Basic magnetic nanoparticles as efficient catalysts for the preparation of naphthopyrane derivatives

Hossein Yarahmadi and Hamid Reza Shaterian*

Department of Chemistry, Faculty of Sciences, University of Sistan and Baluchestan, PO Box 98135-674, Zahedan, Iran

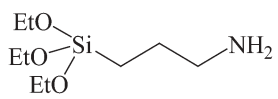
Aminosilane-functionalised spinel ferrite oxide (Fe_2O_3) magnetic nanoparticles have been synthesised and used as efficient heterogeneous base catalysts for the condensation of aromatic aldehydes with malonitrile and α (or β) naphthole via a three-component reaction under solvent-free conditions at 80 °C. Quantitative conversion of the reactants is achieved under mild conditions. Recovery of the catalyst is easily achieved by magnetic decantation. The supported catalyst is reused four times without significant degradation in catalytic activity. Naphthopyrans are polyfunctionalised benzopyran derivatives that have many biological and pharmacological properties.

Keywords: multi-component reactions, magnetic nanoparticles, naphthopyran, green chemistry

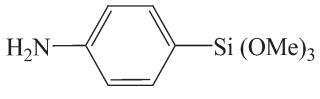
In recent years, research has moved towards the development of environmentally benign reactions. One of the tools used to combine the economic aspects of new reactions with green chemistry and environmental aspects is the multi-component reaction (MCR) strategy.[1] Recently, MCRs have emerged as a valuable synthetic tool in modern drug discovery.[2,3] Another tool is heterogeneous catalysis. These concepts are at the centre of chemical activity, and the research on high selectivity is the driving force for the conception of all new catalytic processes.[1,4]

Naphthopyrans are polyfunctionalised benzopyran derivatives which constitute structural units of several natural products. The biological and pharmacological properties of naphthopyrans include anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactin activities.[5–8] The most straightforward synthesis of this heterocyclic system involves a three-component coupling of aromatic aldehyde, malononitrile and activated phenol. Traditionally, this reaction was catalysed by acidic or basic catalysts such as ammonium salts,[9–12] $TiCl_4$,[13] K_2CO_3,[14] Et_3N,[15] $InCl_3$,[16] I_2/K_2CO_3,[17] heteropolyacid[18] and 4A° MS.[19] However, some of the reported methods require prolonged reaction time, reagents in stoichiometric amounts, toxic solvents, and generate moderate yields in the final product. However, a few heterogeneous catalysts have been used for this transformation. Recently, nano-sized catalysts have also been shown to be effective catalysts for this reaction.[20–22]

Good biocompatibility and biodegradability as well as basic magnetic characteristics can be denoted for surface functional organic materials grafted to iron oxide magnetic nanoparticles (MNPs).[23–25] These catalysts can be easily separated and recycled from the products by an external magnet. The silane agents such as 3-aminopropyltriethyloxysilane (APTES) and 4-aminophenyl trimethoxysilane (APTS) are often considered as potential candidates for modifying the surface of MNPs directly.[26,27]



APTES



APTS

Existence of many hydroxyl groups on the MNPs' surface leads to a reaction with alkoxysilane reagents and formation of Si–O bonds which support terminal functional groups available for the immobilisation of other substances.[28] In continuation of our works on the application of heterogeneous catalysts,[29–34] as part of our program aimed at developing useful new selective and synthesis methods based on the use of APTES functionalised magnetic nanoparticles as catalysts. In this work, we have considered the MCR strategy for the synthesis of substituted naphthopyrans using the basic nano-magnetic catalyst under solvent-free conditions (Scheme 1).

Result and discussion

Our initial study focused on the development of the optimal reaction conditions for this transformation. To determine the best weight of the catalyst and temperature, the synthesis of **6** was carried out in presence of different amounts of catalyst and at different temperatures. Initially, the reaction could start without any catalyst at 100 °C leading to poor yield (23%) of the final product **6** (Table 1, Entry 1). Table 1 shows a remarkable increase in outputs according to the increase in the quantity of the catalyst.

In order to use the minimum mass of the catalyst and temperature, we determined the optimum conditions to be 15 mg mol^{-1} of catalyst at 80 °C (Table 1, entry 12) for the synthesis of a variety of substrates (Table 2).

