

Regioselective Synthesis of Fused Azo-linked
Pyrazolo[4,3-*e*]pyridines Using Nano-Fe₃O₄Nikpassand, Mohammad^{*,a} Zare, Leila^b Shafaati, Tamila^a Shariati, Shahab^a^a Department of Chemistry, Rasht Branch, Islamic Azad University, Rasht, Iran^b Department of Chemistry, Payame Noor University, PO Box 19395-3697 Tehran, Iran

A multicomponent reaction for the synthesis of fused azo-linked pyrazolo[4,3-*e*]pyridines from 3-amino-5-methylpyrazole, indan-1,3-dione and synthesized azo-linked aldehydes using nano-Fe₃O₄ as an effective and reusable catalyst is reported. The present methodology offers several advantages, such as a simple procedure with an easy work-up, short reaction times, high yields, and the absence of any volatile and hazardous organic solvents.

Keywords multicomponent, pyrazolo[4,3-*e*]pyridines, 3-amino-5-methylpyrazole, indan-1,3-dione

Introduction

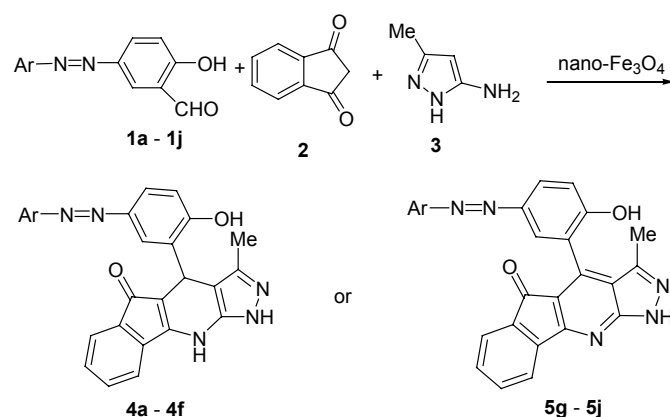
Pyrazolopyridines have received more and more attention in the recent years. Pharmaceutical researches of this kind of compounds have been reported, such as a potent cyclin dependent kinase 1 (CDK1) inhibitor,^[1] HIV reverse transcriptase inhibitors,^[2] CCR1 antagonists,^[3] protein kinase inhibitors^[4] and inhibitors of cGMP degradation, together with several herbicidal and fungicidal activities.^[5] Some derivatives exhibit potential antimalarial^[6] and antiviral properties.^[7,8] Others show intense fluorescence in the bluegreen region and have been considered for applications as fluorescence standards and luminophores in organic light emitting experimental diodes.^[9] Numerous methods for the synthesis of pyrazolopyridines in the last twenty years have been reported with respect to their different structures.^[10]

The main disadvantages of most of these procedures are harsh reaction condition, tedious workup, low yield, high reaction time, multi-step reaction, use of large quantity of volatile organic solvents and low regioselectivity. Due to these problems, development of an efficient and versatile method for the preparation of novel derivatives of pyrazolopyridines is an important aspect and there is a scope for the further improvement towards milder reaction conditions, improved yields and green procedure.

Recent development in the pyrazolopyridines chemistry and our continued interest in the development of efficient and environmentally friendly procedure for the synthesis of pharmaceutical compound^[11-14] triggered us to describe here an efficient method for the regioselective synthesis of new derivatives of pyrazolopyridines

through multicomponent reactions of 3-amino-5-methylpyrazole, azo-linked aldehydes and active methylene compounds using nano-Fe₃O₄ (Scheme 1).

Scheme 1 Multicomponent synthesis of pyrazolopyridine



Experimental

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzu IR-470 spectrometer. ¹H NMR spectra were recorded on a 500 MHz Bruker DRX-500 and ¹³C NMR spectra were recorded on a 250 MHz Bruker DRX-500 in DMSO-*d*₆ as solvent. Chemicals were purchased from Merck and Fluka. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyser and agreed with the calculated values. All solvents used were dried and distilled according to standard procedures.

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Received July 29, 2011; accepted September 14, 2011.

