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Silica-Supported Sodium Sulfonate with Ionic Liquid: A Neutral Catalyst System for Michael Reactions of Indoles in Water

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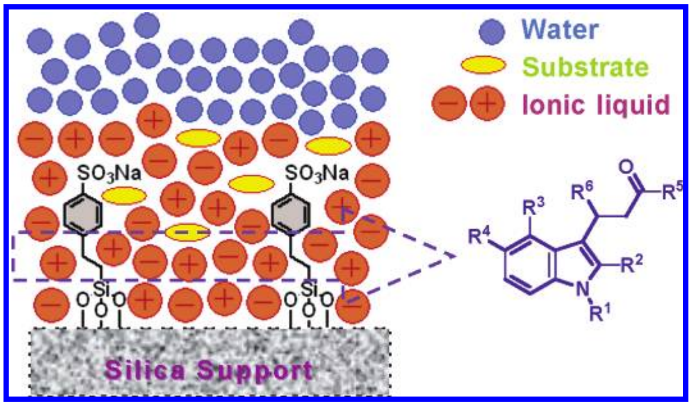
ABSTRACT



A neutral catalytic system for Michael reactions of indoles has been developed by combining silica-supported benzenesulfonic acid sodium salt with hydrophobic ionic liquid in water. An efficient hydrophobic environment could be created on the surface of the silica–sodium material under the conditions. Various indole derivatives and α,β-unsaturated carbonyl compounds including some acid-labile substrates were successfully applied to this system with water as the sole solvent to afford the desired Michael adducts in high yields.

The Michael reaction of indoles with α,β-unsaturated carbonyl compounds provides easy access to 3-substituted indoles, which are important building blocks for the synthesis of biologically important compounds and natural products. While the reaction proceeds in the presence of either protic[1] or Lewis acids in many cases,[2] the acid-catalyzed conjugate addition requires careful control of acidity to prevent side reactions such as dimerization, isomerization, and polymerization, etc. Furthermore, acidic conditions also prevent the use of acid-labile substrates. Despite recent advances in this field, no general methods to address these problems have been reported. As a result, excess amounts of indoles or α,β-unsaturated carbonyl compounds are required to obtain high yields in many cases. Therefore a new method to promote the reactions more efficiently, for example, the reactions with equimolar amounts of indoles with α,β-unsaturated carbonyl compounds, is desired.

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(1) (a) Szmuszkovicz, J. *J. Am. Chem. Soc.* **1975**, *79*, 2819. (b) Noland, W. E.; Christensen, G. M.; Sauer, G. L.; Dutton, G. G. S. *J. Am. Chem. Soc.* **1955**, *77*, 456. (c) Iqbal, Z.; Jackson, A. H.; Rao, K. R. N. *Tetrahedron Lett.* **1988**, *29*, 2577.

(2) (a) Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F. *Chem. Commun.* **2005**, 789. (b) Zhan, Z. P.; Yang, R. F.; Lang, K. *Tetrahedron Lett.* **2005**, *46*, 3859. (c) Reddy, A. V.; Ravinder, K.; Goud, V.; Kishnaiah, P.; Raju, T. V.; Venkateswarlu, Y. *Tetrahedron Lett.* **2003**, *44*, 6257. (d) Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115. (e) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594.

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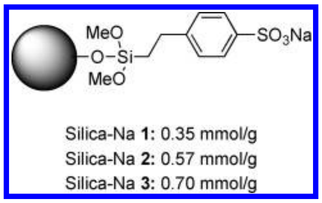
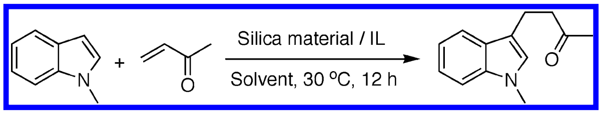


Figure 1. Silica-supported sodium materials.

