Barium chloride dispersed on silica gel nanoparticles: an efficient catalyst for the preparation of 2,4,6-triarylpyridines under solvent-free conditions

Mohammad Reza Mohammad Shafiee* and Raheleh Moloudi

Faculty of Sciences, Islamic Azad University –Najafabad Branch, PO Box: 517, Najafabad, Esfahan, Iran

$BaCl_2$ dispersed on a nano-structural type of silica gel ($BaCl_2$-nano SiO_2) was found to be an effective catalyst for the rapid and high yielding preparation of substituted 2,4,6-triarylpyridine frameworks by the reaction of various acetophenones, benzaldehydes and ammonium acetate. The prepared catalyst was characterised by X-ray diffraction and scanning electron microscopy analysis.

Keywords: $BaCl_2$-nano SiO_2, nano SiO_2, barium chloride, 2,4,6-triaryl pyridine, Krohnke pyridines

Compounds containing pyridine rings are of considerable interest for the synthesis of pharmacological and biologically active materials. For example, these structures show different activities such as having anaesthetic, antimalarial, antioxidant, anticonvulsant, antibacterial and antiparasitic properties.[1–3] Therefore, preparation of pyridine derivatives has attracted considerable attention in recent years.

Despite their importance from a pharmacological and synthetic point of view, comparatively few methods for the preparation of 2,4,6-triarylpyridines (commonly named as Krohnke pyridines) have been reported in the literature.[4–9] New amongst these methods is the cyclo-condensation reaction of acetophenones, benzaldehydes and NH_4OAc using conventional heating in the presence of Brønsted and Lewis acid catalysts.[10–13]

The overall aim of this study was to develop and validate an efficient protocol for the synthesis and easy purification of 2,4,6-triarylpyridines from the cyclo-condensation reaction of acetophenones, benzaldehydes and NH_4OAc in the presence of $BaCl_2$-nano SiO_2 as an efficient catalyst (Scheme 1).

Results and discussion

The crystallinity of pure $BaCl_2$-nano SiO_2 was examined by XRD studies. The XRD pattern of $BaCl_2$-nano SiO_2 is shown in Fig. 1. As shown in Fig. 1, the actual phases were silicon oxide (SiO_2) (tetragonal) and $BaCl_2$ (hexagonal). The powder XRD measurement of $BaCl_2$-nano SiO_2 exhibited a diffraction pattern characteristic of the SiO_2 type tetragonal nanopowder structure with pronounced 22.06, 31.52, 36.18, 38.74, 44.91, 47.12, 48.68, 57.18, 60.41, 62.06, 65.13, 66.98, 68.67, 69.83, 72.79, 74.01, 77.35 and 78.14 peaks (Fig. 1). The peaks at 22.06, 23.09, 29.38, 32.08, 38.74, 39.29, 44.91, 55.94 and 57.18 are believed to arise from the phase of $BaCl_2$ (hexagonal) (Fig. 1).

The dispersal state of the $BaCl_2$-nano silica was characterised by SEM. Figure 2 shows the SEM micrographs of the barium chloride dispersed on silica gel nanoparticles ($BaCl_2$-nano SiO_2). Based on the SEM observation, the $BaCl_2$ particles dispersed on nano-silica contain irregular shapes with a wide size distribution.

Preparation of 2,4,6-triaryl pyridines

Initially, we found that catalyst-free and solvent-free reactions did not yield a product when 4-bromoacetophenone was heated with 4-chlorobenzaldehyde and ammonium acetate at 120 °C. Our investigations show that the use of a catalyst is unavoidable for this transformation.

When silica gel nanoparticles (particle size 29–43 nm) are mixed with 10% by weight of hydrated barium chloride ($BaC1_2.2H_2O$) dissolved in water, followed by evaporation at 80 °C under high vacuum (0.1 Torr) for 1 h, a dry white powder is obtained. This powder is an effective catalyst for the preparation of 2,4,6-triarylpyridine derivatives.

To establish of the most appropriate reaction conditions and to evaluate the catalytic productivity of $BaCl_2$-nano SiO_2 as a catalyst, firstly a model study was executed on the synthesis of 2,6-bis(4-bromophenyl)-4-(4-chlorophenyl)pyridine (Table 1, Scheme 2).

Among the solvents tested such as ethanol, *n*-hexane and dichloromethane and a solvent-free system, the condensation of acetophenone, benzaldehyde and ammonium acetate is more facile and proceeds in the highest yield, under solvent-free conditions (Table 1, entries 1–4).

Next, the effect of temperature and the amount of catalyst on the rate of the reaction was investigated (Table 1, entries 4–10). Finally, we achieved an optimised set of reaction conditions using 0.08 g of $BaCl_2$-nano SiO_2 as the catalyst and 120 °C. The results are summarised in Table 1.

