verma, M.; Nath Pandeya, S.; Nand Singh, K.; Stables, J. P. *Acta Pharm.* **2004**, *54*, 49–54.
8. (a) Quiroga, J.; Trilleras, J.; Insuasty, B.; Abonía, R.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2008**, *49*, 2689–2691; (b) Quiroga, J.; Trilleras, J.; Insuasty, B.; Abonía, R.; Nogueras, M.; Marchal, A.; Cobo, J. *Tetrahedron Lett.* **2008**, *49*, 3257–3259; (c) Quiroga, J.; Insuasty, B.; Insuasty, H.; Abonía, R.; Ortíz, A. J.; Sánchez, A.; Nogueras, M. *J. Heterocycl. Chem.* **2001**, *38*, 339–341; (d) Quiroga, J.; Hormaza, A.; Insuasty, B.; Ortíz, A. J.; Sánchez, A.; Nogueras, M. *J. Heterocycl. Chem.* **1998**, *35*, 231–233; (e) Quiroga, J.; Hormaza, A.; Insuasty, B.; Saitz, C.; Jullian, C. *J. Heterocycl. Chem.* **1998**, *35*, 575–578; (f) Quiroga, J.; Mejía, D.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *Tetrahedron* **2001**, *57*, 6947–6953.
9. (a) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Hernandez, P.; Bolaños, A.; Moreno, R. *J. Heterocycl. Chem.* **1998**, *35*, 333–338; Orlov, V. D.; Quiroga, J.; Kolos, N. N. *Khim. Geterosikl. Soedin.* **1987**, 1247–1251. CA: 88, 167373; (c) Quiroga, J.; Portilla, J.; Serrano, H.; Abonía, R.; Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2007**, *48*, 1987–1990; (d) Quiroga, J.; Cobo, D.; Insuasty, B.; Abonía, R.; Cruz, S.; Nogueras, M.; Cobo, J. *J. Heterocycl. Chem.* **2008**, *45*, 155–159; (e) Quiroga, J.; Trilleras, J.; Sánchez, A. I.; Insuasty, B.; Abonía, R.; Nogueras, M.; Cobo, J. *Lett. Org. Chem.* **2009**, *6*, 381–383.
10. *General procedure for the preparation of pyrazolopyridine-spiroindolinones* **7a–g** and **8a–j**. A solution of 5-aminopyrazole **5a–c** (0.1 mmol), β-diketone **3** (0.1 mmol) and isatin **6** (0.1 mmol) in $H_2O$/EtOH [5:1 (v/v))] and a catalytic amounts of PTSA (0.1 g) was heated at 80 °C (water bath) for 6–12 h. Then, the reaction mixture was filtered hot and the resulting solid products were washed with ethanol, dried in air and recrystallized from ethanol.
*Data for (±)-3,7,7-trimethyl-1-phenyl-6,7,8,9-tetrahydrospiro[pyrazolo[3,4-b]quinoline-4,3′-indoline]-2′,5(1H)-dione* **7a**: Beige solid, yield 75%, 241–243 °C. $^1$H NMR (400 MHz DMSO-$d_6$) $\delta$: 1.00 (s, 3H, $CH_3$-7), 1.03 (s, 3H, $CH_3$-7), 1.57 (s, 3H, $CH_3$-3), 2.00 (d, 1H, H-6 $J$ = 16.0 Hz), 2.11 (d, 1H, H-6 $J$ = 16.0 Hz), 2.58 (s, 2H, H-8), 6.81 (d, 1H, H-7′), 6.85–6.87 (m, 2H, H-4′, H-5′), 7.09–7.13 (m, 1H, H-6′), 7.40–7.44 (m, 1H, $H_p$), 7.51–7.57 (m, 4H, $H_m$, $H_o$), 9.68 (s, 1H, H-9), 10.32 (s, 1H, H-1′). $^{13}$C NMR (100 MHz DMSO-$d_6$) $\delta$: 11.8 ($CH_3$-3), 27.4 ($CH_3$-7), 28.6 ($CH_3$-7), 32.6 (C-7), 41.4 (C-8), 49.2 ($C_{spiro}$), 50.9 ($CH_2$-6), 102.1 (C-3a), 108.4 (C-4a), 109.0 (C-7′), 121.9 (C-5′), 123.6 (C-4′), 123.9 ($C_o$), 127.6 ($C_p$), 127.7 (C-6′), 129.9 ($C_m$), 137.1 (C-3a′), 137.5 ($C_i$), 138.3 (C-9a), 142.2 (C-7a′), 145.5 (C-3), 153.5 (C-8a), 180.0 (C-2′), 193.8 (C-5). IE EM: $m/z$: 424 ($M^+$, 7), 380 (8), 340 (100), 312 (19). Anal. Calcd for $C_{26}H_{24}N_4O_2.H_2O$: C, 70.57; H, 5.92; N, 12.66; found: C, 70.81; H, 5.99; N, 12.70.
*Data for (±)-3,7,7-trimethyl-6,7,8,9-tetrahydrospiro[pyrazolo[3,4-b]quinoline-4,3′-indoline]-2′,5(1H)-dione* **8a**: Beige solid, yield 78%, 320–322 °C. $^1$H NMR (400 MHz DMSO-$d_6$) $\delta$: 1.00 (s, 3H, $CH_3$-7), 1.03 (s, 3H, $CH_3$-7), 1.58 (s, 3H, $CH_3$-3), 1.94 (d, 1H, H-6 $J$ = 16.00 Hz), 2.06 (d, 1H, H-6 $J$ = 16.0 Hz), 2.44 (s, 1H, H-8 $J$ = 16.0 Hz), 2.51 (s, 1H, H-8 $J$ = 16.0 Hz), 6.73–6.81 (m, 3H, H-7′, H-4′, H-5′), 7.05 (dd, 1H, H-6′), 9.94 (s, 1H, H-9), 10.16 (s, 1H, H-1′), 11.89 (s, 1H, H-1). $^{13}$C NMR (100 MHz DMSO-$d_6$) $\delta$: 9.1 ($CH_3$-3), 27.5 ($CH_3$-7), 28.7 ($CH_3$-7), 32,5 (C-7), 41.8 (C-8), 48.7 ($C_{spiro}$), 50.9 (C-6), 101.9 (C-3a), 105.7 (C-4a), 108.8 (C-7′), 121.7 (C-5′), 123.0 (C-4′), 127.2 (C-6′), 134.9 (C-9a), 138.1 (C-3a′), 142.1 (C-7a′), 146.5 (C-3), 154.6 (C-8a),180.2 (C-2′), 192,6 (C-5). IE EM: $m/z$: 348 ($M^+$, 20), 304 (10), 264 (100), 236 (15). Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08; found: C, 68.97; H, 5.75; N, 16.09.