Available online on 15.08.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

An efficient bentonite clay catalyzed multicomponent synthesis of substituted spirooxindoles in water/ethanol solvent system

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Article Info:

Article History:

Received 22 May 2024
Reviewed 06 July 2024
Accepted 26 July 2024
Published 15 August 2024

Abstract

The present report demonstrates an efficient use of bentonite clay to bring about multicomponent synthesis of substituted spirooxindoles **4a-h** in Water/ ethanol solvent system under the mild reaction conditions.

Keywords: Bentonite clay, multicomponent synthesis, spirooxindoles

Cite this article as:

Bajpai S, Bhatia S, Bajpai AK, Asthana SN, An efficient bentonite clay catalyzed multicomponent synthesis of substituted spirooxindoles in water/ethanol solvent system, Journal of Drug Delivery and Therapeutics. 2024; 14(8):119-122 *DOI: http://dx.doi.org/10.22270/jddt.v14i8.6754*

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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] 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.[2, 3] Multicomponent reactions (MCR) have been proved an important tool for organic transformations due to their ability to incorporate three or more substrates into a single target in one operation.[4] In recent years, these are widely used in drug discovery[5] as well as in the total synthesis of natural products.[6] The spirooxindole ring system is a widely distributed structural framework present in numerous pharmaceuticals and natural products[7], including such cytostatic alkaloids as spirotryprostatins A, B, and strychnophylline.[8] Due to the unique structural array and the highly pronounced biological activity, spirooxindoles have become attractive synthetic targets for many scientists and researchers.[9] Among the oxygen-containing heterocycles, 4*H*-chromenes heterocyclic scaffolds represent a "*privileged*" structural motif well-distributed in natural products with a broad spectrum of strong biological activities.[10] Substituted 4*H*-chromenes have received considerable attention due to their broad range of pharmacological properties, such as spasmolitic, diuretic, anticoagulant, anticancer and antianaphylactic activities.[11, 12]

Several methodologies have been reported in literature for the synthesis of spirooxindole fused 4*H*-chromenes[13-16], but bentonite clay induced multicomponent synthesis of substituted spirooxindoles in water/ ethanol solvent system is still not fully explored.

EXPERIMENTAL

General: All chemicals were procured from Aldrich, USA, and E. Merck, Germany and used without further purification. TLC was carried out on SiO_2 gel (HF254, 200 mesh). The solvent system employed was ethyl acetate: n hexane (2: 1) and the spots were identified by placing the plate in Iodine chamber. IR spectra were recorded on a PerkinElmer FT/IR version 10.03.05 spectrometer. NMR spectra were run on a JEOL AL300 FTNMR spectrometer; chemical shifts are given in δ ppm, relative to TMS as internal standard. Elemental microanalysis was performed on Exeter Analytical Inc Model CE- 440 CHN Analyzer. Melting points were measured in open capillaries and are uncorrected.

General procedure for synthesis of compounds 4a-h

Dimedone **2** (0.01mol) and ethylcyanoacetate/malononitrile **3a, b** (0.01 mol) were added to a mixture of isatin derivatives (**1a–g**, 0.01 mol), bentonite clay (25 mol%) and H_2O / EtOH (v/v, 3:1, 20 mL). The reaction mixture was stirred at 60°C for 80 min. The progress of the reaction was monitored by TLC. After completion of reaction 50 mL of acetone was added in order to dissolve the product; the catalyst was separated by filtration and then washed with several times by acetone (4×10 mL), dried at 100 ºC for 12 h and reuse again. The liquid portion was evaporated and dried in order to get crude product. The crude products were recrystallised from ethanol.

