doi:10.1246/cl.130370

Cellulose–Sulfonic Acid: An Efficient, Recyclable, and Biodegradable Solid Acid Catalyst for the Synthesis of 3-Aminoalkylindoles

S. Satyanarayana,[1] K. Praveen Kumar,[1] P. Lakshmi Reddy,[1] R. Narender,*[1] G. Narasimhulu,[2] and B. V. Subba Reddy*[2]
[1] *Crop Protection Chemicals, Indian Institute of Chemical Technology, Hyderabad-500 007, India*
[2] *Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India*

(Received April 20, 2013; CL-130370; E-mail: basireddy@iict.res.in)

Three-component coupling (3CC) of indoles, aldehydes, and *N*-alkylanilines has been accomplished using a catalytic amount of cellulose–sulfonic acid under mild reaction conditions to furnish the 3-aminoalkylindoles at room temperature in short reaction times and in relatively good to excellent yields and selectivity. The use of biodegradable cellulose–sulfonic acid makes this method quite simple, convenient, and economically viable for the synthesis of 3-aminoalkylindoles.

Indole derivatives are known to exhibit a wide range of physiological properties such as antioxidant, antibacterial, and insecticidal.[1–3] They are found to exhibit anticancer activity against human cancer cell lines[4] and are also used as valuable antibiotics.[1] Among various derivatives of indoles, 3-substituted indoles are of great importance as they are widely distributed in nature and show a broad range of biological activities.[5,6] Therefore, there is a growing interest in the development of improved methods for the synthesis of 3-substituted indoles.[7,8] In particular, 3-aminoalkyl or aryl-substituted indoles are considered to be privileged scaffolds in medicinal chemistry.[1] Furthermore, 3-aminoalkylindole core is often found in many indole alkaloids such as gramine **A**, aspidospermine **B**, and 12-chloro-19,20-dihydroakuammicine **C** (Figure 1).[9]

Despite several methods being reported for the synthesis of 3-substituted indoles,[7,8] only a few synthetic methods are available for the preparation of 3-aminoalkylindoles via three-component reaction.[4b,10] Generally, acid catalysts are known to catalyze the reaction of aromatic aldehyde, *N*-alkylaniline, and indole. Therefore, the development of simple and efficient methods would expand the scope of the synthesis of 3-aminoalkylindoles, which are very useful synthetic targets for drug discovery.

Recently, the use of heterogeneous catalysts has received particular attention as user-friendly catalysts because of their recyclability, operational simplicity, and minimal waste disposal.[11] In particular, cellulose–sulfonic acid (cellulose–SO_3H) is a biodegradable solid acid catalyst that has been used for the synthesis of α-amino nitriles, quinolines, aryl-14*H*-dibenzo[*a*,*j*]-xanthenes, tetrahydroquinolines, and functionalized pyrrolidines.[12,13] However, there are no reports on the use of cellulose–SO_3H for the preparation of 3-aminoalkylindoles under mild reaction conditions.

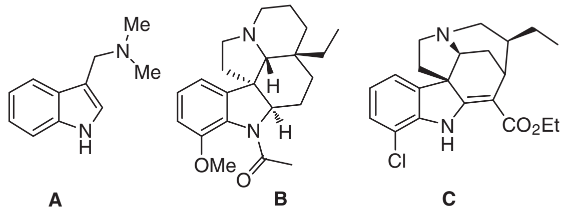
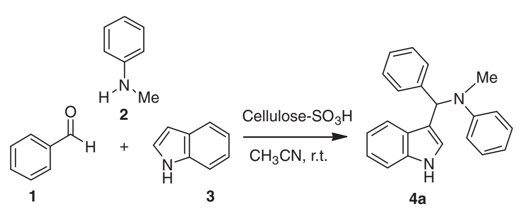


Figure 1. Representative examples of 3-aminoalkylindole alkaloids.

