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Silica-bonded *S*-sulfonic acid: an efficient and recyclable solid acid catalyst for the synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols)

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ABSTRACT

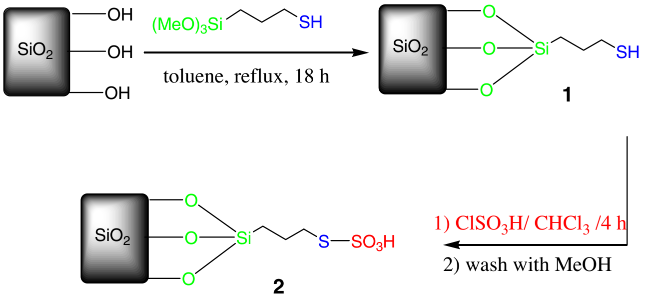
Silica-bonded *S*-sulfonic acid (SBSSA) is employed as a recyclable catalyst for the condensation reaction of aromatic aldehydes with 3-methyl-l-phenyl-5-pyrazolone. This condensation reaction was performed in ethanol under refluxing conditions giving 4,4′-alkylmethylene-bis(3-methyl-5-pyrazolones) in 75–90% yields.

1. Introduction

Pyrazoles are an important class of bio-active drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds.[1–3] For example, they exhibit anti-anxiety, antipyretic, analgesic, and anti-inflammatory properties. 2,4-Dihydro-3*H*-pyrazol-3-one derivatives including 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) have a broad spectrum of approved biological activity, being used as anti-inflammatory,[4] antipyretic,[5] gastric secretion stimulatory,[6] antidepressant,[7] antibacterial[8], and antifilarial agents.[9] Moreover, the corresponding 4,4′(arylmethylene)-bis-(1*H*-pyrazol-5-ols) are applied as fungicides,[10] pesticides,[11] insecticides[12], and dyestuffs[13–15], and as the chelating and extracting reagents for different metal ions.[16,17]

The conventional chemical approach to 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-pyrazol-5-ols) involves the successive Knoevenagel synthesis of the corresponding arylidenepyrazolones and its base-promoted Michael reaction, and also one-pot tandem Knoevenagel–Michael reaction of arylaldehydes with 2 equiv of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one performed under a variety of reaction conditions.[18,19] The first set of procedures utilizes the catalysis of the components with piperidine in ethanolic solution.[20,21] The second set of methods involve the non-catalyzed tandem Knoevenagel–Michael reaction under neutral conditions in either ethanol[22] or benzene[23] solutions. Although it affords the corresponding 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) in reliable 70–90% yields, the reaction requires 3–12 h of initial reflux with a further 24 h under ambient temperature to go to completion. Wang et al.[24] reported its synthesis in water using sodium dodecyl sulfate as the surfactant catalyst over a one-hour period, but the process needs a temperature of 100 °C. Finally, Elinson et al. utilized electrocatalytic procedure for its synthesis.[25] Further, Perumal and co-workers reported the synthesis and antiviral activity of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) using CAN as a catalyst.[26] However, most of the methods suffer from at least one limitation that may include moderate yields, long reaction times, harsh reaction conditions, or tedious workup procedures.

In continuation of our work to develop new catalysts for organic transformations,[27–31] herein we report mild, efficient, and



Scheme 1. Preparation of silica-bonded *S*-sulfonic acid (SBSSA).

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Table 1
Condensation reaction of *p*-chlorobenzaldehyde with 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in the presence of different amounts of catalysts[a]

Entry	Catalyst	Catalyst loading (g)	Time (min)	Yield[b]
1	No catalyst	—	24 h	<10
2	**SBSSA**	0.05	100	80
3	**SBSSA**	0.1	50	90
4	Zeolite-HY	0.1	120	45
5	Zeolite-HY	0.2	120	71
6	Zeolite-HY	0.3	120	87
7	Amberlyst	0.1	120	35
8	Amberlyst	0.2	120	55
9	Amberlyst	0.3	120	73

[a] Reaction conditions: *p*-chlorobenzaldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol), EtOH (10 ml), reflux conditions.
[b] Isolated yield.

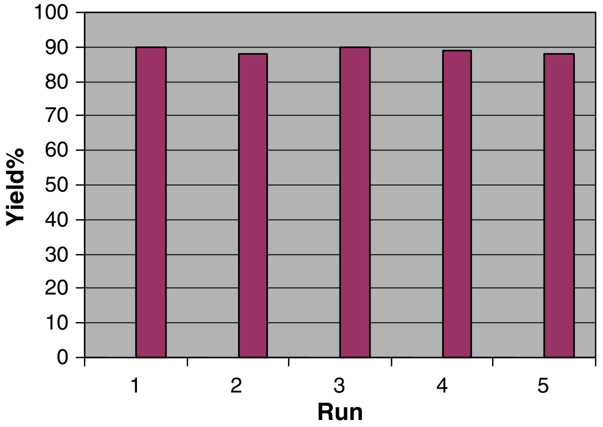
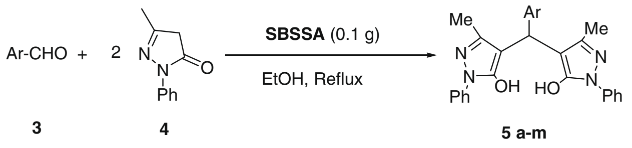


Figure 1. Recyclability of SBSSA (0.1 g) in the reaction of *p*-chlorobenzaldehyde (1 mmol) and 5-methyl-2-phenyl-2,4-dihydro-3*H*pyrazol-3-one (2 mmol) in EtOH under refluxing conditions. Reaction time = 120 min.