2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4a): White solid; ^{1}H NMR (300 MHz, DMSO-d6): δH (ppm) 0.99 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.11- 2.15 (2H, m, CH_2), 2.48-257 (2H, m, CH_2), 6.80–7.27 (4H, m, ArH), 7.20 (2H, s, NH_2), 11.10 (1H, s, NH). ^{13}C NMR (75.45 MHz, DMSO-d6): δC (ppm) 27.8, 28.6, 32.1 ,47.6, 50.1, 56.8, 110.8, 111.3, 118.8, 123.3, 124.5, 127.9, 135.8, 143.1, 160.2, 165.6, 177.1,196.3. IR (KBr), ν_{max},: 3401, 3245, 2859, 2208, 1715, 1669, 1247. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.0; H, 5.16; N, 12.53. Found: C, 67.90; H, 5.30; N, 12.61.

Ethyl-2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate (4b): White solid; ^{1}H NMR (300 MHz,DMSO-d6): δH (ppm) 0.77 (3H, t, *J*= 6.5 Hz, CH_3), 0.99 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.04- 2.11 (2H, m,CH_2), 2.61-2.65 (2H, m, CH_2), 3.84 (2H, q, *J*= 6.9 Hz, CH_2), 6.66–7.06 (4H, m, ArH), 7.76 (2H, s, NH_2), 10.54 (1H, s, NH). ^{13}C NMR (75.45 MHz, DMSO-d6): δC (ppm) 13.6, 28.0, 28.7, 32.0, 47.7, 51.0, 58.9, 76.7, 108.8, 114.0, 122.0, 123.6, 128.0, 137.1, 144.4, 160.0, 162.7, 168.3 , 180.1, 193.1. IR (KBr), ν_{max},: 3399, 3216, 2932, 1661, 1623, 1235. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 66.00; H, 5.77; N, 7.3. Found: C, 65.80; H, 6.03; N, 7.65%.

2-Amino-5-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4c): White solid; ^{1}H NMR (300 MHz, DMSO-d6) δ 0.94 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.13-2.20 (m, 2H, CH_2), 2.52-2.57 (m, 2H, CH_2), 6.83 -7.25(3H, m, ArH), 7.27 (s, 2H, NH_2), 11.00 (s, 1H, NH). ^{13}C NMR (75.45 MHz, DMSO-d6) δ: 28.2, 28.8, 32.9, 49.1, 50.4, 57.3, 111.8, 111.9, 116.5, 124.4, 127.5, 128.6, 137.8, 142.0, 160.9, 164.8, 170.9, 192.2. IR (KBr), ν_{max},: 3480, 3309, 2959, 1691, 1630, 1241. Anal. calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.61; H, 4.45; N, 11.37. Found: C, 61.60; H, 4.48, N, 11.42.

Ethyl-2-amino-5-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxlate (4d): White solid; ^{1}H NMR (300 MHz, DMSO-d6) δ 0.90 (t, *J* = 6.9 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.15-2.22 (m, 2H, CH_2), 2.50- 2.59 (m, 2H, CH_2), 3.70 (q, *J* = 7.2 Hz, 2H, CH_2), 6.69- 7.15 (3H, m, ArH), 7.95 (s, 2H, NH_2), 10.90 (s, 1H, NH). ^{13}C NMR (75.45 MHz, DMSO-d6) δ 15.6, 29.0, 30.1, 31.8, 46.2, 50.5, 60.5, 77.6, 110.4, 114.3, 122.1, 123.8, 128.8, 139.2, 144.5, 160.9, 164.3, 168.4, 180.0, 195.5. . IR (KBr), ν_{max},: 3393, 3263, 2995, 1699, 1621, 1265. Anal. calcd. For $C_{21}H_{21}ClN_2O_5$: C, 60.50; H, 5.10; N, 6.71. Found: C, 60.48; H, 5.18, N, 6.65.

2-Amino-1′,7,7-trimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4e): White solid; ^{1}H-NMR (300 MHz, DMSO-d6) δH 1.08 (6H, s, 2 CH_3), 2.26-2.32 (2H, m, CH_2), 2.58-265 (2H, m, CH_2), 3.94 (3H, s, NCH_3), 6.90–7.32 (4H, m, ArH), 7.50 (2H, s, NH_2) ppm; δC (75.45 MHz, DMSO-d6) 23.0, 27.9, 27.9, 32.9, 41.0, 49.1, 50.6, 57.8, 109.8, 110.7, 118.4, 122.3, 123.7, 129.5, 135.1, 146.2, 161.5, 167.0, 176.9, 193.3 ppm. IR (KBr): ν_{max}, 3460, 3312, 3117, 2972, 2200, 1693, 1641, 1256 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_3O_3$ calcd: C 68.70, H 5.53, N 12.03; found: C 68.65, H 5.53, N 12.00.

