3-Aroylindoles via Copper-Catalyzed Cyclization of *N*-(2-Iodoaryl)enaminones

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Abstract: 3-Aroylindoles have been prepared via copper-catalyzed cyclization of *N*-(2-iodoaryl)enaminones, readily available from 2-iodoanilines and α,β-ynones. The reaction tolerates a variety of useful functionalities including ether, keto, cyano, bromo, and chloro substituents. This indole synthesis can also be carried out from 2-iodoanilines and α,β-ynones through a sequential process that omits the isolation of enaminone intermediates.

Key words: indoles, enaminones, cyclization, copper, catalysis

3-Acylindoles are useful intermediates for the preparation of pyridocarbazole alkaloids[1] and important therapeutic agents.[2] For example, A-85783 is a potent and selective antagonist of PAF[2e] and pravadoline (Figure 1) is a non-acidic analogue of nonsteroidal anti-inflammatory drugs (NAID).[2a]

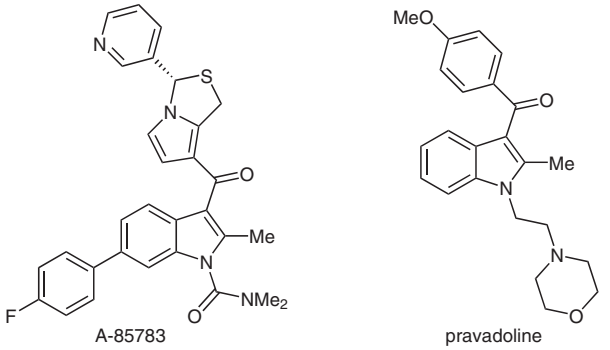

Figure 1

A variety of methods have been used for their preparation. The vast majority of them rely on the acylation of preformed indole derivatives.[3] Direct construction of the 3-acylindole skeleton from acyclic precursors has received less attention. This protocol has been used in the palladium-catalyzed cyclization of 2-(alkynyl)trifluoroacetanilides in the presence of carbon monoxide and aryl halides or vinyl triflates[4] and in the copper-promoted[5] cyclization of *N*-(2-haloaryl)enaminones. As to the latter, only two *N*-(2-haloaryl)enaminones, derived from acyclic β-diketones, were converted into the corresponding 3-acylindoles using 1.5–2.0 equivalents of CuI and NaH as the base in HMPA at 100–170 °C.

During the past few years there have been remarkable advances in the use of copper in organic synthesis.[6] Particularly, it has been shown that by using appropriate ligands a large number of reactions can be carried out in the presence of catalytic amounts of copper, often providing an attractive economic alternative to palladium-catalyzed reactions. Therefore, because of our continuing interest in indole synthesis[7,8] and our recent studies on the chemistry of enaminones,[9] we became interested in investigating the feasibility of a copper-catalyzed cyclization of *N*-(2-haloaryl)enaminones via substitution of the C–C bond for the C–halogen bond. Herein we report the results of this study.

N-(2-Haloaryl)enaminones **1** were prepared via Sonogashira cross-coupling of terminal alkynes with aroyl chlorides[10] followed by the conjugate addition of 2-haloanilines with the resultant α,β-ynones[4a] (Scheme 1). *N*-(2-Haloaryl)enaminones **1** have always been isolated as single isomers. The *Z*-stereochemistry of **1a** has been assigned by NOESY experiments which showed also the presence of an intramolecular hydrogen bond (N–H···O). That of the other enaminones has been assigned on the basis of these data.

We started our study by examining the conversion of **1a** into the corresponding indole derivative **2a** using CuI as the precatalyst, K_2CO_3 as the base at 100 °C, and exploring the influence of solvents and ligands on the reaction outcome. No indole formation was observed omitting copper and ligands (Table 1, entry 1) whereas moderate to good yields were obtained with 0.05 equivalents of CuI and omitting ligands in DMSO and DMF (Table 1, entries 2 and 3). Utilization of phosphine ligands (Table 1, entries 5–7) showed that **2a** could form in high yield with dppp (Table 1, entry 7) but the best result in terms of yield and reaction time was achieved using 0.05 equivalents of CuI and 0.05 equivalents of 1,10-phenanthroline: **2a** was isolated in 92% yield after 2.5 hours at 100 °C in DMF (Table 1, entry 11).