Recently, we have found that combination of a silica-supported scandium catalyst with hydrophobic ionic liquid can create a hydrophobic environment on the surface of silica in water, which allows many organic reactions to proceed well with water as a solvent.[3] As an extension of this work, we focused on a combination of silica gel-supported sodium materials with ionic liquid as a neutral catalyst in water. Herein we report the combination as a neutral heterogeneous catalyst system for Michael reactions of indoles with α,*β*-unsaturated carbonyl compounds in water.[4]

Preparation of silica gel-supported sodium materials was performed according to a modified literature method.[5] The Silica-Na catalysts thus prepared were added to an ethyl acetate solution of ionic liquid, and the solvent was removed under reduced pressure to afford powdery and free-flowing solid, silica gel-supported sodium sulfonate with ionic liquid (Silica-Na-IL).As shown in Table 1, use of a standard Silica-Na catalyst (Silica-Na **3**) alone gave a low yield for Michael reaction of *N*-methylindole and methyl vinyl ketone (MVK) in water (Table 1, entry 1). To our delight, a great improvement on the yield was observed when 25 wt % of [DBIm]SbF_6 was loaded on the Silica-Na **3** (entry 2). When half the amount of the ionic liquid was used, the reaction was also accelerated, but was not complete within 12 h (entry 3). It is noted that the reaction proceeded smoothly without using any acidic species, and that high yields were obtained by using 1 equiv of MVK (refer to *N*-methylindole). We also examined the effect of solvents (entries 4 and 5). While the best yield was obtained in water, much lower yields were observed with other solvents (dichloromethane and toluene). It was also found that loading amounts of Na influenced the

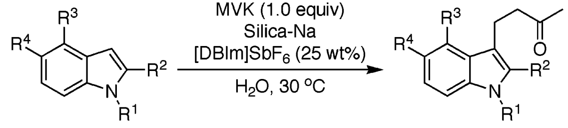
Table 1. Silica-Na Catalyzed Michael Reaction of 1-Methylindole with MVK[a]

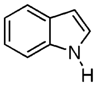
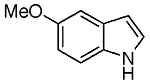
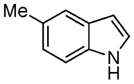
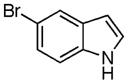
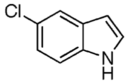
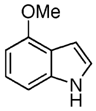
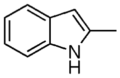
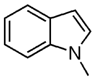


entry	silica material	IL loading[d] (wt %)	solvent	yield (%)
1	Silica-Na **3**	0	H_2O	10
2	Silica-Na **3**	25.0	H_2O	95
3	Silica-Na **3**	12.5	H_2O	61
4	Silica-Na **3**	25.0	CH_2Cl_2	31
5	Silica-Na **3**	25.0	toluene	9
6	Silica-Na **1**	25.0	H_2O	38
7	Silica-Na **2**	25.0	H_2O	73
8[b]	Silica	25.0	H_2O	0
9[c]	Silica-Na **3**	25.0	H_2O	94

[a] Reaction conditions: 50 mg of silica material, 0.25 mmol of *N*-methylindole, 0.25 mmol of MVK, 0.25 mL of solvent. [b] The starting silica gel was used. See the Supporting Information. [c] Reused in the second run. [d] [DBIm]SbF_6 was used. [DBIm] = 1-butyl-3-decylimidazolium.

Table 2. Michael Reactions of Several Indole Derivatives with MVK in Water



entry	indole	catalyst (mol %)	time (h)	yield (%)
1		Silica-Na **2** (11 mol %)	24	96
2		Silica-Na **2** (11 mol %)	12	92
3		Silica-Na **3** (14 mol %)	16	94
4		Silica-Na **2** (11 mol %)	12	95
5		Silica-Na **2** (11 mol %)	12	97
6		Silica-Na **3** (14 mol %)	20	83
7		Silica-Na **3** (14 mol %)	16	86
8[a]		Silica-Na **3** (14 mol %)	12	94

[a] Experiment in a 10 mmol scale.

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(3) Gu, Y.; Ogawa, C.; Kobayashi, J.; Mori, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7217.

