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Aqueous Suspension of Basic Alumina: An Efficient Catalytic System for the Synthesis of Poly Functionalized Pyridines

Pravin V. Shinde, Bapurao B. Shingate, and Murlidhar S. Shingare*

Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad - 431004, Maharashtra, India
**E-mail: prof_msshingare@rediffmail.com*
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In the present work, catalytic activity of basic alumina in water has been demonstrated for the synthesis of poly functionalized pyridines. This strategy has some remarkable advantages, such as use of heterogeneous catalyst in aqueous media, reusability of catalyst and scalable approach.

Key Words: Basic alumina, Pyridines, Water chemistry, Thiols

Introduction

Organic reactions on solid support represent a viable and convenient alternative to traditional synthetic processes realized under homogeneous conditions.[1] In the last decades, new classes of solid adsorbents have been developed as microporous and nanoporous materials, such as silica gel, activated carbon fibers, zeolites, clays, alumina, polymer resins, *etc*.[2] Current development in the use of these heterogeneous catalysts in combination with aqueous media is attracting a great deal of interest.[3] In the view of green chemistry, use of such catalytic systems to carry out the organic transformations offers significant environmental impact and is becoming an intense area of research.

Aluminas and their surface chemistry play a vital role in their performance as catalysts and catalyst supports.[4] In addition, it has also been proved to be an interesting metal oxide due to its widespread industrial use as filler, adsorbent, and drying agent. γ-Alumina is the transition alumina most commonly utilized to carry out surface organic chemistry. Unlike clays and zeolites, this material does not contain accessible channels or cavities and possess large surface area and highly porous exterior available to substrates.[5a] Alumina would be effective as an organic reaction media in water because, the organic substrates would be expected to get adsorbed on the large surface of alumina by hydrophobic interactions of the surface of alumina and organic molecules with water. Various synthetic protocols[5] have recently been explored based upon the adsorptive nature of alumina and these reports encouraged us to study the catalytic applications of alumina in order to expand the utility of this potentially valuable strategy for the synthesis of bioactive heterocycles.

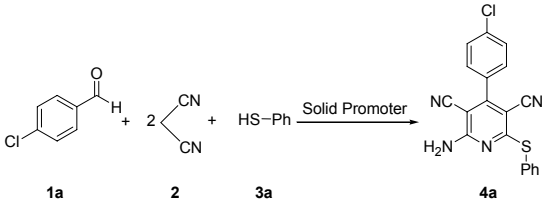
Pyridines constitute a versatile class of nitrogen containing bioactive heterocycles and continue to attract the attention of organic chemists due to its highly pronounced biological and physiological activities.[6-14] Poly functionalized pyridine derivatives especially bearing nitrile functionality have been reported to be endowed with their potential applications as potassium channel openers in the treatment of urinary incontinence,[8] and their use as *anti*-prion,[7a,9] *anti*-hepatitis B virus,[7c] *anti*-bacterial,[10] and *anti*-cancer[11] agents.

One of the most attractive routes for the synthesis of these compounds involves the cyclocondensation of aldehyde, malononitrile and thiol. Various synthetic protocols have been developed following this route with intervention of different basic[9a,14] as well as acidic catalysts[15] with their own merits and demerits. Few notable drawbacks of these routes are non-reusability of catalytic systems, non-scalable approach and use of non-aqueous solvents. Even though some heterogeneous catalysts like silica nanoparticles[16a] and nanocrystaline magnesium oxide[16b] have been utilized in this endeavor, some limitations like commercial unavailability, longer reaction times and use of non-aqueous solvents hamper their application at industrial level. Above discussed drawbacks of the reported methods prompted us to undertake the work for the development of highly efficient route for this cyclocondensation.

Considering the significance of basic alumina in water and in continuation of our interest towards the synthesis of biodynamic compounds,[17] herein, attempt has been made to carry out the cyclocondensation of aldehyde, malononitrile and thiol using basic alumina in water for obtaining the desired poly functionalized pyridine derivatives.

