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Synthesis of novel cyano quinoline derivatives

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ABSTRACT

6,8-Dibromo-1,2,3,4-tetrahydroquinoline (**2**) and 3,6,8-tribromoquinoline (**3**) were converted into the corresponding cyano derivatives via copper assisted nucleophilic substitution reactions. While bromination of 6-bromo-8-cyanotetrahydroquinoline (**11**) gave 3,6-dibromo-8-cyanoquinoline (**8**), the reaction of dicyano-1,2,3,4-tetrahydroquinoline (**12**) resulted in the formation of an unexpected dimer (**15**).

Introduction

The quinoline moiety forms the key skeleton of several natural and pharmacologically active compounds which display a broad spectrum of biological activities.[1–4] Notably, cyano quinoline compounds substituted at the C-3 position can act to deactivate the action of growth factor receptor protein tyrosine kinases.[5–8] Agents with cyano groups also act as small molecule inhibitors, binding with biological systems.[9] A significant body of work has been reported on the synthesis and derivatization of the quinoline substructure. The most common strategies are cyclization reactions of *N*-functionalized benzene or cyclohexane.[10–13] The asymmetric syntheses of 2-cyano substituted dihydro and tetrahydroquinolines have been accomplished using the Reissert reaction[14] while 8-cyano substituted quinoline compounds have been synthesized by the treatment of cyano aniline with ketone functionalized alkynes in polar solvents.[15] However, cyclizations using cyano substituted *N*-functionalized aromatics, allow only the synthesis of mono cyano substituted quinolines.[16] Due to this, the synthesis of poly cyano substituted quinolines has been restricted.

The work presented is a continuation of our ongoing research[17,18] and focuses on the synthesis of polysubstituted quinolines, starting from substituted 1,2,3,4-tetrahydroquinoline 5, which provides an efficient synthesis of C-3 bromoderivatives 6 (Scheme 1). Herein, we present preliminary results focused on the generality and application of this strategy.

Results and discussions

Previously, we have reported the one pot synthesis of 3,6,8-tribromoquinoline **3** by bromination of 6,8-dibromo-1,2,3,4-tetrahydroquinoline **2** which proceeded in high yield (90%).[19] As a continuation of this, we initially studied in detail both this reaction and alternative approaches towards the synthesis of **3**. Interestingly, 1,2,3,4-tetrahydroquinoline **1** was found to react with 5 equiv of bromine at ambient temperature to afford the 3,6,8-tribromoquinoline **3** in good yield (82%) (Scheme 2). As an alternate method for the synthesis of **3**, 6,8-dibromoquinoline **4**[17,20] was brominated using Eisch's procedure.[21] It is proposed that 6,8-dibromoquinoline **4** initially reacts to produce bromine salt **7** which upon heating at reflux in the presence of pyridine undergoes conversion to 3,6,8-tribromoquinoline **3** via substitution at the C-3 position (Scheme 2).

In our previous publication,[18] the copper induced cyanation of 6,8-dibromoquinoline **4** was investigated and we initially applied the same strategy to 3,6,8-tribromoquinoline **3** (Scheme 3) and 6,8-dibromo-1,2,3,4-tetrahydroquinoline **2** (Scheme 4). Tribromo compound **3** was reacted with CuCN in refluxing DMF to afford a mixture of cyanoquinolines **8**, **9** and **10** (Scheme 3). The effect of reaction duration on the product ratio was investigated and it was observed that a reaction time of 6 h gave monocyanide **8** in good yield (76%, entry 1), whereas prolonged reaction times (14 h) yielded a mixture of cyanoquinolines **9** and **10** (entry 2). Gratifyingly after 24 h, tricyanide **10** was obtained as the sole product albeit in low yield (36%, entry 3).

