Rapid synthesis of the indole-indolone scaffold via [3+2] annulation of arynes by methyl indole-2-carboxylates

Donald C. Rogness, Richard C. Larock *

Department of Chemistry, Iowa State University, Ames, IA 50011, USA

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ABSTRACT

The reaction of methyl indole-2-carboxylates and arynes affords a very efficient, high yielding synthesis of a novel indole-indolone ring system, which tolerates considerable functionality, is broad in scope, and proceeds under mild reaction conditions.

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Nitrogen-containing heterocycles exhibit a diverse array of favorable biological and pharmacological properties. The indole core, in particular, is the foundation for many well-known medicinally active compounds.[1] Convenient methods for constructing fused indoles are of great value to medicinal chemists.[1,2] In addition, indolone derivatives possess potent biological activities. Thus, new methodologies for their synthesis contribute significantly to the pursuit of new drugs.[3] Of considerable current interest to medicinal chemists is the synthesis of new drug-like compounds in which two separate biologically interesting scaffolds, both independently known for their favorable activities, are fused.[2,4] Since both indoles and indolones are relevant core structures for pharmaceuticals, a hybrid thereof could potentially lead to a series of biologically active compounds (Fig. 1).

Arynes have been used extensively in recent years in the construction of many heteroaromatic structures.[5] The highly electrophilic nature of benzyne is most suitable for cross coupling with various nucleophilic heteroatoms. If the substrate containing the nucleophilic heteroatom is tethered with a neighboring electrophile, such as a carbonyl group, intramolecular annulations often take place.[6] Recently, our group has reported annulations between *ortho*-heteroatom (N, O, and S) benzoates with arynes, producing a diverse array of medicinally relevant acridones, xanthones, and thioxanthones in good to excellent yields.[7] The proven success and utility of this novel methodology led us to envision a related [3+2] annulation involving the reaction of indole-2-carboxylate esters and arynes. Herein, we report the synthesis of a novel indole-
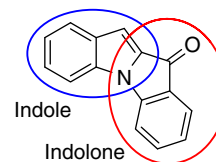

Figure 1. Indole-indolone scaffold.

indolone hybrid, a previously unexplored scaffold with respect to biological activity and materials applications, via the annulation of arynes by methyl indole-2-carboxylates (Scheme 1).

Initial experiments began with ethyl indole-2-carboxylate as our test substrate, but little success was realized using conditions similar to those of our previous annulation chemistry.[7] Switching to the methyl ester, however, produced a slight increase in yield of the desired product (Table 1, entry 1). It was not until we switched to 1,2-dimethoxyethane (DME) as a solvent that decent results were obtained (entry 3). The addition of various bases was examined and a significant improvement in yield was realized when 2 equiv of Cs_2CO_3 was utilized (entry 6). The success of this base over others (entries 7–9) may be attributed to its superior solubility in DME. The success of aryne annulation chemistry often depends heavily on the relative rate of aryne formation versus bimolecular coupling of the substrate and the aryne. For that reason, both the quantity and the nature of the fluoride source, as well as the solvent and temperature, are often critical. CsF has generally been the most popular source of fluoride used in benzyne chemistry and, in fact, it seems to work best for our methodology. Other sources of fluoride, such as tetrabutylammonium reagents have

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* Corresponding author. Tel.: +1 515 294 4660; fax: +1 515 294 0105.
E-mail address: larock@iastate.edu (R.C. Larock).
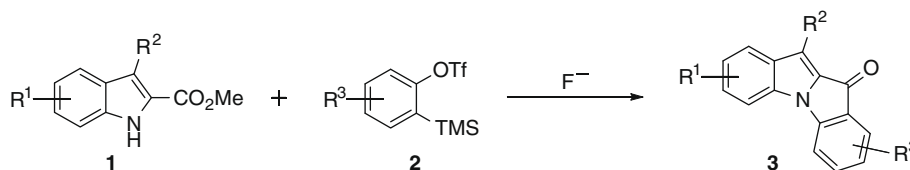
Scheme 1. General reaction of arynes with methyl indole-2-carboxylates.

