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Synthesis of Indolequinones from Bromoquinones and Enamines Mediated by $Cu(OAc)_2 \cdot H_2O$

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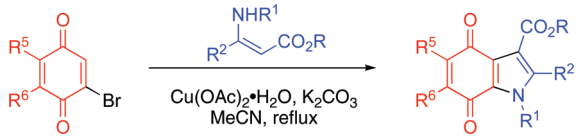


A Cu(II)-mediated synthesis of indolequinones from the corresponding bromoquinones and enamines is reported. The key oxidative cyclization proceeds in good yield for a broad range of substrates and can be performed on a multigram scale, allowing access to biologically interesting structures.

Since the discovery of the naturally occurring, clinically used antitumor agent mitomycin C (MMC) **1**,[1−3] the indolequinone pharmacophore has attracted considerable attention owing to the biological activity associated with such compounds (Figure 1). For example, the indolequinone EO9 (apaziquone) **2**[4] is currently in phase II clinical trials for bladder cancer,[5] and ES936 **3** and related compounds have shown some early promise against pancreatic cancer.[6,7] The fact that many anticancer indolequinones require reductive activation to form electrophilic species toxic to cells is well-known, and the drugs act as substrates for one or more of the reductases present in most cells. Mitomycin C has long been regarded as the archetypal quinone bioreductive anticancer agent, and more recently, the concept has been extended to bioreductive drug delivery systems, indolequinones that

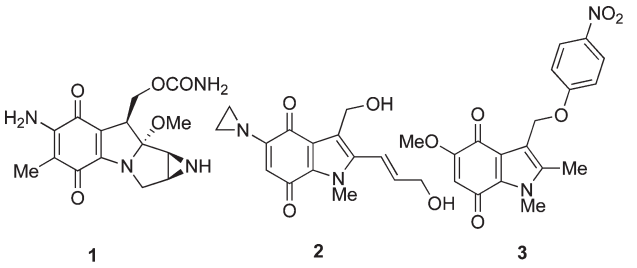
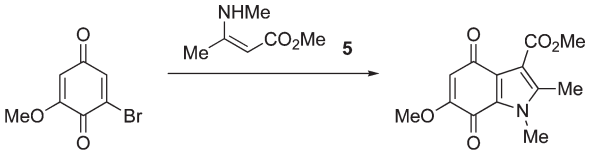


FIGURE 1. Indolequinones with anticancer properties.

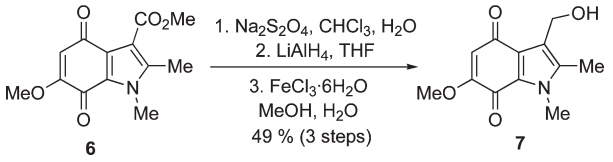
TABLE 1. Optimization of Indolequinone 6 Formation from Bromoquinone 4 and Enamine 5[a]



oxidant (equiv)	solvent	base (equiv)	time/h	T/°C	yield/%
$CuBr_2$ (0.2)	MeOH	K_2CO_3 (3.5)	2	rt	39
$CuBr_2$ (1)	MeOH	K_2CO_3 (3.5)	2	rt	22
$CuBr_2$ (0.2)	MeOH	NEt_3 (3.5)	2	rt	0
$CuBr_2$ (0.2)	MeCN	K_2CO_3 (3.5)	24	rt	41
$CuBr_2$ (1.5)	MeCN	K_2CO_3 (3.5)	2.5	80	46
$Cu(OAc)_2 \cdot H_2O$ (3)	DMF	K_2CO_3 (3)	0.17	140	62
$Cu(OAc)_2 \cdot H_2O$ (3)	DMF	K_2CO_3 (3)	0.25	100	63
$Cu(OAc)_2 \cdot H_2O$ (0.2)	MeCN	K_2CO_3 (3)	2.5	80	60
$Cu(OAc)_2 \cdot H_2O$ (3)	MeCN	K_2CO_3 (3)	2.5	80	78
$Cu(OAc)_2 \cdot H_2O$ (1.5)	MeCN	K_2CO_3 (3)	3.5	80	89

[a]Reactions were carried out in air, and the product was isolated by chromatography in all cases.

