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A new strategy for the synthesis of coumarin- and quinolone-annulated pyrroles via Pd(0) mediated cross-coupling followed by Cu(I) catalyzed heteroannulation

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Abstract

The sequential coupling and cyclization reactions between aryl halides and (trimethylsilyl)acetylene (TMSA) with concurrent elimination of the TMS substituent, allows a straightforward synthesis of substituted pyrano[3,2-*e*]indolone and pyrrolo[3,2-*f*]quinolone derivatives in excellent yields.

Keywords: Sonogashira coupling; Palladium catalyst; Heteroannulation; Indoles

Coumarin and quinolone sub-units are found in a large number of natural products possessing broad-spectrum biological activity and which exhibit antifungal, antibacterial, antiviral, antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, antiarrhythmic and sedative properties.[1–5] In particular, pyranoindole bearing heterocycles have been used for their antibacterial, monoamine oxidase (MAO) inhibitory and anthelminitic activities.[6] Therefore, in continuation of our long-standing interest in coumarin and quinolone chemistry,[7–9] we became interested in developing an efficient protocol for synthesizing substituted pyrano[3,2-*e*]indolone and pyrrolo[3,2-*f*]quinolone derivatives.

So far, we have utilized the Claisen rearrangement,[10,11] radical cyclization,[12] ene-yne ring- closing metathesis[13] and Heck reaction[14,15] for the synthesis of polynuclear coumarin and quinolone annulated heterocycles. We have recently reported the synthesis of novel pyrrolopyridines by palladium-catalyzed cross-coupling between aryl halides and alkynes.[16] Generally an electron withdrawing group is required for the heteroannulation of acetylenic amines to increase the nucleophilicity of nitrogen[17–21] and a few examples of the heteroannulation of acetylenic amines have been reported with free amines.[22–24] To the best of our knowledge, there is no report of the heteroannulation of acetylenic amines possessing an electron donating group. Herein, we report the results of our investigation on the synthesis of biologically important substituted pyranoindolones and pyrroloquinolones via Cu(I) catalyzed cyclization of acetylenic amines possessing an electron donating group on the nitrogen atom.

The required precursors for heteroannulation **3a**–**e** were synthesized in moderate to good yields by Sonogashira coupling of **2a**–**e** with (trimethylsilyl)acetylene using $Pd(PPh_3)_2Cl_2$ as catalyst and CuI as the co-catalyst in anhydrous THF/DMF mixed solvent containing Et_3N with heating for 6–8 h. Compounds **2a**–**e** were prepared by bromination of the corresponding amines **1a**–**e** with NBS in CH_3CN at 25 °C for 30 min (Scheme 1). The starting amino-coumarin and quinolones **1a**–**e** were prepared from commercially available coumarin and quinoline, respectively, using a standard procedure.[25,26] However, we initially encountered trouble with the Sonogashira reactions of **2a**–**e** and the optimum conditions were found through

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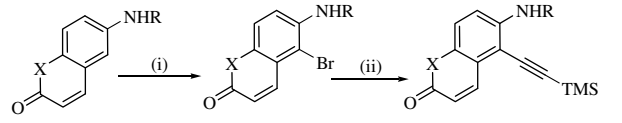
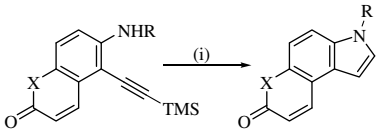


1a, R = Et, X = O
b, R = Me, X = O
c, R = H, X = O
d, R = Et, X = NMe
e, R = Me, X = NMe

2a, R = Et, X = O, 82%
b, R = Me, X = O, 80%
c, R = H, X = O, 75%
d, R = Et, X = NMe, 79%
e, R = Me, X = NMe, 78%

3a, R = Et, X = O, 80%
b, R = Me, X = O, 79%
c, R = H, X = O, 70%
d, R = Et, X = NMe,75%
e, R = Me, X = NMe, 72%

Scheme 1. Synthesis of heteroannulated precursors **3a**–**e**. Reagents and conditions: (i) NBS, CH_3CN, rt, 30 min; (ii) (trimethylsilyl)acetylene, 5 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI, 5:3:2 DMF/THF/Et_3N, 70 °C, sealed tube, 6–8 h.



