



Accessing benzo[*f*]indole-4,9-diones via a ring expansion strategy: silver-catalyzed tandem reaction of tosylmethyl isocyanide (TosMIC) with 2-methyleneindene-1,3-diones



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ABSTRACT

A silver-catalyzed tandem reaction of TosMIC with 2-methyleneindene-1,3-diones was developed for the direct synthesis of benzo[*f*]indole-4,9-diones. In this reaction, a domino [3+2]-cycloaddition/imidoyl anion cyclization/ring opening of cyclopropanolate/aromatization is proposed and three C–C bonds are formed successively.

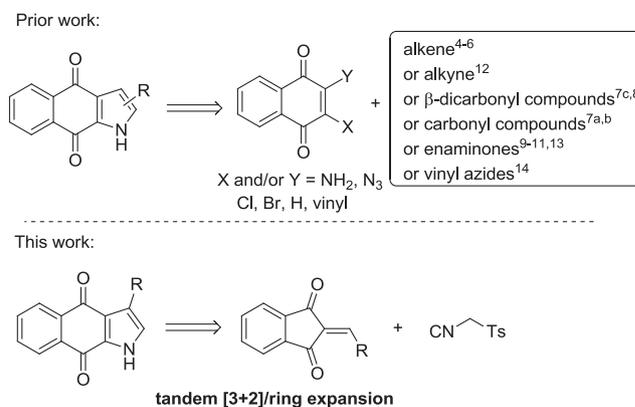
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1. Introduction

Benzo[*f*]indole-4,9-dione is the core structure of natural product Utahmycin B,¹ and 3-methyl-1H-benzo[*f*]indole-4,9-dione was found in *Goniothalamus tapis* Miq.² Meanwhile, many synthesized benzo[*f*]indole-4,9-dione derivatives have diversified biological activity.^{1–3} As a consequence, the synthesis of this scaffold has drawn much attention and numerous synthetic methods have been developed in the literature.^{3–14} These include, intramolecular thermal conversion of 2-azido-3-vinyl-1,4-naphthoquinones,⁴ intermolecular photochemical reaction of 2-azido-⁵ or 2-amino-1,4-naphthoquinones⁶ with alkenes, manganese⁷ or cerium salts⁸ initiated oxidative free radical reactions between 2-amino-1,4-naphthoquinones and β-dicarbonyl compounds or carbonyl compounds, C,N-dialkylation of enamines by 2,3-dichloronaphthoquinone,⁹ CAN-catalyzed multicomponent reaction of 2-bromo-1,4-naphthoquinone, primary amine and β-dicarbonyl compounds,¹⁰ Cu(II)-mediated reaction of 2-bromonaphthoquinone with enamines,¹¹ Pd-catalyzed Sonogashira coupling/cyclization cascade reaction of 2-amino-3-bromo/iodo-1,4-naphthoquinones with alkynes,¹² copper(II)-catalyzed sequential C,N-difunctionalization of 1,4-naphthoquinone with enamines¹³ and Mn(II)-catalyzed annulation of vinyl azides with 2-

hydroxynaphthoquinone.¹⁴ Generally, these existing methods focused on the construction of the pyrrole rings onto the 1,4-naphthoquinone moieties by the sequential formation of C–N and C–C bonds (Scheme 1, top). Therefore, the development of conceptually distinct methods for the synthesis of this tricyclic framework is still of great interest.

Isocyanides are versatile building blocks in organic synthesis.¹⁵ We have been interested in isonitrile chemistry for years,¹⁶ and recently



Scheme 1. Synthetic protocols for benzo[*f*]indole-4,9-diones.

