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Clean, simple and efficient synthesis of spiro-2-amino-4*H*-pyran-3-carbonitrile *via* HBF_4–SiO_2 nanoparticles: a green protocol

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We have reported that fluoroboric acid adsorbed on nano silica-gel (HBF_4–SiO_2 NPs) catalyzed the one-pot synthesis of spiropyrans by condensation of ninhydrin, malononitrile and enolizable systems in good to excellent yields. This new protocol employing HBF_4–SiO_2 NPs, which are a solid acidic, green and inexpensive catalyst, offers advantages such as mild reaction conditions, short reaction times and easy work-up. The catalyst is recyclable with reproducible results without any loss of its activity.

Keywords: HBF_4–SiO_2 NPs, solid acid, ninhydrin, malononitrile, enolizable systems, green chemistry

INTRODUCTION

Multi-component one-pot syntheses have emerged as powerful tools owing to their ability to give products in a single operation step from three or more reactants with high atom economy. These reactions are widely applied in biological and pharmaceutical chemistry for producing different structures and combinatorial libraries for drug discovery[1]. Spiro compounds are an important class of structural motifs of numerous natural products with biological properties [2,3]. On the other hand, the pyran ring is important from pharmaceutical point-of-view and exhibits promising biological activities such as antiviral [4], anticancer [5,6], anti-HIV [7], antimicrobial [8] and calcium channel antagonist activity [9].

Spiropyrans in particular, have attracted strong interest owing to their potential activity as hypertensive, analgesic agents and their applications in industrial fields such as photochromic materials in data recording [10]. In recent years, a variety of synthetic procedures for spiro-2-amino-4H-pyran-3-carbonitriles synthesis have been reported [11,12]. Each of these methods has merits but the development of facile, green and economical synthetic methodologies is still essential. There are many limitations, such as the use of expensive and excess amounts of catalysts, elevated temperatures, long reaction times, and low yields. Hence, we have developed an efficient procedure for the one-pot three-component synthesis of biologically active spiro-2-amino-4*H*-pyran-3-carbonitrile derivatives in the presence of HBF_4–SiO_2 nanoparticles as a solid-phase acidic catalyst. The application of environmentally benign water and solid acid catalyst represents a powerful green procedure.

EXPERIMENTAL

Instruments

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser. 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. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer for solutions in d_6-DMSO using TMS as an internal standard. The morphologies of the products were observed using SEM with a Holland Philips XL30 microscope at an accelerating voltage of 25 kV. The chemicals for this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Stable silica nanoparticles were obtained according to [17] and used for preparation of the catalyst HBF_4–SiO_2 NPs.

Synthesis of HBF_4–SiO_2 nanocrystals

A magnetically stirred suspension of nano silica-gel (2.67 g) in diethyl ether (50 mL) was treated with 40% aq HBF_4 (0.3 g) for 3 h. The mixture was concentrated and the residue dried under vacuum at 100 ºC for 72 h to afford HBF_4–SiO_2 NPs. The dimensions of the nanoparticles were observed by SEM (Scheme 1). The catalyst resembles a net, which is considered as an advantage, since the reactants are situated in the mesh vents and reactions are performed with certain regularity.

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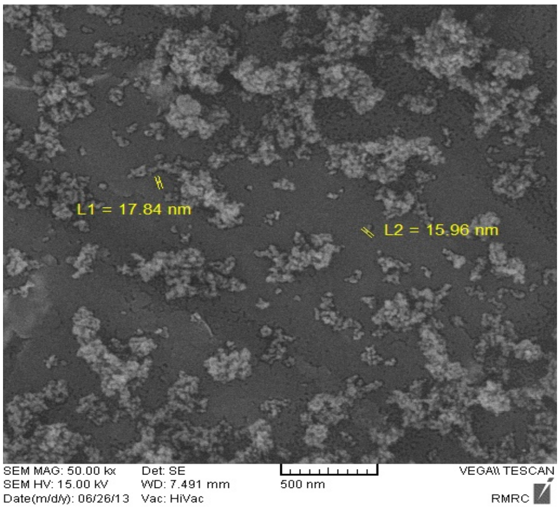