SCHEME 1



fragment to release an active drug upon reductive activation.[8−11]

In continuation of our studies into the anticancer activity of indolequinones and, in particular, their ability to serve as substrates or inhibitors of the human quinone reductase

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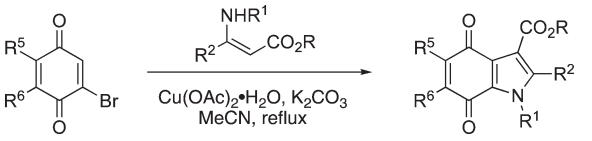
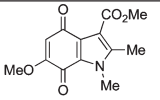
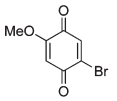
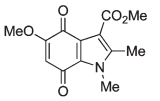
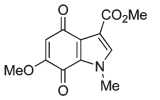
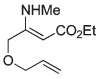
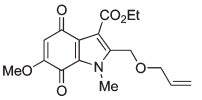
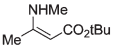
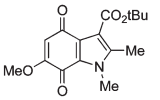
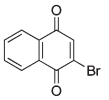
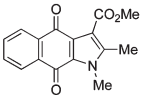
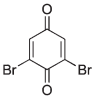
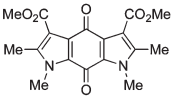
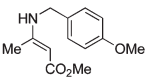
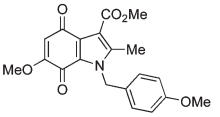
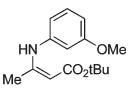
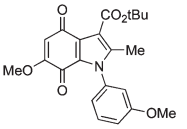
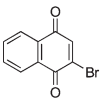
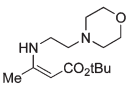
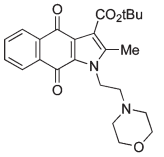
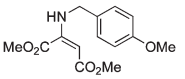
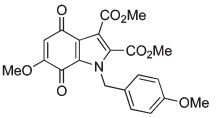
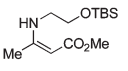
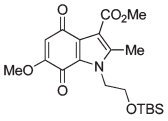
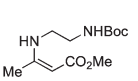
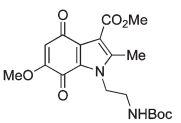
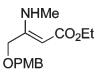
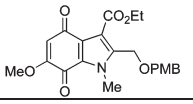
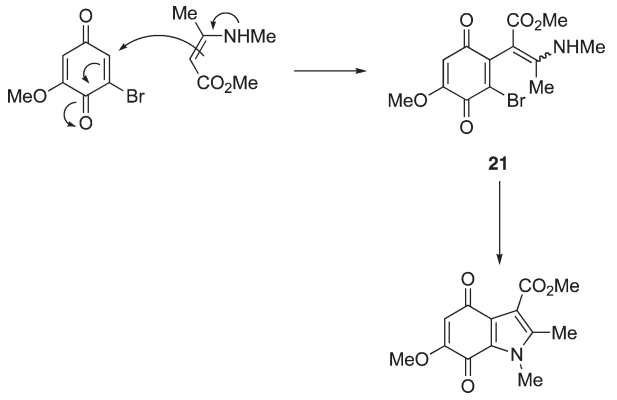
TABLE 2. Indolequinone Synthesis by Copper(II) Acetate Mediated Addition of Enamines to Bromoquinones



entry	bromoquinone	enamine	time (h)		indolequinone	yield %
1	**4**	**5**	3.5	**6**		89
2		**5**	7	**8**		49
3	**4**		20	**9**		64
4	**4**		16	**10**		64
5	**4**		6	**11**		72
6		**5**	4.5	**12**		71
7		**5**	6	**13**		35
8	**4**		4.5	**14**		89
9	**4**		4	**15**		73
10			4	**16**		71
11	**4**		4	**17**		52
12	**4**		2.5	**18**		78
13	**4**		4	**19**		90
14	**4**		14	**20**		75

SCHEME 2



NAD(P)H:quinone oxidoreductase 1 (NQO1),[12−17] we required a scalable and general route to the heterocyclic framework. We report here an efficient, convergent, and general procedure for the synthesis of indolequinone-3-carboxylate esters that can be readily converted into a range of biologically active derivatives.

In their approach to the synthesis of mitosenes related to MMC, Luly and Rapoport reported the reaction of 2,3-dibromo-1,4-benzoquinones with enamine derivatives to give the indolequinone core structure.[18] Subsequently, in their synthesis of EO9 and related mitosenes, Murphy et al. reported a synthesis of indolequinone esters by oxidative annulation of monobromoquinones with enamines, using catalytic amounts of copper(II) bromide and utilizing air as the terminal oxidant.[19,20] Although this appears to be an attractive route, the procedure proved extremely sensitive to structural changes in the substrates and generally gave unsatisfactory yields in our hands. Therefore, we initiated a series of optimization experiments using the reaction of 2-bromo-6-methoxy-1,4-benzoquinone **4** and methyl *N*-methylamino-crotonate **5** (to give the indolequinone **6**) under a range of conditions employing copper(II) salts (Table 1). The results suggest that copper(II) acetate is superior to the bromide in mediating the reaction, with the optimum conditions (89% yield of indolequinone **6**) employing 1.5 equiv of copper(II) acetate monohydrate with K_2CO_3 in boiling acetonitrile. When the reaction was carried out under argon, the yield was reduced to 62%. The reaction still proceeds with catalytic amounts of copper, suggesting that either air or the copper(II) salt can act as the terminal oxidant.