A heterogeneous catalyst is more interesting when it can be easily recovered and re-used. For this purpose, the synthesis of **6** was carried out using fresh and recovered MNPs catalyst for a four-cycle run. After 20 min reaction, the product **6** was isolated and identified. The recovered catalyst was washed with acetone and dried at 100 °C. The obtained yield after the four-cycle run is almost stable and unchangeable (92, 89, 86 and 85%) which demonstrates that MNPs can be easily recovered and re-used without any loss of its activity.

As can be seen from Table 2, electronic effects and the nature of substituent on the aromatic rings showed strong effects in terms of reaction time under the reaction conditions mentioned above. Aromatic aldehydes substituted by electron-donating groups (Table 2, entries **f–i**) require a longer reaction time than those of electron-withdrawing groups (Table 2, entries **b–e**).

The basic magnetic catalyst could be easily isolated from the reaction mixture by simple magnetic decantation using a permanent magnet and it could be reused several times without significant degradation in activity.

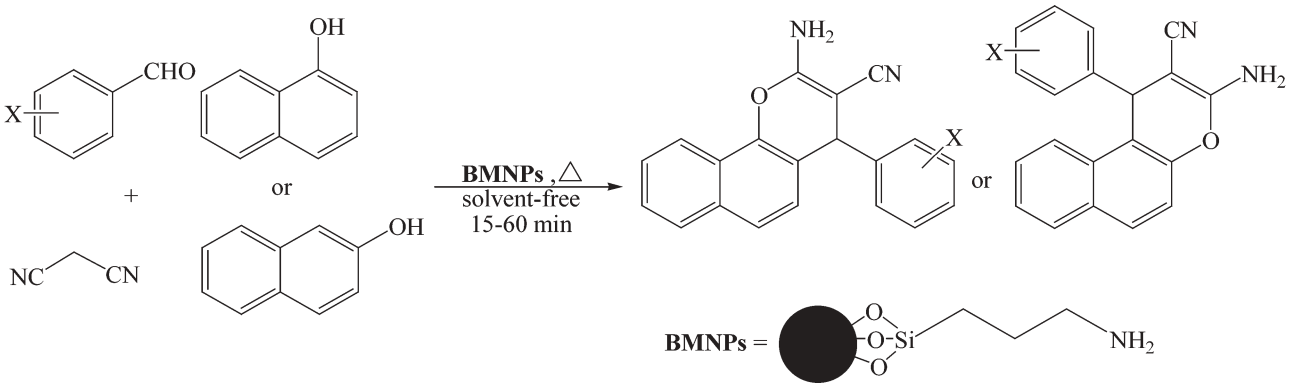
Experimental

Amino coated magnetic nanoparticles were produced according to reported procedure.[26]

Synthesis of 2-amino-2-chromenes; general procedure

An equimolar (1 mmol) mixture of an aromatic aldehyde (**1**), malononitrile (**2**), α (or β) -naphthol (**3**) and 15 mg of catalyst were vigorously stirred at 80 °C for the specified time. The end of the reaction was monitored by TLC. After completion, the mixture reaction was diluted by 5 mL dichloromethane; then the catalytic system was

* Correspondent. E-mail: hshaterian@yahoo.com; hshaterian@chem.usb.ac.ir



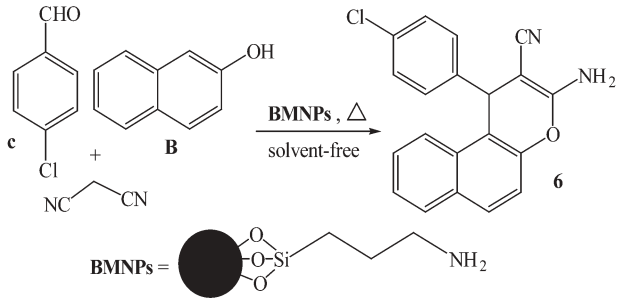
Scheme 1 Synthesis of naphthopyranes using MNPs under solvent-free conditions.

removed by an external magnet and reused as such for the next experiment. The organic layer was washed with aq. solution 10% $NaHCO_3$ and water, dried with Na_2SO_4 and concentrated to give the crude products. Consequently the desired naphthopyran recrystallised in ethanol: water (25% v/v). The desired pure product(s) were characterised by comparison of their physical data with those of known compounds.[9–22] The spectral data of some representative naphthopyranes are as follows.

