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SULFAMIC ACID (H_2NSO_3H): A LOW-COST, MILD, AND EFFICIENT CATALYST FOR THE SYNTHESIS OF SUBSTITUTED N-PHENYLPYRAZOLES UNDER SOLVENT-FREE CONDITIONS

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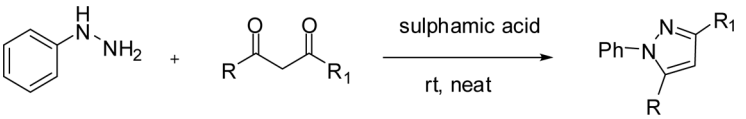
GRAPHICAL ABSTRACT



Abstract *N-Phenylpyrazoles are synthesized by condensing phenylhydrazine and 1,3-diketones in the presence of a catalytic amount of sulfamic acid, a mild and an efficient solid acid catalyst, under solvent-free conditions. This condensation proceeds smoothly in shorter reaction time.*

Keywords N-Phenylpyrazoles; solid acid catalysis; sulfamic acid

INTRODUCTION

Pyrazoles are an important class of drug intermediates in the pharmaceutical industry, as the pyrazole core structure is found in numerous biologically active molecules. They possess a number of biological activities such as antimicrobial, antiviral, antifungal, antitumor, antidepressant, antidiabetic, and anti-inflammatory activities.[1] Recently, they have been reported as potential atypical antipsychotics.[1] One of the classic examples is the blockbuster drug Celebrex, which was the first cyclooxygenase-2 (COX-2) inhibitor approved for the treatment of rheumatism and osteoarthritis.[2] Many synthetic pyrazoles are dye intermediates. N-Phenylpyrazole is the basic component of the antiflea and antitick external treatments for cats and dogs.[3]

Among the various syntheses of pyrazoles, the most convenient is the condensation of 1,3-diketones with hydrazines.[4] However, there are a few other routes that do not employ the use of 1,3-diketones.[5] Acidic catalysts, such as ion exchange

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Table 1. Reaction of phenylhydrazine and pentane-2,5-dione in the presence of different solid acid catalysts

Entry	Catalyst	Time (min)	Yield of N-phenylpyrazole (%)
1	Sulfamic acid	05	91
2	Amberlyst-15	05	80
3	H-ZSM	20	72
4	Mont-K10	20	73
5	Hβ-Zeolite	30	69
6	SiO_2-$HClO_4$	10	73
7	SiO_2-H_2SO_4	10	78
8	SiO_2-H_3PO_4	10	77
9	SiO_2 -HCl	15	76
10	No catalyst	420	45

Note. Reaction conditions: phenylhydrazine (10 mmol, 0.108 g), pentane-2,5-dione (10 mmol, 0.100 g), catalyst (10 wt% of phenylhydrazine), room temperature (32 °C).

resins, heteropoly acids,[6] SiO_2-H_2SO_4,[7] zeolite,[8] para-toluenesulfonic acid (p-TSA), and K10[9] have also been used for the synthesis of pyrazole derivatives. However, supported catalysts have leaching problems. Ion exchange resins are expensive and require longer reaction times, and the reactions are generally carried out in organic solvents. Better results are obtained using homogeneous liquid-phase catalysts; however, these are considerably corrosive and are not environmentally benign. Herein we report a greener method for the synthesis of N-phenylpyrazoles by condensation of phenylhydrazines with 1,3-diketones using a low-cost, mild, and efficient solid acid catalyst: sulfamic acid.

The development of mild, low-cost, and high-performance acid catalysts has recently attracted much interest. Sulfamic acid (NH_2SO_3H) is a heterogeneous acid catalyst in a nonaqueous medium with mild acidity, nonvolatility, and noncorrosivity. It is inexpensive, insoluble in common organic solvents, and very stable. However, not much attention has been paid to the use of sulfamic acid as a catalyst in organic reactions. Earlier, we used sulfamic acid for the Pechmann reaction and to synthesize bis(1H-indol-3-yl)methanes.[10] With this background, we have used sulfamic acid as a solid acid catalyst for the condensation of phenylhydrazine and 1,3-diketone to prepare N-phenylpyrazoles.

