Cellulose Sulfuric Acid Catalyzed One-Pot Three-Component Synthesis of Imidazoazines

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Imidazoazines have been synthesized by a one-pot three-component condensation reaction of an aldehyde, a 2-aminoazine and an isocyanide in the presence of the cellulose sulfuric acid, as an effective bio-supported catalyst in excellent yields. The reaction work-up is simple and the catalyst can be easily separated from the product and reused in several times.

Key words cellulose sulfuric acid; bio-supported catalyst; imidazo[1,2-*a*]pyridine; isocyanide; multi-component reaction

Imidazo[1,2-*a*]pyridines, as an important class of versatile pharmaceutically and biologically active compounds spanning applications in anti-inflammatory[1,2] and antibacterial agents,[3] inhibitors of gastric acids secretion,[4] calcium channel blockers,[5] and antiulcer based therapies.[6] As a result, numerous two- and three-component approaches for their synthesis have been reported.[7—14]

Biopolymers, especially cellulose and its derivatives,[15] have some unique properties, which make them attractive alternatives for conventional organic or inorganic supports for catalytic applications. Among others, they are extremely inert, inexpensive, biodegradable and environmentally benign allowing various reaction conditions to be employed. Cellulose is the most abundant natural material in the world and it has been widely studied during the past decades because it is a biodegradable material and a renewable resource.

In recent years, the emphasis of science and technology is shifting more towards environmentally friendly and sustainable resources and processes; in this regard, biopolymers are attractive candidates to explore for supported catalysis.[16,17]

Several interesting biopolymers for example alginate,[18] gelatin,[19,20] starch[21] and chistosan[22] derivatives have been utilized as a support for catalytic applications.

During the course of our studies on the development of new routes for the synthesis of organic compounds using solid acid catalysts in organic transformations[23—27] and our interest in isocyanide-based MCRs,[28—31] we developed the synthesis of imidazoazines **4a—j** *via* the three-component condensation of an aldehyde **1**, a 2-aminoazine **2** and an isocyanide **3** in the presence of catalytic amount of cellulose sulfuric acid at room temperature (Chart 1).

Experimental

Apparatus Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. All the products (except **4g**) are known compounds, which were identified by IR and ^{1}H-NMR spectral data and comparing their melting points with literature reports.

Preparation of Cellulose Sulfuric Acid To a magnetically stirred mixture of 5.00 g of cellulose (DEAE for column chromatography, Merck) in 20 ml of *n*-hexane, 1.00 g of chlorosulfonic acid (9 mmol) was added dropwise at 0 °C during 2 h. HCl gas was removed from the reaction vessel immediately. After the addition was complete, the mixture was stirred for 2 h. Then, the mixture was filtered and washed with 30 ml of acetonitrile and dried at room temperature to obtain 5.47 g cellulose sulfuric acid as white powder. This white homogeneous solid acid is very stable and is not affected by air, water and light. Sulfur content of sample obtained by conventional elemental analysis, was 0.68 mmol/g. The number of H^+ site of cellulose–SO_3H determined by acid-base titration was 0.65 meq/g. This value corresponds to about 0.96% of the sulfur content, indicating that most of the sulfur species on the sample are in the form sulfonic acid groups.

Synthesis of Imidazoazines (4a—j) To a solution of 2-aminoazine (1 mmol), aldehyde (1.2 mmol) and isocyanide (1.1 mmol), in 3 ml of MeOH, was added cellulose sulfuric acid (0.05 g). The resulting mixture was stirred for 2 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1), the reaction mixture was filtered and washed with CH_2Cl_2 (10 ml) to separate the catalyst. Then the filtrate's solvent was evaporated under reduced pressure and followed by crystallization from ethyl acetate to give the imidazoazines as pure product.

Characterization of *N*-Cyclohexyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine (4g, $C_{19}H_{21}N_3$) Yellow solid (0.274 g, 94%); mp 200—202 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.97 (10H, m), 2.94 (1H, m), 3.76 (1H, br), 7.06—8.15 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 24.73, 25.61, 34.10, 56.82, 107.87, 117.75, 123.02, 125.23, 127.03, 127.72, 128.62, 128.64, 133.36, 135.89, 137.53. IR (KBr) cm^{-1}: 3250, 2920, 1602. MS *m/z*: 291 (M^+), 259, 158, 76.