2-Amino-4-(3,4-dimethoxy phenyl)-4H-benzo[h]chromene-3-carbonitrile (**11**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.8 (S, 3H), 3.9 (s, 3H), 4.8 (s, 2H), 4.9 (s, 1H), 6.8 (d, *J* = 1.2 Hz, 1H), 6.8–6.9 (m, 2H), 7.1 (d, *J* = 8.8 Hz, 1H), 7.5–7.6 (m, 3H), 7.8 (d, *J* = 7.6 Hz, 1H), 8.2 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 41.1, 55.1, 56.0, 61.5, 111.2, 117.3, 119.9, 120.5, 120.8, 123.2, 124.6, 126.2, 126.7, 126.8, 127.8, 133.3, 137.1, 143.2, 148.4, 149.3, 158.8 ppm; FT-IR (KBr, cm^{-1}): 3382 (N–H), 3326 (N–H), 3211, 3056, 2934, 2192 (CN), 1661; Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.69; H, 5.01; N, 7.84%.

3-Amino-1-(3,4-dimethoxyphenyl)-1H-benzo[f]chromene-2-carbonitrile (**12**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.8 (s, 6H), 4.7 (S, 2H), 5.2 (s, 1H), 6.7 (d, *J* = 7.6 Hz, 1H), 6.8 (d, *J* = 7.6 Hz, 2H), 7.3 (d, *J* = 8.8 Hz, 1H), 7.4 (2H, br), 7.7 (br, 1H), 7.8 (d, *J* = 6.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 38.5, 55.8, 55.9, 62.4, 110.5, 111.4, 115.0, 116.6, 119.3, 120.1, 123.9, 125.2, 127.2, 128.5, 129.6, 130.9, 131.49, 137.2, 147.1, 148.0, 149.3, 158.6 ppm; FT-IR (KBr, cm^{-1}): 3428 (N–H), 3336 (N–H), 3193, 3065, 2955, 2184 (CN), 1649; Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.70; H, 5.02; N, 7.79%. 2-amino-4-(3,4,5-trimethoxyphenyl)-4H-benzo[h] chromene-3-carbonitrile (**13**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.8 (s, 6H), 3.8 (s, 3H), 4.8 (s, 1H), 4.9 (s, 2H), 6.5 (s, 2H), 7.1 (d, *J* = 8.8 Hz,1H), 7.5–7.6 (m, 3H), 7.8 (dd, *J* = 1.2, 7.2 Hz, 1H), 8.2 (d, *J* = 8 Hz, 1H,) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 41.8, 45.0, 56.1, 60.8, 105.3, 116.9, 119.9, 120.8, 123.2, 124.6, 126.2, 126.7, 126.8, 127.8, 133.4, 137.2, 140.1, 143.2, 153.5, 159.1 ppm; FT-IR (KBr, cm^{-1}): 3485, 3331, 3203, 3066, 2187, 1664; Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.08; H, 5.15; N, 7.24%.

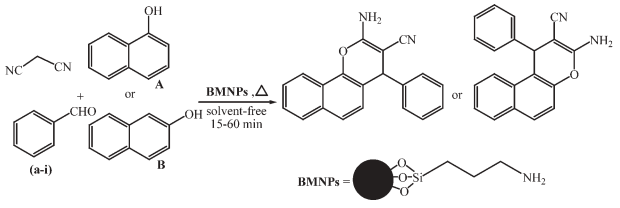
Table 1 Catalyst and temperature screening for the synthesis of **6**[a,b]



Entry	Temperature /°C	Catalyst /mg	Yield of **6** /%[c]
1	100	-	26
2	35	200	41
3	50	200	53
4	65	200	78
5	80	200	93
6	100	200	94
7	120	200	94
8	80	150	95
9	80	100	93
10	80	50	91
11	80	25	92
12	**80**	**15**	**92**
13	80	10	83
14	80	5	80
15	80	1	71

[a] All reactions were conducted with the 4-chlorobenzaldehyde **c** (1 mmol), 2-naphthol **2** (1 mmol), malonitrile (1 mmol) and basic nanomagnetic catalyst in solvent-free conditions.
[b] The time of all reactions is 1 h.
[c] Isolated yields.

