Communication

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A Modified and Practical Synthetic Route to Indazoles and Pyrazoles Using Tungstate Sulfuric Acid

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Tungstate sulfuric acid-catalyzed Knorr reaction have been used as a simple, rapid, atom economic and green method for the synthesis of indazole and pyrazole derivatives based on the condensation of hydrazine derivatives and β-dicarbonyl compounds under solvent-free conditions. It was found that the catalyst could be recovered and reused without significant loss of its activity. The use of this method provides a novel and improved modification of Knorr synthesis in terms of clean reaction profile, use of a safe catalyst and solvent-free conditions.

Keywords: Tungstate sulfuric acid; Hydrazine; Knorr; Indazole; Pyrazole.

INTRODUCTION

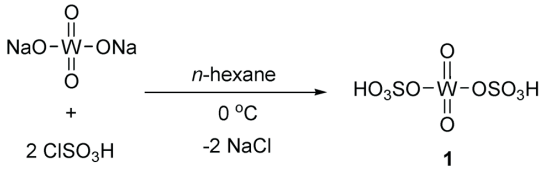
Among the organic compounds, aza-heterocycles such as pyrazole and indazole derivatives, which present considerable biological importance,[1,2] are embedded in a wide range of natural products and medicinal synthetic compounds exerting anti-aggregatory,[3] anti-arrhythmic,[4] muscle relaxing,[5] and anti-diabetic activities.[6] For example, *Celecoxib* is a pyrazole derivative used as an analgesic.[7] The term "pyrazole" was given to this class of compounds by Ludwig Knorr in 1883.[8] Although there are many ways to prepare pyrazole ring, the condensation of the 1,3-dicarbonyls with hydrazine derivatives remains the most common and facile method to assemble this ring system. Many of the reported methods for the Knorr synthesis of pyrazoles suffer from drawbacks, such as the use of organic solvent and unrecoverable catalyst,[9] harsh reaction conditions,[10] and long reaction times.[11]

RESULTS AND DISCUSSION

The challenge in chemistry is to develop practical methods with convenient conditions and reagents, and the concept of "green chemistry" is becoming ever important in the scientific community. We found that anhydrous sodium tungstate reacts with chlorosulfonic acid (1:2 mole ratio) to give tungstate sulfuric acid (TSA **1**). The reaction is easy and clean and no gas is generated during the reaction (Scheme 1).[12]

In connection with our studies on the catalyzed organic reactions,[13-16] herein, we describe a new and green strategy for the synthesis of pyrazole derivatives **9-13** and indazoles **14** from the reaction of hydrazine derivatives **2** with β-dicarbonyls **3-8** using tungstate sulfuric acid (TSA) (Scheme 2). TSA has proved as a powerful, safe, and recyclable catalyst under solvent-free conditions. Solid phase reactions are considered "green" because they eliminate a huge amount of waste (the spent solvent) and require less energy to isolate the product (solvent removal is obviously not an issue).[17]

Scheme 1 Preparation of tungstate sulfuric acid (**1**)



Interests in the environmental control of chemical processes have increased remarkably during the last three decades as a response to public concern about the use of hazardous chemicals. Therefore, to improve the effectiveness of this method in preventing chemical waste, it is important to investigate optimal reaction conditions. To determine the suitable reaction conditions, the reaction of hydrazine (**2a**) with acetylacetone (**3**) was taken as a model reaction. At first, we found that in the absence of TSA **1**, the reaction did not complete in long reaction times (240 min) even at a high temperature (Table 1). After examination of the various amounts of **1** at 80 °C, we found that the reaction can be efficiently carried out by adding 10 mol% of the