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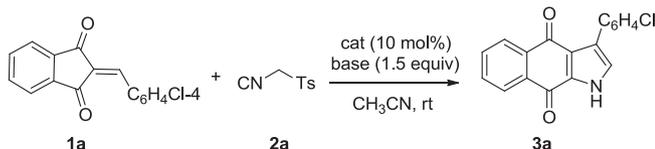
developed a Michael addition/formal isocyanide insertion into the acyl C–C bond cascade for the expedient synthesis of 2-acyl pyrroles and medium-ring fused pyrroles.¹⁷ Thus, it was envisioned that benzo[*f*]indole-4,9-diones could be prepared from the tandem reaction of 2-methyleneindene-1,3-diones and TosMIC via a ring expansion strategy (Scheme 1, bottom). Although the reaction of cyclic oxoketene dithioacetals derived from 1,3-indanedione with methyl isocyanides was reported for the synthesis of 3-(methylthio)-1*H*-benzo[*f*]indole-4,9-diones, the reaction was performed at high temperature (120 °C) and only four examples were presented.¹⁸ Herein, we describe a silver-catalyzed tandem reaction of 2-methyleneindene-1,3-diones and TosMIC for the practical construction of benzo[*f*]indole-4,9-diones in high to excellent yields (Scheme 1, bottom).

2. Results and discussion

Initially, the reaction of 2-(4-chlorobenzylidene)-1*H*-indene-1,3(2*H*)-dione **1a** with TosMIC **2** was tested for the optimization of the reaction conditions. It was found that the reaction of **1a** and **2a** to the formation of annulated indolequinone derivative **3a** in 15% yield (Table 1, entry 1) under our previous reported conditions¹⁷ (in the presence of DBU (1.1 equiv) in CH₃CN at room temperature for 11 h). When CuBr₂ (0.1 equiv) and anhydrous K₂CO₃ (1.5 equiv) were employed, the yield of **3a** was improved to 36% (Table 1, entry 2). Further screening of catalysts revealed that **3a** could be obtained in excellent yield when the reaction of **1a** (1.0 mmol) with TosMIC **2** (1.1 mmol) was catalyzed by AgOAc (0.1 equiv) in acetonitrile (10 mL) at room temperature for 11 h using K₂CO₃ (1.5 equiv) as the base (Table 1, entry 3). The yield of **3a** was lower in the absence of K₂CO₃ (Table 1, entry 4). In contrast, trace amount of **3a** was detected in the absence of AgOAc (Table 1, entry 5). Among the bases tested, anhydrous K₂CO₃ gave the best result (Table 1, entry 3 vs entries 7 and 8).

The above approach features one-carbon-atom ring expansion along with acyl 1,2-migration for the direct synthesis of benzo[*f*]

Table 1
Optimization of reaction conditions for **3a**



Entry	Catalyst (equiv)	Base (equiv)	Time (h)	3a ^a
1	CuCl (0.1)	DBU (1.5)	11	15
2	CuBr ₂ (0.1)	K ₂ CO ₃ (1.5)	18	36
3	AgOAc (0.1)	K₂CO₃ (1.5)	11	95
4	AgOAc (1.1)	—	24	39
5 ^b	—	K ₂ CO ₃ (1.5)	24	Trace
6	AgOAc (0.1)	K ₂ CO ₃ (0.5)	11	71
7	AgOAc (0.1)	NaOH (1.5)	13	— ^c
8	AgOAc (0.1)	DBU (1.5)	12	38

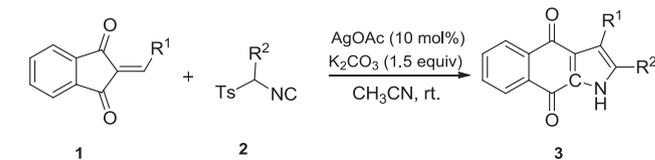
^a Yield of isolated product **3a**.

^b The Michael adduct was obtained in 52%.

