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ORIGINAL PAPER

An efficient and convenient protocol for the synthesis of novel 1′*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione derivatives

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Abstract An efficient and direct procedure for the synthesis of novel spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione derivatives is described. The process employs a condensation reaction of 2-aminobenzamides and isatins in the presence of a catalytic amount of $KAl(SO_4)_2.12H_2O$ (alum) in ethanol under reflux.

Keywords Quinazoline · 2-aminobenzamides · Isatin · $KAl(SO_4)_2.12H_2O$ (alum) · Microwave irradiation

Introduction

2,3-Dihydroquinazoline-4(3*H*)-ones and oxindole derivatives are an important class of heterocyclic compounds. 2,3-Dihydroquinazolin-4(3*H*)-ones possess a broad spectrum of biological and pharmaceutical activities, such as analgesic [1], antitumor [2], anticancer [3], diuretic [4], and herbicidal activities [5]. In addition, these compounds can easily be oxidized to their quinazolin-4(3*H*)-one analogs [6], which also include important pharmacologically active compounds [7, 8]. Several methods have been reported for the synthesis of 2,3-dihydroquinazolinones [8–13].

Oxindoles are useful as antibacterial, antiinflammatory [14] and laxative agents [15]. Furthermore, these heterocycle compounds have recently been isolated from plants. For example, the marine alkaloid convolutamydine A, isolated from the marine bryozoan *Amathia convoluta*, was found to show potent activity in the differentiation of HL-60 human promyelocytic leukemia cells [16]. The synthetic precursors to this type of alkaloid are also isatin derivatives [17].

Oxindole derivatives have been prepared by the reaction of isatins with aromatics in triflic acid [18], the reaction of isatins with diphenyl urea and $AlCl_3$ [19], the reaction of isatins with barbituric acid [20], and by other routes [21, 22].

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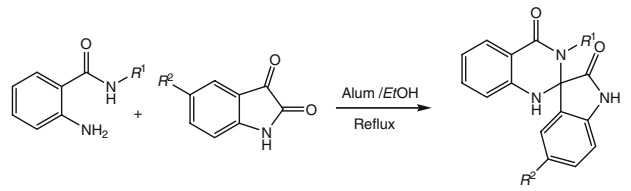
Results and discussion

Very recently, we have reported the preparation of 2,3-dihydroquinazoline-4(3*H*)-ones [23] and oxindoles [24]. Along these lines, we designed the synthesis of 1′*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione. To this end, the use of a $KAl(SO_4)_2.12H_2O$ (alum), which is relatively nontoxic and inexpensive, is the focus of our study [25–28]. In the course of our research on the applications of $KAl(SO_4)_2.12H_2O$ in organic reactions, we have found that alum is an effective promoter in the preparation of 1′*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione.

The 2-aminobenzamides **3a–g** necessary for this investigation were prepared according to [29]; their physical properties were in accordance with those described in [30].

When a mixture of 2-amino-*N*-phenylbenzamide (**3a**) and isatin (**4a**) in ethanol was stirred at reflux in the presence of a catalytic amount of alum, the reaction was completed within 7 h (until **4a** disappeared, as shown by TLC analysis). Workup of the reaction mixture prepared **5a** in 91% yield (Scheme 1).

Encouraged by this success, we extended this reaction of 2-aminobenzamides **3b–g** with a range of other isatins **4a**



	R^1
3a	H
3b	*Ph*
3c	*p*-$CH_3C_6H_4$
3d	*p*-$CH_3OC_6H_4$
3e	*p*-BrC_6H_4
3f	*p*-ClC_6H_4
3g	*Ph*CH_2

	R^2
4a	H
4b	Br

	R^1	R^2
5a	H	H
5b	*Ph*	H
5c	*p*-$CH_3C_6H_4$	H
5d	*p*-$CH_3OC_6H_4$	H
5e	*p*-BrC_6H_4	H
5f	*p*-ClC_6H_4	H
5g	*Ph*CH_2	H
5h	*p*-$CH_3C_6H_4$	Br

Scheme 1

and **b** under similar conditions, furnishing the respective 1′*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-dione **5b–h** with good yields. The optimized results are summarized in Scheme 1. All products were characterized by their ^{1}H, ^{13}C NMR, IR and MS spectral data.