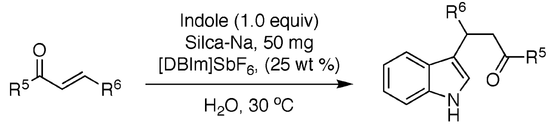
(4) Although supported ionic liquid catalysis has been investigated recently, there has been no example of combination of silica-supported metal catalysts with ionic liquids before our recent report (ref 3). In the supported ionic liquid catalysis, it is reported that silica gel-supported ionic liquids and additional nonsupported ionic liquids form ionic liquid phases on the surface of silica gel due to interactions between supported and nonsupported ionic liquids. For supported ionic liquid catalysis see: (a) Mehnert, C. P.; Cook, R. A.; Dispenziere, N. C.; Afeworki, M. *J. Am. Chem. Soc.* **2002**, *124*, 12932. (b) Riisager, A.; Fehrmann, R.; Flicker, S.; van Hal, R.; Haumann, M.; Wasserscheid, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 815. (c) Hagiwara, H.; Sugawara, Y.; Hoshib, T.; Suzukib, T. *Chem. Commun.* **2005**, 2942. (d) Gruttadauria, M.; Riela, S.; Aprile, C.; Meo, P. L.; D'Anna, F.; Noto, R. *Adv. Synth. Catal.* **2006**, *348*, 82. (e) Mehnert, C. P. *Chem. Eur. J.* **2005**, *11*, 50.

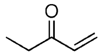
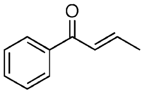
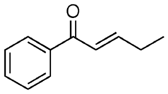
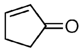
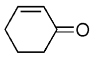
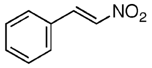
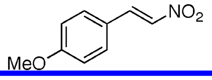
(5) (a) Jones, C. W.; Tsuji, K.; Davis, M. E. *Nature* **1998**, *393*, 52. (b) Sow, B.; Hamoudi, S.; Zahedi-Niaki, H.; Kaliaguine, S. *Miroporous Mesoporous Mater.* **2005**, *79*, 129. (c) Li, P.-H.; Wang, L. *Adv. Synth. Catal.* **2006**, *348*, 681.

yield (entries 2, 6, and 7), while no reaction occurred by using the starting silica without Na (entry 8). These results confirm that the combination of Silica-Na and ionic liquid is key to render the reaction to completion. With Silica-Na **3**/[DBIm]SbF$_6$ the reaction mixture is heterogeneous, and the catalyst was readily filtered off after extraction of the product with a mixture of hexane and ethyl acetate (2:1, v/v). The Silica-Na **3**/[DBIm]SbF$_6$ so recovered could be reused without significant loss of activity (entry 9).

A range of other indoles and α,β-unsaturated carbonyl compounds were then surveyed by using the Silica-Na-IL catalyst systems in water (Tables 2 and 3). It should be noted that various indoles and α,β-unsaturated carbonyl compounds reacted smoothly in water to afford the desired Michael adducts in high yields. While several substituted indoles worked well, both acyclic and cyclic α,β-unsaturated carbonyl compounds are good substrates in the present Michael reaction. For example, 2-cyclohexen-1-one, which is prone to overreact with indoles under acidic conditions,[6] was found to be applicable in the Silica-Na-IL catalyst system (Table 3, entry 5). The Michael reactions with nitrostyrenes as acceptors also proceeded smoothly in water (Table 3, entries 6 and 7). Furthermore, the reaction in a 10 mmol scale was successfully conducted, and the same level of yield compared with that in a preparative scale synthesis was obtained (Table 2, entry 8).

