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Article

Imidazo[1,2-*a*]pyridine A^3-Coupling Catalyzed by a Cu/SiO_2 Material

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In this work, we report the preparation of a copper-silica material (Cu/SiO_2) by a sol-gel methodology and its characterization concerning composition and textural properties. The Cu/SiO_2 material was successfully applied as a Lewis acid heterogeneous catalyst for the A^3-coupling from 2-aminopyridine, aldehydes and alkynes to imidazo[1,2-*a*]pyridines (45-82%), which are relevant pharmacological scaffolds. The synthesis shows a number of advantages, such as easy separation from the reaction media and the minimal formation of metal aqueous wastes. Investigation of the mechanism supports the involvement of the formation of reaction intermediates inside the pores of the mesoporous material prior to 5-exo-dig cyclization.

Keywords: imidazo[1,2-*a*]pyridines, heterogeneous catalyst, A^3-coupling reaction

Introduction

Imidazo[1,2-*a*]pyridine derivatives are known for their wide range of applications in pharmaceutics as a result of their biological properties, including antiviral, antibacterial, antifungal, antiprotozoal and anti-inflammatory activities.[1-4] These heterocycles are also known as gamma-aminobutyric acid (GABA) and benzodiazepine receptor agonists.[5,6] Some of them are well-known commercialized drugs with sedative, anti-hypnotic and anti-psychotic effects, such as Alpidem, Zolpidem and Olprinone.[7] Recent investigations showed that imidazo[1,2-*a*]pyridines are promising drug candidates in cancer treatment.[8,9] The photophysical properties of these heterocyclic scaffolds have also been investigated[10-12] and their potential as fluorescent probes[13] and fluorescent metal sensors has been explored.[14]

Alternatively, different copper species have received considerable attention as catalysts for different kinds of organic transformations involving alkynes, such as homocoupling (Glaser-Hay coupling),[15-18] Huisgen 1,3-dipolar Cu^I-catalyzed alkyne-azide cycloaddition,[19-23] Diels-Alder cycloadditions[24,25] and Sonogashira cross coupling.[26-29] Cu^I salts were successfully applied as catalysts in the synthesis of imidazopyridines from aminopyridine and nitroolefines.[30] Other cyclization methods from aminopyridines involve the combination of Cu^I and Pd^{II} salts, as well as Cu^I and In^{III} under aerobic conditions.[31] Some methods explore the use of Cu^I and ligands, such as bipyridine.[32]

Among the several methods for the synthesis of imidazo[1,2-*a*]pyridines,[33] the multicomponent reaction between 2-aminopyridine, aldehyde and alkyne (A^3-coupling) has received considerable attention as a straight route to products with a wide scope of substituents, with the advantages of atom economy, lower toxic waste generation and an environmental friendly method. In this context, a very mild methodology using a single catalyst as the active specie was published using iodine in water while the use of indium bromide as Lewis acid catalyst requires the presence of triethylamine as additive and molecular sieves yielding a series of substituted imidazo[1,2-*a*]pyridines.[34,35] One report shows a very clean solvent and catalyst-free

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synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridine and α-bromoacetophenone.[36] Copper(II) salts were also proven useful on intramolecular oxidative cyclization from haloalkynes and 2-aminopyridines.[37]

Catalysis of copper sulfate in the presence of *p*-toluenesulfonic acid (10 mol%) leads to moderate to good yields in three and two-component approaches and similar results were observed using a mixture of copper iodide and copper triflate.[38,39] Cherniak and Gevorgyan[40] described the use of binary Cu^I and Cu^{II} catalysts in toluene at high temperature. A mixture of Cu^I-Cu^{II} generated *in situ* from $CuSO_4$ and glucose was shown to be a useful method for the 5-exo-dig cycloisomerization.[41] Also, glucose was found an applicable additive for reactions catalyzed by copper oxide/alumina in heterogeneous strategies.[42]