In conclusion, a novel and efficient method for the condensation of 2-aminobenzamides with isatin derivatives into 1′*H*-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′*H*)-diones was developed. The novelty and synthetic usefulness of this methodology was demonstrated by the efficient synthesis of some novel and interesting dihydroquinazoline-4(3*H*)-ones or oxindoles.

Experimental

Melting points were obtained in open capillary tubes and were measured on an Electrothermal (Southend, UK) 9200 apparatus. Mass spectra were recorded on a Shimadzu (Tokyo, Japan) QP 1100 BX mass spectrometer. The IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker (Rheinstetten, Germany) 300 DRX Avance instrument at 300 and 75 MHz. Elemental analysis for C, H and N were performed using a Heraus (Banau, Germany) CHN rapid analyzer.

General procedure for preparation of 1′H-spiro[isoindoline-1,2′-quinazoline]-3,4′(3′H)-dione

A mixture of 1 mmol **3**, 1 mmol isatin **4**, 0.4 g alum and 5 cm^3 EtOH in a 20 cm^3 flask was stirred at reflux for the time period indicated in Scheme 1. After the reaction had completed (monitored by TLC, ethyl acetate/*n*-hexane, 1/1), EtOH was removed under reduced pressure, 25 cm^3 H_2O was added to the reaction mixture, the resulting solid was separated by filtration and recrystallized from ethanol to afford pure product.

*1′H-Spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**5a**, $C_{22}H_{18}N_2S$)*

Cream powder; mp 261–263 °C dec.; IR (KBr) $\overline{\nu}$ = 3,491 (NH), 3,227(NH), 2,964, 1,725 (C=O), 1,642 (C=O), 1,614, 1,526 cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$) δ = 6.60 (d, 1H, *J* = 8.0, ArH), 6.68(t, 1H, *J* = 7.4, ArH), 6.84 (d, 1H, *J* = 7.7, ArH), 7.05 (t, 1H, *J* = 7.4, ArH), 7.22 (t, 1H, *J* = 7.2, ArH), 7.28 (s, 1H, NH), 7.33 (t, 1H, *J* = 7.8, ArH), 7.47 (d, 1H, *J* = 7.3, ArH), 7.59 (d, 1H, *J* = 7.4, ArH), 8.36 (s, 1H, NH), 10.30 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO-d*$_6$) δ = 71.41, 110.53, 114.31, 114.76, 117.61, 122.73, 125.81, 127.30, 129.89, 131.26, 133.75, 142.58, 147.28, 164.40, and 176.47 ppm; MS: *m/z* (%) = 265 (M$^+$, 25), 263 (50), 237 (100), 119 (95), 92 (60), 63 (35), 50 (30), 39 (40); anal. calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84; found: C, 67.80; H, 4.11; N, 15.73.

*3′-Phenyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**5b**, $C_{21}H_{15}N_3O_2$)*

Yellow powder; mp 251–253 °C dec.; IR (KBr) $\overline{\nu}$ = 3,428 (NH), 3,265 (NH), 2,916, 1,727 (C=O), 1,642 (C=O), 1,616 cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$) δ = 6.63 (d, 1H, *J* = 7.7, ArH), 6.70–6.78 (m, 2H, ArH), 6.92 (t, 1H, *J* = 7.4, ArH), 6.98 (d, 2H, *J* = 7.0, ArH), 7.12–7.23 (m, 4H, ArH), 7.30 (t, 1H, *J* = 7.0, ArH), 7.53 (d, 1H, *J* = 7.3, ArH), 7.63 (s, 1H, NH), 7.66 (d, 1H, *J* = 7.0, ArH), 10.42 (s, 1H, NH) ppm; ^{13}C NMR δ (*DMSO-d*$_6$) δ = 76.85, 110.57, 114.57, 115.04, 118.17, 122.59, 126.96, 127.75, 127.90, 128.10, 129.11, 129.74, 131.29, 134.16, 138.55, 142.12, 146.58, 164.08, and 175.96 ppm; MS: *m/z* (%) = 341 (M$^+$, 5), 313 (100), 269 (15), 249 (15), 221 (25), 194 (25), 167 (15), 120 (60), 92 (30), 77 (80), 63 (35), 51 (50), 39 (40); anal. calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31; found: C, 73.80; H, 4.32; N, 12.25.