The cellulose–SO_3H catalyst shows an excellent catalytic activity and stability. The acidity of the catalyst is not affected by air, water, or light. Due to low solubility and high stability, cellulose acts as an efficient support. Cellulose–SO_3H can easily be prepared from cellulose and chlorosulfonic acid.[12d] To a solution of cellulose (DEAE for column chromatography, Sigma-Aldrich) in absolute ethanol was added chlorosulfonic acid dropwise slowly at 0 °C. The resulting solid was filtered and then washed with acetonitrile. After drying in oven for 3 h at 70 °C, the cellulose–SO_3H was obtained as a white powder.[12c,12d] The number of active acid sites (H^+) of cellulose–SO_3H was determined by acid–base titration, and it was found to be $0.50\,\mathrm{mmol\,g^{-1}}$ ($1\,\mathrm{mequiv} = 1\,\mathrm{mmol/valence}$). This amount corresponds to about 0.90% of the sulfur content, demonstrating that most of the sulfur species are present in the form of sulfonic acid groups.

Following our interest in the catalytic applications of solid acid catalysts,[14] we herein report, for the first time, a novel method for the synthesis of 3-aminoalkylindoles using cellulose–SO_3H as the recyclable catalyst. As a preliminary study, benzaldehyde (**1**) was treated with *N*-methylaniline (**2**) and indole (**3**) in the presence of cellulose–SO_3H in acetonitrile. The reaction proceeded smoothly at room temperature, affording the corresponding product, *N*-[(1*H*-indol-3-yl)(phenyl)methyl]-*N*-methylaniline (**4a**) in 92% yield (Scheme 1). To optimize the reaction conditions, we performed the reaction with various amounts 0.04, 0.05, 0.06, and 0.07 g of cellulose–SO_3H. The best results were obtained with cellulose–SO_3H ($0.06\,\mathrm{mmol\,g^{-1}}$) in terms of reaction time and yields.

In order to realize catalytic efficiency, we performed the above reaction with various catalysts such as CAN, $Mn(OAc)_3$, DDQ, and $CeCl_3{\cdot}7H_2O/LiI$. The reaction was also performed with some commonly used acid catalysts such as *p*-TSA, camphor–sulfonic acid, $Yb(OTf)_3$, $Ce(OTf)_3$, $ZnCl_2$, and Amberlyst-15, and the results are presented in Table 1. However, the use of most of the above catalysts often involves long reaction



Scheme 1. 3CC synthesis of 3-aminoalkylindole **4a**.

Table 1. Screening of various catalysts and solvents for the preparation of **4a**

Entry	Acid catalyst	Quantity /mmol g^{-1} [a]	Solvent	Time/h	Yield/%[b]
a	CAN	0.06	CH_3CN	8.0	62
b	$Mn(OAc)_3$	0.06	CH_3CN	12.0	40
c	DDQ	0.06	DCM	3.5	53
d	Cellulose–SO_3H	0.06	DCM	8.0	65
e	Cellulose–SO_3H	0.06	CH_3NO_2	4.5	80
f	Cellulose–SO_3H	0.06	CH_3CN	2.3	92
g	$CeCl_3 \cdot 7H_2O/LiI$	0.06	CH_3CN	10.0	55
h	*p*-TSA	0.06	CH_3CN	3.0	76
i	Camphor-SO_3H	0.06	CH_3CN	2.0	79
j	$ZnCl_2$	0.06	CH_3CN	2.5	68
k	Amberlyst-15	0.06	CH_3CN	2.5	60
l	$Yb(OTf)_3$	0.06	CH_3CN	4.0	75
m	$Ce(OTf)_3$	0.06	CH_3CN	4.0	65

[a]The reaction was performed at 1 mmol scale at 25 °C. [b]Isolated yield.