The low yield of **10** could be explained by the longer reaction time which caused polymerization/decomposition of tricyanide

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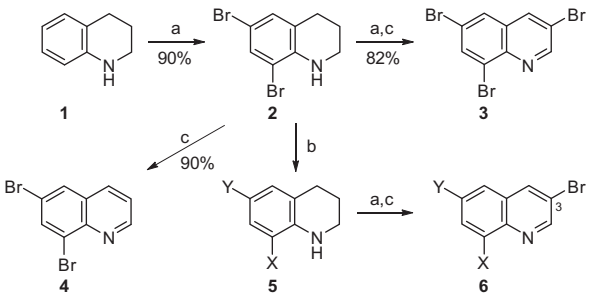
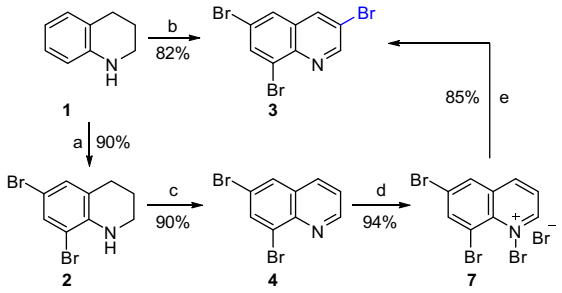
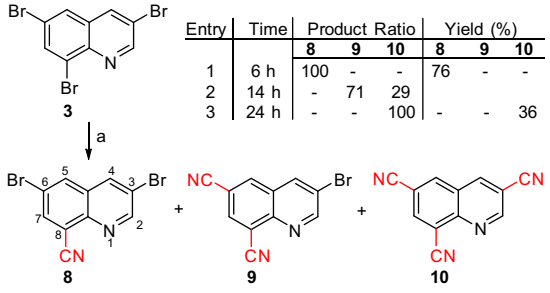


Scheme 1. Approaches to the synthesis and functionalization of quinoline and hydroquinoline derivatives. (a) bromination; (b) substitution; (c) aromatization.

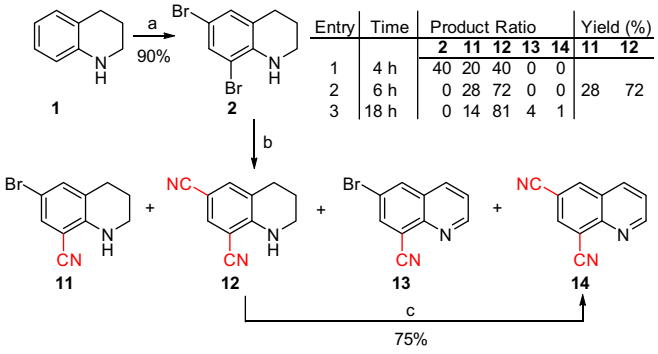


Scheme 2. Reagents and conditions (a) Br_2 (2 equiv), $CHCl_3$, dark, 2 h, rt; (b) Br_2 (5 equiv), $CHCl_3$, dark, 3 d, rt; (c) DDQ (2.5 equiv), benzene, 3 h, reflux; (d) Br_2 (1 equiv), CCl_4, 3 h, rt; (e) pyridine (1 equiv), reflux, 15 h.



Entry	Time	Product Ratio			Yield (%)		
		8	9	10	8	9	10
1	6 h	100	-	-	76	-	-
2	14 h	-	71	29			
3	24 h	-	-	100	-	-	36

Scheme 3. Reagents and conditions (a) CuCN (6 equiv), DMF, reflux.



Entry	Time	Product Ratio					Yield (%)	
		2	11	12	13	14	11	12
1	4 h	40	20	40	0	0		
2	6 h	0	28	72	0	0	28	72
3	18 h	0	14	81	4	1		

Scheme 4. Reagents and conditions (a) Br_2 (2 equiv), CH_2Cl_2, dark, 2 h, rt; (b); CuCN (4 equiv), DMF, reflux; (c) DDQ, benzene, 44 h, reflux.

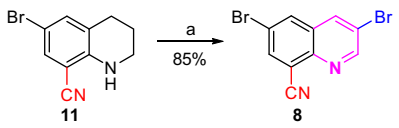
10. Interestingly, the first substitution occurred at the C-8 position instead of C-3 as expected, which was potentially assisted by Cu-N complexation. The ^{1}H NMR of **10** displayed similar signals to tribromide **3**, except they were shifted to a higher field. In the ^{1}H NMR spectra of 3,6,8-tricyanoquinoline **10**, a downfield shift for H-2 (δ_H 9.36, d, $J_{2,4}$ = 1.6 Hz) was observed which was characteristic for a quinoline ring; the doublet of H-4 was observed at δ_H 8.74 ($J_{4,2}$ = 1.6 Hz). Two signals with meta coupling at δ_H 8.56 and 8.45 ($J_{5,7}$ = 2.0 Hz), belonging to H-5 and H-7, respectively, were also in good agreement with the proposed structure. The ^{13}C NMR spectra of **10**, consisted of twelve sp^2 resonances, eight of which were quaternary carbons. ^{1}H NMR of all compounds are listed in Table 1.