Table 1
Optimization studies of the reaction between methyl indole-2-carboxylate and *o*-(trimethylsilyl)phenyl triflate (Scheme 1, $R^1 = R^2 = R^3 = H$)[a]

Entry	Aryne precursor (equiv)	Fluoride source[b] (equiv)	Base (equiv)	Solvent	Temp. (°C)	% Yield[c]
1	1.2	CsF (3)	—	THF	65	22
2	1.2	CsF (3)	—	MeCN	80	34
3	1.2	CsF (3)	—	DME	90	44
4	1.2	CsF (3)	Cs_2CO_3 (1.1)	DME	90	52
5	1.5	CsF (3)	Cs_2CO_3 (1.1)	DME	90	55
6	**1.5**	**CsF (3)**	**Cs_2CO_3 (2.0)**	**DME**	**90**	**70**
7	1.5	CsF (3)	Na_2CO_3 (2.0)	DME	90	34
8	1.5	CsF (3)	K_2CO_3 (2.0)	DME	90	34
9	1.5	CsF (3)	CsOPiv (2.0)	DME	90	39
10	1.5	CsF (3)	NaH (2.0)	DME	90	<10
11	1.5	CsF (3)	Cs_2CO_3 (2.0)	DME	120	62
12	2.0	CsF (3)	Cs_2CO_3 (2.0)	DME	90	62
13	1.5	TBAT (2)	Cs_2CO_3 (2.0)	DME	rt	33
14	1.5	TBAF (2)	Cs_2CO_3 (2.0)	DME	rt	19

[a] Reaction conditions: 0.5 mmol of **1**, 5 mL of solvent, 24 h. optimized conditions are indicated in bold.
[b] Per 1 equiv of benzyne precursor.
[c] Isolated yields.

been examined. However, the overall yields declined (entries 13 and 14), even though these fluorides are more soluble in DME.

With optimized conditions in hand (Table 1, entry 6), we have explored the scope and limitations of our methodology. Suitable indole substrates were easily prepared by the esterification of commercially available 2-indolecarboxylic acids. It was found that indoles containing electron-donating groups generally resulted in lower yields than the unsubstituted indole (Table 1, entries 2–6). Possibly, the electron-donating groups decrease the acidity of the indole, resulting in a weaker nucleophile. In fact, for all substrates containing a methoxy group, it has been observed that a significant amount of the starting material remains after 24 h. Low yields are also obtained with indole **1g**, a substrate containing a highly electron-withdrawing group. It is believed, however, that steric crowding of the nitro group around the nucleophilic nitrogen center is the main reason for the observed decrease in yield (entry 7). On the other hand, a variety of 5-haloindole-2-carboxylates have afforded good yields of the desired products (entries 8–10).[8] Interestingly, even better results were observed when the halogen occupies the 3-position of the indole (entries 11–13). This trend is also observed in substrates **1n** and **1o**, whose 3-positions are substituted (entries 14 and 15) and near quantitative yields are observed. This may be attributed to steric effects, in that a substituent at the 3-position can better help direct the electrophilic ester moiety for intramolecular attack by the intermediate aryl carbanion. As expected, replacement of the *N*–H with a *N*-methyl group prevented any formation of the desired *N*-annulated product (entry 16).

After a number of methyl indolecarboxylates were examined, we turned our attention toward screening various benzyne precursors. Substrate **1l** was chosen for these reactions due to its favorable performance with benzyne precursor **2a** (Table 2, entry 12). A series of symmetrical benzyne precursors were examined first (Table 3, entries 1–4) and good yields were obtained. It was found

that the overall yields depend greatly on the electronics of the aryne precursors. Thus, electron-rich aryne precursor **2c** gave the highest yield (entry 2), whereas electron-poor aryne precursor **2d** gave the lowest yield (entry 3). Unsymmetrical benzyne precursors present an issue of regioselectivity, since a nucleophile can attack either one of the two reactive aryne carbons. Some unsymmetrical benzyne precursors display higher regioselectivity than others. For example, it has been reported in the literature that benzyne precursor **2f** undergoes nucleophilic attack at the *meta*-position for both steric and electronic reasons.[9] As expected, our observations were consistent with the previous reports. Utilizing a 2D-NOESY experiment, the structure of product **3t** was established as shown (entry 6). Benzyne precursor **2g** also presents regioselectivity issues. Here a single product was formed. Although a 2D-NOESY experiment was not performed on the major isolated product, it is assumed that the nitrogen nucleophile would attack at the beta position based on steric hindrance. In addition, previous literature has shown that benzyne precursor **2g** preferably undergoes attack at the beta position.[10,6b]

