Layered Zirconium Sulfophenyl Phosphonate as Heterogeneous Catalyst in the Synthesis of Pyrazoles and 4,5,6,7-Tetrahydro-1(2)*H*-indazoles

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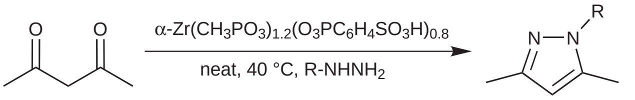
Abstract: Pyrazoles and tetrahydroindazoles may be prepared by condensation of 1,3-diones and hydrazines under layered zirconium sulfophenyl phosphonate catalysis, in solvent-free conditions.

Key words: zirconium sulfophenyl phosphonate, heterogeneous catalysis, solvent free reactions, pyrazoles, indazoles

Surface-mediated solid-phase reactions are of growing interest due to their ease of set-up, mild reaction conditions, rapid reaction, selectivity, increased yield, high purity of compounds and low cost compared with their homogeneous counterparts.[1] We have recently reported that layered zirconium sulfophenyl phosphonate [α-$Zr(CH_3PO_3)_{1,2}(O_3PC_6H_4SO_3H)_{0,8}$] (acid strength H_0 should lie between –5.6 and –8.2)[2] is an excellent heterogeneous catalyst in organic liquid phase synthesis.[3] In continuation of our ongoing effort to develop new methods for the synthesis of heterocyclic compounds using heterogeneous catalysis we decided to investigate the reaction of 1,3-diones with hydrazines for the preparation of pyrazoles using layered zirconium sulfophenyl phosphonate as the catalyst. The interest for this class of compounds is justified by the presence of the pyrazole moiety in a wide variety of biologically active compounds.[4]

Various methods[5] are known for the synthesis of pyrazoles and indazoles using homogeneous catalysis, but only a few examples of heterogeneous catalysis have been reported.[6] Although the reaction of some hydrazines (e.g. phenylhydrazine, methylhydrazine) with 1,3-diketones, often proceeds well in the absence of any added catalyst, less reactive hydrazines, such as 2,4-dinitrophenylhydrazine, take an evident advantage of the use of the catalyst. In the present work we considered the use of usual hydrazine and less reactive hydrazine and compared their reactivity in the presence or absence of the catalyst.

Initially we turn our attention to the condensation of 1,3-pentanedione and hydrazines at room temperature in solvent-free conditions (Scheme 1).[7] Under this condition various hydrazines react with 1,3-pentanedione affording 1*H*-pyrazole derivatives in good yield. As shown in Table 1, the presence of the catalyst in entries 1 and 2 did not lead to particular difference in the reaction yields. Otherwise the reaction of less reactive hydrazines (entries 2, 4 and 5, Table 1) with 1,3-pentanedione took a great advantage from the presence of the catalyst.



Scheme 1

Without the catalyst the reaction of 1,3-pentanedione with 2,4-dinitrophenylhydrazine[8] or 2-hydrazino-4-(trifluoromethyl)pyrimidine stopped at the corresponding hydrazone derivatives, while the methyl hydrazinecarboxylate did not react at all.

In order to verify the regioselectivity of this process we used an asymmetrical 1,3-dione derivative such as 2,4-hexanedione. Condensation of 2,4-hexandione with the hydrazine derivatives gave a mixture of 1*H*-pyrazoles in good yield. As shown in Table 2 this process has a good regioselectivity towards the formation of 3-methyl-5-ethyl-1*H*-pyrazole derivatives. The advantage of the use of the catalyst when less reactive hydrazines are used was also evidenced in this case and in all following reactions.

Since slight differences between the two alkyl groups on 2,4-hexanedione exist, we introduced the use of more complex 1,3-diones to investigate the influence of substitution on the regioselectivity features of this process. A very good regioselectivity was obtained when 1-phenyl-1,3-butanedione was used as the starting material, with the exception of the example where 2,4-dinitrophenylhydrazine was used (Table 3).

The above described method has been successfully applied also to the synthesis of 4,5,6,7-tetrahydro-1(2)*H*-indazole skeleton when 2-acetylcyclohexanone was used as the starting material (Table 4).