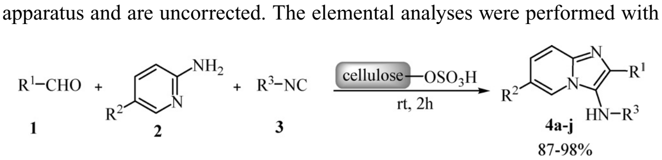

Chart 1. Synthesis of 3-Aminoimidazo[1,2-*a*]pyridines

Results and Discussion

Cellulose sulfuric acid is readily prepared by the dropwise addition of chlorosulfonic acid to *n*-hexane mixture of cellulose at 0 °C. It is important to note that, this reaction is easy and clean without any work-up procedure due to HCl gas is evolved from the reaction vessel immediately. This white homogeneous, nonhygroscopic solid acid is very stable under reaction conditions.

In order to optimize the reaction conditions, we conducted the condensation of benzaldehyde (1.2 mmol), 2-amino-5-methylpyridine (1 mmol) and cyclohexyl isocyanide (1.1 mmol) with stirring at room temperature in various solvents and solvent free conditions. The results showed that the efficiency and the yield of the reaction in MeOH was higher than those obtained in other solvents, such as H_2O, EtOH, CH_2Cl_2, toluene and CH_3CN and or under solvent-free conditions.

As shown in Table 1, the reaction of benzaldehyde, 2-amino-5-bromopyridine and cyclohexyl isocyanide was also carried out in the presence of various protic solid acids (Amberlyst-21, Montmorillonite-K_{10} and cellulose sulfuric acid), liquid acids (HCl, H_2SO_4 and HOAc) and Lewis acid ($AlCl_3$). The best yield was obtained with cellulose sulfuric acid.

To illustrate the need of the cellulose sulfuric acid for these reactions an experiment was conducted in the absence of cellulose sulfuric acid. The yield in this case was trace after 3 h (Table 1, Entry 1). Obviously, the cellulose sulfuric acid is an important component of the reaction.

As indicated in Table 2, the reaction of aldehydes with 2-aminoazines and isocyanides afforded imidazoazines in the presence of cellulose sulfuric acid as a promoter in very high

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yields.

One of the advantages of solid acid catalysts is their ability to perform as a recyclable reaction media. We were able to separate cellulose sulfuric acid from the reaction medium easily by washing with CH_2Cl_2. After drying it was reused for subsequent reactions (Table 2, Entry 1). Thus, this process could be also interesting for large-scale synthesis.

Conclusions

In summary, cellulose sulfuric acid as an efficient and environmentally friendly bio-supported proton source catalyst was prepared and employed for the synthesis of imidazoazines *via* the condensation of an aldehyde, a 2-aminoazine and an isocyanide in the presence of cellulose sulfuric acid in excellent yields with relatively short reaction times at room temperature. To the best our knowledge this is the first report on the synthesis of imidazoazines in a bio-supported catalyst and these new reaction conditions would be a superior proton source comparing to reported inorganic supported solid acids and acidic resins.