General procedure for the synthesis of azo linked pyrazolopyridines using nano-Fe₃O₄

A solution of 3-amino-5-methylpyrazole **3** (1 mmol, 0.097 g), indan-1,3-dione **2** (1 mmol, 0.146 g), synthesized aldehyde **1** (1 mmol) and 0.05 g nano-Fe₃O₄ in H₂O (10 mL) was refluxed for the required reaction times (Table 4). The progress of the reaction was monitored by TLC (EtOAc : petroleum ether, 1 : 4). After completion of the reaction, the mixture was filtered in the presence of an efficient magnetic bar. The crude product was recrystallized from ethanol to produce pyrazolopyridine derivatives **4a–4f** and **5g–5i** as pure crystalline product.

4-(2-Hydroxy-5-((4-iodophenyl)diazenyl)phenyl)-3-methyl-4,10-dihydroindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)-one (4a) Red solid, decomposition 190 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ: 1.9 (s, 3H), 5.3 (s, 1H), 6.97 (d, *J*=8.5 Hz, 1H), 7.17 (d, *J*=6.8 Hz, 1H), 7.30 (t, *J*=7.3 Hz, 1H), 7.39 (t, *J*=7.3 Hz, 1H), 7.50 (d, *J*=8.2 Hz, 2H), 7.54 (s, 1H), 7.58 (d, *J*=8.5 Hz, 1H), 7.67 (d, *J*=7.1 Hz, 1H), 7.81 (d, *J*=8.2 Hz, 2H), 10.4 (s, 1H), 11.2 (s, 1H), 12.06 (s, 1H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ: 10.17, 56.30, 98.01, 105.37, 105.79, 116.91, 120.41 (two carbons), 122.45, 124.89, 126.32, 130.90, 131.83 (two carbons), 135.89, 137.11, 138.96, 139.56, 146.17, 148.03, 152.31, 158.63, 158.73, 190.23; FT-IR (KBr) ν: 3450, 3193, 3056, 2896, 1695, 1660, 1614, 1554, 1485, 1433, 1280, 1080 cm⁻¹. Anal. calcd for C₂₆H₁₈IN₅O₂: C 55.83, H 3.24, N 12.52; found C 55.72, H 3.47, N 12.40.

4-(2-Hydroxy-5-((4-nitrophenyl)diazenyl)phenyl)-3-methyl-4,10-dihydroindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)-one (4b) Red solid, decomposition 245 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ: 1.9 (s, 3H), 5.3 (s, 1H), 7.00 (d, *J*=8.2 Hz, 1H), 7.17 (d, *J*=6.4 Hz, 1H), 7.30 (t, *J*=7.1 Hz, 1H), 7.39 (t, *J*=7.0 Hz, 1H), 7.62 (s, 1H), 7.67 (t, *J*=7.6 Hz, 2H), 7.90 (d, *J*=8.2 Hz, 2H), 8.28 (d, *J*=8.2 Hz, 2H), 10.6 (s, 1H), 11.2 (s, 1H), 12.06 (s, 1H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ: 10.16, 56.23, 105.27, 105.67, 117.05, 119.82, 120.42, 123.28, 123.86, 125.67, 126.95, 130.91, 131.83, 135.87, 136.07, 137.11, 137.44, 146.45, 148.02, 148.46, 156.44, 158.64, 159.81, 190.19; FT-IR (KBr) ν: 3407, 3191, 3058, 2896, 1649, 1612, 1550, 1487, 1427, 1338, 1234, 1188, 1139 cm⁻¹. Anal. calcd for C₂₆H₁₈N₆O₄: C 65.27, H 3.79, N 17.56; found C 65.52, H 3.67, N 17.85.

4-(2-Hydroxy-5-((2-methyl-4-nitrophenyl)diazenyl)phenyl)-3-methyl-4,10-dihydroindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)-one (4c) Red solid, decomposition 221 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ: 1.9 (s, 3H), 2.5 (s, 3H), 5.3 (s, 1H), 6.98 (d, *J*=8.3 Hz, 1H), 7.17 (d, *J*=7.0 Hz, 1H), 7.30 (t, *J*=7.4 Hz, 1H), 7.39 (t, *J*=7.3 Hz, 1H), 7.56 (d, *J*=8.8 Hz, 1H), 7.61 (d, *J*=2.4 Hz, 1H), 7.63 (s, 1H), 7.67 (d, *J*=7.2 Hz, 1H), 8.01 (dd, *J*=2.3, 8.9 Hz, 1H), 8.20 (d, *J*=2.1 Hz, 1H), 10.6 (s, 1H), 11.2 (s, 1H), 12.06 (s, 1H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ: 10.20, 17.70, 56.07, 105.31, 105.75, 117.16, 117.46, 119.78, 120.40 (two

