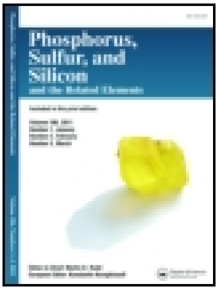

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Silica-Supported $LiHSO_4$ as a Highly Efficient, Mild, Heterogeneous, and Reusable Catalytic System for the Solvent-Free Synthesis of Bis(indolyl)methanes

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Silica-Supported $LiHSO_4$ as a Highly Efficient, Mild, Heterogeneous, and Reusable Catalytic System for the Solvent-Free Synthesis of Bis(indolyl)methanes

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Silica-supported $LiHSO_4$ ($LiHSO_4/SiO_2$) is used as a green, cheap, and efficient catalytic system for the synthesis of bis(indolyl)methanes via the condensation of indoles with carbonyl compounds under solvent-free conditions. The reactions proceed rapidly at room temperature, and the title compounds are obtained in high to excellent yields.

Keywords Bis(indolyl)methane; carbonyl compound; indole; $LiHSO_4/SiO_2$; solvent-free

INTRODUCTION

In recent years, the use of solid-supported catalysts has become popular due to their unique properties such as enhanced reactivity as well as selectivity, straightforward workup, recyclability of the catalyst, and the ecofriendly reaction conditions.[1,2] Silica gel is one of the most interesting solid supports, because it has surface properties that suggest that very rich organic reactions may occur there. SiO_2 is an inexpensive, reusable, commercially available, and environmentally benign support that, accompanied with different catalysts, has been used in a

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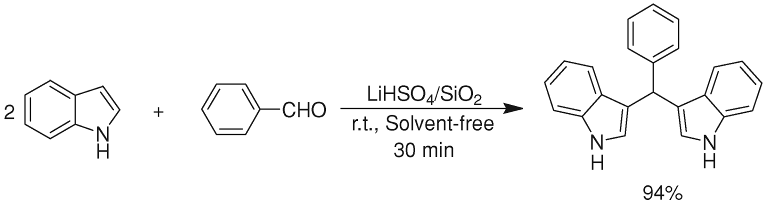
variety of organic transformations.[2] Nevertheless, most of the existing processes in organic synthesis involve toxic and volatile organic solvents as reaction media, and these are environmentally unacceptable from a green chemistry view point. One of the most effective techniques to solve this problem is solvent-free conditions, which makes synthesis simpler, saves energy, and prevents solvent waste, hazards, and toxicity.[3] Consequently, it is important to note that the combination of safe catalysis with the use of solventless technology represents a suitable way toward so-called "ideal synthesis." In this article, we wish to introduce silica-supported $LiHSO_4$ as a new catalyst for organic synthesis. The strong oxophilicity of Li^+ as well as H^+ of HSO_4^- powerfully activates oxygen-containing electrophiles for nucleophilic attack.[4]

Bis(indolyl)methanes are very important compounds, as they have various biological and pharmaceuticals activities.[5] The synthesis of bis(indolyl)methanes via the condensation of indoles with carbonyl compounds is one of the more significant and well-known transformations in organic synthesis.[6,7] In general, this transformation requires a protic[6] or a Lewis acid[7] to activate carbonyl compounds. For this purpose, several reagents and catalysts such as acetic acid,[6a] silica sulfuric acid,[6a] $H_3PMo_{12}O_{40}.xH_2O$,[6c] HY-Zeolite,[6d] $M(HSO_4)_n$ (M = Zn, Mg and Ca),[6e] $ZrOCl_2.8H_2O$,[7a] $AlPW_{12}O_{40}$,[7b] $In(OTf)_3$,[7c] $Dy(OTf)_3$,[7d] $La(PFO)_3$ (PFO = perfluorooctanoates),[7e] Zeokarb-225,[7f] $MgSO_4$,[7g] trityl chloride,[7h] P_2O_5/SiO_2,[7i] and silica chloride have been used.[7j] However, most of the reported methods are associated with one or more of the following disadvantages: (i) the use of expensive reagents, (ii) the necessity of a large or stoichiometric amount of reagent, (iii) long reaction times, and (iv) moderate yields. Moreover, metal hydrogen sulfates have been previously employed for bis(indolyl)methane synthesis,[6e] but this reaction has been performed in solution conditions (EtOH and DMSO) and in relatively long reaction times. Thus, the need for a more efficient and practical alternative use of an inexpensive, copious, and available catalyst is still urgent.