The structure of cyanides **8** and **9** were determined by ^{1}H and ^{13}C NMR, 2D NMR (HMBC, HETCOR), and elemental analysis. The ^{1}H NMR spectrum of dibromide **8** consisted of four signals (Table 1). The resonance for H-2 appeared at δ 9.05 with a coupling constant value ($J_{2,4} = J_{5,7}$ = 1.6 Hz), which is characteristic for a quinoline ring. Meta coupling doublets for H-5 and H-7 (δ_H 8.19, 8.34, respectively, $J_{5,7}$ = 1.6 Hz) as well as H-2 and H-4 (δ_H 9.04, 8.16, respectively, $J_{2,4}$ = 1.6 Hz) were evidence for the position of the two bromine substituents. 2D NMR was used to establish the position of the cyano groups in both **8** and **9**. For example, in the HBMC spectra of **8,** the cyano carbon atom (δ_H 115.2) correlated with H-7 (δ_H 8.34 ppm) but did not correlate with H-5 (δ_H 8.19 ppm) confirming that the cyano group was substituted at C-8. Highly downfield shifts were evidence that the compound contained a cyano group. The ^{13}C NMR studies of compound **8** displayed ten resonances of which six signals were quaternary which was in accordance with the aromatic skeleton being tri substituted.

When 6,8-dibromo-1,2,3,4-tetrahydroquinoline **2** was treated with CuCN in refluxing DMF, the ^{1}H NMR spectrum indicated formation of a mixture of cyano tetrahydroquinolines (**11**, **12**) and quinolines (**13**, **14**) which varied in composition by reaction time. It was observed that after 4 h, two cyano tetrahydroquinoline derivatives **11** and **12** had formed in a 20:40 ratio (conversion 60%, entry 1), as assigned by ^{1}H NMR spectroscopy. The starting material was consumed in 6 h (entry 2) giving **11** and **12** in a

Table 1
Summary of the ^{1}H NMR data of compounds **8**–**14**

Compound	δ_H					J = (Hz)/other signals
	H-2	H-3	H-4	H-5	H-7	
8	9.05 (d)	—	8.16 (d)	8.19. (d)	8.34 (d)	$J_{2,4}$ = 1.6, $J_{7,5}$ = 1.6
9	9.23 (d)	—	8.57 (d)	8.37 (d)	8.33 (d)	$J_{2,4}$ = 2.0, $J_{5,7}$ = 2.0
10	9.36 (d)	—	8.74 (d)	8.56 (d)	8.45 (d)	$J_{2,4}$ = 1.6, $J_{5,7}$ = 2.0
11	3.42 (t)	1.93 (m)	2.74 (t)	7.16 (d)	7.28 (d)	$J_{2,3}$ = 4.4, $J_{4,3}$ = 6.4 $J_{7,5}$ = 2.0; 4.87 (s) *NH*
12	3.50 (t)	1.97 (m)	2.78 (t)	7.50 (s)	7.29 (s)	$J_{2,3}$ = 6.4, $J_{4,3}$ = 6.0 5.48 (s) *NH*
13	9.08 (d)	7.58 (dd)	8.17–8.22 (m)			$J_{2,3}$ = 4.0, $J_{3,4}$ = 8.0
14	9.27 (dd)	7.74 (dd)	8.36 (dd)	8.50 (d)	8.30 (d)	$J_{2,3}$ = 4.0, $J_{3,4}$ = 8.0 $J_{2,4}$ = 1.6, $J_{7,5}$ = 1.6



Scheme 5. Reagents and conditions (a) Br_2 (3 equiv), $CHCl_3$, dark, rt, 2 d.