A possible mechanism for formation of the [3+2] annulated product parallels what has been proposed previously in the literature (Scheme 2).[7] First, immediately following formation of the benzyne, a negatively charged indole nucleophilically attacks the aryne, resulting in intermediate **A**. The newly formed aryl carbanion then intramolecularly attacks the neighboring ester, displacing a methoxy group, which can also aid in deprotonation of the indole starting material.
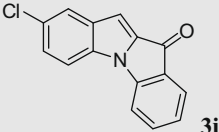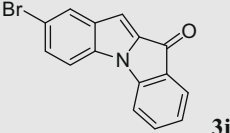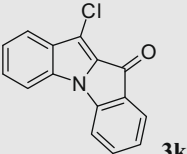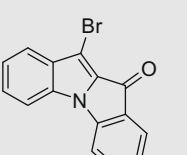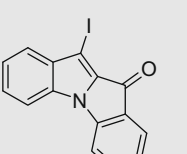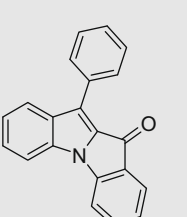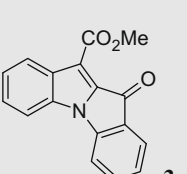
In conclusion, we have demonstrated a new and novel benzyne methodology for the synthesis of a previously unexplored indole-indolone scaffold, which provides good to excellent yields. The reaction involves a [3+2] annulation of arynes by methyl indole-2-carboxylates under mild conditions, producing a variety of functionally diverse compounds. In addition, a variety of substituted benzyne precursors, both symmetrical and unsym-

Table 2
[3+2] Annulations of methyl indole-2-carboxylates[a]
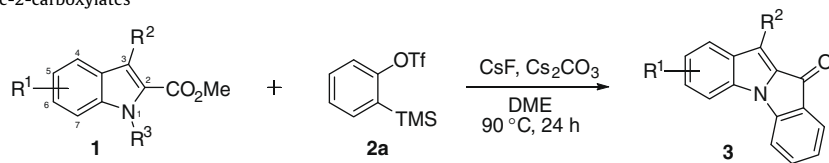
Entry	Substrate	Product	% Yield[b]
1	$R^1 = R^2 = R^3$ = H, **1a**	**3a**	70
2	R^1 = 5-Me, $R^2 = R^3$ = H, **1b**	**3b**	62
3	R^1 = 5-OMe, $R^2 = R^3$ = H, **1c**	**3c**	28
4	R^1 = 4-OMe, $R^2 = R^3$ = H, **1d**	**3d**	45
5	R^1 = 6-OMe, $R^2 = R^3$ = H, **1e**	**3e**	33
6	R^1 = 5,6-(OMe)$_2$, $R^2 = R^3$ = H, **1f**	**3f**	39
7	R^1 = 7-NO$_2$, $R^2 = R^3$ = H, **1g**	**3g**	40
8	R^1 = 5-F, $R^2 = R^3$ = H, **1h**	**3h**	64
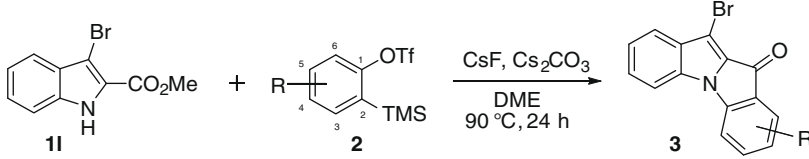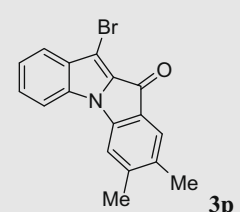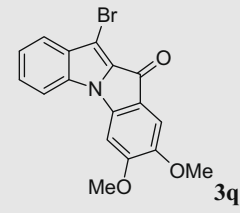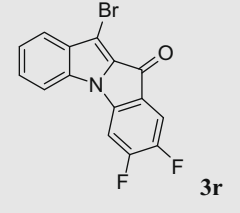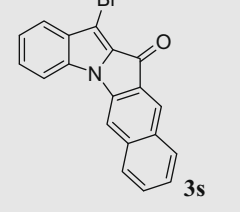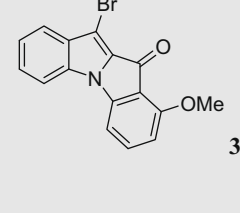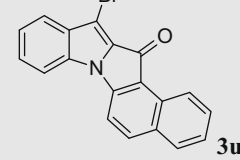
Table 2 (*continued*)