*3′-p-Tolyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**5c**, $C_{22}H_{17}N_3O_2$)*

Cream powder; mp 271–273 °C dec.; IR (KBr) $\overline{\nu}$ = 3,420 (NH), 3,258 (NH), 2,964, 1,708 (C=O), 1,644 (C=O), 1,613, 1,503 cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$) δ = 2.17 (s, 3H, CH_3), 6.63–6.77 (m, 3H, ArH), 6.85 (d, 2H, *J* = 8.2, ArH), 6.93 (d, 2H, *J* = 7.5, ArH), 6.99 (d, 2H, *J* = 8.2, ArH), 7.15 (t, 1H, *J* = 7.2, ArH), 7.29 (t, 1H, *J* = 7.0, ArH), 7.53 (d, 1H, *J* = 7.3, ArH), 7.60 (s, 1H, NH), 7.64 (d, 1H, *J* = 7.0, ArH), 10.40 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO-d*$_6$) δ = 21.00, 76.86, 110.59, 114.51, 115.04, 118.09, 122.60, 126.90, 127.88, 127.96, 129.65, 131.26, 134.08, 135.91, 137.30, 142.10, 146.56, 164.12, and 175.96 ppm; MS: *m/z* (%) = 355 (M$^+$, 5), 353 (15), 327 (100), 249 (15), 235 (25), 208 (25), 120 (50), 91 (35), 77 (20), 65 (45), 51 (30), 39 (30); anal. calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82; found: C, 74.24; H, 4.73; N, 11.74.

*3′-(4-Methoxyphenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**5d**, $C_{22}H_{17}N_3O_3$)*

Cream powder; mp 269–271 °C dec.; IR (KBr) $\overline{v}$ = 3,426 (NH), 3,287(NH), 2,964, 1,726 (C=O), 1,638 (C=O), 1,612, 1,510 cm^{-1}; ^1H NMR (*DMSO-d_6*) δ = 3.64 (s, 3H, OCH_3), 6.67–6.75 (m, 5H, ArH), 6.89–9.91 (m, 3H, ArH), 7.16–7.29 (m, 2H, ArH), 7.55 (s, 1H, NH), 7.59–7.68 (m, 2H, ArH), 10.40 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO-d_6*) δ = 55.54, 77.03, 110.59, 114.23, 114.50, 115.01, 118.09, 122.63, 126.85, 127.92, 128.08, 131.02, 131.23, 134.08, 142.08, 146.59, 158.61, 164.27, and 175.97 ppm; MS: *m/z* (%) = 371 (M^+, 5), 369 (15), 343 (100), 328 (90), 249 (35), 221 (25), 192 (25), 120 (40), 91 (45), 77 (60), 65 (45), 51 (45), 39 (50); anal. calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31; found: C, 71.06; H, 4.53; N, 11.20.

*3′-(4-Bromophenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**5e**, $C_{21}H_{14}BrN_3O_2$)*

Yellow powder; mp 213–215 °C dec.; IR (KBr) $\overline{v}$ = 3,429 (NH), 3,252 (NH), 2,964, 1,725 (C=O), 1,642 (C=O), 1,614 cm^{-1}; ^1H NMR (*DMSO-d_6*) δ = 6.67-6.79 (m, 3H, ArH), 6.93-6.97 (m, 3H, ArH), 7.16 (t, 1H, *J* = 7.6, ArH), 7.31 (t, 1H, *J* = 7.2, ArH), 7.41 (d, 2H, *J* = 8.4, ArH), 7.56 (d, 1H, *J* = 7.3, ArH), 7.67 (s, 1H, NH), 7.69 (d, 1H, *J* = 7.0, ArH), 10.47 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO-d_6*) δ = 76.81, 110.74, 114.65, 114.75, 118.25, 120.71, 121.24, 126.97, 127.46, 127.93, 131.53, 131.99, 132.21, 134.34, 137.91, 142.13, 146.59, 164.08, and 175.77 ppm; MS: *m/z* (%) = 419 (M^+, 5), 391 (100), 301 (15), 272 (15), 249 (35), 221 (15), 194 (25), 171 (35), 155 (20), 120 (90), 92 (45), 77 (60), 63 (65), 51 (65), 39 (55); anal. calcd. for $C_{21}H_{14}BrN_3O_2$: C, 60.02; H, 3.36; N, 10.00; found: C, 59.03; H, 3.26; N, 9.89.