It is noteworthy that Mishra and Ghosh[43] reported the use of CuI and $NaHSO_4.SiO_2$ as binary catalysts, a semi-heterogeneous approach.They have also proved the necessity of both Lewis and Brϕnsted acids in the reaction media to efficiently perform cycloisomerization. Another report by Corma and co-workers[44] shows the ability of Cu^{II}-MOF (MOF: metal-organic framework) on catalyzing the same reaction by a combination of the adsorbed Lewis acid on a microporous and flexible framework. The use of other copper-MOF has shown efficiency on catalyzing imidazo[1,2-*a*]pyridines synthesis although the preparation of the catalysts usually involves harsh conditions.[45] Recently, copper and porphyrin-MOF derivatives were successfully applied on the synthesis of imidazo[1,2-*a*]pyridines, however a copper solution must be periodically replaced for zinc exchange on catalyst preparation.[46] In this context the use of small amounts of copper nanoparticles where also successful, but they suffer of several steps for preparation or low stability for storage.[47,48] Superparamagnetic iron-copper nanoparticles leads to higher yields of imidazo[1,2-*a*]pyridines (75-95%), but the catalyst preparation involves the use of very high range of temperature (500-900 ºC) and they also require the use of euthetic mixture citric acid-dimethyl urea which favors the imine intermediate formation.[49] In addition to copper, other publications[50-52] have reported the use of heterogeneous magnetic nanoparticles of Fe_3O_4, which are easily recovered and recycled from the reaction media. More recently, a synthesis at mild conditions, involving $CuCl_2$/nano-TiO_2 as the catalyst in the reaction between 2-aminopyridines and unactivated ketones, was also described. [53]

Metal/silica materials were employed as catalysts in the synthesis of other types of heterocycles in multicomponent reactions and they have shown advantages such as easy preparation, easy handling and the possibility of recovery. These materials are often prepared by a sol-gel method from an organosilyl precursor in the presence of metal salts.[54,55] In/SiO_2 was applied as a heterogeneous catalyst in a Hantzsch 1,4-dihydropyridine multicomponent synthesis.[56] Later, the same material was employed and successfully recycled in A^3-coupling, leading to propargylamines.[57] Alternatively, a cheaper Cu/SiO_2 material was described and employed in a Biginelli 3,4-dihydropyrimidinone multicomponent synthesis by Russowsky *et al.*[58,59] and more recently, in a 1,2,3-triazole synthesis by click chemistry. In this work, we prepared and characterized a Cu/SiO_2 material with different conditions by sol-gel method and investigated their application as heterogeneous catalysts in the A^3-coupling reaction to produce different substituted imidazo[1,2-*a*]pyridines, without using additives.

Experimental

General experimental methods

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra in $CDCl_3$ were recorded on Varian or Bruker 400 MHz and 100 MHz respectively, using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are expressed in parts *per* million referenced to the residual solvent (i.e., ^1H 7.27, ^{13}C 77.16 ppm for $CDCl_3$). Signal multiplicity is expressed as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet). *J* values are given in hertz (Hz). For novel compounds, the high-resolution mass spectrometry (HRMS) measurement, Bruker Daltonics Micro-TOF instrument was used in electrospray ionization (ESI) mode. All reactions and purity of the synthesized compounds were monitored by thin-layer chromatography (TLC) using silica gel 60 F254 aluminium plates. Visualization was accomplished by UV light, exposure to iodine vapor and by treating the plates with vaniline followed by heating. Unless otherwise indicated, materials and solvents were purchased and used without further purification. The images of Cu/SiO_2 materials were obtained using scanning electron microscopy (SEM) on a JEOL microscope (JSM 5800) connected to a secondary electron detector and energy dispersive X-ray spectroscopy (EDS), performed with Cu/SiO_2 dispersed on a doubled-faced conducting tape on a stainless steel support and coated with gold using Bal-Tec SCD050 Sputter-Coater apparatus. The N_2 adsorption-desorption isotherms of Cu/SiO_2 materials were determined at liquid-nitrogen boiling point, using Tristar II Krypton 3020 Micromeritics equipment. The materials were previously degassed at

120 ºC under vacuum for 10 h. The specific surface areas were determined by the Brunauer-Emmett-Teller (BET) multipoint technique and the pore size distribution curves were obtained by using the Barrett-Joyner-Halenda (BJH) and density functional theory (DFT) methods.