Considering the above facts and also in extension of our previous studies on the application of silica-supported catalysts in organic synthesis,[2a–2h,7i,7j] we introduce here $LiHSO_4/SiO_2$ as a new catalyst for the preparation of bis(indolyl)methanes via the condensation of indoles with aldehydes as well as ketones under solvent-free conditions at room temperature (Scheme 1). It is worth noting that this method has none of the mentioned disadvantages at all.



SCHEME 1

RESULTS AND DISCUSSION

In order to obtain optimal reaction conditions, the condensation of indole with benzaldehyde was selected as a model reaction, and firstly it was examined in the presence of $LiHSO_4$ (20 mol%) under solvent-free conditions at room temperature. However, in these conditions, a highly sticky orange reaction mixture was obtained, and the desired product was produced in 81% yield after 70 min. Prolonging the reaction time did not improve the yield. The yield considerably increased and the reaction time decreased when the reaction was carried out in the presence of silica-supported $LiHSO_4$ (Scheme 1). In this case, the product was obtained in 94% yield within 30 min. Thus, $LiHSO_4/SiO_2$ was applied as catalyst for all other reactions.

The condensation of indole with benzaldehyde was also examined in the presence of $LiHSO_4/SiO_2$ at room temperature in different solvents including H_2O, EtOH, $CHCl_3$, THF, and CH_3CN (Table I). As it can be seen from Table I, the solvent-free method is more efficient.

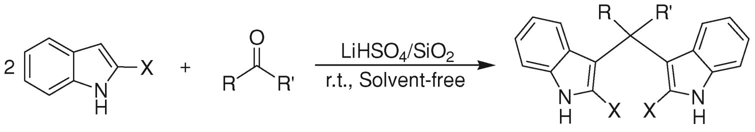
To recognize the efficiency and the capacity of the catalyst, indoles were reacted with structurally diverse aldehydes as well as ketones.

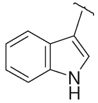
TABLE I Comparison of the Reaction of Indole with Benzaldehyde in the Presence $LiHSO_4/SiO_2$ Under Solution Conditions Versus the Solvent-Free Method

Entry	Solvent	Time (min)	Yield (%)[a]
1	Solvent-free	30	94
2	H_2O	120	23
3	EtOH	60	89
4	$CHCl_3$	120	36
5	THF	120	65
6	CH_3CN	120	59

[a] Isolated yield.

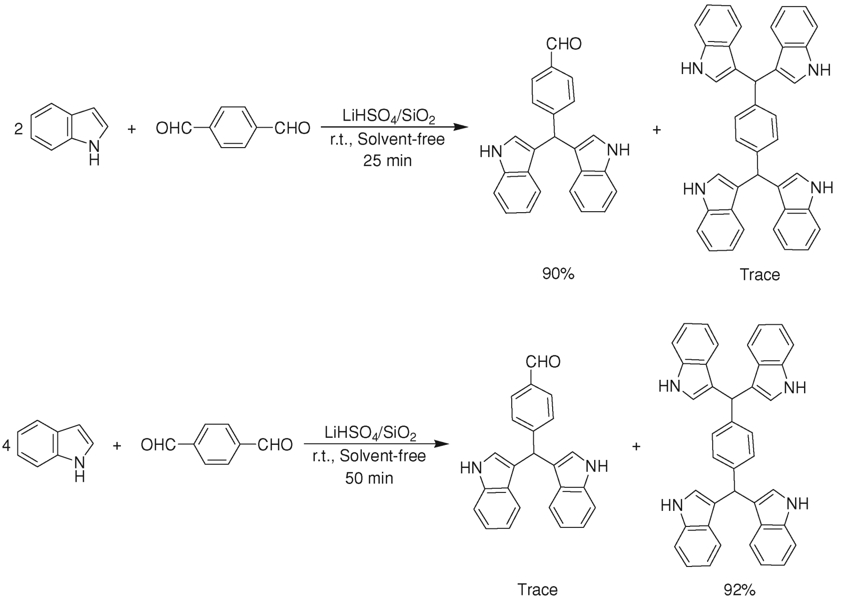
TABLE II Synthesis of Bis(indolyl)methanes via the Condensation of Indoles with Carbonyl Compounds



