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Highly efficient synthesis of 3-pyrrolyl-indolinones and pyrrolyl-indeno[1,2-*b*]quinoxalines catalyzed by heteropolyacids

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ABSTRACT

Simple and improved conditions have been found for the synthesis of 3-pyrrolyl-indolinones and pyrrolyl-indeno[1,2-*b*]quinoxalines by coupling of 4-hydroxyproline with isatins and 11*H*-indeno[1,2-*b*]quinoxalin-11-ones using Keggin ($H_3PW_{12}O_{40}$) and Well–Dawson tungsten heteropolyacids ($H_6P_2W_{18}O_{62}$).

Pyrrole derivatives are important in organic chemistry because they are present in many natural, medicinal and agricultural products, and in semiconductor polymers. They are also very convenient precursors for biologically important compounds such as indolizidine alkaloids, bicyclic lactams and unsaturated γ-lactams.[1–6]

The pyrrole unit is found in many naturally occurring compounds such as heme, chlorophyll and vitamin B_{12}.[6–8] It is also found in various bioactive drug molecules such as atorvastatin, anti-inflammatories, antitumour agents and immunosuppressants.[8–12] They are very useful intermediates not only for the synthesis of drugs, pigments and pharmaceuticals, but also for the development of organic functional materials.[13,14] As a result, a large number of synthetic methods for the preparation of pyrrole derivatives have been reported in the literature.[15–18] Hence, the development of effective and selective methods for obtaining pyrrole derivatives is desirable.

One such method developed by us is the reaction of 4-hydroxyproline with carbonyl compounds such as isatins and 11*H*-indeno[1,2-*b*]quinoxalin-11-ones to generate interesting pyrroles.[19–21] The reactions were carried out on a solid support such as Montmorillonite K10 or silica sulfuric acid under microwave irradiation. Recently, catalysts such as $Dy(OTf)_3$,[22] I_2[23] and $Bi(NO_3)_3{\cdot}5H_2O$[24] were reported for this condensation.

Due to the superacidic properties of heteropolyacids (HPAs), they have found numerous applications as useful and versatile acid catalysts.[25]

They are solids that are insoluble in non-polar solvents but are highly soluble in polar ones. They can be used in bulk or supported forms in both homogeneous and heterogeneous systems. Furthermore, heteropolyacids have several advantages, including high flexibility in modification of the acid strength, ease of handling, environmental compatibility, nontoxicity and experimental simplicity.[25–28]

In spite of the potential utility of the aforementioned routes for the synthesis of 3-pyrrolyl-indolinones and pyrrolyl-indeno[1,2-*b*]-quinoxalines, some of the methods suffer from drawbacks such as use of hazardous organic solvents, toxic catalysts and high cost. Hence, the development of a new and efficient catalyst with high catalytic activity, short reaction time, recyclability and simple work-up procedure for the preparation of the above mentioned compounds under neutral, mild and practical conditions is of prime interest. The aim of this study is to utilize the Keggin (PW) and Well–Dawson (WD) tungsten heteropolyacids as catalysts for the synthesis of 3-pyrrolyl-indolinones **3a–e** and pyrrolyl-indeno[1,2-*b*]quinoxalines **4a–c** by coupling of 4-hydroxyproline with isatins **1a–e** or 11*H*-indeno[1,2-*b*]quinoxalin-11-ones **2a–c** (Scheme 1).

After some experimentation with respect to the catalytic amount of the HPA (PW [$H_3PW_{12}O_{40}$] or WD [$H_6P_2W_{18}O_{62}$]), different solvents and reaction temperatures, optimized conditions were established (Table 1). In the absence of HPA, the reaction did not yield the desired product (Table 1, entry 1).

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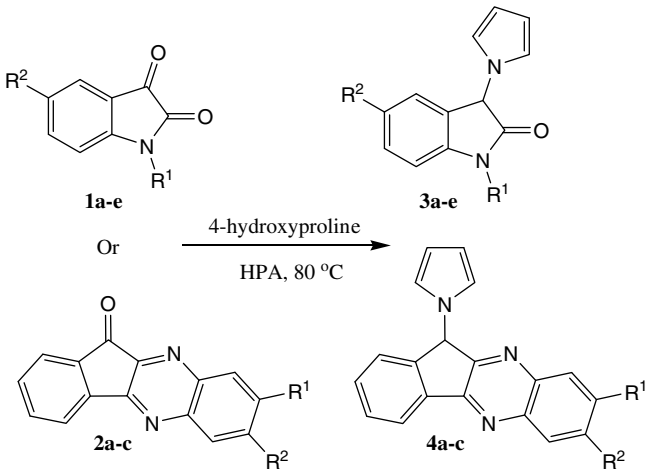
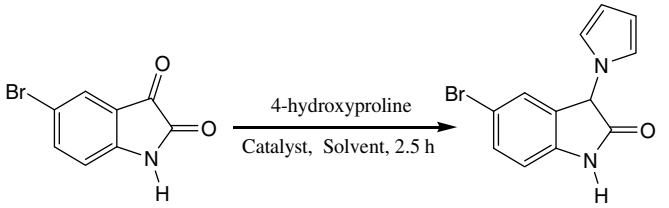


Scheme 1.