Entry	Substrate	Product	% Yield[b]
9	R^1 = 5-Cl, R^2 = R^3 = H, **1i**	**3i**	78
10	R^1 = 5-Br, R^2 = R^3 = H, **1j**	**3j**	76
11	R^1 = R^3 = H, R^2 = Cl, **1k**	**3k**	83
12	R^1 = R^3 = H, R^2 = Br, **1l**	**3l**	88
13	R^1 = H, R^2 = I, R^3 = H, **1m**	**3m**	85
14	R^1 = R^3 = H, R^2 = Ph, **1n**	**3n**	94
15	R^1 = R^3 = H, R^2 = CO$_2$Me, **1o**	**3o**	88
16	R^1 = R^2 = H, R^3 = Me, **1p**	—	0

[a] Reaction conditions: 0.50 mmol of **1**, 0.75 mmol of **2**, 2.25 mmol of CsF, 1.00 mmol of Cs$_2$CO$_3$, DME (5 mL) at rt for 1 d.

[b] Isolated yields.

Table 3
Reactions of indole **1l** with various benzyne precursors

Entry	Benzyne precursor	Product	% Yield[a]
1	R = 4,5-Me$_2$, **2b**	**3p**	67
2	R = 4,5-(OMe)$_2$, **2c**	**3q**	87
3	R = 4,5-F$_2$, **2d**	**3r**	37
4	R = 4,5-(CH)$_4$–, **2e**	**3s**	67
5	R = 3-OMe, **2f**	**3t**	82
6	R = 3,4-(CH)$_4$–, **2g**	**3u**	74

[a] Isolated yields.
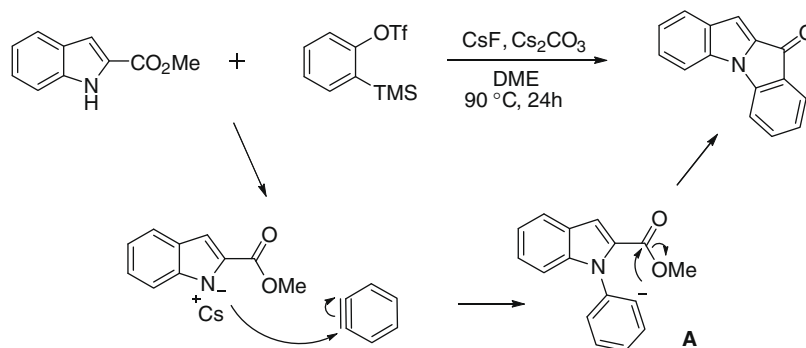
Scheme 2. Proposed mechanism.

metrical, undergo smooth annulations. Single regioisomers have been obtained in good yields for the unsymmetrical benzyne precursors studied. This novel indole-indolone scaffold holds great promise for biological activity. In addition, compounds **3j**, **3l**, **3m**, and **3p–u** are suitable for further elaboration via palladium chemistry if a combinatorial library of these compounds is desired.

Acknowledgments

References and notes

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8. *Representative procedure* (**3i**, Table 2, entry 9): An oven dried 6-dram vial equipped with a stirrer bar was charged with 107.4 mg of **1i** (0.50 mmol) and 223.8 mg of **2a** (0.75 mmol), followed by 2.5 mL of dry DME. The mixture was briefly stirred and 325.8 mg of dry Cs$_2$CO$_3$ and 341.8 mg of dry CsF were added sequentially, followed by an additional 2.5 mL of DME, washing the sidewalls of the vial. The vial was sealed and placed in an oil bath at 90 °C and allowed to stir for 1 d. The resultant mixture was cooled and eluted through a plug of silica gel with ethyl acetate and DCM. The filtrate was dried with anhydrous Na$_2$CO$_3$, decanted, and evaporated. The residue was impregnated with silica gel and purified by column chromatography (35:1–10:1 hexane/ethyl acetate), affording 98.3 mg of the desired product **3i** as a light orange solid; mp 203–204 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, *J* = 7.6 Hz, 1 H), 7.57 (s, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.31–7.39 (m, 2 H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.99 (s, 1 H); ^{13}C NMR (100 MHz CDCl$_3$) δ 181.4, 145.3, 136.8, 135.8, 133.6, 132.5, 129.3, 128.5, 127.7, 125.5, 124.4, 124.4, 112.3, 111.4, 107.0; HRMS (EI): calcd for C$_{15}$H$_8$ClNO 253.0294, found 253.0301.
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