General procedure for the synthesis of Cu/SiO_2 material 2

In a vial flask adapted with a magnetic bar were added 5 mL of ethanol, 2 mL of deionized water and 1 drop (circa 50 μL) of hydrofluoric acid. Then, it was added $CuCl_2$ (1.2 mmol, 0.150 g) and the solution stirred until complete homogenization. The mixture was poured onto tetraethyl orthosilicate (TEOS, 22.4 mmol, 5.0 mL), stirred until complete homogenization and after the formation of a translucid glassy material (gelation), the vial was closed and kept under heating (40 ºC) for 7 days. After this time, the vial cap was removed and kept under mild heating (30 ºC) for more 7 days for slow solvent evaporation. The solid was then removed from the vial, powdered and treated at high temperature (300 ºC) for 4 h while during this process the material color change from green to dark brown. After cooling, the green powder was washed with distilled water (3 × 20 mL) and ethanol (20 mL) and then dried at 100 ºC for 24 h.

General procedure for the A^3-coupling to substituted imidazo[1,2-*a*]pyridines

In a Schlenk tube under inert atmosphere were added 2-aminopyridine (1.1 mmol, 0.112 g), aldehyde (1.0 mmol), Cu/SiO_2 (10 mol%), terminal alkyne (1.5 mmol) and toluene (0.5 mL). The mixture was heated to 120 °C and stirred for 48 h. The mixture was then filtered and the solvent removed under vacuum and the crude product was purified by column chromatography with hexanes, ethyl acetate and triethylamine (84:10:4) as eluent.

3-Benzyl-2-phenylimidazo[1,2-*a*]pyridine (**4a**)[38]

Yield 68% (193.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* 7.4 Hz, 2H), 7.67 (d, *J* 8.7 Hz, 2H), 7.42 (t, *J* 7.5 Hz, 2H), 7.36-7.20 (m, 4H), 7.18-7.10 (m, 3H), 6.67 (t, *J* 6.9 Hz, 1H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 144.1, 136.7, 134.5, 128.9, 128.5, 128.1, 127.6, 126.8, 124.0, 123.3, 117.6, 117.5, 112.1, 29.8.

3-Benzyl-2-(2-methoxyphenyl)imidazo[1,2-*a*]pyridine (**4b**)[35]

Yield 64% (201.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.61 (m, 3H), 7.35 (td, *J* 8.3, 1.8 Hz, 1H), 7.26-7.17 (m, 3H), 7.15-7.10 (m, 3H), 7.05 (td, *J* 7.5, 0.8 Hz, 1H), 6.95 (d, *J* 8.2 Hz, 1H), 6.65 (td, *J* 6.8, 1.0 Hz, 1H), 4.28 (s, 2H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 144.9, 141.6, 137.4, 132.3, 129.5, 128.7, 128.1, 126.5, 123.8, 123.6, 120.8, 119.7, 117.7, 111.9, 110.9, 55.2, 30.3.

3-Benzyl-2-(3-methoxyphenyl)imidazo[1,2-*a*]pyridine (**4c**)[49]

Yield 81% (254.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.65 (m, 2H), 7.38-7.19 (m, 6H), 7.18-7.10 (m, 3H), 6.93-6.87 (m, 1H), 6.68 (t, *J* 6.8 Hz, 1H), 4.48 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 144.9, 143.9, 136.0, 129.5, 129.0, 127.7, 127.0, 124.2, 123.4, 120.6, 117.9, 117.6, 114.1, 113.3, 112.3, 55.3, 29.9.

3-Benzyl-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (**4d**)[38]

Yield 72% (226.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* 8.7 Hz, 2H), 7.67-7.60 (m, 2H), 7.35-7.20 (m, 3H), 7.18-7.07 (m, 2H), 6.96 (d, *J* 8.7 Hz, 2H), 6.66 (td, *J* 6.8, 2.2 Hz, 1H), 4.45 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 144.8, 144.0, 136.9, 129.3, 129.0, 127.7, 127.1, 126.8, 123.9, 123.2, 117.3, 117.0, 114.1, 112.0, 55.3, 29.9.

3-Benzyl-2-(2-fluorophenyl)imidazo[1,2-*a*]pyridine (**4e**)[48]

Yield 78% (236.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (td, *J* 7.5, 1.8 Hz, 1H), 7.69-7.62 (m, 2H), 7.34 (m, 1H), 7.28-7.05 (m, 8H), 6.65 (dt, *J* 6.6, 3.3 Hz, 1H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 158.8, 145.2, 139.1, 136.8, 132.2, 129.9, 129.8, 128.9, 128.0, 126.8, 124.5, 124.4, 124.2, 123.8, 122.7, 122.5, 119.8, 117.8, 116.1, 115.9, 112.2, 30.1.