The best yields were obtained in C_2H_5OH–H_2O (2:1) compared to a variety of other solvents tested (Table 1, entries 3–6). The starting materials were mixed with heteropolyacid (1–2 mol %) in C_2H_5OH–H_2O (2:1), and the solution was kept at 80 °C for the specified time.

A diverse set of pyrroles were synthesized under these optimized conditions (Table 1, entries 3–6). Isatins **1a**–**e** and 11 *H*-indeno[1,2-*b*]quinoxalin-11-ones **2a**–**c** were reacted with 4-hydroxyproline to test the generality of this new method (Table 2).

Table 1
Effect of catalysts under different reaction conditions for the condensation of 4-hydroxyproline with 5-bromoisatin



Entry	Catalyst (mol %)	Temperature (°C)	Solvent	Yield (%)
1	–	80	C_2H_5OH–H_2O (2:1)	–
2	PW (2)	80	C_2H_5OH	25
3	PW (1)	80	C_2H_5OH–H_2O (2:1)	85
4	PW (2)	80	C_2H_5OH–H_2O (2:1)	92
5	WD (1)	80	C_2H_5OH–H_2O (2:1)	86
6	WD (2)	80	C_2H_5OH–H_2O (2:1)	88
7	PW (2)	80	CH_3CN	13
8	PW (2)	80	CH_3CN–H_2O	50
9	WD (1)	80	CH_3CN–H_2O	45
10	PW (2)	80	DMSO	15
11	PW (2)	80	DMSO–H_2O	35
12	PW (2)	rt	C_2H_5OH–H_2O (2:1)	–

The condensation proceeded with Keggin (PW) or Well–Dawson (WD) heteropolyacids and resulted in formation of the corresponding pyrroles in high yields.

A catalytic amount (1–2 mol %) of the catalyst was found to be the most effective. For example, in the presence of 2 mol % of PW,

Table 2
Preparation of 3-pyrrolyl-indolinones and pyrrolyl-indeno[1,2-*b*]quinoxalines catalyzed by heteropolyacids

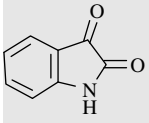
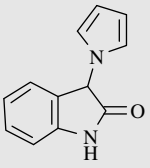
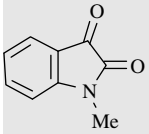
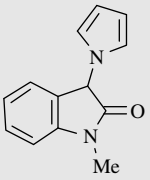
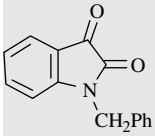
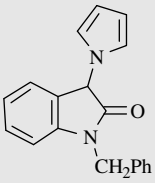
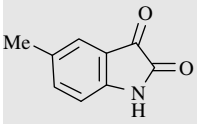
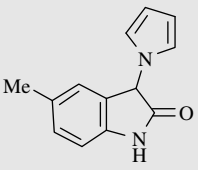
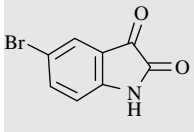
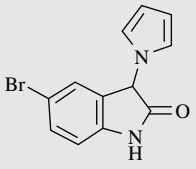
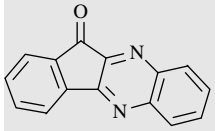
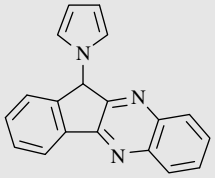
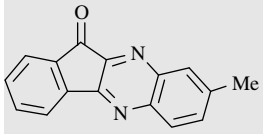
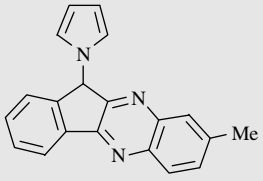
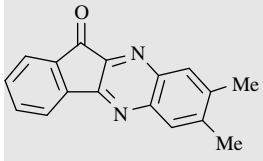
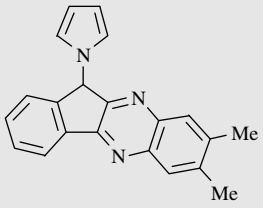
Substrate	Catalyst	Time (h)	Product	Yield (%)	Mp (°C)
 **1a**	PW (2) WD (1)	2.5 2.5	 **3a**	87 82	142–144
 **1b**	PW (2) WD (1)	2.5 2.5	 **3b**	86 82	134–136
 **1c**	PW (2) WD (1)	2.5 2.5	 **3c**	87 83	125–127
 **1d**	PW (2) WD (1)	2.5 2.5	 **3d**	85 82	165–166

Table 2 (*continued*)

Substrate	Catalyst	Time (h)	Product	Yield (%)	Mp (°C)
 **1e**	PW (2) WD (1)	2.5 2.5	 **3e**	92 86	173–174
 **2a**	PW (2) WD (1)	3 3	 **4a**	82 79	181–182
 **2b**	PW (2) WD (1)	3 3	 **4b**	82 78	192–194
 **2c**	PW (2) WD (1)	3 3	 **4c**	81 79	230–232

the reaction of 5-bromoisatin with 4-hydroxyproline in ethanol–water was complete in 2.5 h with 92% conversion of the reactant. Also the Well–Dawson catalyst showed high activity for this reaction (Table 1, entries 5–6).