We then investigated the reaction scope of this catalytic system and its tolerance of functional groups in the case of other acetophenone and benzaldehyde derivatives. As shown

Scheme 1 Preparation of 2,4,6-triarylpyridine derivatives.

* Correspondent. E-mail: mohammadreza.mohammadshafiee@gmail.com

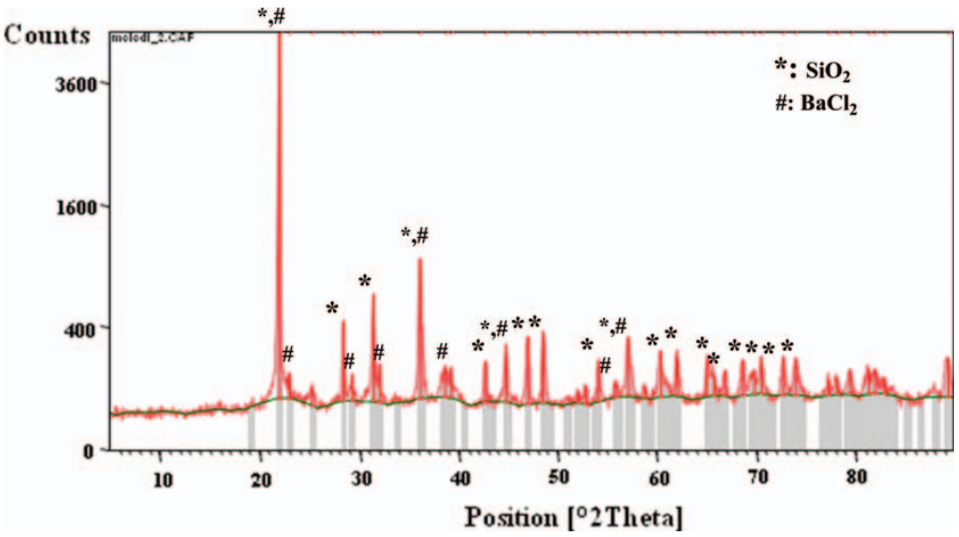


Fig. 1 XRD pattern of $BaCl_2$-nano SiO_2.

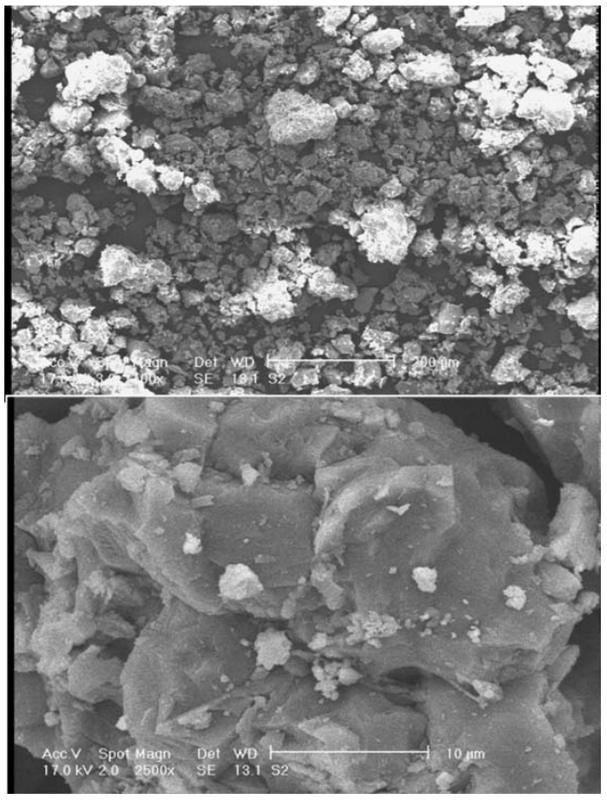


Fig. 2 SEM micrographs of barium chloride dispersed on silica gel nanoparticles ($BaCl_2$-nano SiO2).