3-Benzyl-2-(3-fluorophenyl)imidazo[1,2-*a*]pyridine (**4f**)

Yield 71% (214.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.64 (m, 2H), 7.54 (d, *J* 7.5 Hz, 2H), 7.36 (dd, *J* 14.2, 7.5 Hz, 1H), 7.32-7.21 (m, 3H), 7.21-7.14 (m, 1H), 7.12 (d, *J* 7.4 Hz, 2H), 7.06-6.99 (m, 1H), 6.73-6.66 (m, 1H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 161.9, 145.0, 143.0, 137.0, 136.9, 136.6, 130.2, 130.1, 129.2, 127.7, 126.1, 124.5, 123.8, 123.8, 123.5, 118.2, 117.8, 115.3, 115.1, 114.7, 114.5, 112.5, 29.9; HRMS (ESI) *m/z*, calcd. for $C_{20}H_{15}N_2F$ $[M + H]^+$: 303.1298, found: 303.1293.

3-Benzyl-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (**4g**)[38]

Yield 82% (248.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.71 (m, 2H), 7.71-7.64 (m, 2H), 7.34-7.24 (m, 3H), 7.21-7.15 (m, 1H), 7.14-7.08 (m, 4H), 6.71 (td, *J* 6.8, 1.0 Hz, 1H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 161.5, 145.0, 143.4, 136.8, 130.8, 130.0, 129.9, 129.2, 127.8, 127.1, 124.3, 123.5, 117.7, 115.8, 115.6, 112.4, 29.9.

3-Benzyl-2-(pyridin-3-yl)imidazo[1,2-*a*]pyridine (**4h**)

Yield 80% (228.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.61-8.54 (m, 1H), 8.14-8.09 (m, 1H), 7.78-7.63 (m, 2H), 7.40-7.04 (m, 8H), 6.72 (m, 1H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 148.7, 145.2, 140.9, 136.2, 135.5, 130.6, 129.1, 127.6, 127.1, 124.7, 123.6, 123.5, 118.5, 117.6, 112.6, 29.7; HRMS (ESI) *m/z*, calcd. for $C_{19}H_{15}N_3$ $[M + H]^+$: 286.1344, found: 286.1363.

3-Benzyl-2-cyclohexylimidazo[1,2-*a*]pyridine (**4j**)[38]

Yield 60% (174.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (m, 3H), 7.30-7.17 (m, 3H), 7.12-7.02 (m, 3H), 6.60 (td, *J* 6.8, 0.9 Hz, 1H), 4.28 (s, 2H), 2.89-2.76 (m, 1H), 1.95-1.76 (m, 6H), 1.46-1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 144.5, 137.1, 128.8, 127.8, 126.7, 123.2, 123.1, 117.1, 116.3, 111.6, 36.9, 33.3, 29.0, 26.9, 26.0.

3-(3,5-Bis(trifluoromethyl)benzyl)-2-phenylimidazo [1,2-*a*]pyridine (**4k**)[45]

Yield 75% (315.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.72 (t, *J* 7.8 Hz, 3H), 7.64 (d, *J* 6.9 Hz, 1H), 7.57 (s, 2H), 7.44 (t, *J* 7.5 Hz, 2H), 7.37 (t, *J* 7.3 Hz, 1H), 7.27-7.21 (m, 1H), 6.79 (t, *J* 6.8 Hz, 1H), 4.60 (s, 2H); ^{13}C attached proton test (APT) NMR (100 MHz, $CDCl_3$) δ 145.4, 145.3, 140.0, 134.2, 131.0 (q, $^2J_{C\text{-}F}$ 33.4 Hz), 128.9, 128.3, 128.2, 127.9, 127.3, 124.6, 123.8 (q, $^1J_{C\text{-}F}$ 245.2 Hz), 122.8, 121.3, (q, $^3J_{C\text{-}F}$ 3.6 Hz), 118.1, 115.5, 112.9, 29.8.

3-(4-Methylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (**4l**)[38]

Yield 57% (170.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.77 (m, 2H), 7.68 (m, 2H), 7.42 (m, 2H), 7.33 (m, 1H), 7.18-7.12 (m, 1H), 7.10 (d, *J* 7.9 Hz, 2H), 7.02 (d, *J* 7.9 Hz, 2H), 6.67 (t, *J* 6.7 Hz, 1H), 4.44 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 143.9, 136.4, 134.4, 133.5, 129.6, 128.6, 128.1, 127.6, 127.5, 124.1, 123.4, 117.9, 117.4, 112.1, 29.3, 21.0.

