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Synthesis of 1,2,4,5-tetrasubstituted imidazoles using silica-bonded propylpiperazine *N*-sulfamic acid as a recyclable solid acid catalyst

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ABSTRACT

A simple and efficient procedure for the preparation of silica-bonded propylpiperazine-*N*-sulfamic acid (SBPPSA) by the reaction of 3-piperazine-*N*-propylsilica (3-PNPS) and chlorosulfonic acid in chloroform is described. Silica-bonded propylpiperazine-*N*-sulfamic acid is employed as a recyclable catalyst for the synthesis of highly substituted imidazoles from the reaction of benzil, aromatic aldehydes, ammonium acetate and amines under solvent-free conditions. The heterogeneous catalyst was recycled for five runs upon the reaction of benzil, 4-methylbenzaldehyde, benzylamine, and ammonium acetate without losing its catalytic activity.

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The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds.¹⁻⁵ The members of this class of compounds are known to possess NO synthase inhibition and antifungal, antimycotic, antibiotic, antiulcerative, antibacterial, antitumor, and CB1 receptor antagonistic activities.^{6,7} Various substituted imidazoles act as inhibitors of p38 MAP kinase⁸ and B-Raf kinase,⁹ glucagon receptors,¹⁰ plant growth regulators,¹¹ therapeutic agents,¹ and pesticides.¹² Industrial and academic studies for the preparation of 1,2,4,5-tetrasubstituted imidazoles have led to numerous methodologies for the synthesis of these compounds.^{13,14} The most wellknown and classical method for preparation of these compounds involves four-component condensations of a 1,2-diketone derivative with an aldehyde, primary amine, and ammonium acetate in tive with an aldehyde, primary amine, and ammonium acetate in refluxing HOAc, which is known to have poor yields and long reaction times.¹⁵ Improvements occurred using other acidic conditions, such as silica gel,¹⁶ zeolite,¹⁶ alumina,¹⁷ NaHSO₄–SiO₂,¹⁸ HClO₄·SiO₂,¹⁹ molecular iodine,^{20,21} FeCl₃·6H₂O,²² BF₃·SiO₂,²³ In-Cl₃·3H₂O,²⁴ K₅CoW₁₂O₄₀·3H₂O,²⁵ copper acetate,²⁶ trifluroacetic acid,²⁷ L-proline,²⁸ zeolite supported reagents,²⁹ mercaptopropylsil-ica (MPS),³⁰ Bronsted acidic ionic liquid,³¹ MCM-41 or *p*-TsOH,³² and 1-butyl-3-methylimidazolium bromide³³ under microwave-irradiation, solvent-free or classical conditions.

In continuation of our studies on the design and application of solid acid catalysts in organic transformations,^{34–38} herein, we describe the preparation of silica-bonded propylpiperazine-*N*-sulfamic acid (SBPPSA) and its application as a catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles.

Silica-bonded propylpiperazine-*N*-sulfamic acid (SBPPSA) was prepared by the reaction of 3-piperazine-*N*-propylsilica (3-PNPS) with chlorosulfonic acid in chloroform as illustrated in Scheme 1.

To study the effect of catalyst loading on the four component condensation reactions for the synthesis of 1,2,4,5-tetrasubstituted imidazoles, the reaction of benzil, 4-methylbenzaldehyde, benzylamine, and ammonium acetate was chosen as a model reaction (Table 1). The results show clearly that SBPPSA is an effective catalyst for this four component condensation reaction. The best catalytic loading of SBPPSA was 0.25 g in terms of reaction time and isolated yield. The optimized conditions were chosen as follows: benzil (1 mmol), aldehyde (1 mmol), amine (1 mmol), ammonium acetate (1 mmol), and SBPPSA (0.25 g, equal to 0.31 mmol of H⁺) and heated under solvent-free conditions at 140 °C (Scheme 2). The lower temperature gave the corresponding product in lower yield and longer reaction time (Table 1, entries 5–6).

A wide range of aromatic aldehydes were employed and all imidazoles were obtained in high to excellent yields, which demonstrated that this is a general method that tolerates both electron-withdrawing and electron-donating constituents. Another important aspect is that various aliphatic and aromatic amines, such as aniline, benzyl, cyclohexyl, and ethyl amine were employed



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Scheme 1. Preparation of silica-bonded propylpiperazine-N-sulfamic acid (SBPPSA).

