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An easy and efficient protocol for the condensation reaction of isatin and *N*-substituted isatins with 1,2-diaminobenzene using low cost reusable clay catalyst

Abstract: A green procedure was developed for the condensation of isatin and *N*-substituted isatins with 1,2-diaminobenzene by using reusable bentonite clay in EtOH/H_2O solvent system, under microwave irradiation. This eco-friendly synthesis is characterized by high yields and short reaction times. The catalyst is easily recycled.

Keywords: bentonite clay; microwave irradiation; *N*-substituted isatins; quinoxaline derivatives; spiroindoles.

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Introduction

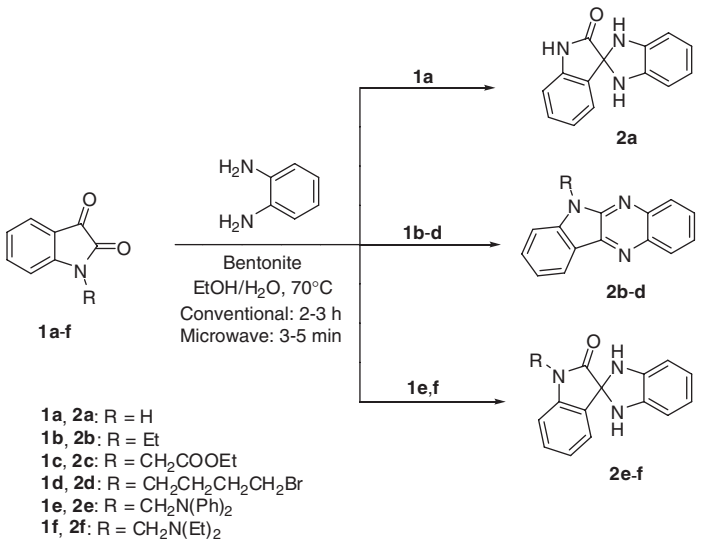
One of the major current challenges is to develop synthetic methods that are less polluting. In particular, the field of heterogeneous catalysis has captivated the interest of researchers due to an increasing demand for more environmentally acceptable processes in the chemical industry [1, 2]. In recent years, the use of solid acid catalyst such as clays, ion-exchange resins and zeolites has received considerable attention in different areas of organic synthesis [3–6]. The chemistry of spiroindoles and quinoxalines has received considerable attention due to their synthetic and biological importance [7, 8]. Such compounds often exhibit potent antiviral and antibacterial [9–12] properties. Although clay has been used as a catalyst in many reactions [13, 14], there is no report of the use of bentonite clay as a catalyst for condensation reaction of isatin and *N*-substituted isatin derivatives with 1,2-diaminobenzene.

Results and discussion

We describe herein a simple and efficient protocol for the condensation reaction of isatin and *N*-substituted isatins with 1,2-diaminobenzene using bentonite clay catalyst in EtOH/H_2O solvent system under conventional and microwave irradiation methods. Spiroindoles and quinoxaline derivatives **2a–f** were synthesized by condensation of **1a–f** [15] with equimolar amount of **2** using bentonite clay in EtOH/H_2O solvent system, under conventional and microwave irradiation methods (Scheme 1).

To optimize the conditions, various parameters such as catalyst amount (10–40 mol%), solvents and solvent systems were investigated in detail by taking condensation reaction between **1a** and **2** as a reference reaction. The best result was obtained for the reaction conducted in EtOH/H_2O (3:1) in the presence of 20 mol% bentonite clay.

Under the optimized conditions, compounds **2a–f** were synthesized in yields of 74–81% by conventional method after 2–3 h. The use of microwave irradiation resulted in higher yields of 86–94% and shortening of the reaction time to 3–5 min. The reaction of **1a** with **2** and analogous reactions have been studied previously [16–19]. Niume et al. [16] have reported that the reaction between isatin and 1,2-diaminobenzene is solvent-dependent. Recently, Alsubari et al. [19] have also reported that treatment of *N*-substituted isatin with 1,2-diaminobenzene produces a quinoxaline product. In our hands, the reaction of **1a** with **2** gave a spiroindole derivative **2a** as sole product by using bentonite clay in EtOH/H_2O solvent system, under both conventional and microwave irradiation methods. When **1b–d** was allowed to react with **2**, the sole product formed was quinoxaline derivatives **2b–d**. However, when **1e** or **1f** was treated with **2**, the expected quinoxaline product was not formed. Instead, the spiroindole derivatives **2e** and **2f** were the sole products. The structures of all isolated products were fully confirmed by elemental and spectroscopic analysis.



Scheme 1

In this reaction, bentonite clay can be reused several times without any appreciable loss in activity. For example, in the reaction of **1a** with **2** no significant loss of product yield (92–88%) was observed when bentonite clay was used after four times of recycling.

Conclusion

The advantages of the developed method are mild reaction conditions, simple isolation procedures, high yields, short reaction times and the reusability of the bentonite clay catalyst.

Experimental

General

All chemicals were procured from Aldrich, USA and E. Merck, Germany and used as such. TLC was carried out on silica gel (HF_{254}, 200 mesh) eluting with ethyl acetate/chloroform (11:9). IR spectra were recorded in KBr pellets on a PerkinElmer FT/IR spectrometer. NMR spectra were run on a JEOL AL 300 spectrometer operating at 300 MHz. Elemental analysis was performed on an Exeter Analytical Model CE-440 CHN analyzer. Melting points were measured in open capillaries and are uncorrected. The microwave assisted reactions were carried out in a MAS-II, Microwave Synthesis System manufactured by Sineo Microwave Chemistry Technology, Ltd, having an output energy range of 0–1000 W.

