$BF_3.SiO_2$ nanoparticles: a solid phase acidic catalyst for efficient one-pot Hantzsch synthesis of 1,4-dihydropyridines

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The solvent-free Hantzsch reaction between ethyl acetoacetate or 1,3-indandione, an aromatic aldehyde and ammonium acetate catalysed by $BF_3.SiO_2$ nanoparticles provided an efficient one-step synthesis of 1,4-dihydropyridines in excellent yields.

Keywords: $BF_3.SiO_2$ nanoparticles, ethyl acetoacetate, 1,3-indandione, ammonium acetate, 1,4-dihydropyridines, Hantzsch reaction

Described more than a century ago by Hantzsch,[1] dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates are the prototypes of a classe of drugs known as the dihydropyridines (DHP) which are vital drugs in the treatment of angina and hypertension. Some of them such as amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nimodipine and nitredipine have been commercialised and it has been shown that their mode of action is as calcium channel blockers.[2] The classical method for the synthesis of 1,4-dihydropyridines is a one-pot condensation of an aldehyde, ethyl acetoacetate, and ammonia either in acetic acid or in refluxing alcohol.[3] However, the yields of 1,4-dihydropyridines obtained in this way are generally low. Over the past 50 years, a number of novel and more efficient procedures have been reported, all of them listed and referenced by Debache and coworkers.[4] These include the use of solvent free conditions, microwave-heating, ionic liquids, high temperatures at reflux, TMSCl–NaI, $InCl_3$, I_2, $SiO_2/NaHSO_4$, $SiO_2/HClO_4$, Na- and Cs-Norit carbons, tetrabutylammonium hydrogen sulfate, fermenting Baker's yeast, and metal triflates. Very recently, Lewis bases such as triphenylphosphine have also been used as catalysts for the synthesis of 1,4-dihydropyridines.[4] We report here the Hantzsch reaction between ammonium acetate, an aromatic aldehyde and two examples of an activated 1,3-dicarbonyl compound using nano-$BF_3.SiO_2$ under solvent-free conditions.

Results and discussion

In continution of our investigations of the application of solid acids in organic synthesis[5–11] we have found that the Hantzsch synthesis of 1,4-dihydropyridine derivatives by the three-component condensation of an aromatic aldehyde **1**, a 1,3-dicarbonyl compound such as ethyl acetoacetate **2**, or indane-1,3-dione **3** and ammonium acetate occurs very rapidly and smoothly in the presence of 0.003 g nano-$BF_3.SiO_2$ as a catalyst (Scheme 1).

The stable catalyst is easily prepared[12] and in order to optimize the reaction conditions, the reaction of 4-nitrobenzaldehyde and ethyl acetoacetate with ammonium acetate was used as a model reaction for 1,4-dihydropyridines synthesis. To demonstrate the better catalytic activity of nano-$BF_3.SiO_2$, initially, we studied the reaction with other catalysts under solvent-free conditions during 20 min at 70 °C, and the results are listed in Table 1.

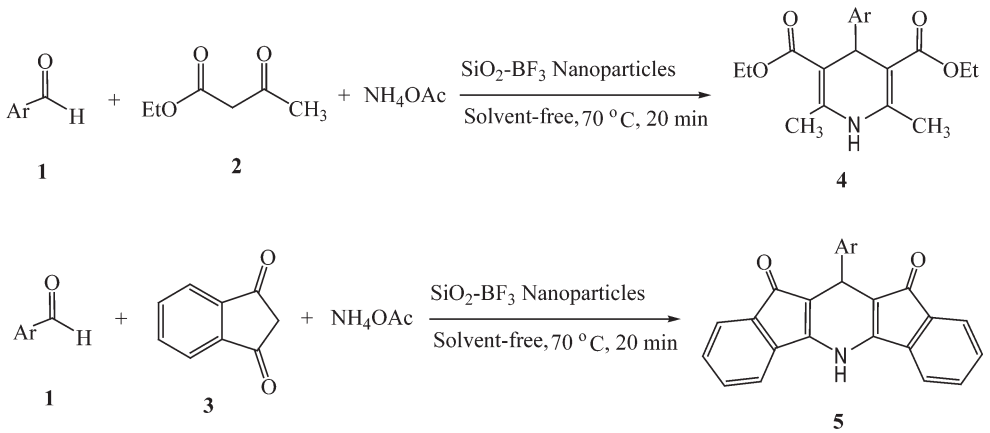
It can be seen that nano-$BF_3.SiO_2$ is a better catalyst than any of the others in terms of yield obtained.

