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Regioselective synthesis of pyridoquinolones and pyridocoumarins via molecular iodine-mediated 6-*endo*-dig electrophilic cylization

K. C. Majumdar *, Inul Ansary, Srikanta Samanta, Brindaban Roy

Department of Chemistry, University of Kalyani, Kalyani 741 235, W.B., India

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ABSTRACT

Angular-pyridoquinolone and pyridocoumarin derivatives have been efficiently synthesized in 60–95% yields by molecular iodine-mediated cyclization of easily available starting materials, 6-(*N*-propargyl)amino quinolone and coumarin derivatives, in the presence of $NaHCO_3$. The reaction was carried out at room temperature.

Coumarins fused with heterocycles have received increasing attention due to their potential biological activities[1] and are common structural motifs in many natural products.[2] In particular, those coumarins fused to pyridines have been reported to possess antiallergic,[3] antidiabetic,[4] and analgesic[5] properties. On the other hand, quinolines and their derivatives occur in numerous natural products and many of them display interesting biological activities.[6] In particular, halogen-containing quinolines are of significant interest because the halogen atom sometimes plays a determinant role in the compound's bioactivity, and such compounds provide further scope for structural elaboration.[7] Nicolaides and co-workers[8] reported the synthesis of some angular pyridocoumarins from the reaction of 8- or 6-quinolinol with triphenylphosphine (PPh_3) and dimethylacetylenedicarboxylate (DMAD). Pyridocoumarin was synthesized in 14% yield by means of a Skraup reaction, carried out on 6-nitrocoumarin.[9] Recently, radical cyclization[10] has become a useful tool to the synthetic organic chemists for the construction of C–C bonds. The most useful mediator of radical cyclization is tributyltin hydride. Despite its widespread applicability, the problem of toxicity and the removal of even a trace of organotin residue from the product are frequently highlighted as reasons to avoid the tin reagents.[11,12] In our laboratory pyridocoumarin derivatives were synthesized by palladium-catalyzed intramolecular Heck reaction[13a,b] as well as organotinhydride-mediated radical cyclization reaction[13c] in excellent yields. On the other hand linear-pyridoquinoline derivatives have been synthesized by several methods[14–20] which are expensive as well as multistep reactions. However, to our knowledge angular-pyridoquinoline derivatives are not reported. In recent years, iodocyclization has emerged as an effective protocol in the preparation of a variety of heterocyclic and carbocyclic compounds.[21–26] This chemistry employs iodine that is cheap and easy to handle. The development of this methodology provides an efficient and mild reaction condition which allows easy isolation of the products from the reaction mixture. In continuation of our interest in the synthesis of nitrogen heterocycles[27] and electrophilic iodocyclization strategy[28] we have undertaken a study on the electrophilic cyclization of 6-(*N*-propargyl)amino quinolone and coumarin derivatives.

The precursors for the iodocyclization reaction, **3a**–**g** were obtained by a two-step approach. The preparation of **2a**,**b** was achieved by the reaction of **1a**,**b** with propargyl bromide in the presence of anhydrous K_2CO_3 and a catalytic amount of NaI in dry acetone under reflux condition, followed by standard Sonogashira coupling reaction[29] using *p*-substituted iodobenzenes. Other precursors **5a**,**b** were synthesized by the reaction of 6-amino quinolone **4a** and 6-amino coumarin **4b** with 1-bromo-2-butyne in the presence of anhydrous K_2CO_3 in dry acetone under refluxing condition and obtained as a 3:1 mixture of compounds **5a**,**b** and **6a**,**b**, respectively (Scheme 1).

When compound **3a**[30] was subjected to iodocyclization reaction in the presence of 3 equiv of I_2 and 3 equiv of $NaHCO_3$ in CH_3CN at room temperature for 13 h, the 6-*endo* cyclized dihydropyridoquinolone derivative **7a**[31] was formed exclusively in excellent yield. Similarly, when the substrate **5a** was condensed with molecular iodine under the reaction condition stated above, the pyridoquinolone **9a** was

* Corresponding author. Tel.: +91 33 2582 7521; fax: +91 33 25828282.
E-mail address: kcm_ku@yahoo.co.in (K.C. Majumdar).

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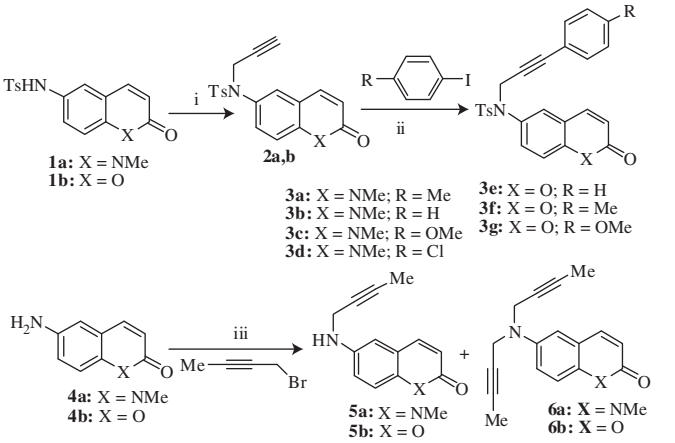
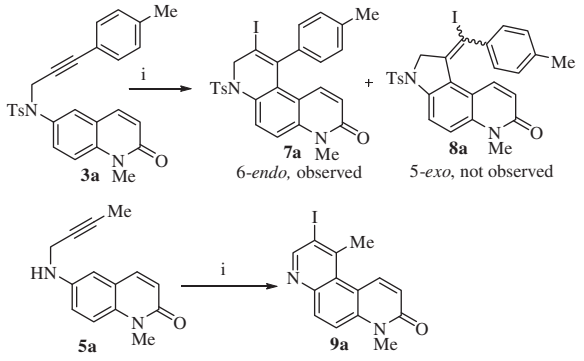


Scheme 1. Reagents and conditions: (i) propargyl bromide, anhydrous K_2CO_3, NaI, dry acetone, reflux, 6 h; (ii) 3 mol % $Pd(PPh_3)_2Cl_2$, 3 mol % CuI, Et_3N, DMF, rt, 2 h; (iii) anhydrous K_2CO_3, dry acetone, reflux 3 h.