Results and Discussion

For our preliminary study, one-pot three-component condensation of 4-chloro benzaldehyde (**1a**), malononitrile (**2**) and thiophenol (**3a**) was considered as a standard model reaction (Scheme 1). To effect the model reaction, evaluation of various solvents were carried out against basic alumina as a catalyst. For this purpose, variety of classical organic solvents, such as, ethanol, methanol, toluene, THF, *etc*. were tested at ambient temperature. Unfortunately, these solvents remained unsuccess-



1a **2** **3a** **4a**

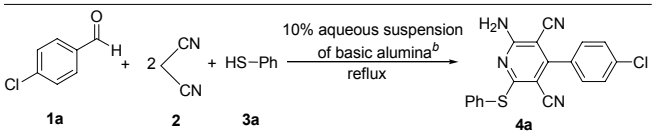
Scheme 1. Standard model reaction

Table 1. Screening of catalysts and temperature effect[a]

Entry	Solid promoter	Temperature (°C)	Time (min)	Yield[b] (%)
1	Basic alumina	rt	8 h	84
2	Basic alumina	60	3 h	52
3	Basic alumina	80	2 h	74
4	Basic alumina	Reflux	60	87
5	Neutral Alumina	Reflux	60	32
6	Acidic Alumina	Reflux	60	48
7	Silica gel 60	Reflux	60	79
8	Amorphous silica	Reflux	60	66

[a]*Reaction conditions:* **1a** (1 mmol), **2** (2 mmol), **3a** (1 mmol), Solid promoter (0.2 gm) in water (2 mL). [b]Isolated yields.

Table 2. Recycling and reuse of catalytic system[a]



Run	1	2	3	4	5
Yield[c] (%)	87	84	81	73	61

[a]Reactions of **1a** (1 mmol), **2** (2 mmol) and **3a** (1 mmol) in 10% aqueous suspension of basic alumina (2 mL) at reflux temperature were conducted for 60 min. Reaction mixture was cooled to RT and extracted with diethyl ether (3 × 2 mL) to remove the product from reaction mass. Thus, remaining clear aqueous suspension with catalyst was reused for next run. [b]10% aqueous suspension of basic alumina was prepared by adding 0.2 gm basic alumina in 2 mL water. [c]Isolated yields.

ful to afford the desired product.

Increasing interest of organic chemists for the use of water as a solvent of choice and its unique properties,[18] turned our attention to examine it for the present reaction. To our surprise, reaction in aqueous media was found to complete after a prolonged reaction time (8 hour) in excellent 84% yield of the desired product (Table 1, entry 1). Therefore, in an attempt to reduce the reaction time, model reaction was tested at higher temperatures like 60 ºC, 80 ºC and reflux condition and enormous decrease in reaction time was observed along with increase in the reaction temperature with respective 52%, 74% and 87% yield (Table 1, entries 2-4).

Careful literature survey reveals that, first step of the reaction, i.e. knoevenagel condensation can be easily achieved in protic solvents like water without need of any catalyst though the net result is dehydration[19] whereas the sub subsequent steps presumably involves Michael addition, *s*-Alkylation and cyclization which requires intervention of catalyst, since uncatalyzed reaction does not lead to final product. Hence, although basic alumina was found to be an effective solid medium for the model reaction in water, variety of solid promoters such as neutral alumina, acidic alumina, silica gel and amorphous silica were examined in order to improve the efficiency of results obtained in our initial study. When neutral and acidic alumina was used in the reaction, the desired product was obtained in only 32% and 48% yields respectively. (Table 1, entries 5, 6) As a matter of fact, silica gel 60 and amorphous silica afforded the product in good yields, i.e., 79% and 66% respectively in agreement with basic alumina (Table 1, entries 7, 8).

Our earlier solvent study for the reaction and report by Singh *et al*[20] reveals that basic alumina fails to catalyze the present reaction in the presence of ethanol as a solvent. However, 10% aqueous suspension of basic alumina effectively catalyzed the reaction in excellent yield and had a dramatic influence on the reaction. This fact could be attributed to the effect of solvent on catalyst for the efficient catalysis. It discloses that water plays a crucial role in the activation of catalyst. In order to understand, the exact role of water, we next carried out the reaction without water. But, reaction did not proceed towards the final product.

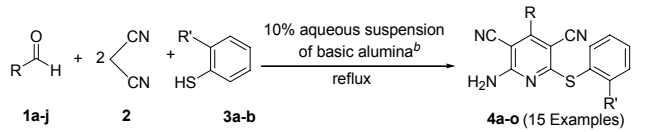
As it is reported, basic alumina when contacted with water yields a basic solution,[21] hence we suspected that the activation of organic substrates in the subsequent steps could be promoted by this basic water solution. Therefore, we performed the same reaction in basic solution obtained after filtration of aqueous suspension of basic alumina and product was obtained in only 46% yield. To this end, it was concluded that not only basic solution but also adsorptive nature of alumina in water supports for completion of the reaction. In addition to this, hydrophobic interactions of organic substrates in water also seem to be reasonable for making the catalytic system an efficient one.

