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Ultrasound-assisted Three-component Synthesis of Spiro[4H-pyrano[3,2-c]quinolin-4,3'-indoline]-2', 5(6H)-diones in Water

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ABSTRACT

A simple and efficient synthesis of the titled spirooxindoles was accomplished via the three-component reaction between isatins, 4-hydroxy-2H-quinolin-2-one, and malononitrile or ethylcyanoacetate in aqueous medium under ultrasound irradiation.

Key words: Spirooxindole, Three-component reaction, Ultrasound irradiation, In water reaction.

INTRODUCTION

Water, after its unique role as solvent in nature, is gaining more and more importance in the recent researches of environmentally benign chemical reactions. It is a cheap and inherently safe solvent relative to more traditional organic liquids. Hydrophobic interactions of water with organic substrates were shown to be the origin of selectivity and rate enhancements of organic reactions in watery solutions or even suspensions[1]. These fascinating features delineate a wide perspective for application of water as solvent in environmentally benign organic syntheses, especially when matched with a clean method of activation such as ultrasound irradiation. Ultrasonic irradiation is a safe transfer of activation energy to reacting molecules providing a unique distribution profile of penetrating waves in matter giving rise to acceleration of numerous catalytic reactions in homogeneous and heterogeneous systems[2-3]. The indole moiety is probably the most known heterocycle, a common and important feature of a variety of natural products and medicinal agents[4]. Among the indole-based heterocycles, those compounds consisted of spirooxindole core represent an important class of naturally occurring substances characterized by highly pronounced biological properties[5]. On the other hand, pyranoquinoline derivatives were found to possess a wide spectrum of biological activities, such as psychotropic, antiallergenic, anti-inflammatory, and estrogenic activity[6]. Furthermore, several pyranoquinoline containing alkaloids exhibit cancer cell growth inhibitory activity and are investigated as potent anticancer agents[7-8]. In this background and in line with ongoing researches devoted to synthesis of spirooxindole compounds[9], we report an efficient one-pot method for synthesis of spiro[4H-

pyrano[3,2-c]quinolin-4,3'-indoline]-2',5(6H)-diones in aqueous media under ultrasound irradiation.

EXPERIMENTAL

Typical procedure for the preparation of (4a)

A tube was charged with 4-hydroxy-2H-quinolone (0.16 g, 1 mmol), isatin (0.15 g, 1 mmol), malanonitrile (0.06 g, 1 mmol), piperidine (5 mol %) and water (5 mL). The reaction mixture was sonicated at 50 ºC for 5 min. After completion of reaction, as monitored by TLC, the reaction mixture was cooled to room temperature, filtered and the solids were wash with water and ethanol to afford the product 4a as white powder (86 %). A library of products (4a-j , see Table 3) were efficiently synthesized by this method among them 4a-e and 4i-j are known compounds,10 but the products 4f-g are reported here for the first time.

Selected data for Ethyl 2-amino-5'-methoxy-2',5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3'-indoline]-3-carboxylate (4f)

Cream powder, Yield, 0.40 g (92 %). mp> 300 °C, IR (KBr), νmax: 3442, 3340, 3180, 2940, 2860, 1687, 1654, 1612, 1480, 1348, 1298, 1104 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 0.87 (t, 3H, J 7.2 Hz, OCH_2CH_3), 3.59 (s, 3H, O-CH_3), 3.73-3.81 (m, 2H, OCH_2CH_3), 6.54 (d, 1H, J 2.4 Hz, 4'-H), 6.60 (d, 1H, J 8.4 Hz, 7'-H), 6.65 (dd, 1H, J 8.4 and 2.4 Hz, 6'-H), 7.30 (t, 1H, J 7.6 Hz, 9-H), 7.31 (d, 1H, J 7.6 Hz, 7-H), 7.59 (t, 1H, J 7.6 Hz, 8-H), 8.02 (d, 1H, J 7.6 Hz, 10-H), 8.05 (s, 2H, NH_2), 10.10 (s, 1H, NH), 11.51 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.6 (OCH_2CH_3), 48.6 (C_{spiro}), 55.7 (OCH_3), 59.4 (OCH_2CH_3), 76.4 (C-C'N), 108.6, 109.9, 110.4, 112.0, 112.2, 115.4, 122.3, 122.6, 132.0, 137.3, 138.1, 138.6, 151.7 (C-5'), 154.8 (C-4b), 159.6, 159.8 (C-2 and C-5), 168.1 (C=O ester), 179.9 (C=O oxindoline). MS (EI) m/z (%): 433 (M^+, 1), 418 (M^+-CH_3, 4), 405 (M^+-CH_2=CH_2, 5), 390 (2), 374 (100), 346 (25), 331 (14), 299 (8), 272 (15). Anal. Calcd for $C_{23}H_{19}N_3O_6$: C, 63.74; H, 4.42; N, 9.70%.Found: C, 63.81; H, 4.49; N, 9.63%.