*3′-(4-Chlorophenyl)-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**5f**, $C_{21}H_{14}ClN_3O_2$)*

Yellow powder; mp 264–266 °C dec.; IR (KBr) $\overline{v}$ = 3,427 (NH), 3,337 (NH), 2,964, 1,739 (C=O), 1,643 (C=O), 1,608, 1,491 cm^{-1}; ^1H NMR (*DMSO-d_6*) δ = 6.66–6.78 (m, 3H, ArH), 6.92–7.02 (m, 3H, ArH), 7.16 (t, 1H, *J* = 7.5, ArH), 7.28–7.33 (m, 3H, ArH), 7.56 (d, 1H, *J* = 7.3, ArH), 7.63(d, 1H, *J* = 7.3, ArH), 7.66 (s, 1H, NH), 10.46 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO-d_6*) δ = 76.86, 110.73, 114.65, 114.76, 118.24, 122.75, 126.98, 127.47, 127.93, 129.25, 131.52, 131.66, 132.66, 134.34, 137.47, 142.14, 146.60, 164.13, and 175.79 ppm; MS: *m/z* (%) = 375 (M^+, 5), 347 (100), 249 (35), 228 (15), 192 (25), 166 (25), 120 (70), 92 (35), 75 (60), 63 (65), 51 (60), 39 (60); anal. calcd. for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18; found: C, 67.01; H, 3.76; N, 11.09.

*3′-Benzyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**5g**, $C_{22}H_{17}N_3O_2$)*

Cream powder; mp 190–192 °C dec.; IR (KBr) $\overline{v}$ = 3,480 (NH), 3,329 (NH), 2,924, 1,729 (C=O), 1,623 (C=O) 1,610 cm^{-1}; ^1H NMR (*DMSO-d_6*) δ = 4.15–4.52 (d,d, *J* = 15.3, 2H, CH_2), 6.67 (d, 1H, *J* = 7.9, ArH), 6.76 (t, 1H, *J* = 7.4, ArH), 6.81 (d, 1H, *J* = 7.6, ArH), 6.90–6.92 (m, 3H, ArH), 7.14–7.16 (t, 2H, ArH), 7.24–7.34 (m, 3H, ArH), 7.48 (s, 1H, NH), 7.73 (d, 1H, *J* = 7.5, ArH), 10.36 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO-d_6*) δ = 46.31, 75.54, 110.91, 114.41, 115.06, 118.12, 122.41, 126.71, 126.76, 127.27, 127.82, 127.87, 128.24, 131.73, 133.86, 137.83, 142.97, 146.47, 164.53, and 175.47 ppm; MS: *m/z* (%) = 355 (M^+, 5), 353 (20), 327 (100), 249 (20), 235 (25), 208 (25), 120 (50), 91 (30), 77 (30), 65 (35), 51 (20), 39 (35); anal. calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82; found: C, 74.23; H, 4.71; N, 11.70.

*5-Bromo-3′-p-tolyl-1′H-spiro[indoline-3,2′-quinazoline]-2,4′(3′H)-dione (**5h**, $C_{22}H_{16}BrN_3O_2$)*

Yellow powder; mp 150–152 °C dec.; IR (KBr) $\overline{v}$ = 3,450 (NH), 3,236 (NH), 1,736 (C=O), 1,645 (C=O), 1,613, 1,512 cm^{-1}; ^1H NMR (*DMSO-d_6*) δ = 2.08 (s, 3H, CH_3), 6.60 (d, 1H, *J* = 8.2, ArH), 6.67 (d, 1H, *J* = 7.7, ArH),6.74 (t, 1H, ArH),6.89 (d, 2H, *J* = 6.7, ArH), 7.03 (d, 1H, *J* = 7.8, ArH), 7.28–7.35 (m, 2H, ArH), 7.65 (m, 2H, ArH), 7.76 (s, 1H, NH), 10.55 (s, 1H, NH) ppm; ^{13}C NMR ***δ*** (*DMSO-d_6*) δ = 21.03, 76.87, 112.66, 114.17, 114.54, 114.98, 118.34, 127.94, 129.68, 129.81, 130.15, 134.03, 134.21, 135.69, 137.61, 141.44, 146.27, 163.91, and 175.64 ppm; MS: *m/z* (%) = 434 (M^+, 10), 405 (95), 327 (25), 286 (35), 250 (15), 209 (15), 192 (25), 166 (25), 146 (20), 120 (100), 91 (85), 77 (60), 65 (95), 51 (60), 39 (70); anal. calcd. for $C_{22}H_{16}BrN_3O_2$: C, 60.84; H, 3.71; N, 9.68; found: C, 60.74; H, 3.62; N, 9.57.

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