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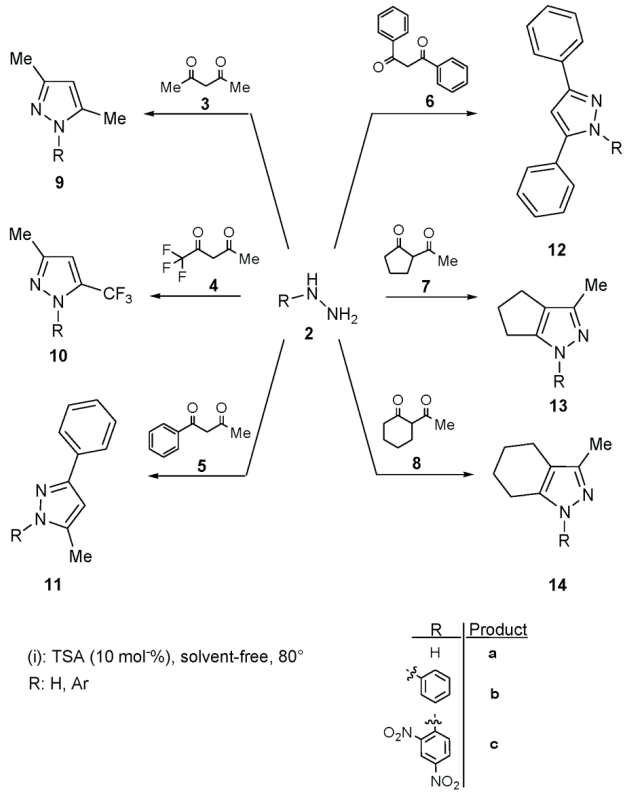
Scheme 2 Preparation of pyrazoles and indazoles using tungstate sulfuric acid (**1**)



catalyst under solvent-free conditions in a short time span of 5 min. The use of excess amounts of the catalyst did not have a marked influence on the product yield or reaction rate. The probable reason for this is the coordination of excessive catalyst to the hydrazine.

According to Table 2, under optimized reaction conditions, various β-dicarbonls were allowed to undergo reaction with hydrazine derivatives in a molar ratio of 1:1 with catalyst affording product **9-14** in good to excellent yields.

The ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of **11c** exhibited a singlet of the methyl group protons (δ = 2.36), a singlet of the pyrazole ring methyne group proton (δ = 6.42). Four doublet signals (7.23, 7.44, 7.68 and 8.34) and multiplet signal (δ = 7.38-7.33) corresponding to the aromatic protons. The proton decoupled ^{13}C NMR spectrum of **11c** also showed 14 distinct resonances in agreement with the proposed structure.

Not only the ecological profile (through helping to decrease hazardous industrial waste), but also the economic profile (through the elimination of expensive organic solvent) is further improved if the catalyst is recyclable and the reaction proceeded under solvent-free conditions. In this process, the recycled catalyst was used for four cycles during which a little appreciable loss was observed in the catalytic activities (Fig. 1).

A plausible mechanism for the synthesis of **9-14** and recyclability of TSA was proposed in Scheme 3.

Table 1. Optimization of the reaction conditions

Entry	Catalyst [mol%]/ Temperature [°C]	Time [min]	Yield [%]
1	-/25	240	trace
2	-/80	240	10
3	-/120	240	25
4	5/25	240	50
5	5/80	25	85
6	5/120	20	70
7	10/25	240	70
8	10/80	5	95
9	10/120	5	85
10	20/80	15	85

Table 2. Synthesis of indazoles and pyrazoles using TSA (**1**) at 80 °C under solvent-free conditions

Entry	Product[a]	Time [min]	Yield [%]	M.p. [°C]
1	**9a**	5	95	109-111 [22]
2	**9b**	5	90	Oil [23]
3	**9c**	40	85	121-123 [23]
4	**10a**	10	90	79-81 [24]
5	**10b**	10	90	Oil [24]
6	**10c**	100	80	94-96 [24]
7	**11a**	10	87	127-128 [25]
8	**11b**	10	85	Oil [23]
9	**11c**	40	85	128 [26]
10	**12a**	30	85	200-202 [25]
11	**12b**	25	87	140-142 [27]
12	**12c**	100	83	152-154 [28]
13	**13b**	30	82	Oil [-]
14	**13c**	20	80	165-167 [-]
15	**14a**	20	80	150-152 [29]
16	**14b**	35	85	Oil [30]
17	**14c**	20	80	175-177 [-]

[a] Yield of Isolated products.

