Unexpected and Divergent Reactions of *N*-Formyl-1,2-dihydroquinolines with Sodium Azide: Highly Chemoselective Formation of 2-Substituted Quinolines and Isoxazolo[4,3-*c*]quinolines

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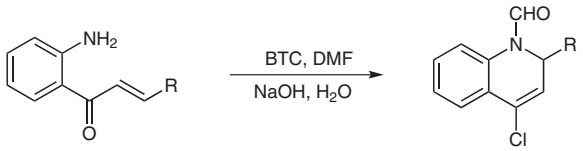
Abstract: Efficient and divergent synthesis of 2-substituted quinolines and isoxazolo[4,3-*c*]quinolines was achieved from *N*-formyl-1,2-dihydroquinolines with the aid of sodium azide. The synthesis is substituent-dependent. Thus *N*-formyl-1,2-dihydroquinolines with a hydrogen atom at the 3-position afforded 2-substituted quinolines in good to excellent yields, while with a 3-formyl group, *N*-formyl-1,2-dihydroquinolines unexpectedly gave isoxazolo[4,3-*c*]quinolines in high yields.

Key words: azides, quinolines, chemoselectivity, deformylation heterocycles

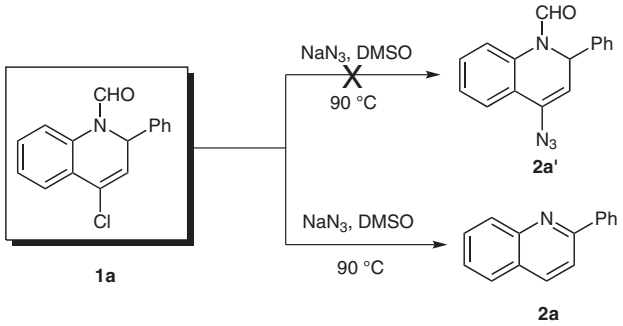
Quinolines and their derivatives represent an important class of organic molecules that attract continuing interest of both synthetic and medicinal chemists. Functionalized quinolines are integral to a large number of biologically active synthetic drug substances.[1] In particular, 2-substituted quinolines are naturally occurring in antiplatelet agents,[2] 5-lipoxygenase inhibitors,[3] LTD4 receptor antagonists,[4] and other biologically active molecules. Despite currently available methodologies for the construction of quinoline derivatives, the development of new synthetic methods is still of considerable ongoing interest.[5]

In our constant medicinal chemistry effort in searching for the compounds with pharmacological importance, we undertook the program of synthesis of a variety of 4-substituted quinolines as key building blocks. Recently, we have reported an efficient method to form 4-chloro 2-substituted *N*-formyl-1,2-dihydroquinolines from 2′-aminochalcones by a new Vilsmeier-type regent, bis-(trichloromethyl) carbonate (BTC)–DMF, as shown in Scheme 1.[6] Since the chlorine atom at the 4-position could be replaced by various groups in producing physiologically activated compounds,[7] we attempted the preparation of 4-azido quinolines from 4-chloro 2-substituted *N*-formyl-1,2-dihydroquinolines.

4-Chloro-2-phenyl-*N*-formyl-1,2-dihydroquinoline (**1a**) was selected as a model substrate to test the reaction. However, the reaction between **1a** and sodium azide did not afford the expected 4-azido products **2a′**, which was in contrast with the reaction between 4-chloro-2-phenylquinoline and sodium azide as previously reported.[8] Instead, 2-phenylquinoline (**2a**), resulting from the one-pot N-deformylation and aromatization, was obtained in excellent yield (95%) (Scheme 2).



Scheme 1



Scheme 2 Reaction of **1a** with sodium azide

According to our knowledge, N-deformylation of formamides is generally achieved by heating of the substrates in strongly acidic or basic solutions.[9] Recently, Perumal et al. developed a novel method for the oxydic deformylation of *N*-formyldihydroquinolines employing ferric chloride hexahydrate.[10] Taking into account the simple and efficient method employed here, we further optimized this unexpected reaction so as to develop a new and convenient metal-free synthesis of quinolines via consecutive N-deformylation and aromatization.