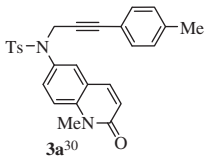
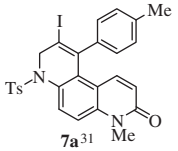
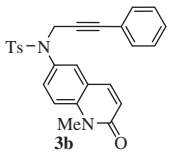
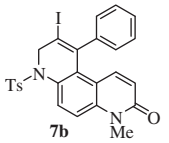
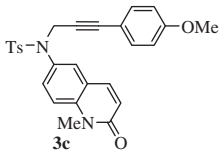
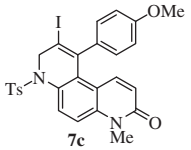
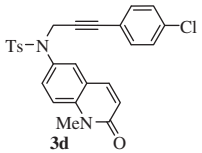
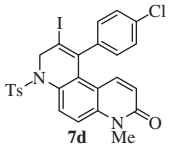
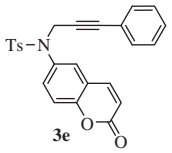
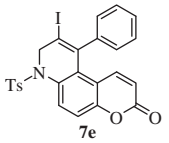
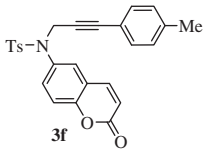
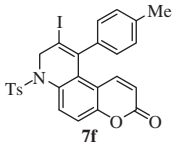
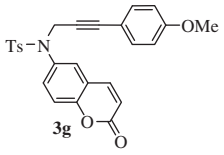
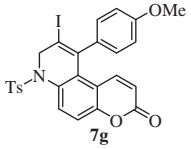
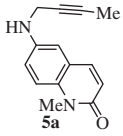
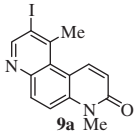
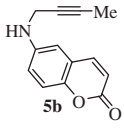
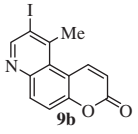
Scheme 2. Reagents and conditions: (i) I_2, $NaHCO_3$, CH_3CN, rt.

Table 1
Optimization of Iodine-mediated reactions

Entry	Solvent	Base (equiv)	I_2 (equiv)	Time (h)	Yield[a] (%)
1	CH_3CN	$NaHCO_3$ (3)	1	13	42
2	CH_3CN	$NaHCO_3$ (3)	1.5	13	60
3	CH_3CN	$NaHCO_3$ (3)	3	24	90
4[b]	CH_3CN	$NaHCO_3$ (3)	3	13	92
5	CH_3CN	$NaHCO_3$ (3)	5	13	88
6	CH_3CN	$NaHCO_3$ (1)	3	13	45
7	CH_3CN	—	3	13	NR[c]
8	CH_3CN	K_2CO_3 (3)	3	13	59
9	CH_2Cl_2	$NaHCO_3$ (3)	3	13	38
10	CH_3OH	$NaHCO_3$ (3)	3	13	42

[a] Isolated yield.
[b] Optimized reaction condition.
[c] NR indicates no reaction.

Table 2
Synthesis of pyridoquinolone and pyridocoumarin derivatives

Entry	Substrate(s)	Product(s)	Time (h)	Yield (%)
1	 **3a**[30]	 **7a**[31]	13	92
2	 **3b**	 **7b**	15	88
3	 **3c**	 **7c**	12	95
4	 **3d**	 **7d**	17	60
5	 **3e**	 **7e**	18	62
6	 **3f**	 **7f**	16	66
7	 **3g**	 **7g**	10	70
8	 **5a**	 **9a**	10	70
9	 **5b**	 **9b**	12	75

obtained. The formation of the product **9a**, supports the 6-*endo* mode of cyclization (Scheme 2).

To standardize the reaction condition a series of experiments were performed with or without the base ($NaHCO_3$/K_2CO_3) and varying amounts of molecular iodine in different solvents, such as CH_3CN, CH_3OH, and CH_2Cl_2. The substrate **3a** was used as a representative for this standardization and the results are summarized in Table 1.

When the substrate **3a** was reacted with 3 equiv of I_2 and 3 equiv of $NaHCO_3$ in CH_3CN (5 mL) at room temperature for 13 h, a 92% isolated yield of the product **7a** was obtained. Solvents, like CH_2Cl_2 and CH_3OH resulted in lower yields of the products. Reducing the amount of I_2 from 3 equiv to 1.5 equiv and 1 equiv afforded the compound **7a** in 60% and 42% yields, respectively. Increase in the amount of iodine from 3 equiv to 5 equiv did not improve the yield. Increasing the reaction time from 13 h to 24 h and longer also did not improve the yield of the cyclized product. The presence of a base proved to be important for the reaction. The reaction does not occur without a base. The effect of K_2CO_3 as a base was also investigated. However, it provided a drastically lower yield of the cyclized product **7a** than that when $NaHCO_3$ was used. Based on the above optimization efforts, the combination of