Scheme 1. SEM image of HBF_4–SiO_2 NPs

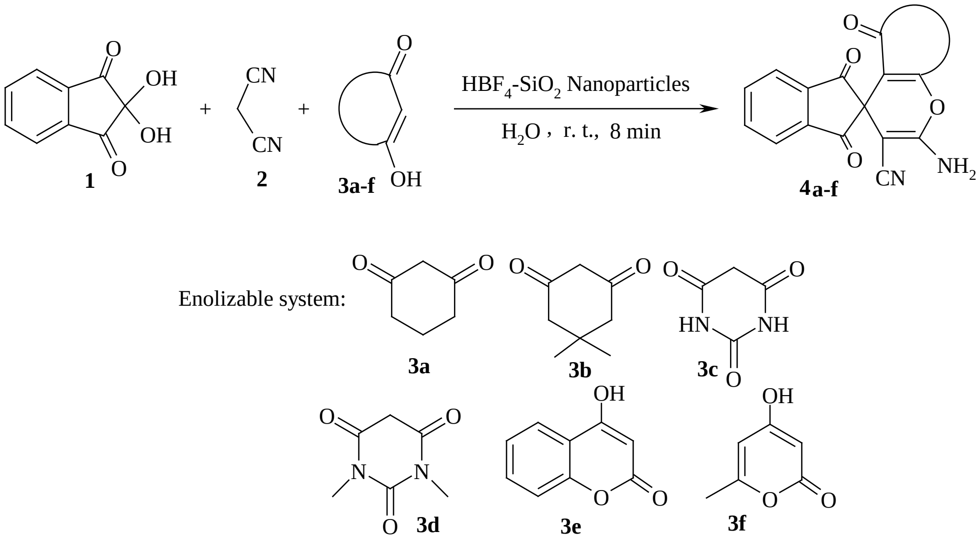
General experimental procedure

A mixture of ninhydrin (1 mmol), malononitrile (1.2 mmol), enolizable system (**3a-f**, 1 mmol), HBF_4–SiO_2 NPs as a catalyst (0.02 g) and H_2O (5 mL) was placed in a round-bottom flask. The materials were magnetically stirred at ambient temperature for the appropriate time, as given in Table 2. After completion of the reaction and evaporation of the solvent, the crude product was recrystallized from hot ethanol to obtain the pure compound.

RESULTS AND DISCUSSION

In continuation of our investigations of the application of solid acids in organic synthesis [13-16] we investigated a novel and efficient method for the synthesis of spiro-2-amino-4*H*-pyran-3-carbonitrile derivatives by three-component condensation of ninhydrin **1**, malononitrile **2** and an enolizable system (**3a-f)**, in the presence of HBF_4–SiO_2 NPs as a catalyst (Scheme 2).

The study was initiated by using ninhydrin, malononitrile and dimedone (**3b**) as model substrates for the preparation of **4b**. There was no reaction without HBF_4–SiO_2 NPs in H_2O at room temperature (Table 1, entry 1). The transformation of ninhydrin with malononitrile and dimedone proceeded smoothly with HBF_4–SiO_2 NPs (0.02 g), and at the end of the reaction (about 8 min later), the product was collected by filtration and recrystallized from ethanol, affording the nicely crystalline **4b** in good yield (94%, Table 1, entry 2). Different solvents (CH_2Cl_2, EtOH and CH_3CN) were screened in the model reaction in the presence of HBF_4–SiO_2 NPs as a catalyst, but they resulted in low yields (Table 1, entries 6-8). Decreasing the catalyst loading from 0.02 to 0.01 g, significantly lowered the yield of the reaction product (Table 1, entries 9, 10). The yields of **4b** were not further improved with increased amount of the catalyst (Table 1, entry 11). Thus, it is clear from the experiments that the best condition for **4b** could be entry 2, employing HBF_4–SiO_2 NPs (0.02 g) as a solid acid in aqueous medium at room temperature. An interesting feature of this method is that the catalyst can be regenerated at the end of the reaction and can be used several times without losing its activity. To recover the catalyst, after completion of the reaction, the mixture was filtered and the catalyst was washed with $CHCl_3$ and then dried. This process was repeated for two cycles and the yield of the product did not change significantly (Table 1, entries 12, 13).