3-(4-Methoxybenzyl)-2-phenylimidazo[1,2-*a*]pyridine (**4m**)[38]

Yield 35% (110.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.79 (m, 2H), 7.72-7.67 (m, 2H), 7.44 (t, *J* 7.6 Hz, 2H), 7.36 (t, *J* 7.3 Hz, 1H), 7.19-7.13 (m, 1H), 7.05 (d, *J* 8.2 Hz, 1H), 6.84 (d, *J* 8.6 Hz, 2H), 6.71-6.65 (m, 1H), 4.42 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 144.8, 143.9, 134.5, 128.7, 128.6, 128.6, 128.2, 127.7, 124.2, 123.5, 118.1, 117.5, 114.4, 112.2, 55.3, 29.0.

4-((2-Phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)benzonitrile (**4n**)

Yield 14% (43.33mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* 4.4 Hz, 1H), 7.76-7.68 (m, 3H), 7.66-7.58 (m, 3H), 7.48-7.35 (m, 4H), 7.29-7.20 (m, 3H), 6.77 (t, *J* 6.8 Hz, 1H), 6.66-6.61 (m, 1H), 6.50 (d, *J* 8.3 Hz, 1H), 4.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 145.2, 144.8, 142.7, 137.8, 134.2, 133.0, 128.9, 128.6, 128.2, 128.1, 124.6, 123.0, 118.7, 117.9, 116.1, 114.0, 112.7, 111. 1, 108.7, 30.1; HRMS (ESI) *m/z*, calcd. for $C_{21}H_{15}N_3$ $[M + H]^+$: 310.134, found: 310.1381.

Results and Discussion

Herein, we propose the preparation and use of Cu/SiO_2 as a unique heterogeneous catalyst for the A^3-coupling of 2-aminopyridines, aldehydes and alkynes to obtain different imidazo[1,2-*a*]pyridine derivatives. Firstly, by employing $CuCl_2$ and tetraethylorthosilicate as precursors in the presence of acid (HCl) or nucleophilic (HF) catalyst for the sol-gel process, Cu/SiO_2 materials 1 and 2 were obtained, respectively. The glassy-like materials achieved after complete gelation at room temperature were powdered and dried to yield pale green solids. These materials were characterized with regards to composition and textural properties.

The scanning electron microscopy with energy dispersive spectroscopy (SEM/EDS) confirm the presence of copper in the materials and showed the irregular surface of both materials (Figure 1).

The choice of catalyst had a less pronounced effect on the material surface area achieved by BET analysis, leading to 490 and 370 $m^2\ g^{-1}$ for the HCl- and HF-catalyzed materials, respectively materials 1 and 2 (Figure 2). However, as shown in Figure 2, material 1 has a typical

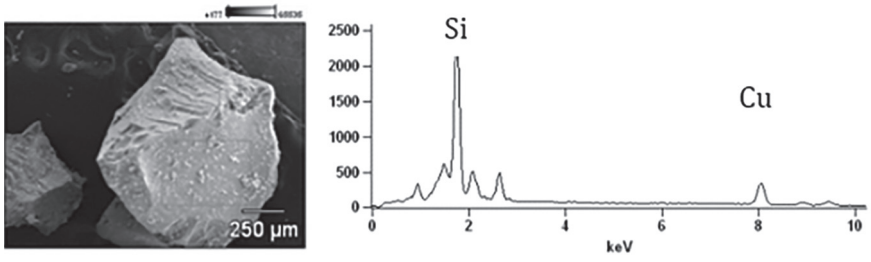


Figure 1. SEM micrograph and EDS graph for material 2.

microporous profile, while material 2 is predominantly mesoporous. The results of BJH and DFT calculations showed that a mesoporous material was obtained using nucleophilic catalysis (pore size of 5.0 nm), while acid catalyst resulted in a microporous material (pore size of 0.9 nm, Figure 3). Similar catalyst effects were reported previously.[60]