carbons), 121.64, 122.86, 126.94, 128.49, 130.90, 131.83, 135.90, 137.06, 137.44, 138.12, 138.60, 148.04, 148.26, 154.56, 158.71, 159.44, 190.23; FT-IR (KBr) ν: 3398, 3064, 2925, 1712, 1668, 1614, 1554, 1512, 1427, 1361, 1224, 1087 cm⁻¹. Anal. calcd for C₂₇H₂₀N₆O₄: C 65.85, H 4.09, N 17.06; found C 65.58, H 4.09, N 17.45.

4-(2-Hydroxy-5-((2-chlorophenyl)diazenyl)phenyl)-3-methyl-4,10-dihydroindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)-one (4d) Dark brown solid, decomposition 200 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ: 1.9 (s, 3H), 5.3 (s, 1H), 6.98 (d, *J*=9.0 Hz, 1H), 7.18 (d, *J*=6.9 Hz, 1H), 7.29–7.33 (m, 1H), 7.36 (d, *J*=7.6 Hz, 1H), 7.38–7.44 (m, 2H), 7.54 (d, *J*=7.7 Hz, 1H), 7.59 (d, *J*=5.7 Hz, 3H), 7.67 (d, *J*=7.1 Hz, 1H), 10.5 (s, 1H), 11.2 (s, 1H), 12.06 (s, 1H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ: 10.20, 56.01, 105.37, 105.79, 117.00, 118.41, 119.76, 120.40, 122.03, 127.36, 128.75, 129.54, 130.89, 131.31, 131.83, 132.30, 133.88, 135.91, 137.06, 137.47, 138.56, 146.71, 148.03, 148.85, 158.70, 190.23; FT-IR (KBr) ν: 3384, 3255, 2927, 1728, 1660, 1614, 1548, 1496, 1465, 1280, 1062 cm⁻¹. Anal. calcd for C₂₆H₁₈ClN₅O₂: C 66.74, H 3.88, N 14.97; found C 66.73, H 3.46, N 14.71.

4-(2-Hydroxy-5-((3-chlorophenyl)diazenyl)phenyl)-3-methyl-4,10-dihydroindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)-one (4e) Brown solid, decomposition 125 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ: 2.06 (s, 3H), 5.2 (s, 1H), 7.20 (d, *J*=8.7 Hz, 1H), 7.46–7.52 (m, 3H), 7.56 (d, *J*=7.1 Hz, 1H), 7.67 (t, *J*=7.3 Hz, 1H), 7.75 (br, 2H), 7.88 (br, 2H), 7.95 (dd, *J*=2.2, 8.7 Hz, 1H), 10.5 (br, 1H), 11.2 (br, 1H), 13.8 (s, 1H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ: 12.28, 56.94, 91.30, 114.04, 117.06, 120.28, 121.45, 121.78, 122.17, 122.91, 123.92, 126.16, 127.77, 130.86, 131.82, 132.45, 134.91, 135.99, 137.71, 141.19, 141.74, 142.85, 145.30, 153.86, 159.70, 164.70, 190.15; FT-IR (KBr) ν: 3332, 3215, 2925, 1704, 1600, 1568, 1452, 1292, 1085 cm⁻¹. Anal. calcd for C₂₆H₁₈ClN₅O₂: C 66.74, H 3.88, N 14.97; found C 66.79, H 3.44, N 14.96.

4-(2-Hydroxy-5-((4-chlorophenyl)diazenyl)phenyl)-3-methyl-4,10-dihydroindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)-one (4f) Dark yellow solid, decomposition 185 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ: 2.0 (s, 3H), 5.1 (s, 1H), 7.21 (d, *J*=8.7 Hz, 1H), 7.54 (t, *J*=7.2 Hz, 1H), 7.58 (d, *J*=5.7 Hz, 1H), 7.60 (d, *J*=8.7 Hz, 2H), 7.73 (t, *J*=7.4 Hz, 1H), 7.82 (d, *J*=8.7 Hz, 2H), 7.84 (d, *J*=2.4 Hz, 1H), 7.92 (d, *J*=7.4 Hz, 1H), 7.97 (dd, *J*=2.4, 8.7 Hz, 1H), 10.8 (s, 1H), 13.7 (s, 1H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ: 12.29, 56.90, 91.23, 117.07, 120.30, 121.83, 122.15, 124.00, 124.67, 125.83, 126.65, 130.31, 132.57, 135.89, 136.13, 137.73, 139.20, 142.85, 145.36, 151.48, 152.15, 159.32, 164.73, 190.18; FT-IR (KBr) ν: 3350, 3213, 2925, 1706, 1641, 1566, 1496, 1427, 1292, 1085 cm⁻¹. Anal. calcd for C₂₆H₁₈ClN₅O₂: C 66.74, H 3.88, N 14.97; found C 66.57, H 3.82, N 14.43.