^c Complex mixture was obtained.

indole-4,9-diones from simple Michael acceptors and methyl isocyanides under very mild conditions. Further experiments showed that the reaction proceeded more efficiently for various 2-methyleneindene-1,3-diones **1** under optimal conditions as in Table 1 (entry 3) and the results are summarized in Table 2. The selected substrates **1** bearing electron-deficient (entries 1 and 2) and electron-rich (entries 4 and 5), aromatic groups, phenyl (entry 3) and hetero aromatic groups (entries 6 and 7) can afford the corresponding indolequinone derivatives **3a–g** in excellent yields. The vinyl and alkyl substituted benzo[*f*]indole-4,9-diones **3h** and **3i** were also obtained in good yields from **1g** and **1f** bearing a phenyl

Table 2
Synthesis of indole-4,7-quinone derivatives **3**



Entry	R ¹	R ²	Time (h)	3	Yield (%) ^a
1	4-ClC ₆ H ₄	H	11	a	95
2	4-BrC ₆ H ₄	H	11	b	91
3	Ph	H	12	c	89
4	4-CH ₃ OC ₆ H ₄	H	17	d	94
5	4-CH ₃ C ₆ H ₄	H	16	e	94
6 ^b	3-CH ₃ C ₆ H ₄	H	3	f	65
7 ^b	2-CH ₃ C ₆ H ₄	H	3	g	69
8	2-furyl	H	12	h	92
9	2-thienyl	H	12	i	96
10 ^c	PhCH=CH	H	24	j	64
11 ^b	cyclohexyl	H	6	k	61
12 ^b	4-BrC ₆ H ₄	Me	6	l	95
13 ^b	4-BrC ₆ H ₄	allyl	5	m	91
14 ^b	4-BrC ₆ H ₄	TolCH ₂	3	n	78
15 ^b	4-BrC ₆ H ₄	Ph	3	o	60

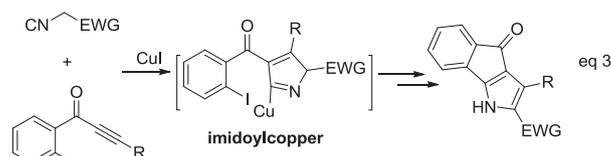
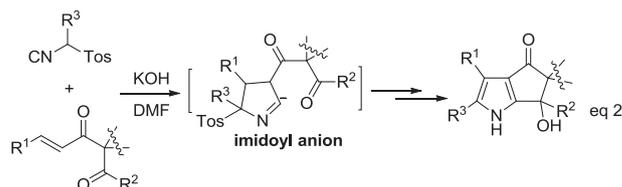
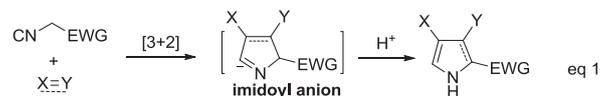
^a Yields of isolated product.

^b 1.1 equiv K₂CO₃ was used.

^c The reaction was performed at 80 °C.

vinyl (entry 8) and cyclohexyl group (entry 9), respectively. In addition, substituted TosMIC **2b** and **2c** gave the 2-methyl- and 2-allyl-benzo[*f*]indole-4,9-diones **3j** and **3k** in excellent yields.

In the formal [3+2]-cycloaddition reaction of TosMIC **2** with activated double or triple bonds, imidoyl anion is generally proposed as a transient intermediate and trapped by a proton to form the final five-membered heterocycles (eq 1).¹⁵ Recently, we reported a protocol for the efficient construction of cyclopenta[*b*]pyrroles by trapping the incipient imidoyl anion with a tethered carbonyl group (eq 2).^{19a} Meanwhile, Cai and Ding reported a formal [3+2] cycloaddition/coupling tandem process for the efficient formation of 4-oxo-indeno[1,2-*b*]pyrroles, in which the reactive imidoylcopper intermediate was involved (eq 2). These results indicate that the imidoyl anions are very reactive intermediates in the [3+2]-cycloaddition of TosMIC, and they could be manipulated for the complex heterocycles synthesis. Thus, it is reasonable that cyclopropanolate intermediates are formed by intramolecular nucleophilic addition of imidoyl anions to carbonyl groups, which are proposed for the possible pathway of acyl migration both in our previous 2-acylpyrrole synthesis¹⁷ and Ila's 3-(methylthio)-1*H*-benzo[*f*]indole-4,9-dione synthesis.¹⁸



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