Table 2 Synthesis of naphthopyrane derivatives (**1–18**) produced via Scheme 1[a]



Entry	X	A/B	Product	Time (min) / Yield (%)[b]	M.p. (lit.)[ref.]
a	H	**A**	**1**	25/88	205–208 (207–210)[10]
		B	**2**	25/89	276–279 (278–279)[19]
b	2-Cl	**A**	**3**	20/87	235–238 (236–237)[10]
		B	**4**	20/90	265–268 (265–267)[19]
c	4-Cl	**A**	**5**	15/93	230–232 (231–232)[10]
		B	**6**	15/92	209–211 (210–211)[19]
d	2,4-Cl	**A**	**7**	12/94	222–225 (222–224)[10]
		B	**8**	15/94	236–239 (239–240)[19]
e	4-NO_2	**A**	**9**	20/92	230–233 (231–234)[10]
		B	**10**	15/90	185–188 (185–186)[19]
f	3,4-OMe	**A**	**11**	16/90	187–190
		B	**12**	18/88	198–201
g	3,4,5-OMe	**A**	**13**	22/91	140–144
		B	**14**	25/92	184–186
h	4-Me	**A**	**15**	40/84	204–206 (205–206)[10]
		B	**16**	40/82	252–255 (253–254)[11]
i	4-OMe	**A**	**17**	60/80	180–183 (182–184)[22]
		B	**18**	70/79	192–195 (194)[19]

[a] All reactions were conducted with the arylaldehyde **a–i** (1 mmol), naphthol **A** or **B** (1 mmol), malonitrile (1 mmol), and nanomagnetic catalyst (20 mg) in solvent-free conditions at 80 °C.
[b] Yield of isolated product afther recrystalisation.

3-Amino-1-(3,4,5-trimethoxyphenyl)-1H-benzo[f] chromene-2-carbonitrile (**14**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.7 (s, 6H), 3.8 (s, 3H), 4.7 (br, 2H), 5.2 (s, 1H), 6.4 (s, 2H), 7.2–7.3 (m, 1H), 7.4–7.5 (m, 2H), 7.7–7.8 (m, 1H), 7.8–7.9 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 39.1, 44.9, 56.1, 60.8, 61.9, 104.2, 114.7, 116.6, 120.1, 123.8, 125.2, 127.3, 128.5, 129.8, 130.9, 131.3, 136.8, 140.2, 147.2, 153.5, 158.8 ppm; FT-IR (KBr, cm^{-1}): 3454 (N–H), 3328 (N–H), 3062, 2936, 2189 (CN), 1659; Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.15; H, 5.14; N, 7.18%.

Conclusion

In conclusion, we have developed a simple, efficient, and green methodology for the synthesis of naphthopyranes using MNPs under solvent-free conditions. The simple experimental procedure, solvent-free reaction conditions, good yields, short time reaction and utilisation of an efficient, easily recoverable and reusable catalyst are the advantages of the present method.

We thank the Sistan and Baluchestan University Research Council for partial support of this work.

Received 20 November 2011; accepted 9 January 2012
Paper 1100994 doi: 10.3184/174751912X13264750348839
Published online: 31 January 2012