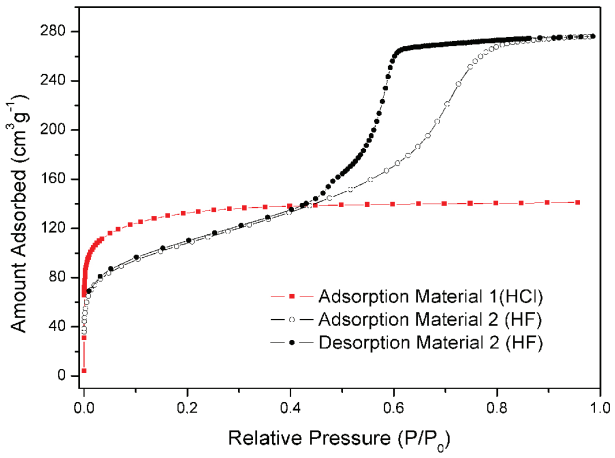


Figure 2. Surface area isotherms of materials 1 and 2.

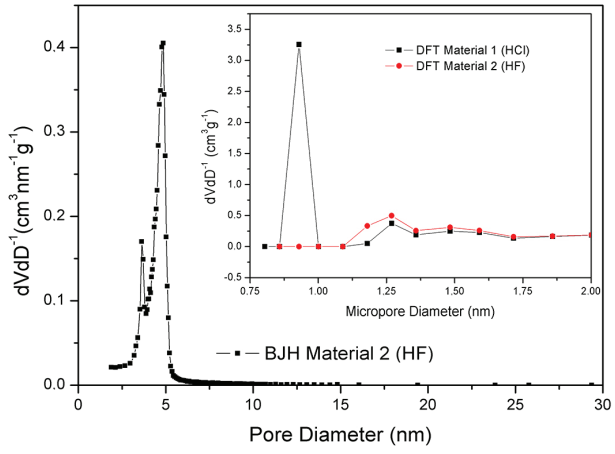


Figure 3. Pore size distribution of materials 1 and 2.

The total amount of copper in the material was determined by flame atomic absorption spectrometry (FAAS) after acidic digestion of the samples, since SEM-EDS furnished a Cu:Si atom ratio on the surface only and not inside the pores of the material. In the case of material 1, more milligrams of copper were achieved *per* gram of sample. The data concerning pore size, surface area and copper amount for materials 1 and 2 are summarized in Table 1.

Table 1. Chemical and textural analyses overview

Material	Pore size[a] / nm	BET surface area / ($m^2 g^{-1}$)	Copper amount / (mg m^{-1})
1	0.9	490	86 ± 3
2	5.0	370	55 ± 3

[a]Obtained from the maximum of pore distribution curves; BET: Brunauer-Emmett-Teller multipoint technique.

Materials 1 and 2 were then applied as catalysts in the three-component reaction between 2-aminopyridine **1**, benzaldehyde **2a** and phenylacetylene **3a**, as depicted in Scheme 1.

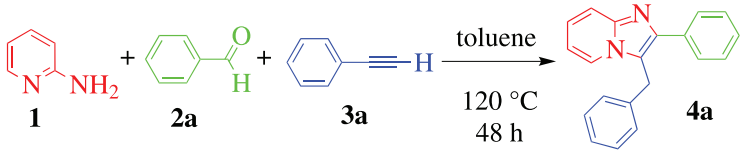
Table 2 summarizes the yields of product **4a** when comparing the same amount of materials 1 and 2 with pure SiO_2 and the reactions in the absence of a catalyst. Non-optimized reaction conditions showed that the higher pore diameter material 2 prepared by HF catalysis resulted in a better product yield without the need for molecular sieves in refluxing toluene after 48 h (Table 2, entry 2). It is worth to mention that the use of free $CuCl_2$ as catalyst leads to similar yields (Table 2, entry 5) but the work-up produces more wastes and requires more steps in comparison to simple filtration of the catalyst in our procedure.

Table 2. Influence of the catalyst on the imidazo[1,2-*a*]pyridine synthesis

entry	Catalyst	Yield[a] / %
1	material 1	56 (63)[b]
2	material 2	68 (68)[b]
3	none	n.r.
4	SiO_2	n.r.
5	$CuCl_2$ (10 mol%)	64

[a]Isolated yield; [b]with molecular sieves 4 Å; n.r.: no reaction.