Due to heterogeneous nature of the catalyst, some additional studies were performed to test the reusability of the catalytic system. Model reaction was carried out over four cycles using the same catalytic system, which was recovered simply by extracting the product from aqueous reaction mixture with diethyl ether. Reused catalytic system was found to be efficient, without much loss in product yield. It is important to point out here that while extraction of the product from reaction mixture formation of emulsion layer takes place in between aqueous and organic phase (Diethyl ether). This emulsion layer needs to be discarded for reusing the same catalytic system for the next run. Small amount of basic alumina goes into the emulsion layer and leads to its loss during extraction of the product, since this layer needs to be discarded. Therefore, practically observed fall in yield after successive runs is attributed to this little bit loss of catalyst during each recovery process (Table 2).

Scalable reactions have been gaining an enormous significance at industrial level. Hence, in order to scale up the efficiency of the present protocol, model reaction was performed on large scale, i.e., 0.1 mole (14 gm) with respect to 4-chloro benzaldehyde and it was found that the reaction proceeds effectively in 81% yield, without apparent loss of yield, but comparatively takes longer reaction time (2.5 h).

To broaden the scope of the established protocol and to generalize the experimental procedure, variety of electronically divergent aldehydes with respect to thiophenol and 2-amino thiophenol were examined. For aromatic aldehydes, the presence of electron-withdrawing and electron-releasing groups on the aromatic rings did not exhibit significant effects on yields. Various hetero aromatic aldehydes were equally amenable and afforded excellent yields. All the results are compiled in Table 3. Formation of the desired product was confirmed with the help of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.

Table 3. Synthesis of poly functionalized pyridine derivatives[a]



1a-j **2** **3a-b** **4a-o** (15 Examples)

Entry	Compounds	R	R'	Time (min)	Yield[c] (%)	mp[d] (^oC)
1	**4a**	4-Cl-Ph	H	60	87	219 - 221
2	**4b**	Ph	H	70	85	217 - 218
3	**4c**	4-F-Ph	H	60	85	224 - 226
4	**4d**	4-OMe-Ph	H	70	83	242 - 243
5	**4e**	4-OH-Ph	H	80	83	313 - 314
6	**4f**	2-NO_2-Ph	H	50	88	288 - 290
7	**4g**	3,4-OMe-Ph	H	60	84	227 - 228
8	**4h**	Piperonyl	H	80	82	233 - 234
9	**4i**	2-Thienyl	H	100	81	208 - 210
10	**4j**	2-Furfuryl	H	100	79	178 - 179
11	**4k**	Ph	NH_2	60	86	225 - 226
12	**4l**	4-Cl-Ph	NH_2	60	85	237 - 239
13	**4m**	4-OMe-Ph	NH_2	70	83	228 - 229
14	**4n**	4-NO_2-Ph	NH_2	50	89	209 - 210
15	**4o**	4-OH-3-OMe-Ph	NH_2	60	90	231 - 233

[a]*Reaction conditions:* **1** (1 mmol), **2** (2 mmol), **3** (1 mmol), 10% Aqueous suspension of basic alumina (2 mL), Reflux. [b]10% aqueous suspension of basic alumina was prepared by adding 0.2 gm basic alumina in 2 mL water. [c]Isolated yields. [d]Melting points matches with literature reports.[14c-e,16]

Conclusion

In summary, an efficient catalytic activity of aqueous suspension of basic alumina for the synthesis of poly functionalized pyridines has been demonstrated. Present synthetic strategy offers some remarkable advantages, such as, non-toxic and economically viable catalyst, aqueous reaction conditions, high isolated yields, reduced reaction times and scalable approach. This catalytic system could be a key for achieving various organic transformations.

Experimental

General. All chemicals were purchased and used without any further purification. Melting points were recorded on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in DMSO-d_6, chemical shifts (δ) are in (parts per million) ppm relative to TMS. ^{13}C NMR spectra were recorded on NMR spectrometer AC 200 in $CDCl_3$. Mass spectra were recorded on a macro mass spectrometer (waters) by electro-spray (ES) method.

Typical Experimental Procedure. A mixture of 4-chloro benzaldehyde **1a** (140 mg, 1 mmol), malononitrile **2** (132 mg, 2 mmol) and thiophenol **3a** (110 mg, 1 mmol) in 10% aqueous suspension of basic alumina (2 mL) was allowed to reflux for 60 min. Reaction progress was monitored by TLC (ethyl acetate/*n*-hexane, 1:7). After completion of the reaction (60 min), product was collected by simple filtration and that solid product was separated from catalyst by dissolving it in warm/boiling ethanol, which also facilitated *in situ* crystallization. Thus obtained product (**4a**) was recrystallized from aq. ethanol to obtain pure product.

Spectroscopic Data.