RESULTS AND DISCUSSION

To optimize the reaction conditions, we carried out the condensation of pentane-2,5-dione with phenylhydrazine.

To study the effect of different heterogeneous catalysts, the reaction was carried out at room temperature in the presence of different solid Brønsted acids and some silica-supported Brønsted acid catalysts (Table 1). The reaction was catalyzed by all the catalysts, and sulfamic acid was found to be the best.

The reaction was carried out using different quantities of sulfamic acid (Table 2). As the catalyst quantity increased, yield of the product increased. Using

Table 2. Reaction of phenylhydrazine and pentane-2,5-dione in the presence of different quantities of sulfamic acid

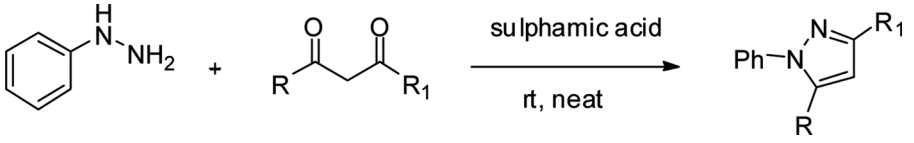
Entry	SA (wt% of phenylhydrazine)	SA (mol% phenylhydrazine)	Yield of N-phenylpyrazole (%)
1	50	5	91
2	25	2.5	89
3	10	1	91
4	5	0.5	79
5	2	0.2	73

Note. Reaction conditions: phenylhydrazine (10 mmol, 0.108 g), pentane-2,5-dione 10 mmol, 0.100 g), time 5 min, room temperature (32 °C).

10 wt% of phenylhydrazine, the maximum yield of the product was obtained. Hence, for further reactions, the same quantity of sulfamic acid was used.

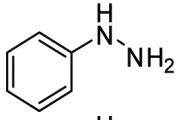
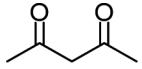
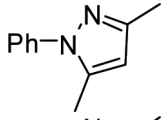
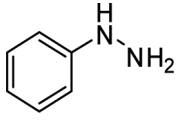
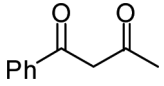
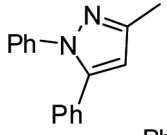
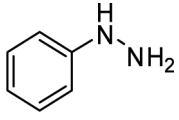
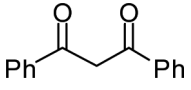
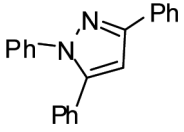
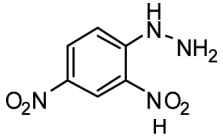
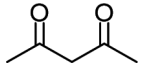
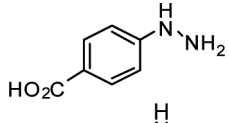
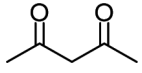
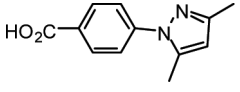
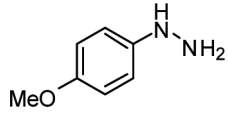
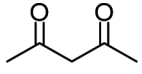
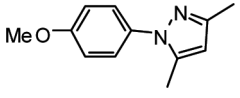
The reaction was tried in ethanol at room temperature, when 84% of the product was obtained. Thus, the reaction without solvent was found to be the best.