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References

1) Maruyama Y., Anami K., Katoh Y., *Arzneim.-Forsch.*, **28**, 2102—2111 (1978).
2) Maruyama Y., Anami K., Terasawa M., Goto K., Imayoshi T., Kadobe Y., Mizushima Y., *Arzneim.-Forsch.*, **31**, 1111—1118 (1981).
3) Rival Y., Grassy G., Michel G., *Chem. Pharm. Bull.*, **40**, 1170—1176 (1992).
4) Kaminski J. J., Wallmark B., Briving C., Andersson B. M., *J. Med. Chem.*, **34**, 533—541 (1991).
5) Sanfilippo P. J., Urbanski M., Press J. B., Dubinsky B., Moore J. B., *J. Med. Chem.*, **31**, 2221—2227 (1988).
6) Almirante L., Polo L., Mugnaini A., Provinciali E., Rugarli P., Biancotti A., Gamba A., Murmann W., *J. Med. Chem.*, **8**, 305—312 (1965).
7) Mosby W. L., "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Wiley, New York, 1961, Part I, p. 460 and Part II, p. 802.
8) Blewitt H. L., "Special Topics in Heterocyclic Chemistry," ed. by Weissberger A., Taylor E. C., Wiley, New York, 1977, p. 117.
9) Spitzer W. A., Victor F., Pollock D. G., Hayers J. S., *J. Med. Chem.*, **31**, 1590—1595 (1988).
10) Elhakmaoui A., Gueiffier A., Milhavet J.-C., Blache Y., Chapat J.-P., Chavignon O., Teulade J.-C., Snoeck R., Andrei G., De Clercq E., *Bioorg. Med. Chem. Lett.*, **4**, 1937—1940 (1994).
11) Gueiffier A., Mavel S., Lhassani M., Elhakmaoui A., Snoeck R., Andrei G., Chavignon O., Teulade J.-C., Witvrouw M., Balzarini J., De Clercq E., Chapat J.-P., *J. Med. Chem.*, **41**, 5108—5112 (1998).
12) Groebke K., Weber L., Mehlin F., *Synlett*, **1998**, 661—663 (1998).
13) Blackburn C., *Tetrahedron Lett.*, **39**, 5469—5472 (1998).
14) Mavel S., Renou J. L., Galtier C., Snoeck R., Andrei G., Balzarini J., De Clercq E., Gueiffier A., *Arzneim.-Forsch.*, **51**, 304—309 (2001).
15) Klemm D., Heublein B., Fink H. P., Bohn A., *Angew. Chem. Int. Ed.*, **44**, 3358—3393 (2005).
16) Breslow R., *Acc. Chem. Res.*, **13**, 170—190 (1980).
17) Clark J. H., Macquarrie D. J., "Green Chemistry and Technology," Blackwell, Abingdon, 2002.
18) Wei W.-L., Zhu H.-Y., Zhao C.-L., Huang M.-Y., Jiang Y.-Y., *React. Funct. Polym.*, **59**, 33—39 (2004).
19) Crecchio C., Ruggiero P., Pizzigallo M. D. R., *Biotechnol. Bioengineering*, **48**, 585—591 (1995).
20) Gliemann H., Nickel U., Schneider S., *J. Raman Spec.*, **29**, 89—96 (1998).
21) Huang K., Xue L., Hu Y.-C., Huang M.-Y., Jiang Y.-Y., *React. Funct. Polym.*, **50**, 199—203 (2002).
22) Guibal E., *Prog. Polym. Sci.*, **30**, 71—109 (2005).
23) Shaabani A., Yavari I., Teimouri M. B., Bazgir A., Bijanzadeh H. R., *Tetrahedron*, **57**, 1375—1378 (2001).
24) Shaabani A., Teimouri M. B., Bijanzadeh H. R., *Tetrahedron Lett.*, **43**, 9151—9154 (2002).
25) Shaabani A., Teimouri M. B., Arab-Ameri S., *Tetrahedron Lett.*, **45**, 8409—8413 (2004).
26) Shaabani A., Soleimani E., Khavasi H. R., Hoffmann R. D., Rodewald U. C., Pöttgen R., *Tetrahedron Lett.*, **47**, 5493—5496 (2006).
27) Shaabani A., Soleimani E., Maleki A., *Tetrahedron Lett.*, **47**, 3031—3034 (2006).
28) Shaabani A., Bazgir A., Teimouri F., Lee D. G., *Tetrahedron Lett.*, **43**, 5165—5167 (2002).
29) Shaabani A., Teimouri F., Lee D. G., *Synth. Commun.*, **33**, 1057—1065 (2003).
30) Shaabani A., Lee D. G., *Synth. Commun.*, **33**, 1255—1260 (2003).
31) Shaabani A., Rahmati A., *J. Mol. Catal. A-Chem.*, **249**, 246—248 (2006).

Table 1. Effect of Catalyst for the Synthesis of **4a** in CH_3OH at Room Temperature

Entry	Catalyst	Time (h)	Yield (%)[a]
1[b]	—	3	Trace
2	Amberlyst-21	24	72
3	Montmorillonite-K_{10}	12	57
4	$AlCl_3$	6	68
5	CH_3COOH	5	36
6	HCl	24	30
7	H_2SO_4	24	10
8	H_2SO_4/SiO_2	3	55
9	Cellulose sulfuric acid	3	98

a) Isolated yield. *b*) In the absence of the catalyst.

Table 2. Synthesis of Imidazoazines **4a**—**j** in the Presence of Cellulose Sulfuric Acid

Entry	R^1	R^2	R^3	Product	Yield (%)
1	Ph	Br	Cyclohexyl	**4a**	(98, 95, 92, 94, 85)[a]
2	Ph	Me	Cyclohexyl	**4b**	89
3	$4-CH_3C_6H_4$	Me	Cyclohexyl	**4c**	92
4	$4-ClC_6H_4$	Me	Cyclohexyl	**4d**	90
5	$3-O_2NC_6H_4$	Me	Cyclohexyl	**4e**	96
6	4-Pyridyl	Me	Cyclohexyl	**4f**	93
7	Ph	H	Cyclohexyl	**4g**	94
8	Ph	Me	*tert*-Butyl	**4h**	90
9	$4-CH_3C_6H_4$	Me	*tert*-Butyl	**4i**	87
10	Ph	Br	*tert*-Butyl	**4j**	98

a) The same catalyst was used for each of the five runs.