Table 1

Condensation reaction of benzil, 4-methylbenzaldehyde, benzylamine, and ammonium acetate in the presence of different amounts of SBPPSA as catalyst under solvent-free conditions and temperatures^a

Entry	Catalyst loading (g)	Temperature (°C)	Time (h)	Conversion ^{b,c} (%)
1	0.05	140	7	70 (63)
2	0.1	140	4	80 (74)
3	0.2	140	1.5	85 (80)
4	0.25	140	1	95 (90)
5	0.25	100	2	75 (69)
6	0.25	80	3	70 (65)
7	0.3	140	1	95 (89)

^a Reaction conditions: benzil (1 mmol), 4-methylbenzaldehyde (1 mmol), benzylamine (1 mmol), and ammonium acetate (2 mmol) under solvent-free conditions at 140 $^{\circ}$ C.

^b Determined by GC analysis.

^c Isolated yields in parenthesis.

in this four component condensation reaction under optimized conditions (Table 2). In each case, no side product formation (for example, 2,4,5-trisubstituted imidazoles) was observed, as is normally the case in such reactions under the influence of strong acids. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution. The results illustrate the high ability of this method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles with different groups.

To show the advantages of SBPPSA as a catalyst in this reaction, our results and reaction conditions for synthesis of 1-benzyl-2-(4-methylphenyl)-4,5-diphenylimidazole (**1a**) were compared with previously reported data in Table 3. The results show that our method is quite comparable with the former methods in yields and reaction times.

The possibility of recycling the catalyst was examined using the reaction of benzil, benzaldehyde, aniline, and ammonium acetate under optimized conditions. Upon completion, the reaction mixture was filtered and the solid was washed with ethanol, and the recycled catalyst was saved for the next reaction. The recycled catalyst could be reused five times without any further treatment. No observation of any appreciable loss in the catalytic activity of SBPPSA was observed (Fig. 1).

In conclusion, we have shown that silica-bonded propylpiperazine-*N*-sulfamic acid (SBPPSA), which can be prepared from commercially available and cheap starting materials, catalyzed efficiently this four component condensation reactions for the synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives. The simplicity of the procedure, eco-friendly, non-volatile, easy handling, safety and reusability of catalyst are the advantages of this method.

All the products were characterized by comparison of their IR, ¹H NMR and ¹³C NMR spectroscopic data and their melting points with reported values.^{11–32} 3-piperazine-*N*-propylsilica (3-PNPS) was prepared according to the procedure reported by Dey.³⁹

Synthesis of silica-bonded propylpiperazine-N-sulfamic acid (SBPPSA): To a magnetically stirred mixture of 3-piperazine-N-propylsilica (3-PNPS) (25 g) in $CHCl_3$ (50 mL), chlorosulfonic acid (25 mL) was added dropwise at 0 °C over 2 h. After the addition was complete, the mixture was stirred for another 2 h and then, the mixture was filtered and washed with ethanol (50 mL) and dried at room temperature to afford silica-bonded propylpiperazine-N-sulfamic acid (SBPPSA) as a cream powder (26.8 g). Elemental analysis showed the *S* content to be 2.85%; C, 8.70%; H, 2.4%; N, 2.1%. The number of H⁺ sites of SBPPSA was determined by pH-ISE conductivity titration (Denver Instrument Model 270) and found to be 1.25 H⁺ sites per 1 g of solid acid at 25 °C (pH 2.30).

General procedure: To a mixture of benzil (1 mmol), aldehyde (1 mmol), amine (1 mmol), and ammonium acetate (2 mmol) was added SBPPSA (0.25 g, equal to 0.31 mmol of H^+) and heated at



Scheme 2. Synthesis of 1,2,4,5-tetrasubstituted imidazoles catalyzed by SBPPSA.