Entry	X	R	R’	Time (min)	Yield (%)[a]	Mp °C (Lit.)
1	H	C_6H_5	H	30	94	140–142 (140–142)[7g]
2	CH_3	C_6H_5	H	50	89	244–246 (245–247)[7j]
3	H	p-$NO_2C_6H_4$	H	25	90	216–218 (217–219)[7i]
4	H	m- $NO_2C_6H_4$	H	25	88	219–221 (218–220)[7g]
5	H	m-CNC_6H_4	H	25	92	99–101 (102–104)[7h]
6	CH_3	p-$NO_2C_6H_4$	H	40	88	241–243 (240–242)[6d]
7	H	p-$CH_3C_6H_4$	H	30	96	94–96 (97–99)[6b]
8	H	p-$OMeC_6H_4$	H	30	93	186–188 (178–181)[6b]
9	H	p-OHC_6H_4	H	30	87	119–121 (119–121)[7i]
10	CH_3	p-$CH_3C_6H_4$	H	50	91	175–177 (176–178)[7g]
11	H	p-ClC_6H_4	H	25	92	78–80 (78–80)[7i]
12	H	o-ClC_6H_4	H	35	90	73–75 (69–71)[7h]
13	H	4-Pyridyl	H	30	94	161–163 (161–163)[7j]
14	H	2-Furyl	H	30	92	317–319 (316–318)[7i]
15	H		H	40	91	163, dec. (162, dec.)[7i]
16	H	E-$C_6H_5CH{=}CH$	H	50	90	99–101 (100–102)[7i]
17	H	$CH_3(CH_2)_3CH_2$	H	50	88	71–73 (71–73)[7g]
18	H	C_6H_5	CH_3	120	74	163–165 (164–166)[7j]
19	H	3-Pyridyl	CH_3	120	76	251–252 (251–252)[7h]
20		$-CH_2(CH_2)_3CH_2-$		60	85	161–163 (163–165)[7i]

[a] Isolated yield.

The results are summarized in Table II. As Table II indicates, indoles were efficiently condensed with a structurally diverse variety of aldehydes including aromatic aldehydes possessing electron-withdrawing and electron-releasing substituents as well as halogen on their aromatic rings and aliphatic aldehydes (Table II, entries 1–17). The reaction of indoles with ketones gave the corresponding bis(indolyl)methanes in lower yields and longer reaction times (Table II, entries 18–20). Our catalyst was also successfully applied for condensation of indole



SCHEME 2

with terephthaldehyde. When, 2.1 equivalents of indole were reacted with terephthalaldehyde, bis(indolyl)methane was obtained as the major product; however, the use of 4.2 equivalents of indole afforded di-bis(indolyl)methane as the main product (Scheme 2).

One of the most interesting properties of $LiHSO_4/SiO_2$ is its ease of recycling. It can be reused after simple washing with Et_2O, thus rendering the process more economical. The yields of the condensation of indole with benzaldehyde in the 2nd, 3rd, and 4th uses of the catalyst were almost as high as in the first use (please see Table III).

TABLE III The Condensation of Indole with Benzaldehyde in the Presence of Recycled $LiHSO_4/SiO_2$

Entry	Cycle	Time (min)	Yield (%)[a]
1	1st use	30	94
2	2nd use	35	91
3	3rd use	40	90
4	4th use	50	88

[a] Isolated yield.

In conclusion, we have introduced $LiHSO_4/SiO_2$ as a new, efficient, green, heterogeneous, and reusable catalyst for organic synthesis. Efficient synthesis of bis(indolyl)methanes via the condensation of indoles with carbonyl compounds is the first application of this cheap catalyst.

EXPERIMENTAL

All chemicals were purchased from Merck or Fluka chemical companies. H_2SO_4 98% was used for the preparation of $LiHSO_4$. Silica gel 60, 0.063–0.200 mm (7–230 mesh ASTM) was applied as support. All products are known, and their structures were identified by comparison of their spectral data and melting points with those in the authentic samples. The ^1H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Bruker Avance DPX-250 FT-NMR spectrometer. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

General Procedure for the Preparation of $LiHSO_4$

A mixture of LiCl (0.848 g, 20 mmol) and H_2SO_4 (2.002 g, 20 mmol) was stirred under N_2 gas for 120 min to give $LiHSO_4$ (2.080 g) as a white powder. The HCl gas produced was trapped with NaOH solution.

