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ORIGINAL PAPER

An efficient synthesis of fluorescent spiro[benzopyrazoloquinoline-indoline]triones and spiro[acenaphthylenebenzopyrazolo-quinoline]triones

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Abstract An efficient and simple synthesis of spiro[11*H*-benzo[*g*]pyrazolo[4,3-*b*]quinoline-11,3′-[3*H*]indole]-2′,5,-10(1′*H*)-triones and spiro[acenaphthylene-1(2*H*),11′-[11*H*]-benzo[*g*]pyrazolo[4,3-*b*]quinoline]-2,5′,10′-triones by a three-component condensation reaction of 2-hydroxy-1,4-naphthoquinone, pyrazol-5-amines, and isatins or acenaphthylene-1,2-dione in the presence of *p*-TSA as an inexpensive and available catalyst in refluxing ethanol is reported.

Keywords Isatin · Spirooxindole · Aminopyrazole · Spiro[benzopyrazoloquinoline-indoline]

Introduction

Fluorescent heterocyclic compounds are of interest in many disciplines; for example, they are used as emitters for electroluminescence devices [1], molecular probes for biochemical research [2], in traditional textile and polymer fields [3], in fluorescent whitening agents [4], and in photoconducting materials [5].

Molecules with a naphthoquinone structure, due to their biological properties, constitute one of the most interesting classes of compounds in organic chemistry. They have also industrial applications and can potentially be used as intermediates in the synthesis of heterocycles [6]. A series of related naphthoquinone pigments (streptocarpone, α-dunnione, dunniol, and dunnione) from *Streptocapus dunnii* have been isolated and characterized [7, 8]. On the other hand, pyrazolo[3,4-*b*]quinolines belong to a class of highly fluorescent compounds which emit mostly in the blue spectral range and have been classified as promising materials for optoelectronics [9]. Attempts have been made to produce redshifts in their fluorescence spectra by changing substituents [10].

Indole and indoline fragments are important moieties in a large number of natural biologically active compounds [11], and some indolines that are spiro-annulated with heterocycles at the 3 position have shown high biological activity [12–15]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [16–19]. Therefore, a number of methods have been reported for the preparation of spirooxindoles [20–23].

Considering the above reports, and as part of our program aiming at the synthesis of heterocycles [24–33], we are currently investigating the synthesis of new spirooxindoles containing pyrazolo[3,4-*b*]quinoline via a facile, atom-economical, and one-pot condensation reaction.

Results and discussion

We found that a mixture of 2-hydroxy-1,4-naphthoquinone (**1**), pyrazol-5-amines **2a**–**2d**, and isatins **3a**–**3e** in the presence of a catalytic amount of *p*-TSA (15 mol%) in refluxing ethanol for 4–5.5 h afforded spiro[11*H*-benzo[*g*]-pyrazolo[4,3-*b*]quinoline-11,3′-[3*H*]indole]-2′,5,10(1′*H*)-triones **4** in good yields (Scheme 1). Using this method, some new spirooxindoles **4a**–**4j** were selectively synthesized by a three-component condensation reaction. The results are summarized in Table 1.

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Scheme 1

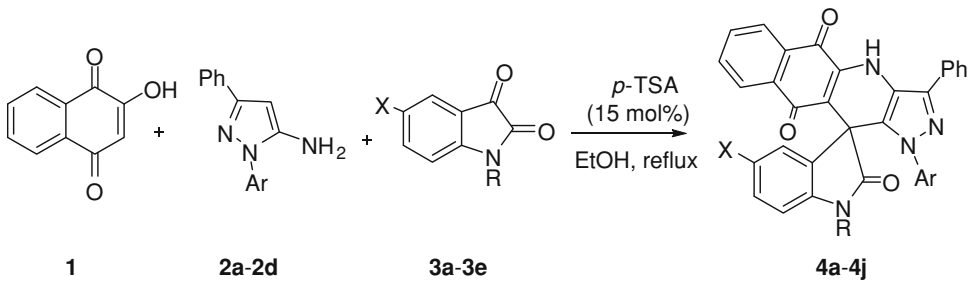


Table 1 Synthesis of spiro[indoline-benzopyrazoloquinoline] derivatives **4a–j**

Derivative	Ar	X	R	Yield/%[a]
4a	C_6H_5	H	H	94
4b	4-MeO–C_6H_4	H	H	87
4c	4-Br–C_6H_4	H	H	83
4d	4-NO_2–C_6H_4	H	H	90
4e	C_6H_5	Br	Et	80
4f	4-MeO–C_6H_4	Br	Et	81
4g	C_6H_5	NO_2	H	80
4h	4-NO_2–C_6H_4	NO_2	H	73
4i	C_6H_5	Me	H	81
4j	4-Br–C_6H_4	H	$PhCH_2$	85

[a] Isolated yields

To the best of our knowledge, this new procedure provides the first example of a synthesis of spirooxindole-annulated benzopyrazoloquinolines. The reactions in ethanol are relatively safe, nontoxic, environmentally friendly, and inexpensive. This method is most simple and convenient, and would be applicable for the synthesis of different types of spiro[benzopyrazoloquinoline-indoline] derivatives. In addition, the workup for these very clean reactions involves only a filtration and a simple washing step with EtOH.

We have not established an exact mechanism for the formation of product **4**, but a reasonable possibility is shown in Scheme 2.

As expected, when the isatin **3** was replaced by acenaphthylene-1,2-dione (**5**), the spiro[acenaphthylene-1(2*H*),11′-[11*H*]benzo[*g*]pyrazolo[4,3-*b*]quinoline]-2,5′,10′-triones **6** were obtained in good yields under the same reaction conditions (Scheme 3).

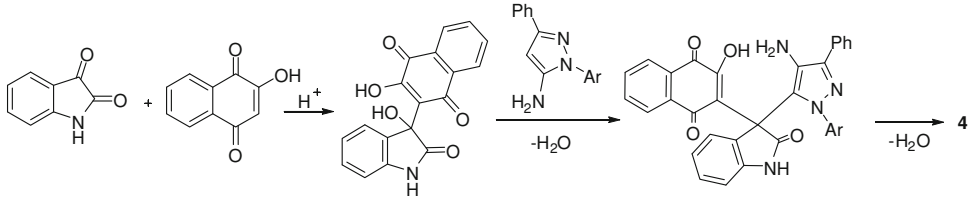
Compounds **4** and **6** are stable solids whose structures were established by IR and ^{1}H NMR spectroscopy and elemental analysis. Electronic absorption and fluorescence spectra of 5×10^{-5} M solutions of the selected products **4** and **6** in methanol were measured, and the results are shown in Table 2. A fluorescence excitation (λ_{ex}) wavelength of 465 nm was used for compounds **4** and **6**. Figures 1, and 2 show the visible and emission spectra of the selected products. From Fig. 2, it can be observed that the products are fluorescent in solution. The λ_{em} values are presented in Table 2.

In conclusion, we have described a facile three-component method for the synthesis of spiro[11*H*-benzo[*g*]-pyrazolo[4,3-*b*]quinoline-11,3′-[3*H*]indole]-2′,5,10(1′*H*)-triones and spiro[acenaphthylene-1(2*H*),11′-[11*H*]benzo[*g*]-pyrazolo[4,3-*b*]quinoline]-2,5′,10′-triones in ethanol using readily available starting materials. Prominent among the advantages of this new method are operational simplicity, good yields in short reaction times, and the easy work-up procedures employed.

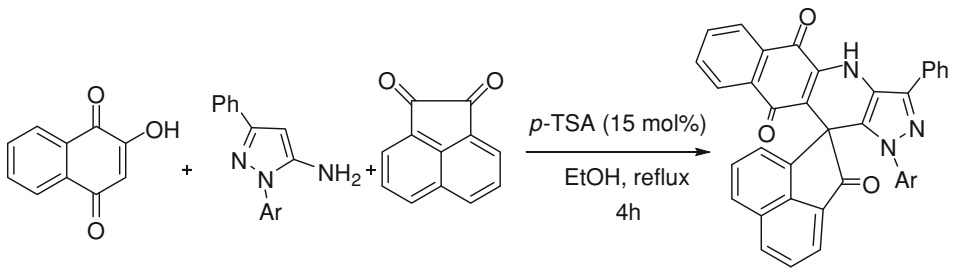
Experimental

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 MHz. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer, and results agreed favorably with calculated values. Absorption spectra were recorded on a Shimadzu UV-2100 spectrophotometer. Fluorescence spectra were recorded using a PerkinElmer LS45 spectrofluorophotometer. Chemicals were purchased from Fluka or Merck and used as received.

Scheme 2



Scheme 3



1 **2a-2c** **5**

Ar= C_6H_5	93%	**6a**
Ar= 4-MeO-C_6H_4	88%	**6b**
Ar= 4-Br-C_6H_4	85%	**6c**

Table 2 UV-vis and fluorescence emission data for compounds **4** and **6** in methanol

Entry	Product	λ_{abs}/nm	log ε	λ_{em}/nm
1	**4a**	462	3.44	628
2	**4b**	475	3.55	626
3	**4c**	471	3.41	629
4	**4d**	471	3.39	630
5	**4e**	473	3.60	631
6	**4f**	476	3.58	626
7	**4g**	477	3.45	635
8	**4h**	463	3.60	619
9	**4i**	470	3.74	628
10	**4j**	477	3.54	633
11	**6a**	478	3.70	626
12	**6b**	477	3.49	633
13	**6c**	484	3.67	648

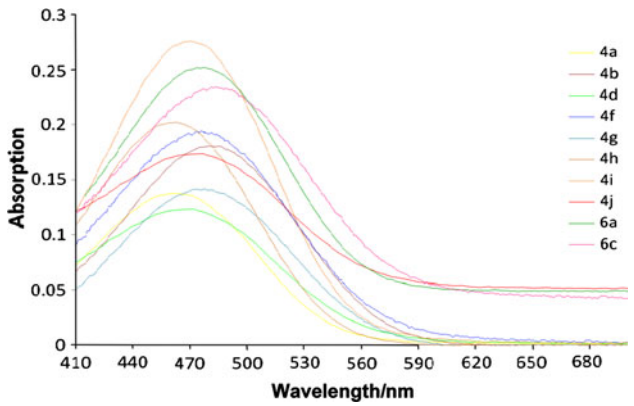


Fig. 1 The visible spectra of the selected compounds **4** and **6** (5×10^{-5} M in methanol)

*Typical procedure for the preparation of compounds **4** and **6***

A mixture of isatin or acenaphthylene-1,2-dione (1 mmol), 1*H*-pyrazol-5-amine (1 mmol), 2-hydroxy-1,4-naphthoquinone (1 mmol), and *p*-TSA (15 mol%) in 5 cm^3 refluxing EtOH was stirred for 4 h. After the reaction had completed, as confirmed by TLC (eluent: EtOAc/*n*-hexane 1:3), the reaction mixture was filtered and the precipitate washed with water and then 5 cm^3 EtOH to afford the pure products. Due to the very low solubility of the products, we are unable to report the ^{13}C NMR data for these products.

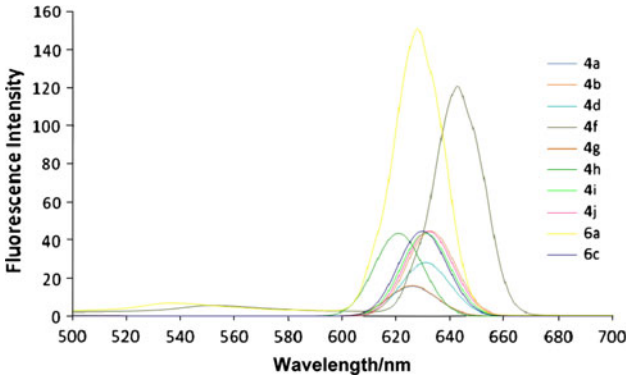


Fig. 2 The emission spectra of the selected compounds **4** and **6** (5×10^{-5} M in methanol)

1,4-Dihydro-1,3-diphenylspiro[11H-benzo[g]pyrazolo-[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4a**, $C_{33}H_{20}N_4O_3$)

Red powder; m.p.: 267–270 °C; IR (KBr): $\bar{\nu}$ = 3,426, 3,343, 1,755, 1,727, 1,678 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 6.61–8.57 (18H, m, arom), 10.46 (1H, s, NH), 11.47 (1H, s, NH) ppm; MS: *m*/*z* = 520 (M^+).

1,4-Dihydro-1-(4-methoxyphenyl)-3-phenylspiro[11H-benzo[g]pyrazolo[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4b**, $C_{34}H_{22}N_4O_4$)

Dark red powder; m.p.: 260–262 °C; IR (KBr): $\bar{\nu}$ = 3,343, 3,200, 1,745, 1,650, 1,615 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.86 (1H, s, OCH_3), 6.67 (3H, d, *J* = 4.6 Hz, arom), 7.15–7.39 (8H, m, arom), 7.60 (2H, d, *J* = 8.1 Hz, arom), 7.79 (3H, bs, arom), 8.07 (1H, d, *J* = 6.5 Hz, arom), 9.90 (1H, s, NH), 10.09 (1H, s, NH) ppm; MS: *m*/*z* = 550 (M^+).

1-(4-Bromophenyl)-1,4-dihydro-3-phenylspiro[11H-benzo-[g]pyrazolo[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4c**, $C_{34}H_{21}BrN_4O_3$)
Orange powder; m.p.: 254–257 °C; IR (KBr): $\bar{\nu}$ = 3,150, 3,056, 1,711, 1,679, 1,644 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 6.44 (1H, d, J = 8.6 Hz, arom), 6.63 (2H, d, J = 7.3 Hz, arom), 6.90–7.82 (13H, m, arom), 8.07 (1H, d, J = 8.7 Hz, arom), 12.10 (1H, s, NH), 12.49 (1H, s, NH) ppm; MS: m/z = 600 ($[M + 2]^+$), 598 (M^+).

1,4-Dihydro-1-(4-nitrophenyl)-3-phenylspiro[11H-benzo[g]pyrazolo[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4d**, $C_{33}H_{19}N_5O_5$)
Red powder; m.p.: >300 °C; IR (KBr): $\bar{\nu}$ = 3,210, 3,061, 1,715, 1,676, 1,644 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.72 (1H, d, J = 9.0 Hz, arom), 8.94 (2H, d, J = 8.1 Hz, arom), 9.36–10.03 (13H, m, arom), 10.25 (1H, d, J = 8.9 Hz, arom), 10.05 (1H, s, NH), 10.18 (1H, s, NH) ppm; MS: m/z = 565 (M^+).

5′-Bromo-1′-ethyl-1,4-dihydro-1,3-diphenylspiro[11H-benzo[g]pyrazolo[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4e**, $C_{35}H_{23}BrN_4O_3$)
Red powder; m.p.: 268–271 °C; IR (KBr): $\bar{\nu}$ = 3,255, 1,722, 1,705, 1,677 cm^{-1}; H NMR (DMSO-d_6): δ = 0.83 (3H, bs, CH_3), 3.15 (2H, bs, CH_2), 6.63–8.05 (17H, m, arom), 9.98 (1H, s, NH) ppm; MS: m/z = 628 ($[M + 2]^+$), 626 (M^+).

5′-Bromo-1′-ethyl-1,4-dihydro-1-(4-methoxyphenyl)-3-phenylspiro[11H-benzo[g]pyrazolo[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4f**, $C_{36}H_{25}BrN_4O_4$)
Dark red powder; m.p.: 253–256 °C; IR (KBr): $\bar{\nu}$ = 3,360, 1,749, 1,705, 1,639 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.05 (3H, bs, CH_3), 3.42 (2H, bs, CH_2), 3.85 (3H, s, OCH_3), 6.68–8.06 (17H, m, arom), 10.01 (1H, s, NH) ppm; MS: m/z = 658 ($[M + 2]^+$), 656 (M^+).

1,4-Dihydro-5′-nitro-1,3-diphenylspiro[11H-benzo[g]-pyrazolo[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4g**, $C_{33}H_{19}N_5O_5$)
Dark red powder; m.p.: 270–273 °C; IR (KBr): $\bar{\nu}$ = 3,426, 3,327, 1,705, 1,672, 1,650 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 6.70 (3H, d, J = 7.4 Hz, arom), 7.15–8.06 (13H, m, arom), 8.51 (1H, d, J = 6.4 Hz, arom), 10.84 (1H, s, NH), 11.16 (1H, s, NH) ppm; MS: m/z = 565 (M^+).

1,4-Dihydro-5′-nitro-1-(4-nitrophenyl)-3-phenylspiro-[11H-benzo[g]pyrazolo[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4h**, $C_{33}H_{18}N_6O_7$)
Dark red powder; m.p.: >300 °C; IR (KBr): $\bar{\nu}$ = 3,418, 3,329, 1,711, 1,670, 1,653 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 6.51 (1H, d, J = 8.3 Hz, arom), 6.75 (2H, d, J = 7.9 Hz, arom), 7.12–7.82 (12H, m, arom), 8.06 (1H, d, J = 6.4 Hz, arom), 10.28 (1H, s, NH), 10.59 (1H, s, NH) ppm; MS: m/z = 610 (M^+).

1,4-Dihydro-5′-methyl-1,3-diphenylspiro[11H-benzo[g]pyrazolo[4,3-b]quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4i**, $C_{34}H_{22}N_4O_3$)
Red powder; m.p.: >300 °C; IR (KBr): $\bar{\nu}$ = 3,194, 3,056, 1,716, 1,678 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.17 (3H, s, CH_3), 6.49–8.05 (17H, m, arom), 10.02 (1H, s, NH), 10.07 (1H, s, NH) ppm; MS: m/z = 534 (M^+).

1-(4-Bromophenyl)-1,4-dihydro-3-phenyl-1′-(phenylmethyl)spiro[11H-benzo[g]pyrazolo[4,3-b]-quinoline-11,3′-[3H]indole]-2′,5,10(1′H)-trione (**4j**, $C_{40}H_{25}BrN_4O_3$)
Red powder; m.p.: >300 °C; IR (KBr): $\bar{\nu}$ = 3,211, 1,710, 1,681, 1,623 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.91 (1H, d, J = 16 Hz, CH_2), 4.79 (1H, d, J = 16 Hz, CH_2), 6.42 (1H, d, J = 8.9 Hz, arom), 6.62 (2H, d, J = 6.5 Hz, arom), 6.91–7.83 (18H, m, arom), 8.09 (1H, d, J = 8.9 Hz, arom), 10.11 (1H, s, NH) ppm; MS: m/z = 690 ($[M + 2]^+$), 688 (M^+).

1′,4′-Dihydro-1′,3′-diphenylspiro[acenaphthylene-1(2H),11′-[11H]benzo[g]pyrazolo[4,3-b]quinoline]-2,5′,10′-trione (**6a**, $C_{37}H_{21}N_3O_3$)
Red powder; m.p.: 252–255 °C; IR (KBr): $\bar{\nu}$ = 3,205, 1,718, 1,670, 1,607 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 6.17 (2H, d, J = 6.6 Hz, arom), 6.60 (2H, t, J = 6.3 Hz, arom), 6.85 (1H, t, J = 6.1 Hz, arom), 7.49–8.12 (15H, m, arom), 10.05 (1H, s, NH) ppm; MS: m/z = 555 (M^+).

1′,4′-Dihydro-1′-(4-methoxyphenyl)-3′-phenylspiro-[acenaphthylene-1(2H),11′-[11H]benzo[g]pyrazolo-[4,3-b]quinoline]-2,5′,10′-trione (**6b**, $C_{38}H_{23}N_3O_4$)
Red powder; m.p.: 263–266 °C; IR (KBr): $\bar{\nu}$ = 3,183, 1,705, 1,678, 1,611 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.86 (3H, s, CH_3), 6.15 (2H, d, J = 8.7 Hz, arom), 6.59 (2H, t, J = 8.9 Hz, arom), 6.85 (1H, t, J = 8.4 Hz, arom), 7.15 (2H, d, J = 8.9 Hz, arom), 7.48–8.13 (12H, m, arom), 9.92 (1H, s, NH) ppm; MS: m/z = 585 (M^+).

1′-(4-Bromophenyl)-1′,4′-dihydro-3′-phenylspiro[acenaphthylene-1(2H),11′-[11H]benzo[g]pyrazolo[4,3-b]quinoline]-2,5′,10′-trione (**6c**, $C_{37}H_{20}BrN_3O_3$)
Red powder; m.p.: 266–269 °C; IR (KBr): $\bar{\nu}$ = 3,200, 1,711, 1,678, 1,617 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 6.14–8.08 (19H, m, arom), 10.26 (1H, s, NH) ppm; MS: m/z = 635 ($[M + 2]^+$), 633 (M^+).

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