3a, R = Et, X = O
b, R = Me, X = O
c, R = H, X = O
d, R = Et, X = NMe
e, R = Me, X = NMe

4a, R = Et, X = O, 99%
b, R = Me, X = O, 98%
c, R = H, X = O, 82%
d, R = Et, X = NMe, 97%
e, R = Me, X = NMe, 96%

Scheme 2. Synthesis of heteroannulated products **4a**–**c**. Reagents and conditions: (i) DMF, 50 mol % CuI, reflux, 1 h.

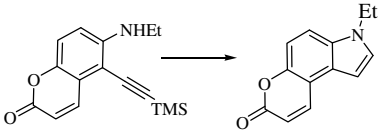
a series of experiments where sequential changes were made to the catalyst, base and the solvent (Table 1). The reactions were optimized by smoothly heating the reaction in a sealed tube.

To achieve the heteroannulation of the acetylenic amines **3a**[27]–**e** in one step, we began our investigation using an iodocyclization strategy and various reagents were used as the iodine source. However, we failed to achieve cyclization by this method. Finally, we succeeded in cyclizing the acetylenic amines **3a**–**e** by refluxing in DMF in the presence of 50 mol % of CuI for 1 h (Scheme 2). Heteroannulation reaction demands higher activation energy. The optimized conditions for the heteroannulation were found through a series of experiments where sequential changes were made to the catalyst, temperature and the solvent used (Table 2).

Using this method, we were able to synthesize biologically important substituted pyrano[3,2-*e*]indolones and pyrrolo[3,2-*f*]quinolones (**4a**[28]–**e**) in three steps and in excellent yields as shown in Table 3.

The mechanistic pathway for the formation of CuI(I) catalyzed heteroannulated product **4a**–**e** is not clear.[29,30] To establish the mechanism, we repeated the conversion of **3c** to **4c** with an electron withdrawing group on nitrogen atom (**3c′**) to see whether the reaction follows a radical or an ionic pathway. We obtain the cyclized product **4c** in excellent yield. The conversion of **3c** to **3c′** was performed by the acylation of **3a** with trifluoroacetic anhydride in the presence of anhydrous K_2CO_3 in dry 1,4-dioxane at 25 °C for 1 h (Scheme 3). As the reaction proceeds smoothly with both electron donating and electron withdrawing groups, we thought that the reaction proceeds through a radical pathway. Thus, we studied the cyclization in the presence of hydroquinone (threefold excess) as a radical inhibitor under identical conditions as stated above to ascertain the involvement of a radical pathway. It was found that the reaction was not affected by the presence of hydroquinone thereby ruling out a radical pathway. Further mechanistic studies are underway.

Table 2
Optimization of the reaction conditions for the cyclization of **3a**



Entry	Catalyst	Solvent	Temp	Time (h)	Yield (%)
1	I_2 (2.5 equiv)	1,4-Dioxane	rt	24	nr
2	I_2 (2.5 equiv)	Ethanol	rt	24	nr
3	I_2 (2.5 equiv)	THF	Reflux	1	ub
4	NIS (2.5 equiv)	MeCN	rt	12	ub
5	TBAI[a] (2.5 equiv)	THF	Reflux	5	ub
6	CuI (2.5 equiv)	DMF	Reflux	3	83
7	CuI (50 mol %)	DMF	Reflux	1	99

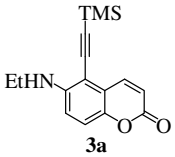
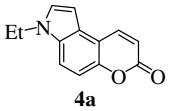
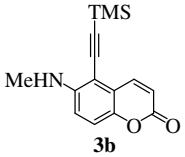
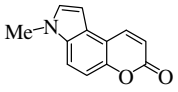
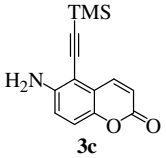
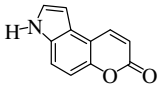
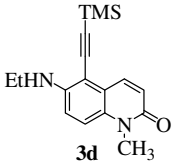
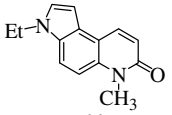
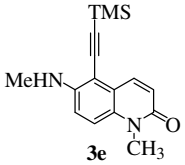
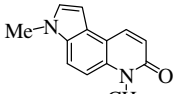
[a] Tetrabutylammonium iodide, nr—no reaction, ub—uncharacterized byproduct.