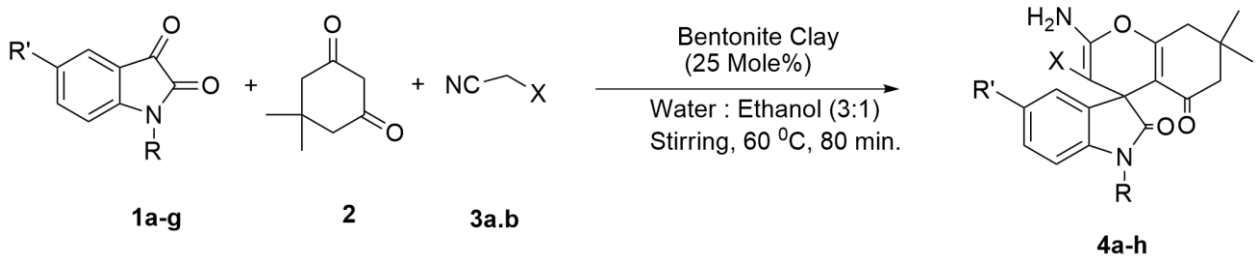
1′-Acetyl-2-amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4f): White solid; ^{1}H-NMR (300 MHz, DMSO-d6) δH 1.03 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.15–2.24 (2H, m, CH_2), 2.54-2.59 (2H, m, CH_2), 2.79 (3H, s, CH_3CO), 7.01–7.30 (3H, m, ArH), 7.51 (2H, s, NH_2), 8.18 (1H, d, *J*= 7.2 Hz, ArH) ppm; δC (75.45 MHz, DMSO-d6) 20.1, 27.2, 28.8, 32.6, 39.3, 46.9, 50.0, 58.1, 111.2, 114.3, 120.1, 123.2, 126.9, 128.9, 132.5, 139.9, 160.5, 164.9, 171.6, 180.8, 195.7 ppm. IR (KBr): ν_{max}, 3407, 3264, 2828, 2217, 1729, 1682, 1616, 1271 cm^{-1}. Anal. Calcd for $C_{21}H_{19}N_3O_4$ calcd: C 65.80, H 7.07, N 14.16; found: C 65.70, H 7.20, N 14.06.

2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-1′-benzyl-indol]-(1′*H*)- 2′-one-3-carbonitrile (4g): White solid; ^{1}H NMR (DMSO-d6, 300 MHz): 0.99 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.15-2.22 (2H, m, CH_2), 2.58–2.64 (m, 2H, CH_2), 5.10 (s, 2H, CH_2) 6.80- 7.25 (m, 4H, ArH), 7.39–7.49 (m, 5H, ArH, NH_2), 7.68 (d, 2H, ArH). IR: 3490, 3352, 3230, 2947, 2231, 1956, 1667, 1632, 1460, 1227 cm^{-1}. Anal. Calcd for $C_{26}H_{23}N_3O_3$: C, 74.38; H, 5.46; N, 8.88. Found: C, 74.30; H, 5.39; N, 8.80.

2-Amino-5-Chloro-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-1′-benzyl-indol]-(1′*H*)- 2′-one-3-carbonitrile (4h): White solid; ^{1}H NMR (DMSO-d6, 300 MHz): 1.12 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.50-2.56 (2H, m, CH_2), 2.85–2.94 (m, 2H, CH_2), 4.95 (s, 2H, CH_2) 6.97- 7.35 (m, 4H, ArH), 7.55–7.80 (m, 5H, ArH, NH_2), 7.95 (d, 2H, ArH). IR: 3458, 3317, 3185, 2923, 2251, 1850, 1672, 1624, 1451, 1241 cm^{-1}. Anal. Calcd for $C_{26}H_{22}ClN_3O_3$: C, 62.37; H, 4.16; N, 10.88. Found: C, 62.35; H, 4.22; N, 10.80.