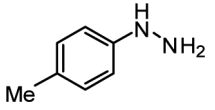
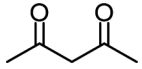
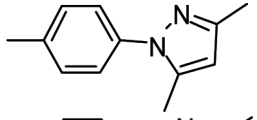
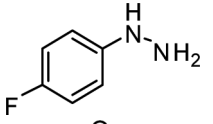
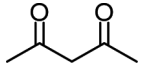
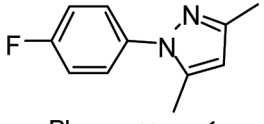
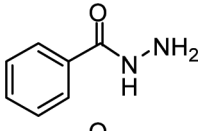
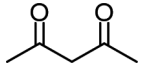
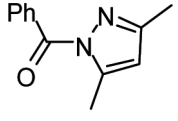
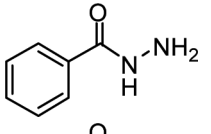
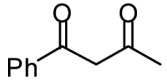
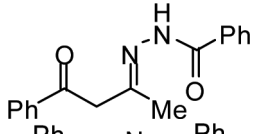
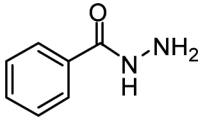
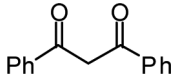
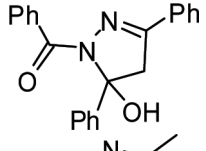
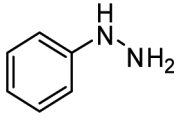
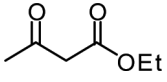
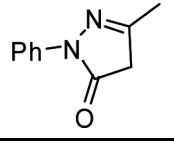
The reaction of phenylhydrazines with different 1,3-dicarbonyl compounds was carried out under the optimized conditions (Scheme 1, Table 3). The reaction of phenylhydrazine with symmetrical 1,3-diketones is expected to give only one N-phenylpyrazole. In the reaction of 1-phenyl-1,3-butanedione (entry 2), only 3-methyl-1,5-diphenylpyrazole (86%) was the isolable product. In literature, in a K10-catalyzed reaction of 1,3-diketone with phenylhydrazine, a mixture of 3-methyl-1,5-diphenylpyrazole (95%) and 5-methyl-1,3-diphenylpyrazole (5%) has been reported. The reaction of 2,4-dinitrophenylhydrazine with pentane-2,5-dione did not give the expected pyrazole, but the reaction stopped at the hydrazone stage, possibly because of poor nucleophilicity of the second nitrogen atom.[4a] The condensation product of phenylhydrazide and benzoylacetone (entry 10) gave the corresponding hydrazone derivative, which was confirmed by ^{1}H NMR and infrared (IR). The reason for the unsuccessful cyclization possibly is the poor nucleophilicity at the second nitrogen atom. The condensation reaction of phenylhydrazide with dibenzoyl methane (entry 11) did not give the dehydrated product, which was confirmed from the spectral analysis. In the literature, the reaction of phenylhydrazine with β-keto esters is reported to give pyrazole derivates.[4c] However, the condensation reaction using sulfamic acid gave N-phenylpyrazolone derivative (entry 12). The known compounds were identified by comparison of reported melting points in the literature and spectral analysis. The liquid compounds were identified by spectral analysis.



Scheme 1. Synthesis of N-phenylpyrazoles by the reaction of phenylhydrazines and 1,3-dicarbonyl compounds in the presence of sulphamic acid.

Table 3. Reaction of phenylhydrazines/hydrazides and 1,3-dicarbonyl compounds in the presence of sulfamic acid

Entry	Hydrazine	Diketone	Product	Mp (°C) (Reported)	Time (min)	Yield (%)
1				Liquid	3	91
2				Liquid	15	86
3				1129–132 (135[9])	20	81
4			Phenyl hydrazone	—	30	—
5				149–151 (147–149[11])	15	84
6				Liquid	5	86

7				Liquid	5	89
8				Liquid	10	80
9				Liquid	20	87
10				135–138	15	81
11				139–141	15	83
12				127–129 (128[12])	30	62

Note. Reaction conditions: phenylhydrazine (10 mmol, 0.108 g), pentane-2,5-dione (10 mmol, 0.100 g), sulfamic acid (10wt% of the phenylhydrazine), room temperature (32 °C).