References

1 J. Zhu and H. Bienayme, *Multicomponent reactions*, Wiley-VCH, Weinheim, Germany, 2005.
2 B.M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259.
3 A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168.
4 B.B.Tourè and D.G. Hall, *Chem. Rev*., 2009, **109**, 4439.
5 E.A.A. Hafez, M.H. Elnagdi, A.G.A. Elagemey and F.M.A.A. El-Taweel, *Heterocycles*, 1987, **26**, 903.
6 M. Kidwai, S. Saxena, M.K.R. Khan and S.S. Thukral, *Bioorg. Med. Chem. Lett*., 2005, **15**, 4295.
7 L. Bonsignore, G. Loy, D. Secci and A. Calignano, *Eur. J. Med. Chem.*, 1993, **28**, 517.
8 G.P. Ellis, *Chromanes and chromones*, eds, A. Weissberger and E.C. Taylor, Wiley, New York, 1997, chap. II, p.11.
9 R. Ballini, G. Bosica, M.L. Conforti, R. Maggi, A. Mazzacanni, P. Righi and G. Sartori, *Tetrahedron*, 2001, **57**, 1395.
10 T.S. Jin, J.C. Xiao, S.J. Wang, T.S. Li and X.R. Song, *Synlett*, 2003, 2001.
11 T.S. Jin, J.C. Xiao, S.J. Wang and T.S. Li, *Ultrason Sonochem.*, 2004, **11**, 393.
12 D.Q. Shi, S. Zhang, Q.Y. Zhuang and X.S. Wang, *Chin. J. Org. Chem.*, 2003, **23**, 1419.
13 B.S. Kumar, N. Srinivasulu, R.H. Udupi, B. Rajitha, Y.T. Reddy, P.N. Reddy and P.S. Kumar, *J. Heterocycl. Chem*., 2006, **43**, 1691.
14 M. Kidwai, S. Saxena, M.K. Rahman Khan and S.S. Thukral, *Bioorg. Med. Chem. Lett*., 2005, **15**, 4295.
15 A. Shaabani, R. Ghadari, S. Ghasemi, M. Pedarpour, A.H. Rezayan, A. Sarvary and S. Weng Ng, *J. Comb. Chem*., 2009, **11**, 956.
16 G. Shanthi and P.T. Perumal, *Tetrahedron Lett*., 2007, **48**, 6785.
17 Y. Ren and C. Cai, *Catal. Commun*., 2008, **9**, 1017.
18 M.M. Heravi, K. Bakhtiari, V. Zadsirjan, F.F. Bamoharram and O.M. Heravi, *Bioorg. Med. Chem. Lett*., 2007, **17**, 4262.
19 X.-S. Wang, G.-S. Yang and G. Zhao, *Tetrahedron: Asymm*., 2008, **19**, 709.
20 D. Kumar, V.B. Reddy, B.G. Mishra, R.K. Rana, M.N. Nadagaouda and R.S. Varma, *Tetrahedron*, 2007, **63**, 3093.
21 M.P. Surpur, S. Kshirsagar and S.D. Samant, *Tetrahedron Lett*., 2009, **50**, 719.
22 A. Solhy, A. Elmakssoudi, R. Tahir, M. Karkouri, M. Larzek, M. Bousmina and M. Zahouily, *Green Chem*., 2010, **12**, 2261.
23 A.H. Lu, E.L. Salabas and F. Schuth, *Angew. Chem. Int. Ed.* 2007, **46**, 1222.
24 B. Hu, J. Pan, H.L. Yu, J.W. Liu and J.H. Xu, *Process Biochem.* 2009, **44**, 1019.
25 S.C. Tsang, V. Caps, I. Paraskevas, D. Chadwick and D. Thompsett, *Angew. Chem. Int. Ed.*, 2004, **43**, 5645.
26 M.Z. Kassaee, H. Masrouri and F. Movahedi, *Appl. Cat. A: Gen.*, 2011, **395**, 28.
27 M. Ma, Y. Zhang, W. Yu, H. Shen, H. Zhang and N. Gu, *Colloid Surf. A*, 2003, **212**, 219.
28 H. Cao, J. He, L. Deng and X. Gao, *Appl. Surf. Sci.*, 2009, **255**, 7974.
29 H.R. Shaterian and H. Yarahmadi, *Tetrahedron Lett*., 2008, **49**, 1297.
30 H.R. Shaterian, H. Yarahmadi and M. Ghashang, *Tetrahedron*, 2008, **64**, 1263.
31 H.R. Shaterian, H. Yarahmadi and M. Ghashang, *Bioorg. Med. Chem. Lett*, 2008, **18**, 788.
32 H.R. Shaterian and H. Yarahmadi, *Arkivoc*, 2008, **ii**, 105.
33 H.R. Shaterian, H. Yarahmadi and M. Ghashang, *Arkivoc*, 2007, **xvi**, 298.
34 H. Yarahmadi and H.R. Shaterian, *J. Chem. Res.*, 2012, **36**, 52–55.