To determine the optimum quantity of nano-$BF_3.SiO_2$, the model reaction was carried out at 70 °C for 20 min using different quantities of nano-$BF_3.SiO_2$ (Table 2). As can be seen, $BF_3.SiO_2$ of 0.003 g gave an excellent yield (Table 2, entry 2) and increasing the amount 5- to 10-fold hardly made any difference.

The reaction was also examined in various solvents and compared with solvent-free conditions (Table 3).

Different solvents clearly affected the efficiency of the reaction, but the best results were obtained when solvent-free conditions were used (Table 3, entry 5).

In summary, using the nano-$BF_3.SiO_2$ (0.003 g) under solvent-free conditions at 70 °C for 20 min are the optimal reaction conditions for the synthesis of 1,4-dihydropyridines.



Scheme 1 Synthesis of 1,4-dihydropyridines by condensation of ethyl acetoacetate or 1,3-indandione with an aromatic aldehyde and ammonium acetate using nano-$BF_3.SiO_2$ as catalyst

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Table 1 Reaction between 4-nitrobenzaldehyde, ethyl acetoacetate and ammonium acetate using different catalysts under solvent-free conditions for 20 min at 70 °C

Entry	Catalyst	Yield/%[a]
1	$FeCl_3.6H_2O$	40
2	$RuCl_3$	32
3	$InBr_3$	37
4	PPh_3	55
5	None	20
6	Nano-$BF_3.SiO_2$	93

[a] Isolated yield.

Table 2 Optimisation of the amount of nano-$BF_3.SiO_2$ on the synthesis of **4e** for 20 min at 70 °C

Entry	Catalyst	Yield/%[a]
1	0.001	74
2	0.003	93
3	0.015	95
4	0.03	95

[a] Isolated yield.

Table 3 Solvent effect on the synthesis of **4e** catalysed by nano-$BF_3.SiO_2$ for 20 min at 70 °C

Entry	Solvent	Yield/%[a]
1	$CHCl_3$	60
2	EtOH	80
3	EtOAC	20
4	H_2O	50
5	Solvent-free	93

[a] Isolated yield.

To study the scope of the reaction, a series of aromatic aldehydes **1** were investigated. The results for ethyl acetoacetate **2** and 2,3-indandione **3** are shown in Tables 4 and 5. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in excellent yields.

The compounds **4a–f** were characterised by their elemental analyses and by their ^{1}H NMR and IR spectral data which were compared with literature data.[4,13–15]

Compounds **4g**, **4h** and **5a–f** were new and their structures were deduced by elemental and spectral analysis, the former two compounds by comparison with data for **4a–f**. The mass spectrum of compound **5a** showed the molecular ion peak at 361. The ^{1}H NMR spectrum of compound **5a** exhibited a methine proton at 4.27 ppm and a NH proton at 9.06 ppm which disappears after addition of D_2O. There are multiplets between 7.25 and 7.88 ppm which are due to aromatic protons. The ^{13}C NMR spectrum of compound **5a** showed 14 signals in agreement with the proposed structure. The IR spectrum of compound **5a** also supported the suggested structure. Compounds **5b–f** showed similar spectral data to those of **5a** and were assigned similar structures.

Table 5 Reaction between 1,3-indandione (2 mmol), aromatic aldehydes (1 mmol) and ammonium acetate (1 mmol) catalysed by nano-$BF_3.SiO_2$ (0.003 g) for 20 min at 70 °C

Entry	Ar	Product	Yield/%[a]
1	C_6H_5	**5a**	85
2	4-NO_2-C_6H_4	**5b**	90
3	4-Br-C_6H_4	**5c**	91
4	2-Cl-C_6H_4	**5d**	92
5	2-MeO-C_6H_4	**5e**	88
6	3-MeO-2-OH-C_6H_3	**5f**	90

[a] Isolated yield.

In summary, we have shown that nano-$BF_3.SiO_2$ has advantages in the preparation of 1,4-dihydropyridines such as shorter reaction times, simple work-up, and much improved yields. Moreover, the solid phase acidic catalyst was re-usable for a number of times without appreciable loss of activity. The present method, which does not involve any hazardous organic solvent, can be classified as green chemistry.

Experimental

IR spectra were recorded on a Shimadzu IR-470 spectrometer in KBr discs. The NMR spectra were obtained on a Bruker Avance DRX-400 FT spectrometer (^{1} H NMR at 400 Hz, ^{13}C NMR at 100 Hz) using $CDCl_3$ as solvent with TMS as internal standard.

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed at the analytical laboratory of Science and Researchs Unite of Islamic Azad University. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Nano-$BF_3.SiO_2$ was prepared as previously described.[12]

General procedure

A mixture of ethyl acetoacetate or 1,3-indandione (2 mmol), aromatic aldehyde (1 mmol), ammonium acetate (1 mmol), and nano-$BF_3.SiO_2$ (0.003 g) was placed in a round bottom flask. The materials were mixed and heated at 70 ºC for 20 min. The progress of the reaction was followed by TLC (*n*-hexane:ethylacetate). After the completion of the reaction, the mixture was filtered to remove the catalyst. Evaporation of the solvent gave the crude product which was recrystallised from hot ethanol to obtain the pure compound.