To set up the standard reaction conditions, the ratio of **1a** to NaN_3, solvent and reaction temperature were then investigated. A series of experiments revealed that using one equivalent of NaN_3 could afford the corresponding product with a preferable yield while reducing the amount of NaN_3 would lead to incomplete conversion. The reaction did not afford **2a** in better yield with higher molar ratio of NaN_3:**1a**. Besides DMSO, a number of other solvents such as DMF and H_2O,[11] DMF,[12] and MeCN were further surveyed under similar conditions. However, no

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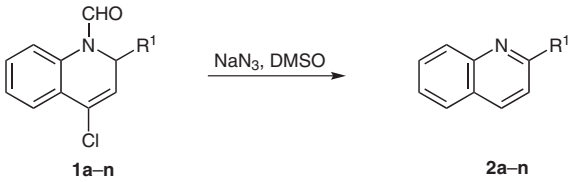
obvious improvement was observed in comparison with DMSO. The optimal results were obtained when the reaction was performed with one equivalent of NaN_3 at 90 °C for 0.5 hour, whereby the yield of **2a** reached 95%.

Table 1 Synthesis of 2-Substituted Quinolines **2**



1a–n **2a–n**

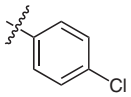
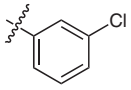
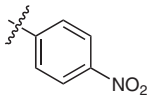
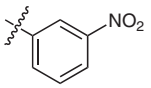
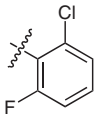
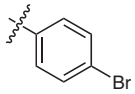
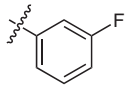
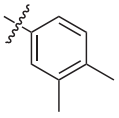
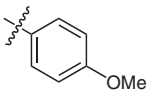
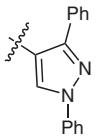
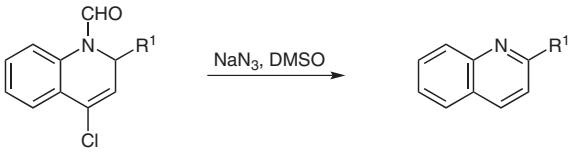
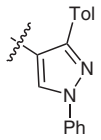
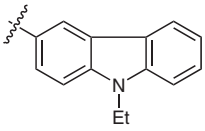
Entry	1	R^1	Product[a]	Time (h)	Yield[b] (%)
1	**1a**		**2a**	0.5	95
2	**1b**		**2b**	0.5	99
3	**1c**		**2c**	0.5	99
4	**1d**		**2d**	0.5	99
5	**1e**		**2e**	0.5	99
6	**1f**		**2f**	0.5	99
7	**1g**		**2g**	0.5	97
8	**1h**		**2h**	0.5	97
9	**1i**		**2i**	1.0	94
10	**1j**		**2j**[c]	3.5	84
11	**1k**		**2k**[c]	3	86
12	**1l**		**2l**[d]	2	86

Table 1 Synthesis of 2-Substituted Quinolines **2** (continued)



1a–n **2a–n**

Entry	1	R^1	Product[a]	Time (h)	Yield[b] (%)
13	**1m**		**2m**[d]	3.5	85
14	**1n**		**2n**[d]	3.5	88

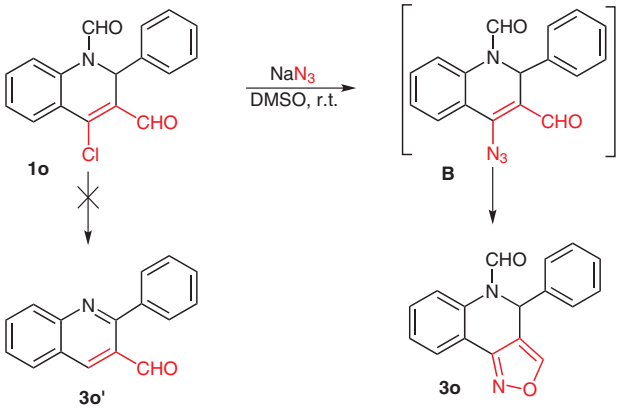
[a] Reactions were carried out with **1** (1.0 mmol) and sodium azide (1.0 mmol) at 90 °C.
[b] Isolated yield based upon **1a**–**n**.
[c] Reaction temperature: 150 °C.
[d] Reaction temperature: 120 °C.