CONCLUSION

We have developed a highly efficient protocol for the synthesis of pyrazoles by the condensation of phenylhydrazines with 1,3-diketones using a low-cost, mild, and efficient catalyst, sulfamic acid (solid acid). The reaction takes place in a short time under solvent-free conditions at ambient temperature.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker 300-MHz and Jeol 60-MHz spectrometers. IR spectra were recorded on a Perkin-Elmer Fourier transform (FT)-IR spectrophotometer. Melting points are uncorrected.

Condensation of Phenylhydrazine and 1,3-Diketone

Phenylhydrazine (10 mmol, 0.108 g), pentane-2,5-dione (10 mmol, 0.100 g), and catalyst (10wt% of the phenylhydrazine) were added to a 50-mL, single-neck, round-bottom flask. The flask was equipped with a calcium chloride guard tube. The contents of the flask were stirred on a magnetic stirrer. After completion of the reaction, the reaction mixture was washed with water to remove the catalyst and then extracted with diethyl ether (3×6 mL). The organic extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in a vacuum. The product obtained was purified using column chromatography (silica gel: 5% EtOAc–petroleum ether).

Selected Data

Compound 1a. FT-IR (KBr): 3062, 2981, 2959, 2923, 2866, 1597 (C=C), 1556, 1500, 1419, 1384, 1131, 1072, 1025, 977, 911, 779, 755, 696, 678, 661, 640 cm^{-1}. ^{1}H NMR (CCl_4, 60 MHz) δ: 2.28 (s, 6H, $2CH_3$), 5.98 (s, 1H, CH=), 7.41 (m, 5H, ArH).

Compound 2a. FT-IR (KBr): 3062, 2924, 2854, 1598, 1551, 1500, 1458, 1413, 1367, 1139, 1084, 1028, 1016, 954, 913, 766, 693, 641 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.41 (s, 3H, CH_3), 6.32 (s, 1H, CH=), 7.22–7.31 (m, 10H, ArH).

Compound 3a. FT-IR (KBr): 3121, 3062, 1596, 1546, 1496, 1457, 1484, 1363, 1214 1175, 1066, 1022, 957, 921, 766, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.85 (s, 1H, CH=), 7.33–7.96 (m, 15H, ArH).

Compound 7a. FT-IR (KBr): 3048, 2922, 2864, 1609, 1593, 1557, 1495, 1466, 1417, 1380, 1364, 1131, 1090, 1023, 976, 857, 788, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.29 (s, 6H, $2CH_3$), 2.27(s, 3H, CH_3), 5.96 (s, 1H, CH=), 7.17–7.26 (d, 4H, ArH).

Compound 8a. FT-IR (KBr): 3066, 2925, 2867, 1604, 1555, 1514, 1416, 1385, 1367, 1289, 1154, 1131, 1094, 1036, 1017, 977, 838, 788, 609 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.29 (s, 6H, $2CH_3$), 2.27 (s, 3H, CH_3), 5.95 (s, 1H, CH=), 7.09–7.35 (d, 4H, ArH).

Compound 10a. FT-IR (KBr): 3232 (NH), 3066, 2836, 1630, 1603, 1554, 1421, 1287, 1131, 1065, 1034, 925, 877, 844, 795, 718.cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.29 (s, 3H, CH_3), 5.98 (s, 1H, CH=), 7.45–7.91 (m, 10H, ArH), 10.87 (s, 1H, NH), 12.24 (s, 1H, NH).

Compound 11a. FT-IR (KBr): 3455 (OH), 3063, 1637, 1598, 1428, 1415, 1337, 1188s, 1069, 923, 860, 795, 759, 718 cm^{-1}. ^1H NMR (DMSO, 300 MHz) δ: 3.48–3.67 (d, 2H, CH_2), 7.12 (s, 1H OH), 7.27–7.82 (m, 15H, ArH).

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