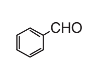
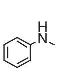
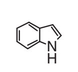
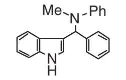
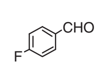
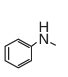
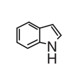
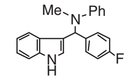
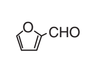
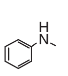
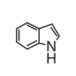
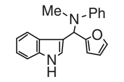
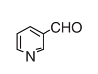
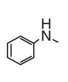
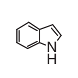
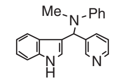
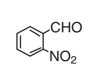
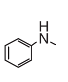
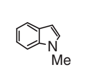
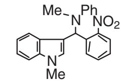
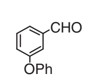
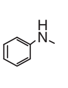
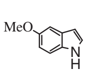
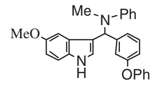
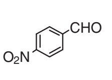
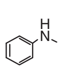
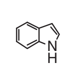
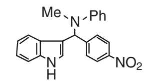
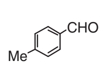
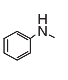
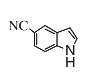
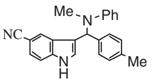
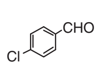
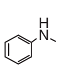
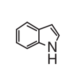
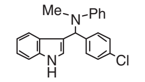
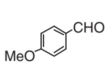
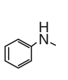
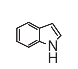
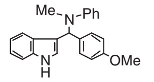
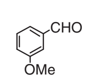
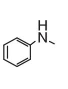
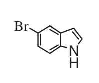
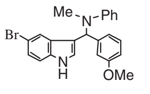
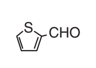
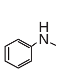
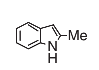
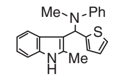
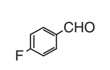
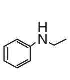
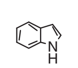
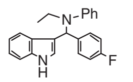
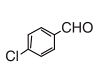
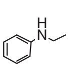
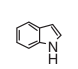
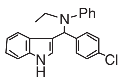
times, high catalyst loading, and lower yields. Thus, the combination of cellulose–SO_3H and acetonitrile gave the 3-aminoalkylindoles in good yields. Furthermore, in the absence of the catalyst, no 3-aminoalkylindole was formed; instead, a trace amount of bis(indolyl)arylmethane was isolated. Therefore, the present method is advantageous over commonly used acid catalysts listed in Table 1.

Next, we examined the effect of various solvents such as dichloromethane, nitromethane, and acetonitrile. Of these, acetonitrile appeared to give the best results with respect to reaction time, yields, and selectivity (Table 1).

Next, we studied this three-component reaction with various aromatic aldehydes. Interestingly, both electron-rich and electron-deficient aryl aldehydes participated well in this reaction. Aromatic aldehydes such as *p*-fluoro-, *o*-nitro-, *m*-phenoxy-, *p*-nitro-, *p*-methyl-, *p*-chloro-, *p*-methoxy-, and *m*-methoxybenzaldehydes gave the products in good yields (Table 2). Other substrates like heteroaromatic aldehydes, including 2-furaldehyde, pyridine-3-carbaldehyde, and thiophene-2-carbaldehyde also worked well for this reaction (Entries c, d, and l, Table 2). Similarly, various indole derivatives such as *N*-methyl-, 5-methoxy-, 5-cyano-, 5-bromo-, and 2-methylindole participated effectively in this reaction to afford the corresponding 3-aminoalkylindoles (Entries e, f, h, k, and l, Table 2). Interestingly, *N*-ethylaniline also gave the desired 3-aminoalkylindoles in good yields (Entries m and n, Table 2). However, the reaction did not proceed with *N*,*N*-diarylamines. Furthermore, *N*-benzylaniline also failed to give the desired product under similar conditions.

Therefore, the reaction was successful only with *N*-alkylanilines such as *N*-methyl- and *N*-ethylanilines. All the products were characterized using ^{1}H, ^{13}C NMR, and mass spectral data and also by comparison with authentic samples.[4b,10]

Table 2. Cellulose–SO_3H-catalyzed synthesis of 3-aminoalkylindoles

Entry	Aldehyde (**1**)	*N*-Alkylaniline (**2**)	Indole (**3**)	Product (**4**)[a]	Time/min	Yield/%[b]
a					2.3	92
b					2.0	86
c					2.5	89
d					2.4	85
e					3.0	87
f					2.3	83
g					2.4	85
h					3.0	89
i					2.2	92
j					3.0	85
k					2.5	82
l					3.0	85
m					2.4	81
n					2.3	89

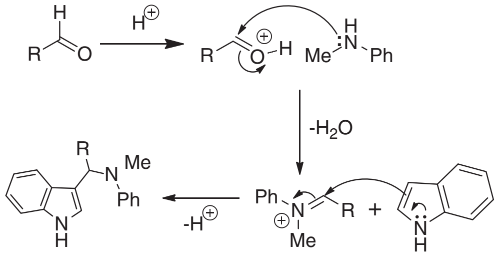
[a]All products were characterized by NMR, IR, and mass spectroscopy. [b]Yield refers to pure products after chromatography.