General procedure for the synthesis of compounds 2a–e

Conventional method 1,2-Diaminobenzene (0.001 mol) was added to a mixture of isatin or *N*-substituted isatins (**1a–f**, 0.001 mol), bentonite clay (20 mol%) and EtOH/H_2O (v/v, 3:1, 20 mL). The reaction mixture was stirred at 70°C for 2–3 h. The progress of the reaction was monitored by TLC. The catalyst was filtered, washed with ethyl acetate and dried. The filtrate was concentrated under reduced pressure, and the residue was crystallized from ethanol.

Microwave irradiation method The mixture, prepared as described above, was stirred at 70°C for 3–5 min under microwave irradiation of 500 W. Workup was conducted as described above.

1,3-Dihydrospiro[benzo[*d*]imidazole-2,3′-indolin]-2′-one (2a) Brown-yellow solid; yield 92%; mp 232°C; ^{1}H NMR (DMSO-d_6): δ 12.02 (s, 1H, NH), 8.35–6.53 (m, 8H, Ar-H), 6.43 [s, 1H (D_2O exchangeable), NH]: IR: ν_{max} 3192, 3090, 3019, 1703, 1614, 1598, 1484, 1339, 718, 671 cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_3O$ (237.26): C, 70.87; H, 4.67; N, 17.71; O, 6.74. Found: C, 70.85; H, 4.68; N, 17.72; O, 6.74.

6-Ethyl-6*H*-indolo[2,3-*b*]quinoxaline (2b) Yellow solid; yield 89%; mp 180°C; ^{1}H NMR ($CDCl_3$): δ 8.49–7.35 (m, 8H, Ar-H), 4.56 (q, 2H, J = 7 Hz, CH_2), 1.52 (t, 3H, J = 7 Hz, CH_3); IR: ν_{max} 2962, 2853, 1660, 1611, 1567, 1482, 1427, 1378, 1331, 757, 738 cm^{-1}. Anal. Calcd for $C_{16}H_{13}N_3$ (247.29): C, 77.71; H, 5.30; N, 16.99. Found: C, 77.73; H, 5.29; N, 16.98.

Ethyl 2-(6*H*-indolo[2,3-*b*]quinoxaline-6-yl)acetate (2c) Yellow solid; yield 91%; mp 160°C; ^{1}H NMR ($CDCl_3$): δ 8.50–7.34 (m, 8H, Ar-H), 5.24 (s, 2H, CH_2), 4.24 (q, 2H, J = 7 Hz, CH_2), 1.28 (t, 3H, J = 7 Hz, CH_3): IR: ν_{max} 2976, 2927, 1734, 1663, 1606, 1565, 1474, 1375, 1203, 760, 743 cm^{-1}. Anal. Calcd for $C_{18}H_{15}N_3O_2$ (305.33): C, 70.81; H, 4.95; N, 13.76; O, 10.48. Found: C, 70.80; H, 4.96; N, 13.75; O, 10.49.

6-(4-Bromobutyl)-6*H*-indolo[2,3-*b*]quinoxaline (2d) Yellow solid; yield 94%; mp 184°C; ^{1}H NMR ($CDCl_3$): δ 8.53–7.38 (m, 8H, Ar-H), 4.42 (t, 2H, *J* = 7 Hz, CH_2), 3.38 (t, 2H, *J* = 7 Hz, CH_2), 2.02 (m, 2H, CH_2), 1.82 (m, 2H, CH_2): IR: ν_{max} 3050, 2930, 1660, 1493, 1485, 1450, 1400, 1330, 1192, 1130, 751, 741 cm^{-1}. Anal. Calcd for $C_{18}H_{16}BrN_3$ (354.24): C, 61.03; H, 4.55; Br, 22.56; N, 11.86. Found: C, 61.01; H, 4.57; Br, 22.57; N, 11.85.

1′-[(Diphenylamino)methyl]-1,3-dihydrospiro[benzo[*d*]imidazole-2,3′-indolin]-2one (2e) Brown solid; yield 88%; mp 228°C; ^{1}H NMR (DMSO-d_6) δ: 8.35–6.56 (m, 18H, Ar-H), 6.45 [s, (D_2O exchangeable), NH], 5.21 (s, 2H, CH_2): IR: ν_{max} 3090, 2980, 2850, 1703, 1614, 1567, 1483, 1350, 744, 752 cm^{-1}. Anal. Calcd for $C_{27}H_{22}N_4O$ (418.49): C, 77.49; H, 5.30; N, 13.39; O, 3.82. Found: C, 77.50; H, 5.30; N, 13.38; O, 3.82.

1′-[(Diethylamino)methyl]-1,3-dihydrospiro[benzo[*d*]imidazole-2,3′-indolin]-2′-one (2f) Yellow solid; yield 86%; mp 246°C; ^{1}H NMR (DMSO-d_6) δ: 8.07–6.53 (m, 8H, Ar-H), 6.42 [s, (D_2O exchangeable), NH], 4.72 (s, 2H, CH_2), 2.89 (q, 4H, *J* = 7 Hz, CH_2), 1.63 (t, 6H, *J* = 7 Hz CH_3): IR: ν_{max} 3384, 2850, 1703, 1613, 1598, 1483, 1322, 759, 743 cm^{-1}. Anal. Calcd for $C_{19}H_{22}N_4O$ (322.40): C, 70.78; H, 6.88; N, 17.38; O, 4.96. Found: C, 70.75; H, 6.89; N, 17.41; O, 4.95.

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