Scheme 2. Synthesis of 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) derivatives catalyzed by SBSSA.

environmentally friendly solid acid catalyst for the preparation of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) from aromatic aldehydes and with 2 equiv of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in the presence of silica-bonded *S*-sulfonic acid (SBSSA) in ethanol under refluxing conditions.

Recently, we reported the preparation of silica-bonded *S*-sulfonic acid (SBSSA) and used it as a catalyst for the synthesis of 1,1-diacetates,[27] quinoxaline,[28] and coumarin derivatives[29] (Scheme 1).

To study the effect of catalyst loading on the condensation reaction of aromatic aldehydes with 3-methyl-l-phenyl-5-pyrazolone, the reaction of *p*-chlorobenzaldehyde and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one was chosen as a model reaction (Table 1). The results clearly show that SBSSA is an effective catalyst for this condensation, and in the absence of SBSSA the condensation reaction gave very low yield after 24 h. Although lower catalyst loading of 0.05 g of SBSSA accomplished this condensation, however, 0.1 g of SBSSA per 1 mmol of aldehyde was optimum in terms of reaction time and isolated yield. Also, the results of this condensation in the presence of commercially available solid acids such as amberlyst and zeolite-HY are shown in Table 1.

Therefore, we employed the optimized conditions (0.1 g mmol^{-1} of SBSSA in ethanol under refluxing conditions) for the condensation reaction of various aryl aldehydes with 3-methyl-l-phenyl-5-pyrazolone into the corresponding 4,4′-(arylmethylene) bis (3-methyl-1-phenyl-1*H*-pyrazol-5-ols) (Scheme 2).

As shown in Table 2, both aromatic and heteroaromatic aldehydes reacted with 3-methyl-l-phenyl-5-pyrazolone to afford 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) in excellent yields. On the other hand, benzaldehydes with electron-donating or electron-withdrawing groups, that is, 3,4-dimethoxybenzaldehyde **3j** or 4-nitrobenzaldehyde **3g**, were condensed into the corresponding 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) **5j** and **5g** in high yields. The acid-sensitive substrate thiophene-2-carbaldehyde **3m** was converted into the corresponding product **5m** in 75% yield (80% conversion) without any by-products (Table 2, entry m).

The possibility of recycling the catalyst was examined using the reaction of *p*-chlorobenzaldehyde and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one under the optimized conditions. Upon completion, the reaction mixture was washed with warm ethanol (3 × 30 mL). The recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs. The recycled catalyst could be reused four times without any additional treatment. No

Table 2
Preparation of 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) derivatives catalyzed by SBSSA in ethanol under refluxing conditions[a]

Entry	Ar (**3**)	Product **5**	Time (min)	Yield[b] (%)	Mp (°C)	Lit. mp (°C)
a	C_6H_5–	**5a**	120	80	170–172	171–172[24]
b	4-Me–C_6H_4–	**5b**	60	82	202–204	203[19]
c	4-Cl–C_6H_4–	**5c**	50	90	215–217	210[19]
d	2-Cl–C_6H_4–	**5d**	80	78	235–237	236–237[24]
e	2,,4-$(Cl)_2$–C_6H_3–	**5e**	240	82	227–229	228–230[24]
f	4-O_2N–C_6H_4–	**5f**	40	90	225–227	224–226[24]
g	3-O_2N–C_6H_4–	**5g**	70	83	151–153	149–150[24]
h	4-HO–C_6H_4–	**5h**	100	82	155–157	152–153[24]
i	3-HO–C_6H_4–	**5i**	160	90	165–168	—
j	3,4-$(MeO)_2$–C_6H_3–	**5j**	120	80	195–197	—
k	4-MeS–C_6H_4–	**5k**	40	84	201–203	—
l	4-(CN)–C_6H_4–	**5l**	50	90	210–212	—
m	2-Thienyl-	**5m**	240	75 (80)[c]	181–183	—

[a] Reaction conditions: aromatic aldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol), EtOH (10 ml), reflux conditions.
[b] Isolated yield.
[c] Conversion.

observation of any appreciable loss in the catalytic activity of SBSSA was made (Fig. 1).

In conclusion, we have prepared some new 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) by a tandem condensation reaction of aromatic aldehydes with 2 equiv of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in the presence of silica-bonded *S*-sulfonic acid in refluxing ethanol.

All the products were characterized by comparison of their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data and their melting points with the reported values.[32] Silica-bonded *S*-sulfonic acid (SBSSA) was prepared according to our previously reported procedure.[27,32]

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.114.

