Chinese Chemical Letters 27 (2016) 575–578

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Three-component reaction for synthesis of functionalized spiro[indoline-3,4′-pyrano[3,2-h]quinolines]

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ARTICLE INFO

Article history:
Received 29 December 2015
Received in revised form 5 February 2016
Accepted 19 February 2016
Available online 2 March 2016

Keywords:
Spirooxindole
Chromene
Isatin
Malononitrile
Three-component reaction

ABSTRACT

The functionalized spiro[indoline-3,4′-pyrano[3,2-h]quinolines] were efficiently prepared in high yields from three-component reaction of 8-hydroxyquinoline, isatins and malononitrile or ethyl cyanoacetate in ethanol at room temperature for about 12 h in the presence of piperidine.

1. Introduction

The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [1,2]. Thus, spirooxindole has been attracted much interest in synthetic and medical chemistry [3,4]. Among the diverse heterocyclic spirooxindole ring system, spiro[indoline-3,4′-chromene] is one of the particular heterocyclic members because they possess important biological activities [5–7]. The conventional reaction for the synthesis of spiro[indoline-3,4′-chromene] derivatives was the three-component reaction of isatin, malononitrile and reactive methylene compounds under various reaction conditions. The conventional procedure for this reaction was employing common organic bases such as triethylamine, piperidine, and DBU as base catalyst in organic solvents [8]. In order to develop more efficient and greener methods, many other catalysts such as surfactant TEBA (triethylbenzylammonium chloride) [9], NH_4Cl [10], sodium stearate [11], mesoporous silica nanoparticles [12,13], $HAuCl_4$ [14], nanocrystalline MgO [15] and sulfated choline [16] have been employed in the reaction. Additionally, the two- and three-component reactions were also carried out in ionic liquid, microwave, and electrocatalytic reaction manner [17,18]. Practically, the three-component reaction could be also successfully applied to α-naphthol, β-naphthol and resorcinol with isatin and malononitrile for preparing benzo-fused spiro[indoline-3,4′-chromene] derivatives [19–25]. However, a literature survey indicated there is only one example describing the reaction of 8-hydroquinoline with isatin and ethyl cyanoacetate for the synthesis of quinoline-fused spiro[indoline-3,4′-chromene] [26]. In continuation of our aim to explore more efficient multicomponent reactions for biological active spiroxondole systems [27–30], herein we report our new investigation for developing the three-component reaction of 8-hydroquinoline, isatin and malononitrile to synthesis of densely substituted spiro[indoline-3,4′-pyrano[3,2-h]quinolines].

2. Experimental

2.1. General procedure for the three-component reaction

8-Hydroxyquinoline (1.0 mmol), isatin (1.1 mmol) and malonitrile or ethyl cyanoacetate (1.0 mmol) was dissolved in ethanol (20.0 mL). Then piperidine (1.0 mmol) was added and the mixture was stirred at room temperature for about 12 h. The resulting precipitates were collected by filtration and washed with cold alcohol to give the pure product. ^{1}H NMR and ^{13}C NMR spectra for all new compounds are available in Supporting information.

2.2. 2′-Amino-2-oxospiro[indoline-3,4′-pyrano[3,2-h]quinoline]-3′-carbonitrile (**1a**)

White solid, 85%, mp 210–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.71 (s, 1H, NH), 9.00–8.99 (m, 1H, ArH), 8.36 (d, 1H, J = 8.0 Hz,

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http://dx.doi.org/10.1016/j.cclet.2016.02.016

ArH), 7.67–7.62 (m, 2H, ArH), 7.49 (s, 2H, NH_2), 7.31 (t, 1H, J = 15.2 Hz, ArH), 7.04–7.00 (m, 2H, ArH), 6.68–6.66 (d, 1H, J = 8.4 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.1, 161.6, 151.0, 144.4, 142.3, 137.9, 136.5, 135.2, 129.8, 128.6, 125.1, 124.6, 124.3, 123.3, 123.1, 119.2, 118.9, 110.5, 54.5, 51.6; IR (KBr, cm^{-1}): υ 3476, 3445, 3295, 3190, 3055, 2194, 1726, 1693, 1656, 1621, 1600, 1568, 1499, 1470, 1403, 1365, 1322, 1268, 1233, 1198, 1170, 1157, 1141, 1118, 1064, 1037, 989, 924, 871, 845, 834, 796, 752; MS (m/z): HRMS (ESI) Calcd. for $C_{20}H_{12}N_4NaO_2$ ([M + Na]$^+$): 363.0852; Found: 363.0860.