Scheme 2. Synthesis of spiro-2-amino-4*H*-pyran-3-carbonitrile derivatives catalyzed by HBF_4–SiO_2 NPs.

Table 1. Optimization of the reaction conditions for the synthesis of **4b**[a].

Entry	Catalyst (amount)	Solvent/ Cond.	Time (min)	Yield (%) [Ref.]
1	HBF_4–SiO_2 NPs (0)	H_2O/ r.t.	60	0
2	HBF_4–SiO_2 NPs (0.02 g)	H_2O/ r.t.	8	94
3	$NaHCO_3$ (0.2 mmol)	EtOH/ Reflux	20	92 [11]
4	DBU (10 mol%)	H_2O/ r.t.	10	85 [12]
5	SiO_2-HBF_4 (0.02 g)	H_2O/ r.t.	8	Trace
6	HBF_4–SiO_2 NPs (0.02 g)	EtOH/ r.t.	8	64
7	HBF_4–SiO_2 NPs (0.02 g)	CH_3CN/ r.t.	8	57
8	HBF_4–SiO_2 NPs (0.02 g)	CH_2Cl_2/ r.t.	8	40
9	HBF_4–SiO_2 NPs (0.015 g)	H_2O/ r.t.	8	90
10	HBF_4–SiO_2 NPs (0.01 g)	H_2O/ r.t.	8	84
11	HBF_4–SiO_2 NPs (0.03 g)	H_2O/ r.t.	8	94
12	HBF_4–SiO_2 NPs (0.02 g)2nd	H_2O/ r.t.	8	90
13	HBF_4–SiO_2 NPs (0.02 g)3rd	H_2O/ r.t.	8	87

[a] Reaction conditions: 1 mmol of ninhydrin, 1 mmol of malononitrile, 1 mmol of dimedone.

Table 2. Synthesis of spiro-2-amino-4*H*-pyran-3-carbonitrile derivatives[a].

Entry	Enolizable system	Product	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found	Reported [Ref.]
1	**3a**	**4a**	10	90	284-285	> 300 [11]
2	**3b**	**4b**	8	94	289-291	> 300 [11]
3	**3c**	**4c**	12	88	273-275	> 300 [11]
4	**3d**	**4d**	10	89	260-262	> 300 [11]
5	**3e**	**4e**	7	90	> 300	> 300 [11]
6	**3f**	**4f**	10	91	290-295	288-292 [12]

[a] Reaction conditions: 1 mmol of ninhydrin, 1.2 mmol of malononitrile, 1 mmol of enolizable system, in aqueous medium at room temperature.

[b] Isolated yields.

After optimizing the reaction conditions, a series of enolizable systems were employed under similar circumstances to evaluate the substrate scope of this reaction. The results are summarized in Table 2. In all cases, the enolizable systems underwent the reaction smoothly and gave products in excellent yields.

The compounds **4a-f** were characterized by ^{1}HNMR and IR spectroscopy and elemental analysis [11,12].

In conclusion, we have successfully developed an efficient, atom-economical and simple methodology for the synthesis of spiro-2-amino-4*H*-pyran-3-carbonitrile derivatives by a three-component reaction in aqueous medium at room temperature. Prominent among the advantages of this method are: operational simplicity, mild reaction conditions, short reaction times, high yields, environmental safety and cheapness of the catalyst. The present method does not involve any hazardous organic solvents and liquid acid catalysts. Therefore, this procedure could be classified as green chemistry.