With the best reaction conditions in hand, the scope of this novel cascade reaction with different *N*-formyl-1,2-dihydroquinolines **1** was examined. Gratifyingly, under the optimized conditions, all the substrates listed in Table 1 afforded the desired N-deformylated products **2** in good yields.

As shown in Table 1, compounds **1** with an electron-withdrawing group at the 2-aryl of quinoline produced the corresponding N-deformylated products in excellent yields (Table 1, entries 2–8). On the other hand, compounds **1i** and **1j** with electron-donating aryl groups afforded **2i** and **2j** in relatively lower yields (Table 1, entries 9 and 10). When this protocol was applied to more substrates, especially various 2-heteroaryl-4-chlorodihydroquinolines, good yields of the desired quinoline products were also isolated (Table 1, entries 11–14). At this stage, it could be concluded that this N-deformylation and aromatization reaction tolerates a wide variety of *N*-formyl-1,2-dihydroquinolines.

To further extend the scope and generality of the reaction, 3-formyl-substituted *N*-formyl-1,2-dihydroquinolines such as 4-chloro-2-phenylquinoline-1,3(2*H*)-dicarbaldehyde (**1o**) was introduced.[13] However, instead of obtaining the desired N-deformylation product **3o′**, 4-phenylisoxazolo[4,3-*c*]quinoline-5(4*H*)-carbaldehyde (**3o**) was isolated as the single product and no azirine was detected.[14a,b] A plausible pathway is therefore suggested in Scheme 3 to rationalize the formation of this unexpected product.

Encouraged by the results that **1o** could undergo a heterocyclization to form **3o** in the presence of sodium azide, we subsequently applied the method for synthesizing more isoxazolo[4,3-*c*]quinolines. It was found that isoxazo-

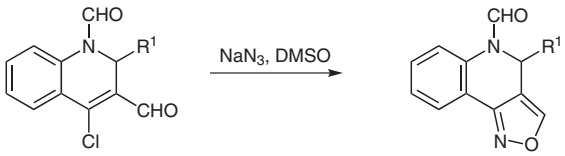


Scheme 3 Reaction pathway for the formation of **3**

lo[4,3-*c*]quinolines **3o–r** were obtained in satisfactory yields (Table 2).

On the basis of the above results, a possible mechanism for these two divergent reactions is presented in Scheme 4. Although it is premature to propose a detailed mechanism at this stage, based on the above results a probable sequence of reactions may be proposed. The overall transformation of route 1 arises from the [1,3]-proton transfer, which is followed by azide nucleophilic attack of **1a–n** to provide an *N*-formyl azide intermediate **A**. Elimination of formyl azide accompanied by elimination of chlorine ion finally produces 2-substituted quinolines **2**. Formation of isoxazolo[4,3-*c*]quinolines **3** (route 2) is not mechanistically consistent with the quinolines produced in route 1. In this case, the above [1,3]-H shift to generate intermediate **C** is disfavored. The formyl at the 3-position of quinoline conjugates with the C=C bond and chlorine, thus forming an electron-deficient α,β-unsaturated carbonyl system.