Under the optimized conditions, the reaction could be repeated on a large scale, and the product could also be isolated by recrystallization from methanol, with a slight reduction in yield to 65%. The regiochemistry of the reaction was confirmed by conversion of the product **6** into the known 3-hydroxymethylindolequinone **7**[16] via a three-step procedure, starting with reduction of the quinone with sodium dithionite followed by reduction of the ester with lithium aluminum hydride and reoxidation of the hydroquinone to the quinone **7** with iron(III) chloride (Scheme 1). Comparison of the ^{13}C NMR spectrum of the alcohol thus derived with an authentic sample confirmed conclusively that the regiochemistry was as shown in Scheme 1.

In order to investigate the generality of this method, a number of bromoquinones were reacted with a wide range of enamines, readily available in excellent yield by condensation of primary amines with β-keto esters or by 1,4-addition of primary amines to electron-deficient alkynes, to give indolequinones **6** and **8**−**20** bearing various functional groups (Table 2). A wide range of functionalities was tolerated, including TBS, allyl and PMB ethers, Boc-protected amines, and methyl, ethyl, and *tert*-butyl esters. The *N*-substituent could be varied to include alkyl and aryl functionalities, but attempts to synthesize 1-unsubstituted derivatives using methyl 3-aminocrotonate proved unsuccessful. Reaction of 2,6-dibromo-1,4-benzoquinone with 2 equiv of the enamine component allowed access to the symmetrical pyrroloindolequinone **13** in moderate yield (Table 2, entry 7).

The inferior reactivity of 2-bromo-5-methoxybenzoquinone, compared with the 6-methoxy isomer, is noteworthy but is consistent with the results reported by Murphy and coworkers[20] and with the proposed mechanism which begins with 1,4-addition of the enamine through carbon to the 3-position of the bromoquinone and reoxidation (Scheme 2). Premature termination of the reaction afforded the intermediate uncyclized enaminoquinone **21**, observed in all reactions as a red component which eventually converted to the product under the reaction conditions.

In summary, we present an efficient, regioselective, and versatile method for the construction of indolequinones from various bromoquinones and enamines. The indolequinones serve as precursors to a range of derivatives with anticancer properties.

Experimental Section

Bromoquinones. 2-Bromo[1,4]naphthoquinone is commercially available; 2-bromo-6-methoxy[1,4]benzoquinone,[21] 2-bromo-5-methoxy[1,4]benzoquinone,[21] and 2,6-dibromo[1,4]benzoquinone[22] were prepared by literature methods.

Preparation of Enamines: Typical Procedure. (*Z*)-*tert*-Butyl 3-(Methylamino)but-2-enoate. A solution of methylamine (25% w/v in water; 3.72 mL, 30 mmol) was added in a single portion to a stirred suspension of silica gel (0.3 g) and *tert*-butyl acetoacetate (3.95 g, 25 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 15 h. The mixture was extracted with dichloromethane (3 × 15 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the title compound as a pale yellow oil (4.15 g, 97%): found $M + H^+$, 172.1342, $C_9H_{18}NO_2$ requires 172.1332; IR ν_{max} ($CHCl_3$)/cm^{-1} 3306, 3005, 2980, 2931, 1595, 1293; NMR δ_H (400 MHz; $CDCl_3$) 8.45 (1H, br s, NH), 4.41 (1H, s, CH), 2.89 (3H, d, J = 4.8 Hz, NMe), 1.89 (3H, s, Me), 1.47 (9H, s, *t*Bu); δ_C (75 MHz; $CDCl_3$) 170.9, 162.2, 83.5 (CH), 77.7, 29.5 (Me), 28.6 (Me), 19.0 (Me); HRMS *m*/*z* (EI) 365 ($2M + Na^+$, 100), 172 ($M + H^+$, 79).

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General Procedure for the Synthesis of Indolequinones. A solution of enamine (1.0−4.0 equiv) in acetonitrile (5−10 mL/mmol) was added to a mixture of bromoquinone (1.0 equiv), copper(II) acetate monohydrate (1.5 equiv), and potassium carbonate (3.0 equiv). The resulting mixture was stirred at reflux under air for the indicated time, cooled to room temperature, diluted with dichloromethane (20 mL/mmol), filtered through Celite, and concentrated in vacuo. Column chromatography of the residue gave the indolequinone.

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Supporting Information Available: Full experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.