REFERENCES

1. N. K. Terret, M. Gardner, D. W. Gordon, R. J. Kobylecki, J. Steel, *Tetrahedron*, **51**, 8135 (1995)
2. K. A. Parker, A. Dermatakis, *J. Org. Chem.*, **62,** 4164 (1997)
3. M. J. Kukla, H. J. Breslin, C. J. Diamond, P. P. Gtous, C. Y. Ho, M. Miranda, J. D. Rodgers, R. G. Sherrill, E. D. Clercq, *J. Med. Chem.*, **34**, 3187 (1991)
4. S. Wang, G. W. Milne, X. Yan, I. J. Posey, M. C. Nicklaus, L. Graham, W. G. Rice, *J. Med. Chem.*, **39**, 2047 (1996)
5. D. R. da Rocha, A. C. G. de Souza, J. A. L. C. Resende, W. C. Santos, E. A. dos Santos, C. Pessoa, M. O. de Moraes, L. V. Costa-Lotufo, R. C. Montenegro, V. F. Ferreira, *Org. Biomol. Chem.*, **9**, 4315 (2011)
6. Y. Dong, Q. Shi, K. Nakagawa-Goto, P.-C. Wu, S. L. Morris-Natschke, A. Brossi, K. F. Bastow, J.-Y. Lang, M.-C. Hung, K.-H. Lee, *Org. Biomol. Chem.*, **18**, 803 (2010)
7. M-z. He, N. Yang, X-J. Yao, C-l. Sun, M. Yang, *Med. Chem. Res.*, **20**, 200 (2010)
8. H. Hussain, S. Aziz, B. Schulz, K. Krohn, *Nat. Prod. Commun.*, **6**, 841 (2011).
9. A. Shahrisa, M. Zirak, A. R. Mehdipour, R. Miri, *Chem. Heterocycl. Compd.*, **46**, 1354 (2011).
10. C. P. McCoy, L. Donnelly, D. S. Jones, S. P. Gorman, *Tetrahedron Lett.*, **28**, 657 (2007).
11. Y. He, H. G, J. Tian, *J. Chem. Res.*, **35**, 528 (2011)
12. P. Saluja, K. Aggarwal, J. M. Khurana, *Synth. Commun.*, **43**, 3239 (2013).
13. B. Sadeghi, B. F. Mirjalili, M. M. Hashemi, *Tetrahedron Lett.*, **49**, 2575 (2008).

14. B. Sadeghi, A. Hassanabadi and M, Kamali, *J. Chem. Res.*, **36**, 9 (2012).
15. B. Sadeghi, S. Zavar and A. Hassanabadi, *J. Chem. Res.*, **36**, 343 (2012).
16. B. Sadeghi, Z. Nasirian and A. Hassanabadi, *J. Chem. Res.*, **36**, 391 (2012).
17. K. Lee, A. N. Sathyagal, A. V. McCormick, *Colloids Surfaces A*, **144**, 115 (1998).

ЧИСТ, ПРОСТ И ЕФЕКТИВЕН СИНТЕЗ НА СПИРО-2-АМИНО-4*H*-ПИРАН-3-КАРБОНИТРИЛ ЧРЕЗ НАНОЧАСТИЦИ HBF_4-SiO_2: ЗЕЛЕН ПРОТОКОЛ

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(Резюме)

Съобщава се, че флуороводородната киселина, адсорбирана върху нано силикагел (HBF4-SiO_2 NPs), катализира едностъпален синтез на спиропирани чрез кондензация на нинхидрин, малононитрил и енолизируеми системи при добри до отлични добиви. Този нов протокол, използващ HBF_4-SiO_2 NPs, който е твърд, киселинен, зелен и евтин катализатор, предлага предимства като меки реакционни условия, кратки реакционни времена и лесна обработка. Катализаторът се рециклира с възпроизводими резултати без загуба на неговата активност.