In all cases, the reactions proceeded well at ambient conditions and the corresponding 3-aminoalkylindoles were obtained in relatively good to excellent yields. The scope and generality of this process is illustrated with respect to various aromatic aldehydes, and the results are presented in Table 2.[15] After complete conversion, as indicated in Table 2, cellulose–SO_3H was recovered from the reaction mixture by simple filtration. The recovered catalyst showed an excellent activity in 3–4 successive runs without any significant loss of its performance under similar reaction conditions (Table 3).[12d] Thus, this process is superior to those involving the use of reported catalysts for large-scale synthesis.

Table 3. Reusability of the cellulose–SO_3H for the preparation of **4a**

Entry	Cycles	Quantity /mmol $g^{-1\,a}$	Solvent	Time /h	Yield /%^{b}
1	1st	0.06	CH_3CN	2.3	92
2	2nd	0.06	CH_3CN	2.3	90
3	3rd	0.06	CH_3CN	2.3	87
4	4th	0.06	CH_3CN	2.3	83

^{a}The reaction was performed at 1 mmol scale at 25 °C. ^{b}Isolated yield.



Scheme 2. A plausible reaction pathway.

Mechanistically, we assume that *N*-methylaniline reacts with aldehyde in the presence of cellulose–SO_3H, to generate the iminium ion. Thus formed iminium ion was trapped by indole to afford the desired 3-aminoalkylindole (Scheme 2).

In summary, cellulose–SO_3H was proved to be an efficient catalyst for the synthesis of 3-aminoalkylindoles at room temperature by means of three-component coupling of indole, aldehydes, and *N*-alkylanilines. The major advantages of the present method are short reaction times, high conversions, operational simplicity, economic viability, environmentally benign nature, and reusability of the catalyst, which make it an attractive process for the preparation of 3-aminoalkylindoles.

S.S., K.P., and G.N. are thankful to CSIR, New Delhi, India, for the award of fellowships. P.L.R. is thankful to UGC, for the award of a fellowship.

References and Notes

1 a) R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**. b) D. J. Faulkner, *Nat. Prod. Rep.* **2001**, *18*, 1R. c) I. Ninomiya, *J. Nat. Prod.* **1992**, *55*, 541. d) A. Casapullo, G. Bifulco, I. Bruno, R. Riccio, *J. Nat. Prod.* **2000**, *63*, 447.

2 a) S. A. Morris, R. J. Andersen, *Tetrahedron* **1990**, *46*, 715. b) I. Mancini, G. Guella, F. Pietra, C. Debitus, J. Waikedre, *Helv. Chim. Acta* **1996**, *79*, 2075. c) H. R. Bokesch, L. K. Pannell, T. C. McKee, M. R. Boyd, *Tetrahedron Lett.* **2000**, *41*, 6305.

3 a) J. Ford, R. J. Capon, *J. Nat. Prod.* **2000**, *63*, 1527. b) A. Cutignano, G. Bifulco, I. Bruno, A. Casapullo, L. Gomez-Paloma, R. Riccio, *Tetrahedron* **2000**, *56*, 3743. c) S. Olgen, E. Akaho, D. Nebioglu, *J. Enzyme Inhib. Med. Chem.* **2003**, *18*, 485.

4 a) H.-C. Zhang, L. V. R. Boñaga, H. Ye, C. K. Derian, B. P. Damiano, B. E. Maryanoff, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2863. b) V. K. Rao, B. S. Chhikara, A. N. Shirazi, R. Tiwari, K. Parang, A. Kumar, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3511. c) A. Ahmad, W. A. Sakr, K. M. W. Rahman, *Curr. Drug Targets* **2010**, *11*, 652.

5 a) B. Jiang, C.-G. Yang, J. Wang, *J. Org. Chem.* **2001**, *66*, 4865. b) H. Zhang, R. C. Larock, *Org. Lett.* **2001**, *3*, 3083. c) M. Sakagami, H. Muratake, M. Natsume, *Chem. Pharm. Bull.* **1994**, *42*, 1393. d) T. Fukuyama, X. Chen, *J. Am. Chem. Soc.* **1994**, *116*, 3125.

6 a) D. J. Faulkner, *Nat. Prod. Rep.* **1999**, *16*, 155. b) M. Lounasmaa, A. Tolvanen, *Nat. Prod. Rep.* **2000**, *17*, 175.

7 a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem., Int. Ed.* **2004**, *43*, 550. b) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172. c) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2001**, *40*, 160.