EXPERIMENTAL

General: Chemicals were purchased from Merck and Aldrich. The TSA was prepared according to our previously published works.[18-21] The progress of the reactions was monitored by TLC (silica gel 60 F_{254}, *n*-hexane/AcOEt). IR spectra (KBr disc) were recorded on a FT-IR Shimadzu-470 spectrometer and the ^{1}H NMR spectra were recorded on a Bruker-Instrument DPX-400

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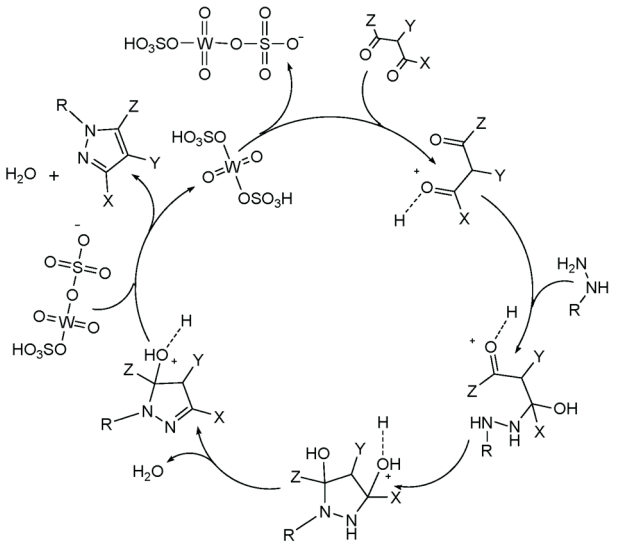
Scheme 3 Proposed mechanism for the hedrazines condensation with β-dicaronyl compounds using TSA (**1**)



Avance 2 model. Known products were characterized by comparison of their spectra and physical data with those reported in the literature.[22-30]

Preparation of Pyrazoles and Indazoles Using TSA (1): A mixture of hydrazine **2** (1 mmol), β-dicarbonyl **3-8** (1 mmol) and TSA (0.1 mmol) was stirred and heated at 80 °C in a preheated oil bath for an appropriate time. After completion of the reaction as indicated by TLC (AcOEt/*n*-hexane, 1:4), the reaction mixture was dissolved in hot EtOH and catalyst was separated by filtration. The solvent was evaporated and the products **9-14** were purified by recrystallization in EtOH. The separated catalyst was washed with diethyl ether, dried at 70 °C for 45 min, and reused in another reaction.