Selected data for 2-Amino-5'-methoxy-6-methyl-2',5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c] quinoline-4,3'-indoline]-3-carbonitrile (4g)

Cream powder, Yield, 0.35 g (88%). mp> 300 °C, IR (KBr), ν_{max}: 3530, 3400, 3300, 3155, 2198, 1709, 1672, 1621, 1590, 1485, 1360 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d6) δ: 3.48 (s, 3H, N-CH_3), 3.63 (s, 3H, OCH_3), 6.68 (br s, 1H, 4'-H), 6.74-6.75 (m, 2H, 6'-H and 7'-H), 7.43 (t, 1H, J 7.6 Hz, 9-H), 7.46 (s, 2H, NH_2), 7.58 (d, 1H, J 8.4 Hz, 7-H), 7.75 (dt, 1H, J 7.8 and 1.6 Hz), 8.06 (dd, 1H, J 8.0 and 1.6 Hz, 10-H), 10.36 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 29.7, 49.1 (C_{spiro}), 55.8 (OCH3), 57.8 (C-C'N), 106.9, 110.0, 110.8, 112.8, 113.4, 115.5, 118.0, 122.8, 122.9, 132.7, 136.0, 136.3, 139.2, 152.0 (C-5'), 155.5 (C-4b), 159.2, 159.3 (C-2 and C-5), 178.2 (C=O oxindoline). MS (EI) m/z (%): 400 (M^+, 9), 381 (2), 368 (1), 322 (4), 236 (9), 216 (15), 149 (17), 97 (79), 57 (100). Anal. Calcd. for $C_{21}H_{14}N_4O_4$: C, 66.00; H, 4.03; N, 13.99 %. Found: C, 65.91; H, 4.09; 14.03 %.

Selected data for 2-Amino-6-methyl-5'-nitro-2',5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3'-indoline]-3-carbonitrile (4h)

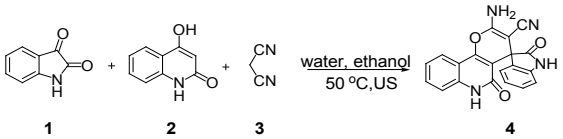
Creamy powder, Yield, 0.33 g (80%). mp> 300 °C, IR (KBr), ν_{max}: 3445, 3304, 3250, 3196, 2198, 1736 (C=O), 1674 (C=O), 1622, 1583, 1506, 1364, 1337, 1160 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d6) δ: 7.06 (d, 1H, J 8.8 Hz, 7'-H), 7.47 (t, 1H, J 7.4 Hz, 9-H), 7.61 (d, 1H, J 8.4 Hz, 7-H), 7.68 (s, 2H, NH_2), 7.78 (dt, 1H, J 7.8 and 1.2 Hz, 8-H), 8.08 (dd, 1H, J 8.0 and 1.2 Hz, 10-H), 8.11 (d, 1H, J 2.4 Hz, 4'-H), 8.18 (dd, 1H, J 8.4 and 2.4 Hz, 6'-H), 11.31 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d6)δ: 29.8 (CH3), 48.8 (Cspiro), 56.1 (C-C'N), 105.7, 109.8, 112.9, 115.6, 117.7, 120.0, 123.02, 123.05, 126.3, 132.9, 135.8, 139.2, 143.0 (C-5'), 149.5 (C-7'a), 152.6 (C-4b), 159.4 (C-2), 159.7 (C=O), 179.0 (C=O oxindoline). MS (EI) m/z (%): 415 (M+, 0.5), 381 (9), 368 (12), 339 (8), 330 (8), 313 (28), 264 (20), 236 (30), 194 (100), 175 (33). Anal. Calcd for C21H13N5O5: C, 60.72; H, 3.15; N, 16.86 %. Found: C, 60.76; H, 3.22; N, 16.73 %.

RESULTS AND DISCUSSION

At the onset of this study, the reaction of isatin, 4-hydroxy-2(1H)-quinolone and malononitrile was used as the model to explore the optimum reaction conditions (Table 1).

As Table 1 show, better results were obtained with the aid of basic catalysts especially piperidine and triethylamine. In the absence of any

Table 1: Optimization of reaction conditions for the model reaction in 1:5 ethanol:water solution under ultrasound irradiation (45 KHz)



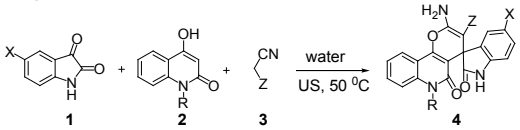
1 2 3 4

Entry	Catalyst (X mol %)	Time	Yield (%)
1	Pipiridine (5)	10 min	79
2	NEt_3 (5)	10 min	78
3	KBr (15)	45 min	48
4	Al_2O_3 (30)	45 min	32
5	Na_2CO_3 (30)	45 min	80
6	L-Proline	20 min	77
7	-	45 min	53

Table 2. Further optimizations of the trial reaction at 50 ºC under sonication (unless specified).