General Procedure for the Preparation of $LiHSO_4/SiO_2$ Catalytic System

A mixture of $LiHSO_4$ (0.5 g) and SiO_2 (9.5 g) was ground vigorously to give $LiHSO_4/SiO_2$ catalytic system as a white powder (10 g).

General Procedure for the Synthesis of Bis(indolyl)methanes

To a mixture of carbonyl compound (1 mmol) and $LiHSO_4/SiO_2$ (0.416 g, 20 mol%) in a mortar, indole (2.1 mmol) was added, and the resulting mixture was ground at room temperature for the times reported in Table II. Then, the reaction mixture was suspended in EtOAc (25 mL), filtered, and the filtrate was washed with a saturated solution of $NaHCO_3$ (2 × 20 mL), saturated solution of $NaHSO_3$ (2 × 20 mL), and water (2 × 20 mL). The organic layer was separated and dried with $CaCl_2$. The solvent was evaporated, and the crude product was purified by recrystallization from EtOAc:petroleum ether (1:2) or plate chromatography on silica gel eluted with EtOAc:petroleum ether (1:2).

After isolation of the products, the remaining $LiHSO_4/SiO_2$ was dried and used for the next run under identical reaction conditions.

REFERENCES

[1] (a) J. H. Clark and C. N. Rhodes, *Clean Synthesis Using Porous Inorganic Solid Catalysts and Supported Reagents* (Royal Society of Chemistry, UK, 2000); (b) R. A. Sheldon and H. van Bekkum, *Fine Chemicals Through Heterogeneous Catalysis*, (Wiley-VCH, Weinheim, Germany, 2001); (c) A. P. Kybett and D. C. Sherrington, *Supported Catalysts and Their Applications* (Royal Society of Chemistry, UK, 2001); (d) M. S. Silva, R. G. Lara, J. M. Marczewski, R. G. Jacob, E. J. Lenardão, and G. Perin, *Tetrahedron Lett.*, **49,** 1927 (2008); (e) R. Hosseinzadeh, Y. Sarrafi, M. Mohadjerani, and F. Mohammadpourmir, *Tetrahedron Lett.*, **49,** 840 (2008).

[2] (a) A. Hasaninejad, A. Zare, H. Sharghi, and M. Shekouhy, *ARKIVOC*, **xi,** 64 (2008); (b) A. Hasaninejad and H. Sharghi, *Phosphorus, Sulfur, and Silicon*, **182,** 873 (2007); (c) A. Khalafi-Nezhad, A. Zare, A. Parhami, M. N. Soltani Rad, and G. R. Nejabat, *Phosphorus, Sulfur, and Silicon*, **182,** 657 (2007); (d) A. Khalafi-Nezhad, A. Parhami, M. N. Soltani Rad, M. A. Zolfigol, and A. Zare, *Tetrahedron Lett.*, **48,** 5219 (2007); (e) A. Khalafi-Nezhad, A. Zare, A. Parhami, M. N. Soltani Rad, and G. R. Nejabat, *J. Iran. Chem. Soc.*, **4,** 271 (2007); (f) A. Hasaninejad and A. Zare, *J. Sulfur Chem.*, **28,** 357 (2007); (g) A. Khalafi-Nezhad, A. Zare, A. Parhami, M. N. Soltani Rad, and G. R. Nejabat, *Synth. Commun.*, **36,** 3549 (2006); (h) A. Khalafi-Nezhad, A. Zare, A. Parhami, M. N. Soltani Rad, and G. R. Nejabat, *Can. J. Chem.*, **84,** 979 (2006); (i) F. Shirini, K. Marjani, H. Taherpour Nahzomi, and M. A. Zolfigol, *Phosphorus, Sulfur, and Silicon*, **183**, 168 (2008); (j) H. Ghafuri, B. Eftekhari-Sis, and M. M. Hashemi, *Phosphorus, Sulfur, and Silicon*, **182,** 1645 (2007); (k) F. Shirini, K. Marjani, H. Taherpour Nahzomi, M. A. Zolfigol, *Phosphorus, Sulfur, and Silicon*, **182,** 1245 (2007); (l) P. Salehi, M. A. Zolfigol, F. Shirini, and M. Baghbanzadeh, *Curr. Org. Chem.*, **10,** 2171 (2006) (Review).