Acetonitrile, ethanol and DMSO as solvent resulted in poor yields of the desired pyrroles (Table 1, entries 2, 7 and 10).

The products **3a–e** and **4a–c** are known compounds, and their structures were deduced by comparison of their physical and spectroscopic data with those previously reported.[20–22,29]

In conclusion, we have demonstrated an alternative and simple procedure for the synthesis of some interesting pyrroles using Keggin or Well–Dawson heteropolyacids as ecofriendly, reusable, inexpensive and efficient catalysts. High yields, relatively short reaction times and easy work-up are some advantages of this protocol.

Acknowledgement

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References and notes

1. Ragno, R.; Marshall, G. R.; Di Santo, R.; Costi, R.; Massa, S.; Rompei, R.; Artico, M. *Bioorg. Med. Chem.* **2000**, *8*, 1423.
2. Franc, C.; Denone, F.; Cuisiner, C.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 4555.
3. Liu, J.; Yang, Q.; Mak, T. C.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587.
4. Dieter, R. K.; Yu, H. *Org. Lett.* **2000**, *2*, 2283.
5. Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511.
6. Amos, R. I. J.; Gourlay, B. S.; Molesworth, P. P.; Smith, J. A.; Sprod, O. R. *Tetrahedron* **2005**, *61*, 8226.
7. Di Santo, R.; Costi, R.; Artico, M.; Massa, S.; Lampis, G.; Deidda, D.; Rompei, R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2931.
8. De Leon, C. Y.; Ganem, B. *Tetrahedron* **1997**, *53*, 7731.
9. Thompson, R. B. *FASEB J.* **2001**, *15*, 1671.
10. Cozzi, P.; Mongelli, N. *Curr. Pharm. Des.* **1998**, *4*, 181.
11. Furstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305.
12. Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109.
13. Lainton, J. A. H.; Hoffman, J. W.; Martin, B. R.; Compton, D. R. *Tetrahedron Lett.* **1995**, *36*, 1401.
14. Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977; pp 1–5.
15. Gilchrist, T. L. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 615.
16. Yu, S.-X.; Le Quesne, P. W. *Tetrahedron Lett.* **1995**, *36*, 6205.
17. Paal, C. *Chem. Ber.* **1884**, *17*, 2756.
18. Knorr, L. *Chem. Ber.* **1884**, *17*, 2863.
19. Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *J. Org. Chem.* **2005**, *70*, 1471.
20. Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Tetrahedron Lett.* **2005**, *46*, 6155.
21. Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Synthesis* **2005**, 1095.
22. Yadav, J. S.; Subba Reddy, B. V.; Jain, R.; Suresh Reddy, Ch. *Tetrahedron Lett.* **2007**, *48*, 3295.
23. Yadav, J. S.; Subba Reddy, B. V.; Jain, R.; Subba Reddy, U. V. *J. Mol. Catal. A: Chem.* **2007**, *278*, 38.
24. Banik, B. K.; Cardona, M. *Tetrahedron Lett.* **2006**, *47*, 7385.
25. Kozhhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171.
26. Kozhhevnikov, I. V. In *Catalysis for Fine Chemical Synthesis, Catalysis by Polyoxometalates 2*; Derouane, E., Ed.; Wiley: New York, 2002.
27. Romanelli, G. P.; Bennardi, D.; Ruiz, D. M.; Baronetti, G.; Thomas, H. J.; Autino, J. C. *Tetrahedron Lett.* **2004**, *45*, 8935.
28. Amini, M. M.; Shaabani, A. *Catal. Commun.* **2006**, *7*, 843.
29. *General procedure for the preparation of products*: A mixture of 4-hydroxyproline (1 mmol), isatin **1a** (1 mmol) and PW acid (2 mol %, 0.06 g) or WD acid (1 mol %, 0.05 g) in 15 mL of ethanol–water (2:1) was stirred at

80 °C for 2.5 h (Table 2). On completion of the reaction, as indicated by TLC, the resulting mixture was poured into water, and the product was separated and recrystallized from ethanol–water (5:1) to yield pure 3-(1*H*-pyrrol-1-yl)indolin-2-one **3a**. The products were identified by ^{1}H NMR, and by comparison with physical data with those reported in the literature.[15–17]

Spectral data for compound **3e**: mp 173–175 °C, IR (KBr) (ν_{max}, cm^{-1}): 3241, 1712, 1614, 1488; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H: 5.52 (1H, s, CH), 6.29 (2H, br s, $CH_{pyrrole}$), 6.70 (2H, br s, $CH_{pyrrole}$), 6.87–7.48 (3H, m, Arom), 8.63 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C: 60.72 (CH), 109.87, 111.95 (4$CH_{pyrrole}$), 115.84, 120.41, 127.16, 128.44, 133.18, 140.29 (arom), 173.98 (C=O).