Using the optimized conditions, we next explored the scope and generality of the process.[11] As shown in Table 2, a variety of indoles can be prepared in high to excellent yields. Several useful functionalities are tolerated,

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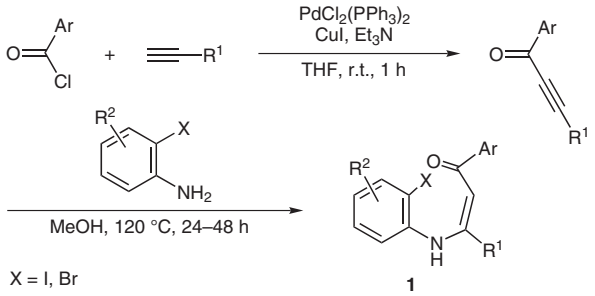
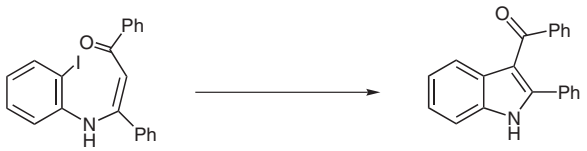


Scheme 1

Table 1 Optimization of Reaction Conditions[a]



1a **2a**

Entry	Ligand (equiv)	Solvent	Time (h)	Yield (%)[b]
1	–	DMF	7	–[c]
2	–	DMSO	8	51
3	–	DMF	8	69
4	–	dioxane	8	–[d]
5	Ph_3P (0.05)	DMF	6	67
6	dppe (0.05)	DMF	7	47
7	dppp (0.05)	DMF	7	80
8	TMEDA (0.05)	DMF	7	65
9	DMEDA (0.05)	DMF	7	69
10	L-proline (0.1)	DMF	20	63
11	1,10-phenanthroline (0.05)	DMF	2.5	92

[a] Unless otherwise stated, reactions were carried out at 100 °C on a 0.25 mmol scale using 0.05 equiv of CuI, 2 equiv of K_2CO_3, in 2.5 mL of solvent.
[b] Yields are given for isolated products.
[c] In the absence of CuI.
[d] Compound **1a** was recovered in 93% yield.

including ether, keto, cyano, bromo, and chloro substituents.

We next explored the extension of this indole synthesis to bromo-containing enaminones. However, when the *N*-(2-bromoaryl)enaminone **1a′** (R^1 = Ar = Ph; R^2 = H; X = Br) was subjected to our standard conditions, we were surprised to find that the formation of the expected indole product was accompanied by the formation of the benzoxazepine derivative **3** (Scheme 2). Most probably its formation involves an intramolecular copper-catalyzed substitution of the C–O bond for the C–Br bond.[12] No such a competition between C- and O-cyclization was observed with the iodo derivatives that we have investigated.

Table 2 Synthesis of 3-Acylindoles **2** via Copper-Catalyzed Cyclization of *N*-(2-Iodoaryl)enaminones **1**[a]

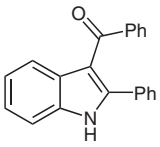
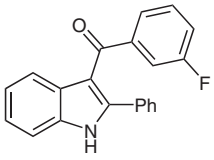
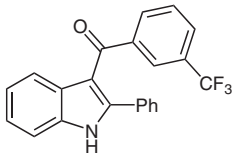
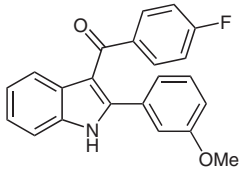
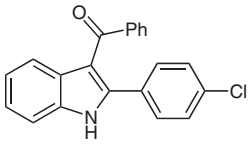
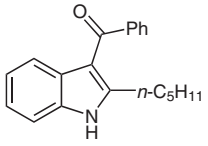
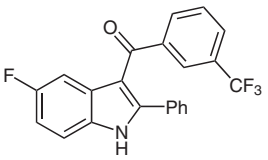
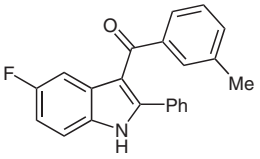
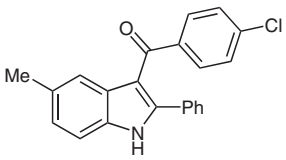
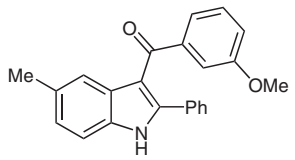
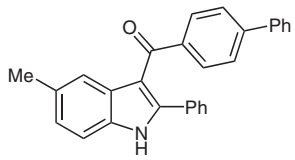
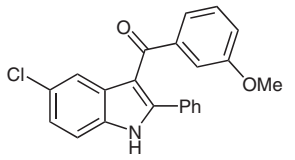
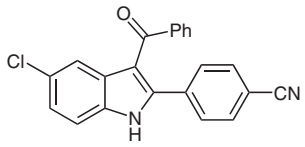
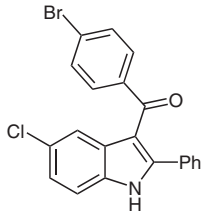
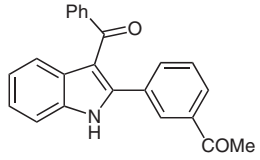
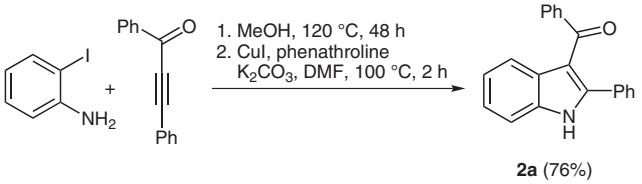
Entry	Product		Time (h)	Yield (%)[b]
1		**2a**	2.5	92
2		**2b**	5	95
3		**2c**	3.5	93
4		**2d**	10	96
5		**2e**	10	91
6		**2f**	3	87
7		**2g**	4	89
8		**2h**	13	86
9		**2i**	8	88