[3] (a) K. Tanaka, *Solvent-Free Organic Synthesis* (Wiley-VCH, GmbH and KGaA, Weinheim, Germany, 2004); (b) A. Loupy, *Microwave in Organic Synthesis* (Wiley-VCH, Weinheim, Germany, 2006); (c) A. R. Kazemizadeh, E. Ahmadi, F. Marandi, and A. Ramazani, *Phosphorus, Sulfur, and Silicon*, **182,** 2855 (2007); (d) P. Salehi, M. Dabiri, A. R. Khosropour, and P. Roozbehniya, *J. Iran. Chem. Soc.*, **3,** 98 (2006); (e) M. M. Mojtahedi, M. S. Abaee, M. Bolourtchian, and H. Abbasi, *Phosphorus, Sulfur, and Silicon*, **182,** 905 (2007).

[4] (a) A. Basak (née Nandi), M. K. Nayak, and A. K. Chakraborti, *Tetrahedron Lett.*, **39,** 4883 (1998); (b) A. K. Chakraborti, A. Basak (née Nandi), and V. Grover, *J. Org. Chem.*, **64,** 8014 (1999).

[5] (a) J. J. Michnovicz, H. L. Bradlow, M. J. Huang, T. Osawa, C. T. Ho, and R. T. Rosen (eds), *Food Phytochemicals for Cancer Prevention 1: Fruits and Vegetables* (American Chemical Society, Washington, DC, 1994); (b) T. Osawa and M. Namiki, *Tetrahedron Lett.*, **24,** 4719 (1983); (c) R. Bell, S. Carmell, and N. Sar, *J. Nat. Prod.*, **57,** 1587 (1994); (d) G. Bifulco, I. Bruno, R. Riccio, J. Lavayre, and G. Bourdy, *J. Nat. Prod.*, **58,** 1254 (1995); (e) A. Ramirez and S. Garcia-Rubio, *Curr. Med. Chem.*, **10,** 1891 (2003); (f) S. Zhao, X. Liao, and J. M. Cook, *Org. Lett.*, **4,** 687 (2002).

[6] (a) A. Kamal and A. A. Qureshi, *Tetrahedron*, **19,** 513 (1963); (b) D. M. Pore, U. V. Desai, T. S. Thopate, and P. P. Wadgaonkar, *ARKIVOC*, **xii,** 75 (2006); (c) M. A. Zolfigol, P. Salehi, and M. Shiri, *Phosphorus, Sulfur, and Silicon*, **179,** 2273 (2004); (d) A. V. Reddy, K. Ravinder, V. L. N. Reddy, T. V. Goud, V. Ravikanth, and Y.

Venkateswarlu, *Synth. Commun.*, **33,** 3687 (2003); (e) K. Niknam, M. A. Zolfigol, T. Sadabadi, and A. Nejati, *J. Iran. Chem. Soc.*, **3,** 318 (2006).

[7] (a) H. Firouzabadi, N. Iranpoor, M. Jafarpour, and A. Ghadiri, *J. Mol. Cat. A: Chem.*, **253,** 249 (2006); (b) H. Firouzabadi, N. Iranpoor, and A. A. Jafari, *J. Mol. Catal. A: Chem.*, **244,** 168 (2006); (c) R. Nagarajan and P. T. Perumal, *Tetrahedron*, **58,** 1229 (2002); (d) X. Mi, S. Luo, J. He, and J. P. Cheng, *Tetrahedron Lett.*, **45,** 4567 (2004); (e) L. Wang, J. H. Han, T. Sheng, J. Z. Fan, and X. Tang, *Synlett*, 337 (2005); (f) C. J. Magesh, R. Nagarajan, M. Karthik, and P. T. Perumal, *Applied Catal. A: General*, **266,** 1 (2004); (g) A. Hasaninejad, A. Parhami, A. Zare, A. Khalafi-Nezhad, A. Nasrolahi Shirazi, and A. R. Moosavi Zare, *Polish J. Chem.*, **82,** 565 (2008); (h) A. Khalafi-Nezhad, A. Parhami, A. Zare, A. R. Moosavi Zare, A. Hasaninejad, and F. Panahi, *Synthesis*, 617 (2008); (i) A. Hasaninejad, A. Zare, H. Sharghi, K. Niknam, and M. Shekouhy, *ARKIVOC*, **xiv,** 39 (2007); (j) A. Hasaninejad, A. Zare, H. Sharghi, M. Shekouhy, R. Khalifeh, A. Salimi Beni, and A. R. Moosavi Zare, *Can. J. Chem.*, **85,** 416 (2007).