4-(2-Hydroxy-5-(phenyldiazenyl)phenyl)-3-methylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)-one

(5g) Red solid, decomposition 305 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ : 2.02 (s, 3H), 7.20 (d, $J=8.7$ Hz, 1H), 7.46 (d, $J=7.1$ Hz, 1H), 7.52 (t, $J=7.5$ Hz, 3H), 7.57 (d, $J=7.2$ Hz, 1H), 7.69 (t, $J=7.4$ Hz, 1H), 7.80 (d, $J=7.6$ Hz, 2H), 7.85 (d, $J=2.2$ Hz, 1H), 7.91 (d, $J=7.4$ Hz, 1H), 7.97 (dd, $J=2.3$, 8.7 Hz, 1H), 10.6 (s, 1H), 13.7 (s, 1H); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ : 14.46, 114.00, 117.00, 120.34, 121.81, 122.07, 123.03, 123.97, 125.72, 126.46, 130.17, 131.48, 132.52, 136.06, 137.73, 141.90, 142.86, 145.24, 145.52, 152.89, 155.49, 158.94, 164.75, 190.19; FT-IR (KBr) ν : 3450, 3195, 2995, 1704, 1660, 1564, 1487, 1431, 1315, 1153 cm^{-1} . Anal. calcd for $\text{C}_{26}\text{H}_{17}\text{N}_5\text{O}_2$: C 72.38, H 3.97, N 16.23; found C 72.17, H 3.45, N 16.83.

4-(2-Hydroxy-5-(*p*-tolylidiazonyl)phenyl)-3-methylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (5h) Drown solid, decomposition 260 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ : 2.01 (s, 3H), 2.35 (s, 3H), 7.18 (d, $J=8.7$ Hz, 1H), 7.31 (d, $J=8.1$ Hz, 2H), 7.50 (t, $J=7.6$ Hz, 1H), 7.53 (d, $J=7.3$ Hz, 1H), 7.70 (d, $J=8.1$ Hz, 3H), 7.92 (t, $J=7.8$ Hz, 2H), 10.5 (s, 1H), 11.5 (br, 1H), 13.7 (s, 1H); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ : 14.37, 21.81, 114.00, 114.90, 116.97, 120.31, 121.81, 122.01, 123.03, 123.97, 125.49, 126.00, 126.27, 130.69, 132.54, 136.09, 137.74, 141.57, 142.00, 142.87, 145.47, 150.95, 158.70, 164.74, 190.18; FT-IR (KBr) ν : 3452, 1708, 1647, 1554, 1427, 1298 cm^{-1} . Anal. calcd for $\text{C}_{27}\text{H}_{19}\text{N}_5\text{O}_2$: C 72.80, H 4.30, N 15.72; found C 72.55, H 4.47, N 15.15.

4-(2-Hydroxy-5-((4-methoxyphenyl)diazonyl)-phenyl)-3-methylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (5i) Brown solid, decomposition 163 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ : 2.01 (s, 3H), 3.8 (s, 3H), 7.03 (d, $J=8.05$ Hz, 2H), 7.16 (d, $J=8.35$ Hz, 1H), 7.50 (d, $J=6.77$ Hz, 1H), 7.56 (d, $J=6.52$ Hz, 1H), 7.68 (br, 1H), 7.79 (br, 3H), 7.89 (d, $J=7.07$ Hz, 2H), 10.47 (s, 1H), 13.71 (s, 1H); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ : 25.96, 67.86, 114.00, 115.29, 116.90, 120.31, 121.78, 121.97, 123.93, 124.85, 125.23, 126.02, 132.47, 132.80, 136.02, 137.74, 142.30, 142.87, 145.20, 145.53, 147.05, 158.26, 162.17, 164.74, 190.17; FT-IR (KBr) ν : 3191, 3110, 2935, 1706, 1593, 1568, 1498, 1460, 1253 cm^{-1} . Anal. calcd for $\text{C}_{27}\text{H}_{19}\text{N}_5\text{O}_3$: C 70.27, H 4.15, N 15.18; found C 70.52, H 4.74, N 15.49.