Diethyl-4-)4-cyanophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4g**): Yellow oil; IR (ν_{max}, cm^{-1}): 3480 (NH), 2250 (C=N), 1692 (C=O) ^{1}H NMR: δ 1.22 (6H, t, $^3J_{HH}$ = 7 Hz, 2 × CH_2CH_3), 2.35 (6H, s, 2 × CH_3), 4.03–4.15 (4H, m, 2 × OCH_2), 5.04 (1H, s, CH), 5.08 (1H, br. s, NH), 7.39 (2H, d, $^3J_{HH}$ = 7 Hz, aromatic), 7.52 (2H, d, $^3J_{HH}$ = 7 Hz, aromatic) ppm; ^{13}C NMR: δ 14.2, 19.5, 40.2, 59.9, 103.2, 109.7, 119.3, 128.8, 131.8, 144.6, 153.4 and 167.1 ppm; MS (*m/z*, %): 354 (M^+, 10). Anal Calcd for $C_{20}H_{22}N_2O_4$: C, 67.81; H, 6.21; N, 7.91. Found: C, 67.69; H, 6.26; N, 7.84%.

Table 4 Reaction between ethyl acetoacetate (2 mmol), aromatic aldehydes (1 mmol) and ammonium acetate (1 mmol) catalysed by nano-$BF_3.SiO_2$ (0.003 g) for 20 min at 70 °C

Entry	Ar	Product	Yield/%[a]	M.p./°C	
				Found	Reported
1	C_6H_5	**4a**	91	157–159	158–160 (Ref. 14)
2	2-NO_2-C_6H_4	**4b**	90	169–171	169–170 (Ref. 13)
3	4-MeO-C_6H_4	**4c**	90	160–162	161–163 (Ref. 14)
4	4-OH-C_6H_4	**4d**	88	226–228	227–228 (Ref. 15)
5	4-NO_2-C_6H_4	**4e**	93	131–132	129–130 (Ref. 15)
6	2-Br-C_6H_4	**4f**	92	161–163	162–164 (Ref. 4)
7	4-NC-C_6H_4	**4g**	82	Oil	–
8	4-Cl-3-NO_2-C_6H_3	**4h**	80	Oil	–

[a] Isolated yield.

Diethyl-4-)3-nitro-4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4h**): Yellow oil; IR (ν_{max}, cm^{-1}): 3380 (NH), 1693 (C=O), 1535 and 1364 (NO_2). ^1H NMR: δ 1.20 (6H, t, $^3J_{HH}$ = 7 Hz, 2 × CH_2CH_3), 2.32 (6H, s, 2 × CH_3), 4.02–4.17 (4H, m, 2 × OCH_2), 4.96 (1H, s, CH), 5.53 (1H, br. s, NH), 7.72–8.35 (3H, m, aromatic) ppm; ^{13}C NMR: δ 14.2, 19.6, 39.9, 59.6, 99.3, 104.2, 127.4, 130.0, 140.6, 143.6, 145.1, 150.0 and 167.7 ppm; MS (*m/z*, %): 408 (M^+, 7). Anal Calcd for $C_{19}H_{21}ClN_2O_6$: C, 55.81; H, 5.17; N, 6.85. Found: C, 55.86; H, 5.19; N, 6.76%.

11-Phenyl-5,11-dihydro-diindeno[1,2-b:2',1'-e]pyridine-10,12-dione (**5a**): White powder, m.p. 207–209 °C; IR (ν_{max}, cm^{-1}): 3453 (NH), 1696 (C=O); ^1H NMR: δ 4.27 (1H, s, CH), 7.25–7.88 (13H, m, aromatic), 9.06 (1H, br. s, NH) ppm; ^{13}C NMR: δ 40.2, 91.1, 118.4, 126.2, 127.5, 129.1, 129.7, 130.8, 138.3, 140.5, 140.6, 141.05, 151.1, 190.9 ppm; MS (*m/z*, %): 361 (M^+, 11). Anal Calcd for $C_{25}H_{15}NO_2$: C, 83. 1; H, 4.15; N, 3.87. Found: C, 83.6; H, 4.22; N, 3.79%.