The results reported above show that the use of 1-phenyl-1,3-butanedione in this process involved a better regioselectivity over the use of 2,4-hexanedione and 2-acetylcyclohexanone. Steric hindrance can be acclaimed for all

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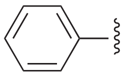
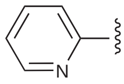
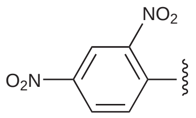
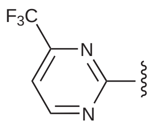
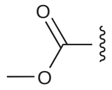
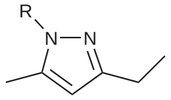
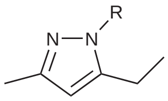
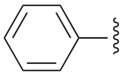
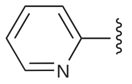
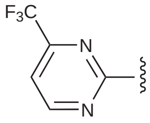
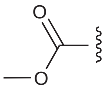
Table 1 Reaction of 1,3-Pentanedione with Hydrazines

Entry	R	Catalyst		No catalyst	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1		2	95[8]	2	89
2		2	91	2	78
3		12 12	37[9] 68[a,9]	12 12	–[b] –[b]
4		7	89	7	–[b]
5		3	67[10]	3	–

[a] Temp = 60 °C.
[b] Hydrazone derivative was formed.

Table 2 Reaction of 2,4-Hexanedione with Hydrazines[a]

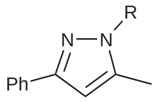
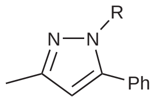
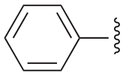
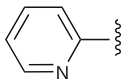
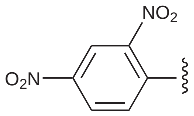
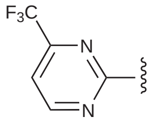
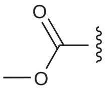
Entry	R	Time (h)	Yield (%)		
1		2	88	27	73
2		2	77	25	75
3		12	86	28	72
4		12	91	26	74

[a] All regioisomers were identified by NOESY experiments.

asymmetric 1,3-diones to explain the influence on the regioselectivity. However, the exception is 1-phenyl-1,3-butanedione where the conjugative effect of aromatic ring that stabilizes the enol-tautomer, can contribute to increase the regioselectivity of this process towards the formation of 3-methyl-1,5-diphenyl-1*H*-pyrazole derivatives (Scheme 2).

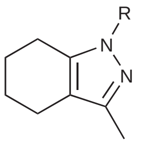
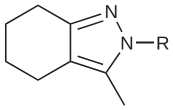
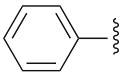
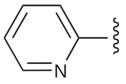
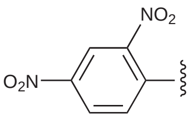
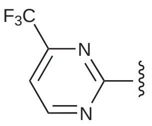
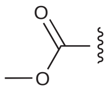
In conclusion, we prepared some pyrazole and 4,5,6,7-tetrahydro-1(2)*H*-indazole derivatives in good yield using layered zirconium sulfophenyl phosphonate as heterogeneous catalyst in solvent free conditions. The important features of our method are: mild reaction condition, good regioselectivity, simple work up and recyclable nature of the catalyst employed[13] whose preparation does not require particular skill.[14] Studies for the application of this method to the synthesis of more complex pyrazoles and 4,5,6,7-tetrahydro-1(2)*H*-indazoles are under investigation in our laboratory.

Table 3 Reaction of 1-Phenyl-1,3-butanedione with Hydrazines

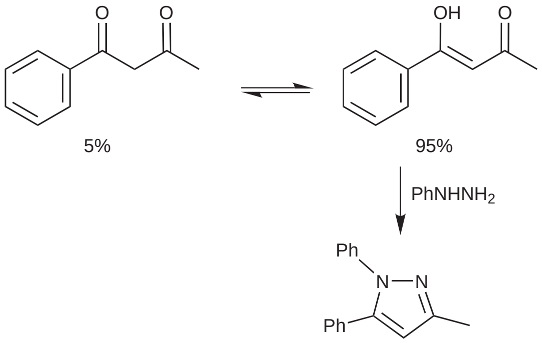
Entry	R	Time (h)	Yield (%)		
1		2	89[8]	7	93
2		12	90	5	95
3		24	73[a,9]	37	63
4		12	87	8	92
5		20	79[10]	–	100

[a] Temp = 60 °C. All regioisomers were identified by NOESY experiments.