2.3. 2′-Amino-1-benzyl-5-chloro-2-oxospiro[indoline-3,4′-pyrano[3,2-h]quinoline]-3′-carbonitrile (**1i**)

White solid, 89%, mp 176–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02–9.01 (m, 1H, ArH), 8.39 (d, 1H, J = 8.4 Hz, ArH), 7.70–7.66 (m, 2H, ArH), 7.64 (s, 2H, NH_2), 7.41–7.30 (m, 7H, ArH), 7.10–7.08 (m, 1H, ArH), 6.64–6.62 (m, 1H, ArH), 5.10 (d, 1H, J = 7.8 Hz, CH_2), 4.95 (d, 1H, J = 8.0 Hz, CH_2) ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.5, 161.8, 151.1, 144.6, 141.7, 138.0, 136.5, 136.2, 136.0, 129.8, 129.1, 128.9, 128.2, 128.0, 127.6, 125.7, 124.8, 124.0, 123.3, 118.9, 118.1, 53.6, 51.4, 43.8; IR (KBr, cm^{-1}): υ 3182, 3063, 3030, 2193, 1720, 1654, 1625, 1603, 1565, 1482, 1409, 1370, 1334, 1255, 1192, 1162, 1112, 1080, 1046, 987, 946, 924, 880, 858, 832, 814, 767; MS (m/z): HRMS (ESI) Calcd. for $C_{27}H_{17}ClN_4NaO_2$ ([M + Na]$^+$): 487.0932; Found 487.0933.

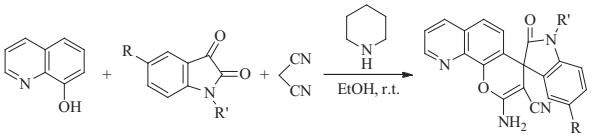
2.4. Ethyl 2′-amino-5-methyl-2-oxospiro[indoline-3,4′-pyrano[3,2-h]quinoline]-3′-carboxylate (**2a**)

White solid, 78%, mp 266–268 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 1H, NH), 8.98–8.97 (m, 1H, ArH), 8.33–8.31 (m, 1H, ArH), 8.16 (s, 2H, NH_2), 7.64–7.57 (m, 2H, ArH), 7.00–6.98 (m, 1H, ArH), 6.83–6.75 (m, 3H, ArH), 3.80–3.75 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 0.81 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.1, 168.2, 161.4, 150.8, 143.1, 139.9, 139.7, 137.9, 136.3, 131.2, 128.6, 128.3, 124.6, 124.3, 124.2, 122.9, 121.0, 109.5, 73.8, 59.2, 51.1, 21.0, 13.7. IR (KBr, cm^{-1}): υ 3545, 3409, 3300, 3033, 2981, 2902, 2865, 1708, 1679, 1580, 1527, 1491, 1408, 1367, 1303, 1264, 1241, 1111, 1064, 1025, 984, 947, 852, 830, 810, 791, 766; MS (m/z): HRMS (ESI) Calcd. for $C_{23}H_{20}N_3O_4$ ([M + H]$^+$): 402.1448; Found 402.1452.