After choosing material 2 as the catalyst for the A^3-coupling reaction between 2-aminopyridine, benzaldehyde and phenylacetylene, a screening of the solvent and temperature was performed (Table 3). Interestingly,



Scheme 1. Multicomponent A^3-coupling synthesis of 3-benzyl-2-phenylimidazo[1,2-*a*]pyridine.

only toluene was found to be suitable for the cyclization reaction, although low conversion was achieved in neat conditions at 120 °C (Table 3, entries 9 and 10). In addition, investigation of the catalyst load was made by varying the amount of catalyst from 2.5-20.0 mol% based on the total amount of copper of the material, as determined by FAAS in Table 4. It is worth to mention that the use of 10 mol% of several homogeneous copper species in the absence of Brønsted acid additives does not lead to considerable yield of imidazo[1,2-*a*]pyridines under the same conditions, as described by Liu *et al.*[38]

Table 3. Screening of solvents on the imidazo[1,2-*a*]pyridine synthesis

entry	Solvent	Conversion / %
1	DMF[a]	–
2	DMSO[a]	trace
3	water	–
4	ethanol	–
5	toluene/water	trace
6	THF	–
7	MeCN	–
8	DCM	–
9	neat[a]	21
10	toluene	68

Reaction conditions: 1.0 mmol benzaldehyde, 1.1 mmol 2-aminopyridine, 1.5 mmol phenylacetylene, 10 mol% Cu/SiO_2, reflux temperature, inert atmosphere, 48 h; [a]120 °C; DMF: dimethylformamide; DMSO: dimethyl sulfoxide; THF: tetrahydrofuran; DCM: dichloromethane.

With these results in hand, we then studied the scope of the reaction (Scheme 2). This protocol was found suitable for a range of aldehydes bearing electron donating or electron withdrawing groups, giving the respective imidazo[1,2-*a*]pyridines with good yields (64-82%, Table 5, entries 1-6). It is worth mentioning that no conversion to product was achieved when using 4-nitrobenzaldehyde (entry 7).

Conversely, heteroaromatic and aliphatic aldehydes also worked well in this protocol, except for 2-pyridinecarboxaldehyde (entries 8-10). Substituted aromatic alkynes gave slightly lower yields (entries 11-14) when compared to phenylacetylene. Substituents with an inductive effect, such as 3,5-bis-trifluoromethyl and

Table 4. Influence of catalyst load on the imidazo[1,2-*a*]pyridine synthesis

entry	Catalyst load / mol%	Yield / %
1	2.5	10
2	5.0	35
3	7.5	45
4	10.0	68
5	20.0	73

Reaction conditions: 1.0 mmol benzaldehyde, 1.1 mmol 2-aminopyridine, 1.5 mmol phenylacetylene, reflux temperature, inert atmosphere, 0.5 mL toluene, 48 h.

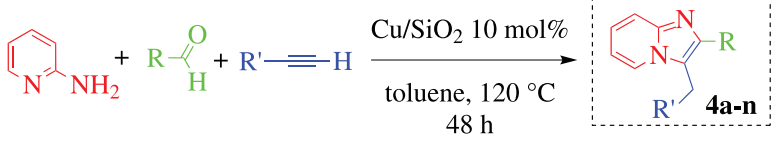
Table 5. Scope of the reaction for different substituted imidazo [1,2-*a*]pyridines

entry	R'	R	Product	Yield[a] / %
1	Ph	2-MeO-C_6H_4	**4b**	64
2	Ph	3-MeO-C_6H_4	**4c**	81
3	Ph	4-MeO-C_6H_4	**4d**	72
4	Ph	2-F-C_6H_4	**4e**	78
5	Ph	3-F-C_6H_4	**4f**	71
6	Ph	4-F-C_6H_4	**4g**	82
7	Ph	4-NO_2-C_6H_4	–	–
8	Ph	3-Py	**4h**	80
9	Ph	2-Py	**4i**	trace
10	Ph	Cy	**4j**	60
11	3,5-CF_3-C_6H_3	Ph	**4k**	75
12	4-Me-C_6H_4	Ph	**4l**	57
13	4-MeO-C_6H_4	Ph	**4m**	35
14	4-CN-C_6H_4	Ph	**4n**	14