Table	2
Table	4

Preparation of various 1.2.4.5-tetrasubstituted imidazoles in the presence of SBF	PPSA under solvent-free conditions at 140 °C ^a
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Entry	Ar	R	Product	Time (min)	Yield ^b (%)	Mp (°C)	Lit. mp (°C)
1	4-Me-C ₆ H ₄ -	C ₆ H ₅ -CH ₂ -	1a	60	90	165-167	165-166 ²²
2	$4-Cl-C_6H_4-$	C ₆ H ₅ -CH ₂ -	1b	70	92	162-164	162-164 ²³
3	$2-Cl-C_6H_4-$	C ₆ H ₅ -CH ₂ -	1c	90	90	140-142	140-142 ²³
4	3,4,5-(MeO) ₃ -C ₆ H ₂ -	C ₆ H ₅ -CH ₂ -	1d	85	90	185-187	184–186 ¹⁹
5	3-HO-C ₆ H ₄ -	C ₆ H ₅ -CH ₂ -	1e	75	89	232-235	-
6	4-MeS-C ₆ H ₄ -	C ₆ H ₅ -CH ₂ -	1f	60	86	164-166	-
7	4-NC-C ₆ H ₄ -	C ₆ H ₅ -CH ₂ -	1g	75	87	208-210	-
8	$4 - O_2 N - C_6 H_4 -$	C_6H_5-	1h	120	89	212-214	159–160 ²⁷
9	3-Br-C ₆ H ₄ -	C_6H_5-	1i	150	85	143-145	_
10	4-NC-C ₆ H ₄ -	C_6H_5-	1j	150	72	194-196	-
11	4-Me-C ₆ H ₄ -	$4-Br-C_6H_4-$	1k	150	88	219-221	-
12	C ₆ H ₅ -	$C_6H_{11}-$	11	300	70	168-170	167–169 ²²
13	4-Me-C ₆ H ₄ -	$C_6H_{11}-$	1m	240	75	164-166	162–164 ²²
14	4-MeO-C ₆ H ₄ -	C ₆ H ₁₁ -	1n	120	75	217-219	-
15	$4-Cl-C_6H_4-$	$C_6H_{11}-$	10	90	78	197-199	_
16	$4 - O_2 N - C_6 H_4 -$	$C_6H_{11}-$	1p	320	77	215-217	_
17	4-HO-C ₆ H ₄ -	C ₆ H ₁₁ -	1q	260	78	283-285	-
18	$4-Cl-C_6H_4-$	Et-	1r	90	72	310-312	_
19	$4-NC-C_6H_4-$	Et–	1s	90	73	155–157	_

a Reaction conditions: benzil (1 mmol), aromatic aldehyde (1 mmol), amine (1 mmol), ammonium acetate (2 mmol), SBPPSA (0.25 g, equal to 0.31 mmol of H⁺), solvent-free at 140 °C.

^b Isolated yield.

Table 3

S	vnthesis of	1-benz	vl-2-	(4-meth	vlı	ohenv	1)-	4.5-di	iphe	nvl	-imidazole	1a	using	different	catal	vsts	and	reaction	condi	tions
			-																	

Entry	Solvent and catalyst (loading)	Time (min)	Yield ^a (%)	Ref.
1	MW, solvent-free, zeolite HY (5 mol %)	6	85	16
2	Solvent-free, 140 °C, NaHSO ₄ –SiO ₂ (18.6 g)	120	92	18
3	Solvent-free, 140 °C, HClO ₄ .SiO ₂ (1 mol %)	6	90	19
4	MeOH, rt, InCl ₃ .3H ₂ O (10 mol %)	480	75	24
5	Solvent-free, 140 °C, K ₅ CoW ₁₂ O ₄₀ .3H ₂ O (0.1 mol %)	120	95	25
6	MeOH, 60 °C, L-proline (15 mol %)	540	88	28
7	Reflux in AcOH, MCM-41(0.04 g)	32	82	32
8	[Bmim]Br (0.5 g, 2.28 mmol), solvent-free, 140 °C	120	90	33
9	Solvent-free, 140 °C, SBPPSA (equal to 0.31 mmol H ⁺)	60	90	This work

^a Isolated yield.



Figure 1. Recyclability of SBPPSA in the reaction of benzil (1 mmol), 4-methylbenzaldehyde (1 mmol), benzylamine (1 mmol) and ammonium acetate (2 mmol) under solvent-free conditions at 140 °C. Reaction time = 60 min.

140 °C under solvent-free conditions. When the reaction was complete as judged by TLC, ethanol (5 mL) was added and the reaction mixture was filtered and the remaining solid was washed with warm ethanol (3×5 mL) in order to separate the catalyst. The products were recrystallized from ethanol. The recovered catalyst was dried and reused for subsequent runs.

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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.2011.06.105.

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