Table 4 Reaction of 2-Acetylcyclohexanone with Hydrazines

Entry	R	Time (h)	Yield (%)		
1		12	87[11]	20	80
2		12	73	22	78
3		21	79[a,12]	24	76
4		12	76	24	76
5		12	69	20	80

[a] Temp = 60 °C. All regioisomers were identified by NOESY experiments.



Scheme 2

Acknowledgment

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References

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(2) Measurement of the acid strength: 0.5 g of zirconium sulfophenyl phosphonate, previously dried at 160 °C for 12 h, were dispersed in 3 mL of benzene in a test tube. Then, 0.2 mg of the chosen Hammet indicator were added to the dispersion held under stirring. The colour changes were evaluated after 30 min. For more detailed information see: (a) Umansky, B.; Engelhardt, J.; Hall, W. K. *J. Catal.* **1991**, *127*, 128. (b) Hammett, L. P.; Deyrup, A. J. *J. Am. Chem. Soc.* **1932**, *54*, 2721.

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(7) **Typical Reaction Procedure**
To the mixture of 1,3-dione (1 mmol) and α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$ (25 mg, ca. 6 mol%) was added hydrazine derivative (1 mmol) under strirring, under nitrogen and in neat. The mixture was left to react at 40 °C (60 °C in the case of 2,4-dinitrophenylhydrazine), and monitored by TLC. The reaction mixture was diluted with CH_2Cl_2, filtered on Buchner funnel, then concentrated under vacuum. In some entries a chromatography on silica gel was required in order to purify the pyrazole or tetrahydroindazole derivatives. The structures of all regioisomers were determined on the basis of the typical ^1H NMR chemical shifts and NOESY experiments.
Selected Experimental Data.
Methyl 5-Ethyl-3-methyl-1*H*-pyrazole-1-carboxylate.
Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.5 Hz, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 2.97 (q, *J* = 14.8, 7.5 Hz, 2 H, CH_2), 4.02 (s, 3 H, OCH_3), 6.02 (s, 1 H, H-pyrazole). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.4, 13.7, 21.2, 54.2, 108.7, 150.6, 151.3, 152.6. GCMS: *m/z* = 168, 153, 137, 123, 109, 95.
1-(2,4-Dinitrophenyl)-3-methyl-5-phenyl-1*H*-pyrazole.
White solid: mp 152–153 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 6.43 (s, 1 H, H-pyrazole), 7.18–7.47 (m, 8 H, ArH), 8.38 (dd, *J* = 9.2, 3.0 Hz, 1 H, PhH), 8.77 (d, *J* = 3.0 Hz, 1 H, PhH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 109.4, 120.8, 127.1, 128.5 (double), 129.0 (double), 129.2, 129.6, 138.2, 145.0, 143.3, 143.8, 152.7. GCMS: *m/z* = 324, 294, 232, 219, 190, 105, 89, 77.
2-(2,4-Dinitrophenyl)-3-methyl-4,5,6,7-tetrahydro-2*H*-indazole.
Pale yellow solid: mp 156–158 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.82 (m, 4 H), 2.20 (s, 3 H, CH_3), 2.52 (m, 2 H), 2.69 (m, 2 H), 7.71 (d, *J* = 8.8 Hz, 1 H, ArH), 8.53 (dd, *J* = 8.8, 2.5 Hz, 1 H, ArH), 8.80 (d, *J* = 2.5 Hz, 1 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.2, 20.4, 23.0 (double), 23.3, 117.7, 121.0, 127.2, 128.8, 135.7, 138.3, 145.2, 145.6, 153.5. GCMS: *m/z* = 302, 285, 255, 209, 181, 135, 115.

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(13) The catalyst, washed with CH_2Cl_2 and dried at 120 °C for 12 h can be reused for several experiments. The reaction of 2,3-hexanedione and phenylhydrazine has been repeated 3 times with the following yields: 82% (2 h), 84% (2 h), 79% (2 h).

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