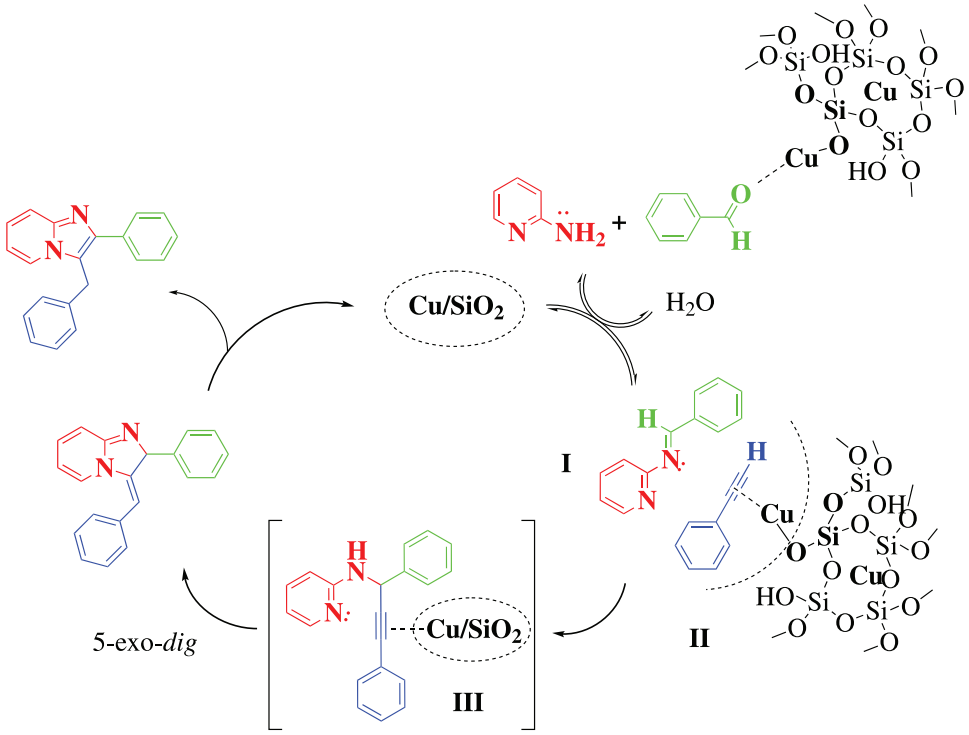
Reaction conditions: 1.0 mmol aldehyde, 1.1 mmol 2-aminopyridine, 1.5 mmol acetylene, reflux temperature, inert atmosphere, 0.5 mL toluene, 48 h; [a]isolated yields; Ph: phenyl.

methyl groups, showed better results than with mesomeric (donating or withdrawing) effect groups in achieving the corresponding imidazo[1,2-*a*]pyridines.

Concerning the mechanism of the reaction, we believe that the major role of the catalyst is in the approximation of the pre-formed imine (**I**) from 2-aminopiridine and benzaldehyde and the π-complex of Cu-phenylacetylene (**II**) (Scheme 3). This step may occur on the surface but mainly inside pores of the catalyst, since it was verified that the



Scheme 2. Multicomponent A^3-coupling synthesis of different substituted imidazo[1,2-*a*]pyridines.



Scheme 3. Proposed reaction mechanism of the A^3-coupling to imidazo[1,2-*a*]pyridines.

pore size distribution of 0.9 nm for material 2 gave slightly better yields when compared to material 1 with a higher surface area and a higher amount of copper *per* gram of material. The formation of intermediate **III** is crucial for 5-exo-dig cyclization, which is also aided by catalyst complexation. Intermediate **I** was readily detected by gas chromatography coupled to mass spectrometry when analyzing crude reaction mixtures, while intermediate **III** was not detected. This result agrees with the mechanistic proposal made by other authors,[35,38,43] with imine formation from aldehyde and amine as a faster step than the propargyl alcohol formed between aldehyde and alkyne which was not observed.

Conclusions

In summary, we have successfully applied mesoporous Cu/SiO_2 material as heterogeneous Lewis acid catalyst on the multicomponent synthesis of imidazo[1,2-*a*]pyridines with good yields, without any additive and co-catalyst as commonly found in the literature. This protocol allows the removal of the catalyst from the reaction media through simple filtration. The very simple sol-gel prepared mesoporous material showed slightly better yield of imidazo[1,2-*a*]pyridines even with lower copper load in comparison to microporous material.

Supplementary Information

Supplementary information (^1H and ^{13}C NMR spectra) is available free of charge at http://jbcs.sbq.org.br as a PDF file.

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