Table 2 Synthesis of 3-Acylindoles **2** via Copper-Catalyzed Cyclization of *N*-(2-Iodoaryl)enaminones **1**[a] (continued)

Entry	Product		Time (h)	Yield (%)[b]
10		**2j**	4	96
11		**2k**	8	88
12		**2l**	3	91
13		**2m**	2	93
14		**2n**	6	92
15		**2o**	1	73

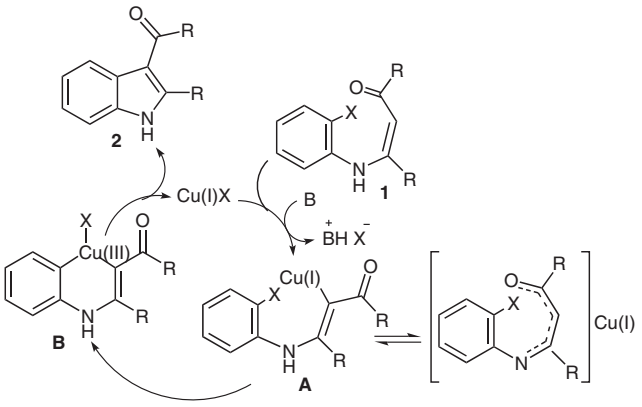
[a] Reactions were carried out at 100 °C on a 0.25 mmol scale using 0.05 equiv of CuI, 0.05 equiv of 1,10-phenathroline, 2 equiv of K_2CO_3 in 2.5 mL of DMF.
[b] Yields are given for isolated products.

This indole synthesis can also be carried out through a process that omits the isolation of the enaminone intermediates. In practice, excellent results can be obtained by adding CuI, 1,10-phenanthroline, K_2CO_3, and DMF to the crude mixture derived from the reaction of 2-iodoanilines with α,β-ynones after evaporation of the volatile materials.[13] Under these conditions, **2a** was isolated in 76% overall yield (Scheme 3).



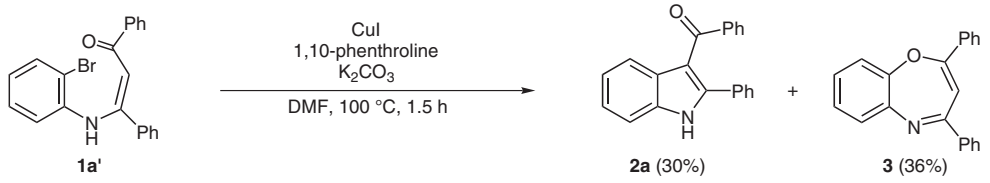
Scheme 3

On the basis of the recently reported tendency of *N*-aryl enaminones to coordinate to palladium(II) electrophiles[14] and previous observations on related Cu-catalyzed heterocyclizations involving $C_{aromatic}$–X bonds,[15] a plausible mechanism for this indole ring formation begins with the initial coordination of carbon with copper (Scheme 4). The resulting complex **A** undergoes an oxidative addition of the C–X bond to copper to afford the Cu(III) intermediate **B**. Subsequent reductive elimination releases the product with concomitant regeneration of the Cu(I) species. Another possible mechanism involves the formation of **B** via oxidative addition of the C–I bond to CuI to produce a Cu(III) intermediate followed by nucleophilic displacement of iodide by the anionic fragment.