Table 2 Synthesis of Isoxazolo[4,3-*c*]quinolines **3**

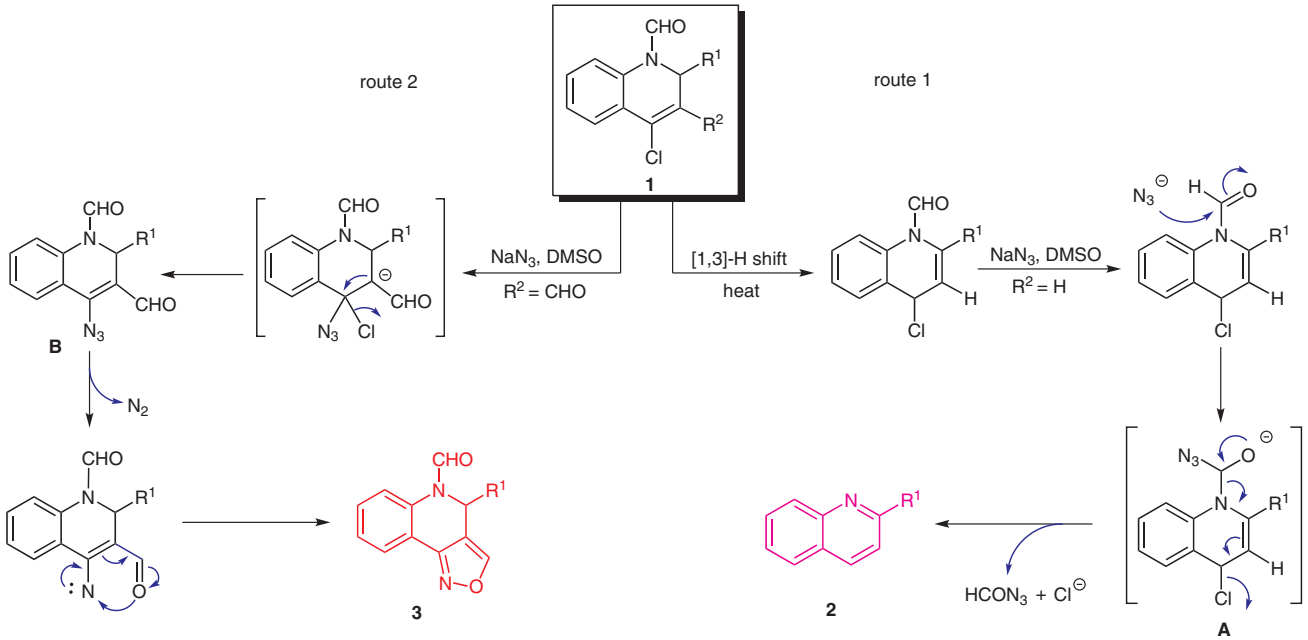


Entry	**1**	R^1	Product[a]	Time (h)	Yield[b] (%)
1	**1o**	Ph	**3o**	0.5	88
2	**1p**	4-ClC_6H_4	**3p**	0.5	90
3	**1q**	3,4-$Me_2C_6H_3$	**3q**	0.5	89
4	**1r**	4-$MeOC_6H_4$	**3r**	0.5	89

[a] Reactions were carried out with **1o–r** (1.0 mmol) and sodium azide (1.5 mmol) at r.t.
[b] Isolated yield based upon **1o–r**.

The azide anion attacks in a way of conjugate addition and subsequent elimination of the chlorine would lead to intermediate **B**.[14] The azido-aldehyde intermediate **B** then undergoes spontaneous denitrogenation and ring closure to isoxazolo[4,3-*c*]quinolines **3**. The details of the reaction mechanism and the role of sodium azide are currently under investigation.

In summary, we have developed a new and convenient approach to the construction of quinoline derivatives from the readily accessible *N*-formyldihydroquinolines by treatment with sodium azide. Depending upon the 3-substituent on the substrates, the protocol could give either 2-substituted quinolines[15] or 4-substituted isoxazolo[4,3-*c*]quinolines-5(4*H*)-carbaldehydes[16] in good to excellent yields.