Selected Spectral Data: 5-Methyl-1,3-diphenyl-1H-pyrazole (**11b**): IR (KBr): 3095, 2950, 1650, 1500, 1390. ^{1}H-NMR (400 MHz, DMSO-d_6): 7.33-7.24 (m, 10 H); 6.35 (s, 1 H); 2.43 (s, 3 H). ^{13}C-NMR (100 MHz, DMSO-d_6): 149.47, 143.73, 140.21, 130.79, 128.9, 128.68, 128.47, 127.14, 127.07, 125.17, 107.86, 13.67. **1-(2,4-Dinitrophenyl)-5-methyl-3-phenyl-1H-pyrazole** (**11c**): IR: 3120, 2990, 1650, 1610, 1510v*s*, 1390. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.68 (d, J = 2, 1 H); 8.33 (d, J = 8.4, 1 H); 7.43 (d, J = 8.4, 1 H); 7.35-7.22 (m, 5 H); 6.42 (s, 1 H); 2.36 (s, 3 H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.69. 145.73, 145.29, 145.00, 139.2, 129.69, 129.56, 129.23, 127.00, 120.85, 109.43. **3,5-Diphenyl-1H-pyrazole** (**12a**): IR (KBr): 3300, 3100, 2920, 1490. ^{1}H-NMR (400 MHz, DMSO-d_6): 7.20 (s, 1 H); 7.51-7.31 (m, 5 H); 7.90, 7.83 (two d, J = 7.2, 5 H,); 13.41 (s, 1 H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.30, 146.03, 145.37, 137.18, 136.28, 128.77, 128.29, 121.52, 117.08. **3-Methyl-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole** (**13b**): IR (KBr): 3114, 2987, 1649, 1598, 1463, 1221. ^{1}H-NMR (400 MHz, DMSO-d_6): 7.14-7.61 (m, 5 H); 2.98 (m, 2 H); 2.56 (s, 4 H); 2.15 (s, 3 H). ^{13}C-NMR (100 MHz, DMSO-d_6): 148.98, 143.44, 140.46, 129.34, 128.35, 122.37, 118.37, 30.97, 26.70, 22.19, 13.01. **1-(2,4-Dinitrophenyl)-3-methyl-1,4,5,6-tetrahydrocyclopenta [c]pyrazole** (**13c**): IR (KBr): 3055, 2990, 1610, 1510, 1370. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.95 (*s*, J = 2.4, 1 H); 8.66 (*dd*, J = 8.2, 2.4, 1 H); 7.75 (*d*, J = 8.4, 1 H); 2.80 (m, 2 H); 2.62 (s, 4 H); 2.21 (s, 3 H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.30, 146.03, 145.37, 137.28, 126.28, 128.77, 128.28, 121.52, 117.08, 32.15, 23.19, 20.34, 12.40. **1-(2,4-Dinitrophenyl)-3-methyl-4,5,6,7-tetrahydro-1H-indazole** (**14c**): IR (KBr): 3060, 2980, 1600, 1510, 1380. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.84 (d, J = 2.4, 1 H); 8.57 (dd, J = 8.8, 2.4, 1 H); 7.99 (d, J = 8.8, 1 H); 2.48 (s, 3 H); 2.25 (*s*, 3 H); 1.72 (d, J = 4.4, 5 H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.30, 146.03, 145.37, 137.28, 126.28, 128.77, 128.28, 121.52, 117.08, 33.35, 23.16, 23.09, 20.29, 10.41.

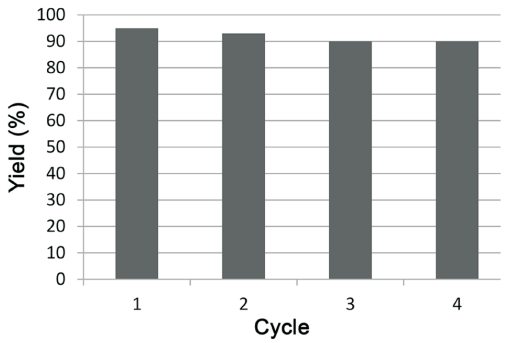


Fig. 1. Recyclability of TSA in the synthesis of **9a** under uptimized conditions.

CONCLUSIONS

In summary, a new catalytic application of TSA as a highly efficient and green solid acid catalyst to synthesize indazoles and pyrazoles was presented. Simple experimental procedure, utilization of a clean and recyclable catalyst, the use of readily available starting materials, short period of reactions and good to excellent yields make this method a valid contribution to the existing methodologies.