2.5. Ethyl 2′-amino-1-butyl-5-chloro-2-oxospiro[indoline-3,4′-pyrano[3,2-h]quinoline]-3′-carboxylate (**2f**)

White solid, 90%, mp 146–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95–8.94 (m, 1H, ArH), 8.30–8.28 (m, 1H, ArH), 8.22 (s, 2H, NH_2), 7.62–7.54 (m, 2H, ArH), 7.32–7.30 (m, 1H, ArH) 7.16–7.07 (m, 2H, ArH), 6.61–6.58 (m, 1H, ArH), 3.79–3.76 (m, 2H, CH_2), 3.67–3.58 (m, 2H, CH_2), 1.65–1.62 (m, 2H, CH_2), 1.42–1.35 (m, 2H, CH_2), 0.91 (t, 3H, J = 7.2 Hz, CH_3), 0.67 (t, 3H, J = 6.8 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.9, 167.9, 161.6, 150.9, 143.4, 142.3, 140.6, 137.9, 136.3, 128.5, 128.4. 127.0, 124.4, 123.9, 123.1, 119.7, 110.3, 72.9, 59.0, 50.6, 29.7, 20.2, 14.1. IR (KBr, cm^{-1}): υ 3539, 3401, 3270, 2995, 2952, 2929, 2869, 1710, 1667, 1644, 1614, 1581, 1529, 1481, 1430, 1409,1376, 1339, 1288, 1226, 1205, 1169, 1105, 1034, 981, 928, 880, 827, 789, 773, 759; MS(m/z): HRMS (ESI) Calcd. for $C_{26}H_{25}ClN_3O_4$ ([M + H]$^+$): 478.1528; Found 478.1533.

Table 1
Synthesis of spiro compounds **1a–1i** *via* three-component reaction[a].



Entry	Compd	*R*	*R′*	Yield (%)[b]
1	**1a**	H	H	85
2	**1b**	CH_3	H	87
3	**1c**	F	H	81
4	**1d**	Cl	H	86
5	**1e**	CH_3	*n*-Bu	94
6	**1f**	F	*n*-Bu	91
7	**1g**	Cl	*n*-Bu	89
8	**1h**	F	Bn	86
9	**1i**	Cl	Bn	89

[a] Reaction conditions: 8-Hydroxyquinoline (1.0 mmol), isatin (1.1 mmol), malononitrile (1.0 mmol), piperidine (1.0 mmol) in ethanol (20.0 mL), r.t., 12 h.
[b] Isolated yield.

3. Results and discussion

Initially, the reaction conditions of three-component reaction of 8-hydroquinoline, isatin and malononitrile were examined according to the previous reported procedure for the similar reaction of β-naphthol [20]. When the three-component reaction was carried out in ethanol at room temperature in the presence of equivalent common organic bases such as triethylamine, piperidine, DABCO and DBU, the expected spiro[indoline-3,4′-pyrano[3,2-h]quinoline] **1a** was obtained in 70%, 85%, 75% and 63% yields, respectively. When less amount of piperidine was employed, the yield of product **1a** was decreased, which showed that the piperidine was not simply described as a catalyst, but as a base promoter. Under this mild reaction conditions, various substituted isatins reacted smoothly to give the products **1a–1i** in 81%–94% yields (Table 1). It should be pointed out that the products **1a–1i** can be obtained in very pure state by simple filtration and washing with a little cold alcohol, and further separation with chromatography was not needed. The structures of obtained spiro compounds **1a–1i** were fully characterized by IR, HRMS, ^{1}H NMR and ^{13}C NMR spectra. The single crystal structures

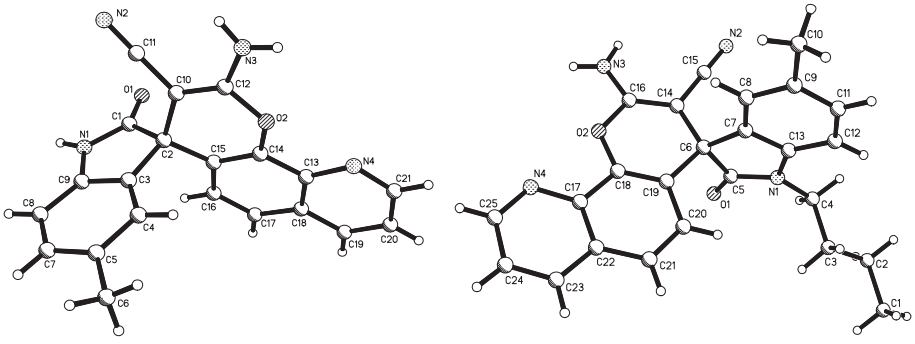


Fig. 1. Single crystal structures of spiro compounds **1b** and **1e**.