RESULTS AND DISCUSSION

In light of the above, we report herein easy and efficient one-pot synthesis of substituted spirooxindoles *via* bentonite clay catalyzed reaction between isatin derivatives **1a-g** with cyclic 1, 3-diketone **2** and malononitrile/ethylcyanoacetate **3a,b** in water/ ethanol solvent system at 60 ^{0}C (**Scheme 1, Table 1**).



1a-g **2** **3a.b** **4a-h**

Table 1: Synthesis of spirooxindole derivatives **(4a-h).**

Entry	R	R′	X	% Yield	M P (Reported)
4a	H	H	CN	78	268–270 (268-270) [13]
4b	H	H	COOEt	80	258-260 (257-258) [13]
4c	H	Cl	CN	76	296 (293-295) [14]
4d	H	Cl	COOEt	77	290 (292-293 [14]
4e	CH_3	H	CN	74	251 (248-250) [15]
4f	CH_2COOEt	H	CN	79	237 (233–234) [15]
4g	CH_2Ph	H	CN	76	269-271(267-269) [16]
4h	CH_2Ph	H	CN	79	323

In order to find optimum reaction conditions, several parameters were investigated. Expectedly, efficiency of the catalytic system was affected by the catalyst amount. Therefore, a set of experiments using different amounts of bentonite clay was taken into account for the multicomponent reaction of isatin, dimedone and ethylcyanoacetate at 60 ^{0}C in water/ ethanol solvent system (3: 1). The synthetic route was drastically dependent on the presence of catalyst and only poor yield was observed in the absence of catalyst. It was found that product yield was increased with enhancing catalyst concentration. The best yield of 80% was obtained with 25 mol% of bentonite clay catalyst. However, further addition of catalyst concentration (> 25 mol%) did not improve the reaction rate and product yield.

To investigate the effect of solvents, for the multicomponent reaction of isatin, dimedone and ethylcyanoacetate in various organic solvents at refluxing temperature using 25 mol% bentonite clay was carried out. About 58% of the expected product was obtained when the solvent was ethanol while in the case of water it was only 54%. It was observed further that when water/ ethanol solvent system was tried, the product yield was increased under mild temperature condition. This encourages us to investigate ethanol water solvent system for the model reaction. The best result was obtain when water/ ethanol was used in **3: 1** proportion at 60 ^{0}C.

Under the optimized set of reaction conditions, isatin derivatives **1a-g** were made to undergo smooth coupling with cyclic 1,3-diketone **2** and malononitrile/ethylcyanoacetate **3a,b** in the presence of bentonite clay in water/ ethanol solvent system at 60 ^{0}C to afford substituted spirooxindoles **4a-h.**

Chemical structure of all synthesized compounds was fully established by their physical and spectral data.

The reusability of bentonite clay was examined under optimized reaction conditions. The catalyst was separated by filtration, washed, dried and reused for a fresh reaction mixture up to run no. 4. The results showed that there is no appreciable decrease in product yield in subsequent reuse which proves the reusability and recyclability of the catalyst.

CONCLUSIONS

In conclusion, a novel and mild approach for the one-pot synthesis of substituted spirooxindoles has been achieved by using bentonite clay in water/ ethanol solvent system, employing isatin derivatives, cyclic 1,3-diketone and malononitrile /ethyl cyanoacetate at 60 ^{0}C in good to excellent yield. The advantage of proposed method is its facile reaction conditions, the product can be isolated very easily without the use of column chromatography and the catalyst is recyclable. The simplicity of the present protocol makes it an interesting alternative to other approaches. The catalyst is expected to contribute to the development of environmentally benign methods.

Declaration of Interest:

There is no conflict of interest among the authors. The authors alone are responsible for the content and writing of the paper.

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