8 a) N. Srivastava, B. K. Banik, *J. Org. Chem.* **2003**, *68*, 2109. b) G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem.* **2003**, *68*, 4594. c) K. R. Campos, J. C. S. Woo, S. Lee, R. D. Tillyer, *Org. Lett.* **2004**, *6*, 79. d) K. B. Hong, C. W. Lee, E. K. Yum, *Tetrahedron Lett.* **2004**, *45*, 693. e) P. Köhling, A. M. Schmidt, P. Eilbracht, *Org. Lett.* **2003**, *5*, 3213. f) A. Arcadi, G. Bianchi, M. Chiarini, G. D'Anniballe, F. Marinelli, *Synlett* **2004**, 944.

9 J. S. Bello, D. F. Amado, V. V. Kouznetsov, *Rev. Soc. Quim. Peru* **2008**, *74*, 190.

10 a) A. Olyaei, B. Shams, M. Sadeghpour, F. Gesmati, Z. Razaziane, *Tetrahedron Lett.* **2010**, *51*, 6086. b) D. K. Yadav, R. Patel, V. P. Srivastava, G. Watal, L. D. S. Yadav, *Tetrahedron Lett.* **2010**, *51*, 5701. c) B. Das, J. N. Kumar, A. S. Kumar, K. Damodar, *Synthesis* **2010**, 914. d) P. Srihari, V. K. Singh, D. C. Bhunia, J. S. Yadav, *Tetrahedron Lett.* **2009**, *50*, 3763. e) V. K. Rao, M. S. Rao, N. Jain, J. Panwar, A. Kumar, *Org. Med. Chem. Lett.* **2011**, *1*, 10. f) D. Kundu, A. K. Bagdi, A. Majee, A. Hajra, *Synlett* **2011**, *8*, 1165. g) C. L. Devi, V. J. Rao, S. Palaniappan, *Synth. Commun.* **2012**, *42*, 1593. h) A. Ravindran, R. Kore, R. Srivastava, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2013**, *52*, 129.

11 a) I. V. Kozhevnikov, *Chem. Rev.* **1998**, *98*, 171. b) O. De Paolis, L. Teixeira, B. Török, *Tetrahedron Lett.* **2009**, *50*, 2939. c) K. Niknam, D. Saberi, M. N. Sefat, *Tetrahedron Lett.* **2010**, *51*, 2959.

12 a) A. Shaabani, A. Rahmati, Z. Badri, *Catal. Commun.* **2008**, *9*, 13. b) J. V. Madhav, Y. T. Reddy, P. N. Reddy, M. N. Reddy, S. Kuarm, P. A. Crooks, B. Rajitha, *J. Mol. Catal. A: Chem.* **2009**, *304*, 85. c) A. Kumar, S. Srivastava, G. Gupta, *Tetrahedron Lett.* **2010**, *51*, 517. d) A. Kumar, G. Gupta, S. Srivastava, *J. Comb. Chem.* **2010**, *12*, 458.

13 a) A. Shaabani, A. Maleki, *Appl. Catal., A* **2007**, *331*, 149. b) A. Shaabani, A. Maleki, J. Moghimi, E. Soleimani, *Chem. Pharm. Bull.* **2007**, *55*, 957.

14 a) B. V. S. Reddy, A. Venkateswarlu, Ch. Madan, A. Vinu, *Tetrahedron Lett.* **2011**, *52*, 1891. b) B. V. S. Reddy, A. Venkateswarlu, G. G. K. S. N. Kumar, A. Vinu, *Tetrahedron Lett.* **2010**, *51*, 6511. c) J. S. Yadav, B. V. S. Reddy, D. N. Chaya, G. G. K. S. N. Kumar, P. Naresh, B. Jagadeesh, *Tetrahedron Lett.* **2009**, *50*, 1799. d) J. S. Yadav, B. V. S. Reddy, G. Satheesh, *Tetrahedron Lett.* **2004**, *45*, 3673. e) J. S. Yadav, B. V. S. Reddy, M. Srinivas, A. Prabhakar, B. Jagadeesh, *Tetrahedron Lett.* **2004**, *45*, 6033. f) J. S. Yadav, B. V. S. Reddy, V. Sunitha, K. S. Reddy, K. V. S. Ramakrishna, *Tetrahedron Lett.* **2004**, *45*, 7947.

15 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.