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REFERENCES

1. Mangalagiu, I. I. *Curr. Org. Chem.* **2011**, *15*, 730.

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2. Eller, G. A.; Holzer, W. *Molecules* **2007**, *12*, 60.
3. Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; de Ocariz, C. O. *Mini Rev. Med. Chem.* **2005**, *5*, 869.
4. Bondavalli, F.; Bruno, O.; Ranise, A.; Schenone, P.; Addonizio, P.; De, N. V.; Loffreda, A.; Marmo, E. *Farmaco Sci.* **1988**, *43*, 725
5. Ram, V. J.; Pandey, H. *Arch. der Pharma.* **1979**, *312*, 703.
6. Rathish, G. I.; Javed, K.; Bano, S.; Ahmad, S.; Alam, M. S.; Pillai, K. K. *Eur. J. Med. Chem.* **2009**, *44*, 2673.
7. Reuben, S. S.; Buvanendran, A.; Kroin, J. S.; Raghunathan, K. *Pain. Med.* **2006**, *103*, 1271.
8. Knorr, L. *Ber Dtsch. Chem. Ges.* **1883**, *16*, 2597.
9. Stoit, A. R.; Lange, J. H. M.; den Hartog, A. P.; Ronken, E.; Tipker, K.; van Stuivenberg, H. H.; Dijksman, J. A. R.; Wals, H. C.; Kruse, C. G. *Chem. Pharm. Bull.* **2002**, *50*, 1109.
10. Gosselin, F.; O'Shea, P. D.; Webster, R. A.; Reamer, R. A.; Tillyer, R. D.; Grabowski, E. J. J. *Synlett* **2006**, 3267.
11. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogbum, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem*. **1997**, *40*, 1347.
12. Karami, B.; Khodabakhshi, S.; Nikrooz, M. *J. Chin. Chem. Soc.* **2012**, *59*, 187.
13. Khodabakhshi S.; Baghernejad, M. *J. Chin. Chem. Soc.* **2013**, *60*, 495.
14. Karami, B.; Khodabakhshi, S.; Nikrooz, M. *Polycyclic Aromat. Compds.* **2011**, *31*, 97.
15. Khodabakhshi, S.; Karami, B. *Catal. Sci. Technol.* **2012**, *2*, 1940.
16. Khodabakhshi, S.; Baghernejad, M. *J. Chin. Chem. Soc.* **2014**, *61*, 521.
17. Jacob, R. G.; Radatz, C. S.; Rodrigues, M. B.; Alves, D.; Perin, G.; Lenardão, E. J.; Savegnago, L. *Heteroat. Chem.* **2011**, *22*, 180.
18. Karami, B.; Khodabakhshi, S.; Haghighijou, Z. *Chem. Pap.* **2012**, *66*, 684.
19. Karami, B.; Taei, M.; Khodabakhshi, S.; Jamshidi, M. *J. Sulfur Chem.* **2012**, *33*, 65.
20. Karami, B.; Khodabakhshi, S.; Safikhani, N.; Arami, A. *Bull. Korean Chem. Soc.* **2012**, *33*, 123.
21. Kamaei, V.; Karami, B.; Khodabakhshi, S. *Polycyclic Aromat. Compds.* **2014**, *34*, 1.
22. Chen, X.; She, J.; Shang, Z.; Wu, J.; Wu, H.; Zhang, P. *Synthesis* **2008**, *21*, 3478.
23. Xiong, W.; Chen, J. X.; Liu, M. C.; Ding, J. C.; Wu, H. Y.; Su, W. K. *J. Braz. Chem. Soc.* **2009**, *20*, 367.
24. Sloop, J. C.; Lechner, B.; Washington, G.; Bumgardner, C. L.; Creasy, W.; Loehle, W. D. *Int. J. Chem. Kinet.* **2008**, *40*, 370
25. Wang, Z.; Qin, H. *Green Chem*. **2004**, *6*, 90.
26. Curini, M.; Rosati, O.; Campagna, V.; Montanari, F.; Cravotto, G.; Boccalini, M. *Synlett* **2005**, *19*, 2927.
27. Sreekumar, R.; Padmakumar, R. *Synth. Commun*. **1998**, *28*, 1661.
28. Mirjalili, B. F.; Bamoniri, A.; Amrollahi, M. A.; Emtiazi, H. *Dig. J. Nanomat. Bios.* **2010**, *5*, 897.
29. Nakhai, A. Bergman, J. *Tetrahedron* **2009**, *65*, 2298.
30. Curini, M.; Rosati, O.; Campagna, V.; Montanari, F.; Cravotto, G.; Boccalini, M. *Synlett* **2005**, *19*, 2927.

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