11-(4-Nitrophenyl)-5,11-dihydro-diindeno[1,2-b:2',1'-e]pyridine-10,12-dione (**5b**): White powder, m.p. 192–194 °C; IR (ν_{max}, cm^{-1}): 3455 (NH), 1708 (C=O), 1558 and 1343 (NO_2); ^1H NMR: δ 4.22 (1H, s, CH), 7.23–7.82 (12H, m, aromatic), 9.01 (1H, br. s, NH) ppm; ^{13}C NMR: δ 41.3, 91.2, 118.1, 124.4, 129.4, 129.9, 130.9, 138.5, 140.6, 140.8, 141.1, 147.8, 151.3, 191.1 ppm; MS (*m/z*, %): 406 (M^+, 5). Anal Calcd for $C_{25}H_{14}N_2O_4$: C, 73.89; H, 3.47; N, 6.89. Found: C, 73.78; H, 3.53; N, 6.72%.

11-(4-Bromophenyl)-5,11-dihydro-diindeno[1,2-b:2',1'-e]pyridine-10,12-dione (**5c**): White powder, m.p. 120–122 °C; IR (ν_{max}, cm^{-1}): 3405 (NH), 1697 (C=O). ^1H NMR: δ 3.42 (1H, s, CH), 7.02–7.79 (12H, m, aromatic), 8.75 (1H, br. s, NH) ppm; ^{13}C NMR: δ 43.5, 91.6, 121.4, 122.9, 123.1, 128.8, 129.6, 130.9, 131.2, 132.4, 135.1, 136.4, 136.7, 196.4 ppm; MS (*m/z*, %): 440 (M^+, 8). Anal Calcd for $C_{25}H_{14}BrNO_2$: C, 68.19; H, 3.2; N, 3.18. Found: C, 68.23; H, 3.27; N, 3.07%.

11-(2-chlorophenyl)-5,11-dihydro-diindeno[1,2-b:2',1'-e]pyridine-10,12-dione (**5d**)*:* White powder, m.p. 109-111; IR (ν_{max}, cm^{-1}): 3450 (NH), 1699 (C=O). ^1H NMR: δ 3.67 (1H, s, CH), 7.08-7.68 (12H, m, aromatic), 8.70 (1H, br. s, NH) ppm; ^{13}C NMR: δ 41.6, 91.7, 122.1, 125.9, 127.8, 129.8, 130.7, 131.5, 132.7, 133.4, 135.2, 136.5, 136.8, 140.1, 142.2, 196.2 ppm; MS (*m/z*, %): 395 (M^+, 7). Anal Calcd for $C_{25}H_{14}ClNO_2$: C, 75.85; H, 3.56; N, 3.53. Found: C, 75.79; H, 3.62; N, 3.49%.

11-(2-Methoxyphenyl)-5,11-dihydro-diindeno[1,2-b:2',1'-e]pyridine-10,12-dione (**5e**): White powder, m.p. 144–146; IR (ν_{max}, cm^{-1}): 3490 (NH), 1725 (C=O). ^1H NMR: δ 3.86 (1H, s, CH), 7.12–8.24 (12H, m, aromatic), 8.62 (1H, br. s, NH) ppm; ^{13}C NMR: δ 40.9, 91.2, 111.8, 120.6, 122.1, 128.5, 129.7, 130.8, 131.3, 132.4, 135.0, 136.2, 136.7, 140.3, 157.6, 195.8 ppm; MS (*m/z*, %): 391 (M^+, 4). Anal Calcd for $C_{26}H_{17}NO_3$: C, 79.78; H, 4.37; N, 3.57. Found: C, 79.81; H, 4.41; N, 3.46%.

11-(2-Hydroxy-3-methoxyphenyl)-5,11-dihydro-diindeno[1,2-b:2',1'-e]pyridine-10,12-dione (**5f**): White powder, m.p. 160–162; IR (ν_{max}, cm^{-1}): 3475 and 3065 (NH, OH), 1706 (C=O). ^1H NMR: δ 1.39 (1H, br. s, OH), 3.39 (1H, s, OCH_3), 4.36 (1H, s, CH), 6.72-7.76 (11H, m, aromatic), 9.01 (1H, br. s, NH) ppm; ^{13}C NMR: δ 40.3, 50.4, 118.1, 119.1, 120.0, 122.1, 122.1, 128.6, 131.5, 131.6,131.7, 135.1, 136.2, 136.1, 140.6, 166.9, 200.4 ppm; MS (*m/z*, %): 407 (M^+, 8). Anal Calcd for $C_{26}H_{17}NO_4$: C, 76.64; H, 4.2; N, 3.43. Found: C, 79.57; H, 4.17; N, 3.52%.

We gratefully acknowledge financial support from the Research Council of the Islamic Azad University of Yazd and The Islamic Azad University of Zahedan of Iran.

Received 5 October 2012; accepted 30 October 2012
Paper 1201557 doi: 10.3184/174751912X13542975429543
Published online: 15 January 2013

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