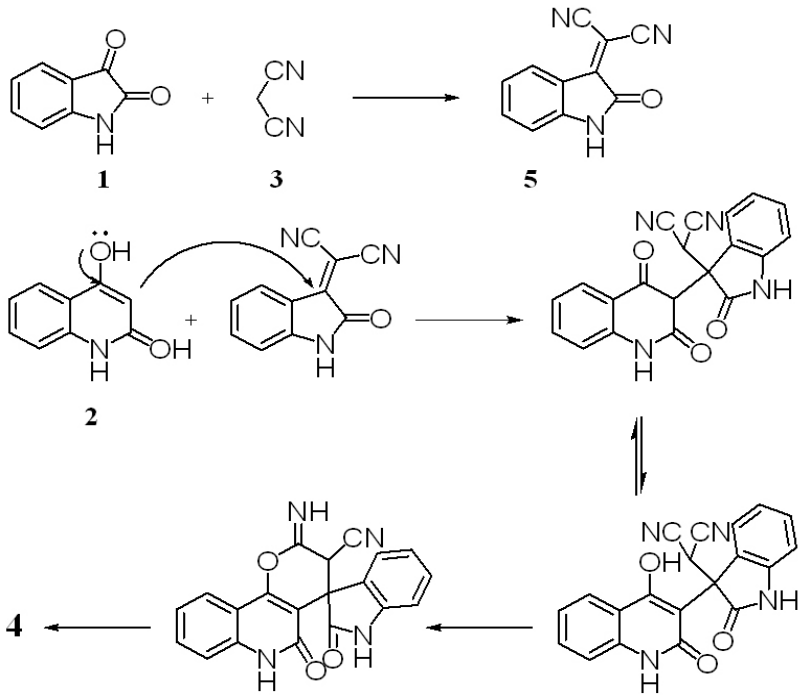
Entry	Solvent	Time	Yield (%)
1	H_2O	5 min	86
2	H_2O without US	80 min	82
3	H_2O- EtOH (5:1)	10 min	79
4	MeCN	20 min	68
5	CH_2Cl_2	10 min	78

Table 3: The library of the spiro-products synthesized under the optimal conditions



1 2 3 4

Yield (%)	Time	Z	R	X	Product
86	5	CN	H	H	4a
85	5	CO_2Et	H	H	4b
83	5	CN	CH_3	H	4c
82	5	CO_2Et	CH_3	H	4d
90	5	CN	H	OCH_3	4e
92	5	CO_2Et	H	OCH_3	4f
88	5	CN	CH_3	OCH_3	4g
80	7	CN	CH_3	NO_2	4h
82	7	CO_2Et	H	NO_2	4i
84	7	CN	H	NO_2	4j



Scheme 1: A proposed mechanism for the reaction

catalyst, the reaction takes a longer time and gives lower yield. Upon further examination of the trial reaction, water has been proved to be the superior solvent in spite of its lower solvability (Table 2). The best result was obtained with piperidine (5 mol %) as catalyst under ultrasonic irradiation for 5 min at 50 ºC. To verify the role of ultrasounds, the reaction was also run in water at 50 ºC without soniaction. As this table show, ultrasound irradiation improves the yield of the reaction (entry 2).

Encouraged by this success, a variety of isatin derivatives, quinolones, and malononitrile or ethyl cyanoacetate were employed under similar circumstances to evaluate the applicability of this method. The results summarized in Table 3 show the viability of this method. It is evident from this table that both electron-deficient and electron-rich isatins afford fairly high yields of the desired spiro-condensates in reaction with malononitrile and a variety of 1,3-dicarbonyl compounds in a few minutes at ambient temperature. Nevertheless, the electron-donating methoxy group at the 5-position of isatin substrate renders the reaction to give slightly higher yields, whilst presence of the electron-accepting nitro group at the same position have a retardation effect on the rate of the reaction. Moreover, employing ethyl cyanoacetate in place of malononitrile furnishes similar connective assembly of spiro-annulated pyran-oxindole products. The general aspect of the present method partially lies on the fact that amidic N-H group of 4-hydroxy-2H-quinolone did not affect on the course of reactions, as N-substituted and unsubstituted quinolones take part similarly into the reaction to give the corresponding products. The structures of some products were confirmed by comparison of their IR and ^{1}H NMR spectroscopic as well as physical data with those of authentic samples prepared from previously reported method,8 however the new products 4f-h were fully characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data as well as their elemental microanalyses.

The synthesis hinged on a cascade of reactions in which first isatin 1 condenses with malononitrile 3 to afford the intermediate isatylidenemalononitrile 5. This intermediate undergoes a Michael type addition at its exocyclic C=C bond with the 4-hydroxyquinolin-2(1H)-one 2 followed by a cyclization through addition of the OH

and cyano groups existing on the resultant adduct (Scheme 1).

CONCLUSION

In conclusion, we have developed a quick, clean, and simple method for the synthesis of spiro[4H-pyrano[3,2-c]quinoline-4,3'-indoline]-2',5(6H)-dione in water under ultrasound irradiation. Prominent among the advantages of this method are operational simplicity, good yields, easy workup and using water as solvent. The reactions gain acceleration and give better yields under ultrasound irradiation.

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