Scheme 4 Plausible mechanism

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(13) **Experimental Procedure for the Synthesis of 4-Chloro-2-substituted Quinolines; 1,3-(2*H*)-dicarbaldehyde 1o–r**: To an ice-cold magnetically stirred solution of DMF (10 mL) and 2-arylquinoline (5.0 mmol), $POCl_3$ (30 mmol, 2.8 mL) was added dropwise. The reaction mixture was heated to 50 °C for 3 h. After which it was poured into the crush ice, neutralized with sat. K_2CO_3 solution and extracted with EtOAc. After drying and condensation of the organic layer , the crude reaction product was purified by column chromatography using 5% EtOAc in PE as eluent to afford pure **1o–r**.

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(15) **General Procedure for the Synthesis of 2-Substituted Quinolines 2a–n**: To a solution of DMSO (5 mL) and 4-chloro-*N*-formyl-1,2-dihydroquinolines **1a–n** (1.0 mmol), NaN_3 (1 mmol, 0.065 g) was added at r.t. The solution was then heated at the indicated temperature (90 °C or 120 °C or 150 °C) for the indicated time. After completion of the reaction (monitored by TLC) the mixture was treated with ice-water and extracted with EtOAc. The organic layer was washed with H_2O, and then with brine. After condensation of the organic layer, the products **2a–n** were obtained by column chromatography (PE–EtOAc).
2-(2-Chloro-6-fluorophenyl)quinoline (2f)
New compound. Yield: 99%; light yellow oil; R_f 0.53 (PE–EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (1 H, d, *J* = 8.0 Hz), 8.20 (1 H, d, *J* = 8.4 Hz), 7.89 (1 H, d, *J* = 8.0 Hz), 7.74–7.79 (1 H, m), 7.60 (1 H, t, *J* = 8.0 Hz), 7.50 (1 H, d, *J* = 8.0 Hz), 7.32–7.38 (2 H, m), 7.11–7.16 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (d, $^1J_{C-F}$ = 248.7 Hz), 152.5, 147.9, 136.4, 134.3, 130.2 (d, $^3J_{C-F}$ = 9.9 Hz), 129.8, 129.6, 127.6, 127.3, 127.1, 125.6 (d, $^4J_{C-F}$ = 3.1 Hz), 123.0, 114.6 (d, $^2J_{C-F}$ = 22.0 Hz). HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{10}ClFN$: 258.0408; found: 258.0477.

(16) **General Procedure for the Synthesis of 4-Substituted Isoxazolo[4,3-*c*]quinolines-5-(4*H*)-carbaldehyde 3o–r**: To a solution of DMSO (5 mL) and 4-chloro-2-substituted quinolines-1,3 (2*H*)-dicarbaldehyde **1o–r** (1.0 mmol), NaN_3 (1.5 mmol, 0.098 g) was added at r.t. and the reaction mixture was kept at this temperature for 0.5 h. After completion of the reaction (monitored by TLC) the mixture was treated with ice-water and extracted with EtOAc. The organic layer was washed with H_2O, and then with brine. After condensation of the organic layer, the products **3o–r** were obtained by column chromatography (PE–EtOAc).
4-Phenylisoxazolo[4,3-*c*]quinoline-5-(4*H*)-carbaldehyde (3o)
New compound. Yield: 88%; white crystals; mp 176–178 °C; R_f 0.46 (PE–EtOAc, 3:1). IR (KBr): 3121, 3057, 2851, 1677, 1609, 1574, 1475 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 9.21 (1 H, s), 8.86 (1 H, s), 7.94 (1 H, d, *J* = 8.0 Hz), 7.73 (1 H, d, *J* = 8.0 Hz), 7.54–7.59 (1 H, m), 7.37–7.41 (1 H, m), 7.22–7.30 (3 H, m), 7.16 (2 H, d, *J* = 8.0 Hz), 7.10 (1 H, s). ^{13}C NMR (100 MHz, DMSO): δ = 162.4, 156.0, 153.8, 138.8, 136.1, 132.2, 128.7, 127.8, 126.3, 126.1, 124.6, 121.2, 117.1, 114.7, 46.9. HRMS (EI): *m/z* [M$^+$] calcd for $C_{17}H_{12}N_2O_2$: 276.0899; found: 276.0899.

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