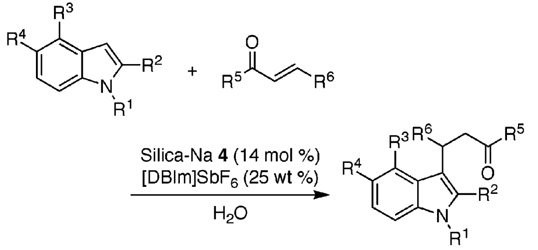
Table 3. Michael Reactions of Several α,β-Unsaturated Carbonyl Compounds with Indole in Water

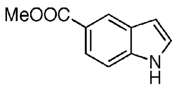
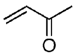
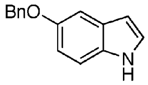
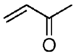
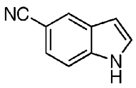
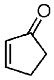
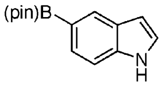
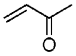
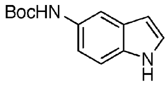
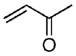
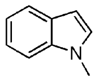
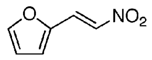
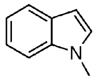
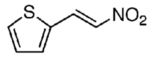
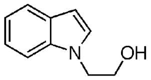
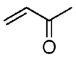
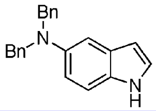
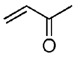


entry	enone	catalyst (mol %)	Time (h)	Yield (%)
1		Silica-Na **2** (11 mol %)	12	89
2		Silica-Na **3** (14 mol %)	20	77
3		Silica-Na **3** (14 mol %)	24	63
4		Silica-Na **3** (14 mol %)	20	95
5[a]		Silica-Na **3** (14 mol %)	20	70
6[b]		Silica-Na **3** (14 mol %)	24	64
7[b]		Silica-Na **3** (14 mol %)	24	82

[a] 2-Methylindole was used instead of indole. [b] *N*-Methylindole and 50 wt % of ionic liquid were used at 50 °C.

Table 4. Michael Reactions of Acid-Labile Substrates in the Silica-Na-IL System in Water



entry	indole	enone	yield (%)
1[a]			80
2[a]			89
3[a]			91
4[b]			85
5[b]			94
6[c, d]			80
7[c, d]			81
8[a]			85
9[a]			90

[a] 30 °C, 20 h. [b] 30 °C, 12 h. [c] 50 °C, 20 h. [d] 50 wt % of ionic liquid was used.

The Silica-Na-IL catalyst system does not require the inclusion of Lewis or Brønsted acid species, which allows us to use some acid-labile substrates. This is particularly an issue in cases where substrates or products are sensitive and decompose under acidic conditions. As shown in Table 4, several indole derivatives with acid-labile functions were all successfully converted to the corresponding Michael adducts by using the Silica-Na-IL catalyst in water without any

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[6] Paul, H.; Michael, K. *Can. J. Chem.* **1998**. *76*, 1256.

damage of acid-labile functions (entries 1 to 5). The Michael reactions of 1-methylindole with 2-(2-nitrovinyl)furan and 2-(2-nitrovinyl)thiophene were also examined to give the corresponding adducts in 80% and 81% yields, respectively (entries 6 and 7). Furthermore, the Michael reaction of *N*-(2-hydroxyethyl)indole with MVK proceeded smoothly without formation of a ketalization product (entry 8). As shown in entry 9, an indol with tertiary amine moiety reacted with MVK in the Silica-Na-IL system to afford the desired Michael adduct in excellent yield. These results indicated the usefulness of the Silica-Na-IL as a neutral catalyst for the title reactions.

In summary, we have developed a novel neutral catalyst system derived from silica gel-supported sodium sulfonate with ionic liquid for Michael reactions of indoles with α,β-unsaturated carbonyl compounds in water. The use of ionic liquid supports the formation of a hydrophobic environment on the surface of the silica material. The system can be readily recycled without appreciable loss of reactivity. Simplicity of operation as well as the neutral, mild, and environmentally benign nature of the reaction could enable expansion to a wide variety of acid-labile substrates, even to a larger scale reaction.[7] This novel concept is expected to contribute to the development of more benign reactions in water, and the related work is underway in our group.

Acknowledgment. This work was partially supported by Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Sciences (JSPS).

Supporting Information Available: Preparation of catalysts, experimental details, and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] At this stage, we use organic solvents in workup processes. This is a drawback as an environmentally benign reaction, and the development of a novel workup process without using any organic solvents is now in progress in our laboratory.