Results and Discussion

Initially, the condensation reaction of 2-hydroxy-5-(phenyldiazonyl)benzaldehyde (**1g**), indan-1,3-dione (**2**) and 3-methyl-5-aminopyrazole (**3**) (i) in a catalyst free reaction and (ii) in the presence of Fe_3O_4 and (iii) in the presence of nano- Fe_3O_4 was done and the results are listed in Table 1.

As depicted, nano- Fe_3O_4 proved to be better catalyst than Fe_3O_4 for the synthesis of pyrazolopyridines. With the best catalyst in hand, we moved to study the effects of catalyst amount on the model reaction and the results are listed in Table 1. 50 mg of nano- Fe_3O_4 is sufficient

Table 1 Effect of amount of nano- Fe_3O_4 on synthesizing **5g**

Entry	Catalyst	Catalyst amount	Time/min	Yield ^a /%
1	—	—	240	70
2	Fe_3O_4	0.05 g	60	77
3	Nano- Fe_3O_4	0.05 g	2	86
4	Nano- Fe_3O_4	0.01 g	15	81
5	Nano- Fe_3O_4	0.03 g	10	86
6	Nano- Fe_3O_4	0.1 g	2	87

^a Isolated yield.

to push the reaction forward completion and 10 or 30 mg of catalyst was not enough. Higher amount of catalyst did not lead to significant change in the reaction yields.

Furthermore, the reaction was carried out in different solvents. As shown in Table 2, the yields of the reaction in H_2O were greater and the reaction times were generally shorter than the conventional methods.

Table 2 Synthesis of pyrazolopyridine **5g** in the presence of nano- Fe_3O_4 (0.05 g) in different solvents

Entry	Solvent	Time/min	Yield ^a /%
1	MeOH	25	66
2	EtOH	15	78
3	CH_3CN	35	56
4	toluene	75	53
5	H_2O	2	86

^a Isolated yields.

The same model reaction in the presence of 0.05 g of the catalyst was carried out at different temperatures in H_2O to assess the effect of temperatures on the reaction yield. It was observed that yield is a function of temperature since the yield was increased as the reaction temperature was raised (Table 3).

Table 3 Synthesis of pyrazolopyridine **5g** in the presence of nano- Fe_3O_4 (0.05 g) at different temperatures in water

Entry	Temperature	Time/min	Yield ^a /%
1	r.t.	45	75
2	60	10	79
3	100	2	86

^a Isolated yield.

With the best optimized condition in hand, we were interested in synthesis of several pyrazolopyridines refluxing at 100 °C using nano- Fe_3O_4 in H_2O . The results are summarized in Table 4.

It is important to point out the fact that when 3-amino-5-methylpyrazole (**3**), indan-1,3-dione (**2**) and azo-linked benzaldehyde containing electron releasing substituents **1g**—**1i** were refluxed for required reaction time, the reaction leads to the formation of the aromatized pyrazolopyridine **5**, which were isolated and char-

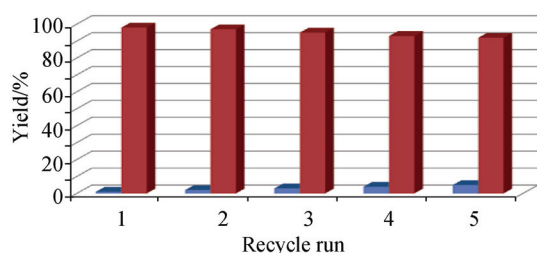
Table 4 Synthesis of pyrazolopyridine using catalytic amount of nano-Fe₃O₄

Entry	Product	Ar	Time/min	Yield/%
1	4a	4-I-C ₆ H ₄ -	5	75
2	4b	4-NO ₂ -C ₆ H ₄	8	83
3	4c	2-Me-4-NO ₂ -C ₆ H ₃ -8		75
4	4d	2-Cl-C ₆ H ₄ -	5	83
5	4e	3-Cl-C ₆ H ₄ -	5	95
6	4f	4-Cl-C ₆ H ₄ -	5	84
7	5g	C ₆ H ₅ -	2	86
8	5h	4-Me-C ₆ H ₄ -	1	79
9	5i	4-MeO-C ₆ H ₄ -	1	87

acterized, but in the case of using azo-linked aldehydes containing electron withdrawing substituents **1a–1f**, just pyrazolopyridine **4** were observed.