Scheme 4

In conclusion, we have shown that *N*-(2-iodoaryl)enaminones can be converted into the corresponding 3-acylindoles in the presence of catalytic amounts of CuI.[16,17] The new method tolerates a variety of useful functionalities including ether, keto, cyano, bromo, and chloro substituents. 3-Acylindoles can also be prepared via a sequential process from α,β-ynones and 2-iodoanilines, omitting the isolation of the enaminone intermediates. Since multisubstituted indoles are essentially formed by



Scheme 2

assembling 2-iodoanilines, aroyl chlorides, and terminal alkynes, a wide variety of indole derivatives can be synthesized by using this protocol that can be particularly useful for the preparation of libraries.

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(11) **Typical Procedure for the Cyclization of *N*-(2-Iodoaryl)-enaminones 1 to 3-Acylindoles 2**
To a stirred solution of **1d** (118.2 mg, 0.25 mmol) in DMF (2.5 mL), CuI (2.4 mg, 0.0125 mmol), 1,10-phenanthroline (2.3 mg, 0.0125 mmol), and K_2CO_3 (69.0 mg, 0.50 mmol) were added at r.t. The reaction mixture was warmed at 100 °C and stirred for 10 h. After cooling, the reaction mixture was diluted with Et_2O, washed with 1 N HCl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 [*n*-hexane–EtOAc, 70:30] to afford 82.8 mg (96% yield) of **2d**: white solid; mp 184–185 °C. IR (KBr): 3423, 2927, 1601, 1562, 1435, 1223 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.22 (br s, 1 H), 7.84 (d, *J* = 7.9 Hz, 1 H), 7.60–7.57 (m, 2 H), 7.52 (d, *J* = 7.9 Hz, 1 H), 7.27 (t, *J* = 7.9 Hz, 1 H), 7.18 (t, *J* = 7.8 Hz, 2 H), 7.04–6.92 (m, 4 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 3.67 (s, 1 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 191.2, 164.3 (d, J_{CF} = 251 Hz), 159.3, 144.4, 137.1 (d, J_{CF} = 22 Hz), 136.3, 133.2, 132.2 (d, J_{CF} = 9 Hz), 129.7, 128.7, 123.5, 122.5, 122.0, 121.1, 115.4, 115.3, 115.1 (d, J_{CF} = 4 Hz), 112.6, 112.4, 55.6. ^{19}F NMR (376 MHz, DMSO-d_6): δ = –108.6. Anal. Calcd for $C_{22}H_{16}FNO_2$: C, 76.51; H, 4.67. Found: C, 76.40; H, 4.58.

(12) Compounds **2a** and **3** were isolated in 30% and 60% yield, respectively, when the reaction was carried out in DMA at 120 °C (3 h).

(13) **Typical Procedure for the Preparation of 3-Acylindoles 2 Omitting the Isolation of Enaminone Intermediates**
To a stirred solution of 2-iodoaniline (109.5 mg, 0.5 mmol) in MeOH (1.0 mL), 1,3-diphenylprop-2-yn-1-one (154.5 mg, 0.75 mmol) was added at r.t. The reaction mixture was warmed at 120 °C and stirred for 48 h. After that period the volatile materials were evaporated at reduced pressure, and CuI (4.8 mg, 0.025 mmol), 1,10-phenanthroline (4.5 mg, 0.025 mmol), K_2CO_3 (138.0 mg, 1.0 mmol), and DMF (4 mL) were added. The reaction mixture was warmed at 100 °C and stirred for 2.5 h. After cooling, the reaction mixture was diluted with Et_2O, washed with1 N HCl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 [*n*-hexane–EtOAc, 75:25] to afford 106 mg (76% yield) of **2a**: white solid; mp 223–224 °C. IR (KBr): 3055, 1593, 1564, 1450, 1421 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.19 (br s, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 7.54–7.51 (m, 3 H), 7.40–7.35 (m, 3 H), 7.26–7.10 (m, 7 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 192.6, 144.6, 140.3, 136.3, 132.1, 131.8, 130.1, 129.6, 129.0, 128.7, 128.5, 128.3, 123.4, 121.9, 121.1, 112.7, 112.4. Anal. Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08. Found: C, 84.71; H, 5.19.

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