Table 1 Optimisation of the reaction conditions in the preparation of 2,6-bis(4-bromophenyl)-4-(4-chlorophenyl)pyridine

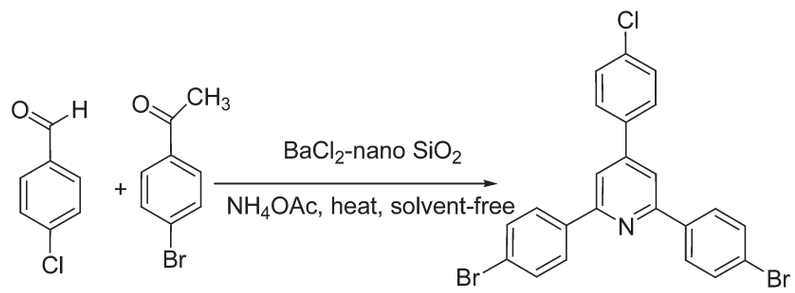
Entry	Catalyst /g	T /°C)	Solvent	Time /min	Yield /%[a]
1	0.08	Reflux	CH_2Cl_2	150	85
2	0.08	Reflux	*n*-hexane	150	73
3	0.08	Reflux	Ethanol	300	84
4	0.08	120	–	40	91
5	0.08	100	–	60	87
6	0.08	80	–	90	85
7	0.08	r.t.	–	480	trace
8	0.05	120	–	180	80
9	0.03	120	–	150	74
10	0.01	120	–	210	62

[a]Isolated yield.

in Table 2, the optimised reaction conditions were applicable to various substrates. Whether using various acetophenones or various benzaldehydes, $BaCl_2$-nano SiO_2 efficiently promoted the reaction with good to excellent yields. The substituent on the aromatic ring had no noticeable effect on the reaction as all products were obtained in high yields with short reaction times.

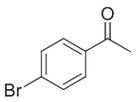
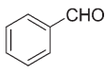
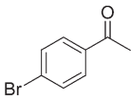
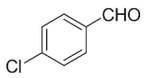
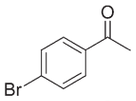
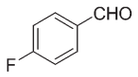
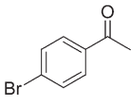
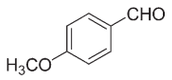
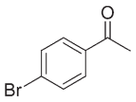
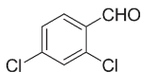
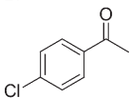
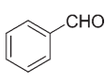
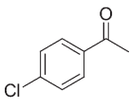
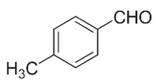
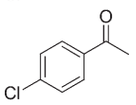
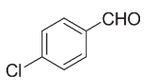
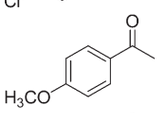
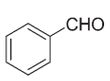
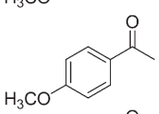
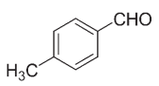
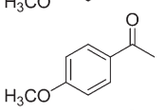
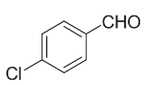
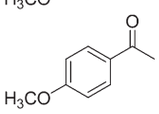
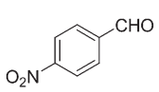
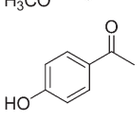
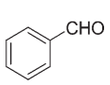
Conclusion

In conclusion, we have presented a highly efficient and powerful method for the preparation of 2,4,6-triarylpyridines catalysed by $BaCl_2$-nano SiO_2. The present protocol features simple operations, short reaction time, environmental friendliness and good yields.



Scheme 2 Preparation of 2,6-bis(4-bromophenyl)-4-(4-chlorophenyl)pyridine using $BaCl_2$-nano SiO_2 as catalyst under solvent-free conditions.

Table 2 Preparation of 2,4,6-triarylpyridine derivatives using $BaCl_2$-nano SiO_2

Entry	Acethophenone	Aldehyde	Time /min	Yield /%[a]	m.p. /°C [lit. m.p.][ref]
1			60	83	103–105 [103–105][12]
2			40	91	166–168
3			40	89	146–148
4			45	88	149–150
5			110	87	226–228
6			60	90	125–127 [125–127][9]
7			43	88	202–204 [201–203][11]
8			65	86	260–262 [264–265][13]
9			90	81	102–104 [100–103][9]
10			95	85	157–159 [155–157][9]
11			15	94	112–114 [115–116][9]
12			20	91	146–148 [143–144][9]
13			120	70	199–201 [197][10]

[a]Isolated yield.

Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. The NMR spectra were recorded on a Bruker Avance DPX 300 and 400 MHz instruments. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Elemental analysis was performed on a Heraeus CHN–O-Rapid analyser. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel polygram SIL G/UV 254 plates. The powder X-ray diffraction patterns were measured with Bruker D_8 Advance, Bruker, AXS, diffractometer using CuKα irradiation. Scanning electron micrographs were taken on a Philips (XL30 model).