2-Amino-4-(4-chlorophenyl)-6-phenylsulfanylpyridine-3,5-dicarbo-nitrile (4a): ^1H NMR (400 MHz, DMSO-d_6) δ 7.46-7.49 (m, 3H, Ar-H), 7.57 (d, 2H, J = 8 Hz, Ar-H), 7.59 (d, 2H, J = 8 Hz, Ar-H), 7.64 (d, 2H, J = 8 Hz.) 7.83 (brs, 2H, -NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 87.19, 93.32, 114.78, 115.19, 117.12, 125.38, 127.61, 128.92, 130.18, 130.43, 132.74, 135.29, 157.82, 159.61, 166.09; IR (KBr, cm^{-1}): 3489, 3342, 3221, 2216, 1628, 1544, 1487, 1259, 1091, 839, 791; ES-MS: 363.04 (M^+), 365.03 (M+2).

2-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (4h): ^1H NMR (400 MHz, DMSO-d_6) δ 6.12 (s, 2H, -O-CH_2-O-), 7.00-7.03 (m, 1H, Ar-H), 7.07 (d, 1H, J = 8Hz, Ar-H), 7.14 (d, 1H, J = 1.2 Hz, Ar-H) 7.46-7.48 (m, 3H, Ar-H), 7.55-7.57 (m, 2H, Ar-H), 7.72 (brs, 2H, -NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 92.42, 98.74, 107.08, 113.79, 114.13, 120.40, 120.65, 128.29, 132.40, 132.51, 134.67, 134.89, 140.07, 152.62, 154.25, 163.37, 164.95, 171.38; IR (KBr, cm^{-1}): 3458, 3338, 3229, 2907, 2217, 1636, 1558, 1492, 1251, 1037, 825; ES-MS: 373.14 (M^+).

2-Amino-4-(thiophene-2-yl)-6-phenylsulfanylpyridine-3,5-dicarbo-nitrile (4i): ^1H NMR (400 MHz, DMSO- d_6) δ 6.68 (t, 1H, J = 4Hz, Ar-H), 7.24 (d, 1H, J = 4Hz, Ar-H), 7.32-7.35 (m, 3H, Ar-H), 7.42-7.45 (m, 2H, Ar-H), 7.61 (brs, 2H, -NH_2), 7.94 (d, 1H, J = 4.8 Hz, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 82.46, 91.10, 112.92, 115.65, 116.13, 117.32, 127.30, 129.36, 129.96, 135.89, 143.38, 145.46, 145.91, 159.98, 169.98; IR (KBr, cm^{-1}): 3438, 3360, 3210, 2984, 2210, 1617, 1512, 1257, 1064, 722; ES-MS: 335.07 (M^+).

2-Amino-4-(furan-2-yl)-6-phenylsulfanylpyridine-3,5-di-carbo-nitrile (4j): ^1H NMR (400 MHz, DMSO-d_6) δ 7.26 (t, 1H, J = 4Hz, Ar-H), 7.46-7.48 (m, 3H, Ar-H), 7.54-7.58 (m, 3H, Ar-H), 7.79 (brs, 2H, -NH_2), 7.93 (d, 1H, J = 5.2 Hz, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 87.17, 99.01, 114.65, 115.07, 119.06, 126.99, 129.42, 129.52, 130.81, 131.52, 135.83, 137.47, 157.16, 159.27, 159.72, 169.41; IR (KBr, cm^{-1}): 3380, 3328, 3210, 2992, 2215, 1650, 1518, 1264, 1029, 766; ES-MS: 319.09 (M^+).

2-Amino-4-(4-hydroxy-3-methoxyphenyl)-6-(2-amino-phenylsulfa-nyl)pyridine-3,5-dicarbonitrile (4o): ^1H NMR (400 MHz, DMSO-d_6) δ 3.80 (s, 3H, -OCH_3), 5.37 (brs, 2H, -NH_2 (-thiophenol ring)), 6.57 (t, 1H, J = 8 Hz, Ar-H), 6.77 (d, 1H, J = 8 Hz, Ar-H), 6.91-6.98 (m, 2H, Ar-H), 7.12 (d, 1H, J = 1.6 Hz, Ar-H), 7.15-7.20 (t, 1H, J = 8 Hz, Ar-H), 7.23-7.25 (dd, 1H, J = 1.6 Hz, 8 Hz, Ar-H), 7.57 (brs, 2H, -NH_2(-pyridine ring)), 9.65 (brs, 1H, -OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 57.43, 83.34, 96.01, 111.99, 115.61, 127.15, 127.55, 128.08, 129.38, 130.02, 130.52, 131.47, 135.85, 150.43, 159.54, 163.21, 169.71, 170.61; IR (KBr, cm^{-1}): 3473, 3348, 3290, 2958, 2212, 1625, 1533, 1281, 1020, 756; ES-MS: 390.02 (M^+).

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