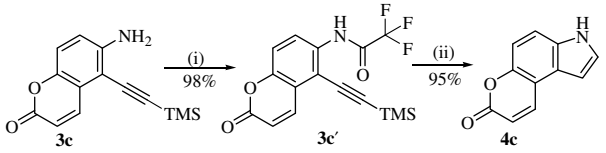
Table 1
Optimized conditions for the Sonogashira reaction of **2a**

Entry	Catalytic system	Temp (°C)	Time (h)	Yield (%)
1	5 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI	rt	36	10[a]
2	10 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI	rt	36	10[a]
3	5 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI	Reflux	10	Trace[a]
4	2.5 mol % Pd_2dba_3, 15 mol % PPh_3, 5 mol % CuI	Reflux	8	12[b]
5	5 mol % $Pd(PPh_3)_4$, 5 mol % CuI	rt	20	Trace[c]
6	2 mol % Pd–C (10%), 2.5 mol % PPh_3, 5 mol % CuI	Reflux	8	nr[a]
7	5 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI	50	12	55[d]
8	5 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI	70	8	80[e]
9	10 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI	70	8	80[e]

nr—No reaction.
[a] THF/Et_3N, 5:2.
[b] $CHCl_3$/Et_3N, 5:2.
[c] CH_3CN/Et_3N, 5:2.
[d] THF/Et_3N, 5:2, in a sealed tube.
[e] DMF/THF/Et_3N, 5:3:2, in a sealed tube.

Table 3
Heteroannulated products

Entry	Heteroannulated precursor	Heteroannulated product	Yield (%)
1	 **3a**	 **4a**	99
2	 **3b**	 **4b**	98
3	 **3c**	 **4c**	82
4	 **3d**	 **4d**[26]	97
5	 **3e**	 **4e**[26]	96



Scheme 3. Heteroannulation reaction of **3c′** possessing an electron withdrawing group. Reagent and conditions: (i) Trifluoroacetic anhydride, K_2CO_3, 1,4-dioxane, 1 h; (ii) DMF, 50 mol % CuI, reflux, 1 h.

In conclusion, and to the best of our knowledge, the work reported here represents the first example of Cu(I) catalyzed cyclization that allows access to pyrrolocoumarins and pyrroloquinolones in excellent yields. Additionally, application of these heterocycles in natural product synthesis is currently underway and the results will be reported in due course.

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27. *6-(Ethylamino)-5-(2-(trimethylsilyl)ethynyl)-2H-chromen-2-one* (**3a**): Green fluorescent solid, mp 124–126 °C, yield 80%. IR (KBr, cm^{-1}) ν_{max}: 3397, 2139, 1716; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.31 (s, 9H, –Si(CH_3)$_3$), 1.31 (t, 3H, CH_2–CH_3, $J = 7.2$ Hz), 3.19–3.26 (m, 2H, –CH_2–CH_3), 4.52 (s, 1H, N*H*), 6.42 (d, 1H, Ar*H*, $J = 9.7$ Hz), 6.78 (d, 1H, Ar*H*, $J = 9.0$ Hz), 7.17 (d, 1H, Ar*H*, $J = 9.1$ Hz), 8.01 (d, 1H, Ar*H*, $J = 9.4$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.7, 15.1, 38.8, 98.3, 103.2, 107.7, 113.9, 117.6, 118.5, 120.1, 142.3, 146.1, 147.4, 161.4; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{16}H_{19}NO_2SiNa$: 308.1080; found, 308.1094.
28. *3-Ethylpyrano[3,2-e]indol-7(3H)-one* (**4a**): Yellow solid, mp 106–108 °C, yield 99%. IR (KBr, cm^{-1}) ν_{max}: 1715, 1587; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.49 (t, 3H, CH_2–CH_3, $J = 7.2$ Hz), 4.22 (q, 2H, –CH_2–CH_3, $J = 7.3$ Hz), 6.45 (d, 1H, Ar*H*, $J = 9.5$ Hz), 6.71 (d, 1H, Ar*H*, $J = 3.0$ Hz), 7.19 (d, 1H, Ar*H*, $J = 8.9$ Hz), 7.27 (d, 1H, Ar*H*, $J = 3.1$ Hz), 7.48 (d, 1H, Ar*H*, $J = 8.9$ Hz), 8.12 (d, 1H, Ar*H*, $J = 9.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.9, 41.8, 99.1, 111.2, 113.8, 115.2, 125.2, 129.5, 132.3, 141.3, 150.2, 162.3; HRMS: *m/z* $[M+H^+]$ calcd for $C_{13}H_{12}NO_2$: 214.0863; found, 214.0859.
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