Preparation of silica nanoparticles: Silica nanoparticles were prepared by the hydrolysis of tetraethyl orthosilicate (TEOS) with aqueous ethanol catalysed by oxalic acid. Typically, 50 mL of TEOS and 10 mL oxalic acid (35 w%) were added to a stirred mixture of 50 mL of aqueous ethanol (50%) respectively. The mixture was stirred at room temperature until a gel was formed and this was subsequently dried by stirring overnight at 60 °C and 24h at 120 °C to remove the excess solvents, as well as some of the water, from the pores. The dry mixture was ground in a mortar and passed through standard sieves. Finally the xerogel was heated from room temperature to 1400 °C at a rate of 4 °C/min in an argon flow. The temperature was kept at 1400 °C for 1h to remove organic contaminants. Xerogel particles 29–43 nm in size were used in the next preparation procedure.

Barium chloride dispersed on silica gel ($BaCl_2$-nano SiO_2): The actual procedure for the preparation of $BaCl_2$-nano SiO_2 is quite similar to the procedure for the preparation of SiO_2-$FeCl_3$ that was reported by Tal *et al*.[14] Typically, in a 250 mL flask, barium chloride dihydrate ($BaCl_2.2H_2O$) (1 g) was dissolved in water (50 mL) and silica gel nanoparticles (10 g) were added to this mixture which was thenvigorously stirred under rotary evaporation until the water had completely evaporated. This powder was kept in an oven at 100 °C for 1h to give the active catalyst.

Typical procedure

To a mixture of benzaldehyde (1 mmol), 4-bromoacetophenone (2 mmol) and ammonium acetate (1.3 mmol) was added $BaCl_2$-nano SiO_2 (0.08 g) and the mixture was heated at 120 °C in an oil bath for the appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the mass was cooled to 25 °C and the mixture was dissolved in CH_2Cl_2. The catalyst was removed by simple filtration. The solvent was then evaporated off and the solid product was purified by recrystallisation from ethanol.

2,6-bis(4-bromophenyl)-4-(4-chlorophenyl)pyridine (Table 2, entry 2): ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.53 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 4H), 7.94 (d, *J* = 8.5 Hz, 4H), 7.98 (s, 2H), 8.11 (d, *J* = 8.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 123.3, 128.3, 129.8, 131.5, 131.6, 132.7, 134.4, 136.1, 137.2, 143.9, 189.1 ppm; IR (KBr, cm^{-1}): 1655, 1593, 1487, 1402, 1328, 1215, 1096, 1032, 1006, 982, 814. Found: C, 55.33; H, 2.85; N, 2.84 $C_{23}H_{14}Br_2ClN$ requires C, 55.29; H, 2.82; N, 2.80%.

2,6-Bis(4-bromophenyl)-4-(4-fluorophenyl)pyridine (Table 2, entry 3): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.30 (t, *J* = 8.8 Hz, 2H), 7.72–7.82 (m, 5H), 7.88–8.02 (m, 5H), 8.10 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.3, 116.5, 122.0, 127.8, 131.0, 131.7, 131.72, 131.8, 131.9, 132.3, 136.9, 143.7, 162.7, 165.2, 188.6 ppm; IR (KBr, cm^{-1}): 1658, 1592, 1505, 1411, 1330, 1210, 1159, 1107, 1070, 997, 819. Found: C, 57.21; H, 2.97; N, 2.94 $C_{23}H_{14}Br_2FN$ requires C, 57.17; H, 2.92; N, 2.90%.

2,6-Bis(4-bromophenyl)-4-(4-methoxyphenyl)pyridine (Table 2, entry 4): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.82 (s, 3H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.71–7.87 (m, 8H), 8.08 (d, *J* = 8.4 Hz, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.9, 114.9, 119.6, 127.5, 127.7, 130.9, 131.4, 132.2, 137.3, 145.0, 162.0, 188.6 ppm; IR (KBr, cm^{-1}): 3002, 2931, 1655, 1591, 1509, 1459, 1330, 1303, 1255, 1214, 1171, 1032, 1006, 981, 818. Found: C, 58.27; H, 3.49; N, 2.86; $C_{24}H_{17}Br_2NO$ requires C, 58.21; H, 3.46; N, 2.83%.

2,6-Bis(4-bromophenyl)-4-(2,4-dichlorophenyl)pyridine (Table 2, entry 5): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.59–7.87 (m, 7H), 8.06 (s, 2H), 8.22 (d, *J* = 8.0 Hz, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 120.1, 123.6, 128.3, 129.4, 129.9, 132.3, 132.8, 133.3, 134.7, 136.9, 137.8, 148.3, 155.3 ppm; IR (KBr, cm^{-1}): 1601, 1542, 1478, 1417, 1371, 1259, 1178, 1106, 1070, 1007, 816. Found: C, 51.76; H, 2.52; N, 2.65 $C_{23}H_{13}Br_2Cl_2N$ requires C, 51.72; H, 2.45; N, 2.62%.

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