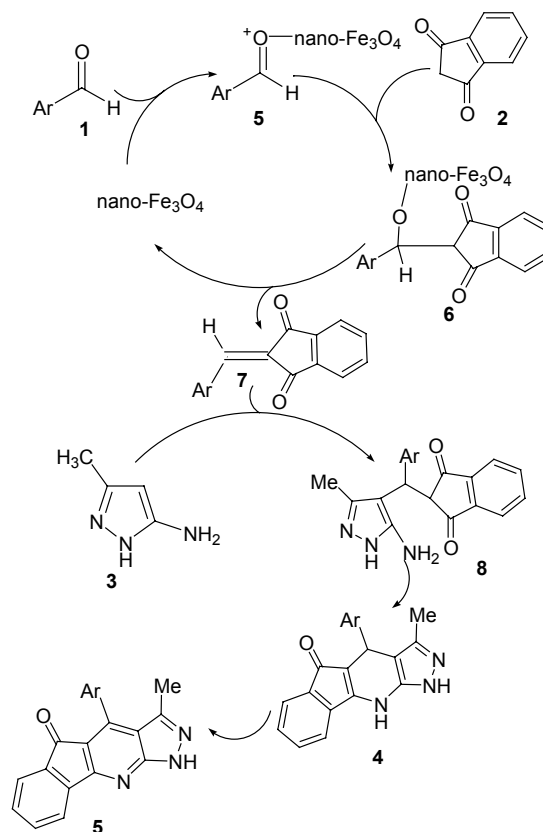
All of compounds summarized in Table 1 were characterized by spectroscopic methods (IR, ¹H NMR, ¹³C NMR) and elemental analysis. In the ¹H NMR spectra of azo-linked pyrazolopyridines **4a–4f**, benzylic C-H proton resonated at δ 5.1–5.3 and in their ¹³C NMR spectra, the benzylic C—H carbon resonated at δ 56.

Apart from the simplicity of the process and its excellent results, the simplicity of product isolation, replacement of carcinogenic solvent with H₂O and the possibility to recycle nano-Fe₃O₄ offer a significant advantage. After the reaction was completed, the catalyst could be easily attracted by an efficient magnetic bar. After further treatments including washing with CHCl₃ and activation at 80 °C, the recycled catalyst has been examined in next run. Studies on the synthesis of **5g** as a model substrate showed that the recovered catalyst could be successively recycled in subsequent reactions without any decrease of yields (Figure 1).

**Figure 1** Reusability of nano-Fe₃O₄ in the synthesis of **5g**.

We propose a possible mechanism for the nano-Fe₃O₄ catalyzed synthesis of fused pyrazolopyridine derivatives (Scheme 2). We suggest that, nano-Fe₃O₄ catalyzes the formation of iminium ion **5** in a reversible reaction with the aldehyde **1**. The higher reactivity of the iminium ion compared to the carbonyl species could facilitate Knoevenagel condensation between aldehyde **1** and indandione **2**, via intermediate **6** and after the elimination of nano-Fe₃O₄, **7** might be

produced as an intermediate. The addition of **7** to 3-amino-5-methyl-pyrazole (**3**) then could furnish the intermediate product **8**, which upon intermolecular cyclization and dehydration would give rise to **4**. Compounds **4** were oxidized to aromatized pyrazolopyridine **5** with electron donating substituted aldehydes.

Scheme 2 Proposed mechanism for the synthesis of pyrazolopyridine

Conclusions

In conclusion, this one-pot three component protocol using nano-Fe₃O₄ in water provides a regioselective, fast and practical method for the preparation of fused pyrazolo pyridines from 5-amino-3-methylpyrazole, indan-1,3-dione and various azo-linked aldehydes in short reaction times and excellent yields. The simplicity, high atom economy, easy execution and work up, productivity, together with the use of inexpensive material and environmentally friendly procedure are the remarkable features of this procedure.

Acknowledgements

We thank the Research Committee of Islamic Azad University of Rasht Branch for partial support given to this study.

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