References and notes

1. McDonald, E.; Jones, K.; Brough, P. A.; Drysdale, M. J.; Workman, P. *Curr. Top. Med. Chem.* **2006**, *6*, 1193–1203.
2. Elguero, J.. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Oxford: Pergamon, 1996; Vol. 5.,.
3. Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst.* **2002**, *6*, 52–98.
4. Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, T.; Asai, H.; Kato, K. *J. Med. Chem.* **1977**, *20*, 80–85.
5. Behr, L. C.; Fusco, R.; Jarboe, C. H. In *The Chemistry of Heterocyclic Compounds, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Weissberger, A., Ed.; Interscience: New York, 1967.
6. Rosiere, C. E.; Grossman, M. I. *Science* **1951**, *113*, 651.
7. Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; Defelice, A. F.; Feigenson, M. E. *J. Med. Chem.* **1985**, *28*, 256–260.
8. Mahajan, R. N.; Havaldar, F. H.; Fernandes, P. S. *J. Indian Chem. Soc.* **1991**, *68*, 245–246.
9. Chauhan, P. M. S.; Singh, S.; Chatterjee, R. K. *Indian J. Chem., Sect. B* **1993**, *32*, 858–861.
10. Singh, D.; Singh, D. *J. Indian Chem. Soc.* **1991**, *68*, 165–167.
11. Londershausen, M. *Pestic. Sci.* **1996**, *48*, 269–292.
12. *The Chemistry of Synthetic Dyes and Pigments*; Lubs, H. A., Ed.; American Chemical Society: Washington, DC, 1970.
13. Uzoukwu, A. B. *Polyhedron* **1993**, *12*, 2719–2724.
14. Maurya, R. C.; Verma, R. *Indian J. Chem., Sect. A* **1997**, *36*, 596–598.
15. Garnovskii, A. D.; Uraev, A. I.; Minkin, V. I. *Arkivoc* **2004**, *iii*, 29–41.
16. Sridhar, R.; Perumal, P. T.; Etti, S.; Shanmugam, G.; Ponnusamy, M. N.; Prabavathy, V. R.; Mathivanan, N. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6035–6040.
17. Sivaprasad, G.; Perumal, P. T.; Prabavathy, V. R.; Mathivanan, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6302–6305.
18. Hamama, W. S. *Synth. Commun.* **2001**, *31*, 1335–1345.
19. Li, X.-L.; Wang, Y.-M.; Tian, B.; Matsuura, T.; Meng, J.-B. *J. Heterocycl. Chem.* **1998**, *35*, 129–134.
20. Singh, D.; Singh, D. *J. Chem. Eng. Data* **1984**, *29*, 355–356.
21. Mitra, A. S.; Rout, M. K. *J. Indian Chem. Soc.* **1961**, *38*, 893.
22. Pavlov, P. T.; Goleneva, A. F.; Lesnov, A. E.; Prokhorova, T. S. *Pharm. Chem. J. (Engl. Trans.)* **1998**, *32*, 370–372.
23. Buzykin, B. I.; Lonshchakova, T. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Trans.)* **1971**, 2224–2226.
24. Wang, W.; Wang, S.-X.; Qin, X.-Y.; Li, J.-T. *Synth. Commun.* **2005**, *35*, 1263–1269.
25. Elinson, M. N.; Dorofeev, A. S.; Nasybullin, R. F.; Nikishin, G. I. *Synthesis* **2008**, *12*, 1933–1937.
26. Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4501–4503.
27. Niknam, K.; Saberi, D.; Nouri Sefat, M. *Tetrahedron Lett.* **2009**, *50*, 4058–4062.
28. Niknam, K.; Saberi, D.; Mohagheghnejad, M. *Molecules* **2009**, *14*, 1915–1926.
29. Niknam, K.; Saberi, D.; Baghernejad, M. *Chin. Chem. Lett.* **2009**, *20*, 1444–1448.
30. Niknam, K.; Saberi, D. *Tetrahedron Lett.* **2009**, *50*, 5210–5214.
31. Niknam, K.; Saberi, D. *Appl. Catal. A: Gen.* **2009**, *366*, 220–225.
32. *pH Analysis of the SBSSA*. To an aqueous suspension of 0.1 g SBSSA, NaOH (1.8 mL, 0.1 M) was added. This is equal to a loading of 1.8 mmol SO_3H g^{-1}. So, all the SH functional groups in 3-mercaptopropylsilica **1** were sulfonated. According to our previous reports,[27,28] the loading of 3-mercaptopropylsilica **1** is 0.33 mmol/g.*General procedure:* A mixture of aromatic aldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol) and SBSSA (0.1 g) in ethanol (10 mL) were added to a flask and heated under refluxing conditions for an appropriate time. After the completion of the reaction, as indicated by TLC, the reaction mixture was washed with warm ethanol (3 × 30 mL). After cooling, the crude products were precipitated. The crude products were purified by recrystallization from ethanol (95%). The recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs.