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Synthesis of benz[*f*]indole-4,9-diones via acetylenic derivatives of 1,4-naphthoquinone

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ABSTRACT

A synthetic route to benz[*f*]indole-4,9-diones from 1,4-naphthoquinone is described. Effective methods for cross-coupling of 3-acetylamino-2-bromo-1,4-naphthoquinone with terminal acetylenes and cyclization of the resulting 3-acetylamino-2-alkynyl-1,4-naphthoquinones are developed.

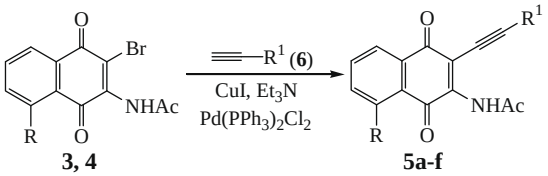
A number of drugs and biologically active compounds, for example, physostigmine, mitomycin, indomethacin, tryptophan, serotonin, and strychnine contain an indole nucleus.[1–6] In medicinal chemistry, indole is considered a privileged structure because of its ability to bind multiple receptors with high affinity.[7,8] As a result of this feature substituted indoles and complex systems possessing an indole moiety show diverse, and often strong biological activity. Therefore, indole compounds represent an important structural class in drug discovery.[8] Continuing investigations in this area stimulate the development of novel and effective methods for the synthesis and derivatization of indoles.

Intramolecular cyclization of *ortho*-alkynylarylamines or -amides has been successfully exploited for preparing indole structures.[9,10] However, the applicability of this method to the synthesis of indolequinones has not been studied, presumably due to the lack of methods available for introducing acetylenic substituents to a quinone ring.

Earlier we described the preparation of *N*-substituted 2-phenylbenz[*f*]indole-4,9-diones via oxidative amination of 2-phenylethynyl-1,4-naphthoquinone with primary amines followed by cyclization in the presence of KOH in boiling pyridine.[11] We have also carried out photochemical heterocyclizations of 2-dialkylamino-3-alkynyl-1,4-quinones.[12,13] Herein, we report the synthesis of 2-substituted benz[*f*]indole-4,9-diones **1** from 1,4-naphthoquinone **2** via its acetylenic derivatives.

We found that 3-acetylamino-2-bromo-1,4-naphthoquinone **3** and its 5-acetylamino derivative **4**, unlike non-acylated bromoamines, reacted smoothly with various cuprous acetylides in the presence of $Pd(PPh_3)_2Cl_2$ in a mixture of DMSO and $CHCl_3$ to yield alkynylnaphthoquinones **5**.[14] The acetylides were prepared in situ from equivalent quantities of terminal acetylenes **6**, CuI, and Et_3N. Acetylides that cannot be isolated in the solid state were obtained in the same way. The condensation reaction was completed within 15–40 min at rt (Scheme 1, Table 1).

Without the Pd-catalyst the condensation proceeded much more slowly and became complicated by side reactions. The cross-coupling of bromides **3** and **4** with terminal acetylenes **6** under standard Sonogashira reaction conditions[15] did not afford the desired products.



Scheme 1.

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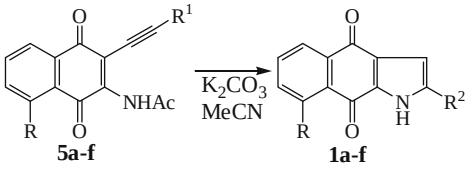
Table 1
Cross-coupling of bromides **3** and **4** with terminal acetylenes **6**

Entry	R	R^1	Product	Yield[a] (%)
1	H	Ph	**5a**	77
2	H	CMe_2OH	**5b**	72
3	H	C(*cyclo*-Pr)MeOH	**5c**	73
4	H	1-HO-cyclohexyl	**5d**	59
5	H	CH_2–OTHP	**5e**	65
6	NHAc	CMe_2OH	**5f**	92

[a] Isolated yield.



Scheme 2.

Cyclization of *ortho*-alkynylarylamines and -amides is usually carried out with transition metal salts or complexes, strong bases and $Bu_4N^+F^-$ as catalysts.[16] Naphthoquinones **5** bearing acetylenic and amido substituents on the non-aromatic quinone ring cyclized in the presence of an equimolar quantity of powdered K_2CO_3 in MeCN at 80 °C in 15–40 min. The cyclization was followed by deacetylation which led to 2-substituted benz[*f*]indole-4,9-diones **1**.[14] Acetylenic alcohols **5b**,**c**,**d**,**f** also underwent dehydration to form alkenyl-substituted indolequinones **1b**,**c**,**d**,**f** (Scheme 2, Table 2).

Under these conditions, 2-alkynyl-3-amino-1,4-naphthoquinones did not cyclize. We suppose that the inability of these compounds to cyclize under the chosen mild conditions is due to the 'push–pull' conjugation $H_2N\!-\!C\!=\!C\!-\!C\!=\!O$. The potential for cyclization probably depends on delocalization of the negative charge which emerges on the α-C atom of the acetylenic substituent during the nucleophilic addition process. Polarization of the C2=C3 double bond and the increased electron density on the C2 carbon atom hamper the delocalization and, hence prevent the reaction occurring. The +M effect of the amido group is noticeably smaller than that of the amino group and acetylation of the latter makes cyclization possible. It is likely that deprotonation of the nucleophile precedes its attack on the triple bond and therefore the greater NH-acidity of the amido group is also of importance. The different reactivities of bromoamide **3** and the corresponding non-acylated bromoamine in the cross-coupling, as with those of amides **5** and the corresponding non-acylated acetylenic amines in cyclizations, are explained by the properties of their conjugated systems.

For derivatization or insertion of the benzindolequinone core in more complex structures it is desirable to activate its benzene ring. This can be achieved by introducing an amino group.[17] The amino group activates the ring toward electrophilic substitution (iodination, etc.) and can itself be replaced by other functions. Acetylenic amide **5f** bearing an additional acetylamino group at position 5 was shown to cyclize easily into indole **1f** (Table 2, entry 6). Thus, the method developed allows the synthesis of benzindolequinones with activated benzene rings.

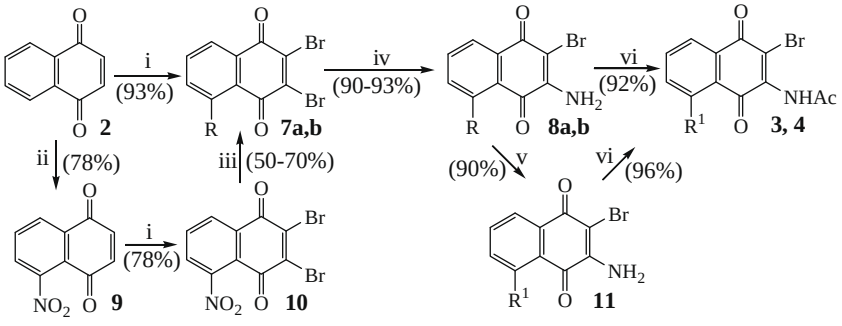
The procedures developed for alkynylation and annulation of the quinone ring of 1,4-naphthoquinone **2** with a pyrrole ring are the key and final steps of the synthesis of benz[*f*]indole-4,9-diones **1**. The preceding steps are shown in Scheme 3.

Naphthoquinone **2** was brominated with Br_2 in AcOH in the presence of a small quantity of I_2.[18] One of the halogen atoms of the resulting dibromide **7a** was substituted by an amino group under the action of aqueous NH_3 in dioxane. Acetylation of bromoamine **8a** using Ac_2O in the presence of a catalytic quantity of H_2SO_4 in $CHCl_3$ led to the pivotal precursor **3**. In order to synthesize

Table 2
Cyclization of acetylenic amides **5**

Entry	Substrate	Product	R	R^1	R^2	Yield[a] (%)
1	**5a**	**1a**	H	Ph	Ph	72
2	**5b**	**1b**	H	CMe_2OH	$C(Me)=CH_2$	64
3	**5c**	**1c**	H	C(*cyclo*-Pr)MeOH	$C(cyclo\text{-}Pr)=CH_2$	53
4	**5d**	**1d**	H	1-HO-cyclohexyl	Cyclohex-1-enyl	70
5	**5e**	**1e**	H	CH_2–OTHP	CH_2–OTHP	61
6	**5f**	**1f**	NHAc	CMe_2OH	$C(Me)=CH_2$	75

[a] Isolated yield.



7a, **8a**: R = H; **3**: R^1 = H

7b, **8b**: R = NH_2; **4**, **11**: R^1 = NHAc

Scheme 3. Reagents and conditions: (i) Br_2/I_2, AcOH, 118 °C; (ii) $NaNO_3$–H_2SO_4, 0–40 °C; (iii) $SnCl_2$, AcOH–HCl, 50–70 °C; (iv) aq NH_3, dioxane, rt; (v) Ac_2O–H_2SO_4, dioxane, 50 °C; (vi) Ac_2O–H_2SO_4, $CHCl_3$, 50 °C.

8-substituted benzindoledione **1f**, naphthoquinone **2** was nitrated using a mixture of $NaNO_3$–H_2SO_4 at 0–40 °C.[19] Bromination of 5-nitro-1,4-naphthoquinone **9**, analogously to quinone **2**, afforded nitrodibromide **10** which was reduced to amine **7b** by $SnCl_2$ in AcOH–HCl at 70 °C. The amino group at position 5 directs an entering nucleophile predominantly to position 3.[20] Treatment of **7b** with aqueous NH_3 gave 3,5-diamino-2-bromo-1,4-naphthoquinone **8b**. Acetylation of **8b** was carried out in two steps. 5-Acetylamino-3-amino-2-bromo-1,4-naphthoquinone **11** was the main product of the first step (Ac_2O, H_2SO_4, dioxane, 50 °C). The second step proceeded readily under the same conditions, but in $CHCl_3$, and yielded bromodiamide **4**.

Thus, a variant of the cross-coupling of 3-acetylamino-2-bromo-substituted 1,4-naphthoquinones with terminal acetylenes and a method for intramolecular cyclization of the resulting amidoacetylenes with closure of a pyrrole ring have been developed leading to the synthesis of benz[*f*]indole-4,9-diones from commercially available 1,4-naphthoquinone.

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14. *All compounds gave satisfactory analytical and spectroscopic data*. Typical ^{1}H NMR and IR spectra are presented below. *Compound* **5c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.40–0.80 (m, 4H, CH_2–CH_2), 1.15–1.30 (m, 1H, CH), 1.66 (s, 3H, CH_3), 2.28 (s, 3H, Ac), 2.60 (br s, 1H, OH), 7.65–7.80 (m, 2H, H-6,7), 7.97 (br s, 1H, NH), 8.00–8.15 (m, 2H, H-5,8); IR ν_{max}($CHCl_3$)/cm^{-1} 1667, 1723 (C=O), 2218 (C≡C), 3366 (NH), 3585 (OH). *Compound* **5f**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.61 (s, 6H, CH_3), 2.28 (s, 3H, NAc-3(5)), 2.29 (s, 3H, NAc-5(3)), 2.72 (br s, 1H, OH), 7.65–7.90 (m, 2H, H-6(8),7), 7.99 (br s, 1H, NH-3), 9.03 (dd, 1H, H-8(6), J_1 = 8.5 Hz, J_2 = 1.3 Hz), 11.59 (br s, 1H, NH-5); IR ν_{max}($CHCl_3$)/cm^{-1}1634, 1666, 1707 (C=O), 2217 (C≡C), 3303, 3369 (NH), 3496 (br OH). *Compound* **1d**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.55–1.85 and 2.15–2.45 (both m, 8H, $(CH_2)_4$), 6.35–6.45 (m, 1H, HC=C), 6.73 (d, 1H, H-3, J = 2.3 Hz), 7.55–7.75 (m, 2H, H-6,7), 8.05–8.20 (m, 2H, H-5,8), 9.90 (br s, 1H, H-1); IR ν_{max}($CHCl_3$)/cm^{-1}1647 (C=O), 3432 (NH). *Compound* **1f**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.14 (s, 3H, CH_3), 2.29 (s, 3H, Ac), 5.23 (d, 1H, =CH-*Z*(*E*), J = 1.5 Hz), 5.46 (s, 1H, =CH-*E*(*Z*)), 6.78 (d, 1H, H-3, J = 2.4 Hz), 7.55–7.70 (m, 1H, H-6), 7.93 (dd, 1H, H-7(5), J_1 = 7.6 Hz, J_2 = 1.2 Hz), 8.97 (dd, 1H, H-5(7), J_1 = 8.5 Hz, J_2 = 1.2 Hz), 9.33 (br s, 1H, H-1), 12.18 (br s, 1H, NH-8); IR ν_{max}($CHCl_3$)/cm^{-1}1628, 1669, 1695 (C=O), 3432 (NH).
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