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SHORT COMMUNICATIONS

Simultaneous Double C^2/C^3 Functionalization of Quinoline with *p*-Nitrobenzoyl(phenyl)acetylene. One-Pot Synthesis of 3-(4-Nitrobenzoyl)-2-phenylquinoline

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Abstract—(4-Nitrophenyl)(2-phenylquinolin-3-yl)methanone has been synthesized in one step by simultaneous double C^2/C^3 functionalization of the pyridine ring of quinoline molecule by the action of *p*-nitrobenzoyl(phenyl)acetylene in aqueous potassium hydroxide.

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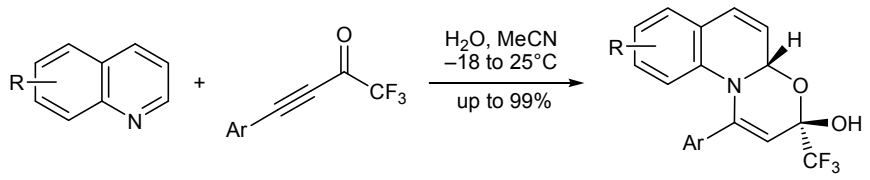
In recent time, increased interest has been observed in reactions of azines with electron-deficient acetylenes, which involve reversible formation of 1,3-dipoles (zwitterions), namely vinylic carbanions with an ammonium counterion located in the same molecule. Depending on the azine structure and acetylene nature, such reactions are accompanied by ring opening [1–4], ring expansion [5], functionalization [6], or fusion to another heterocyclic system [7, 8]. An important advantageous feature of this approach is that it makes it possible to carry out the reactions under mild conditions, often at room temperature, generally in the absence of a catalyst (less frequently, in the presence of bases). As a result, the final products can be obtained with enhanced selectivity and high purity, without transition metal impurities. This is important for potential pharmaceuticals [9] which usually include functionalized and fused azines.

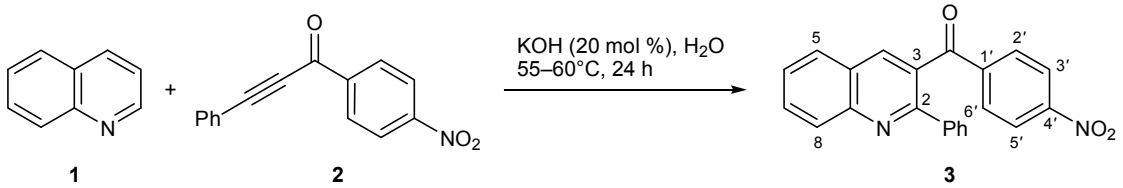
We have recently reported a noncatalytic one-step procedure for the stereoselective synthesis of functionalized hydroxy(trifluoromethyl)oxazinoquinolines by reaction of quinolines with aryl(trifluoroacetyl)acetylenes at –18 to 25°C [8] (Scheme 1). However, quinoline (**1**) reacted with *p*-nitrobenzoyl(phenyl)acetylene (**2**) in the presence of 20 mol % of potassium hydroxide in water (55–60°C, 24 h) in a quite different way, unexpectedly yielding 24% of 3-(4-nitrobenzoyl)-2-phenylquinoline (**3**) (Scheme 2). The yield of **3** was lower (19%) when the reaction was carried out in 70% aqueous acetonitrile for a longer time (48 h), and the reaction mixture contained hydroxy enone **4** resulting from base-catalyzed hydration [10] of **2**. Compound **4** was isolated in 11% yield as a mixture of two tautomers **4a** and **4b**, both having *Z*-configured double bond (Scheme 3). This reaction, as well as other possible base-catalyzed side processes involving electron-deficient acetylene derivative, in particular its anionic polymerization, are likely to be responsible for the low yield of functionalized quinoline **3**.

Formalistically, the observed functionalization can be regarded as replacement of an unsubstituted acetylene molecule in the pyridine ring of quinoline by the disubstituted alkyne fragment. However, no any

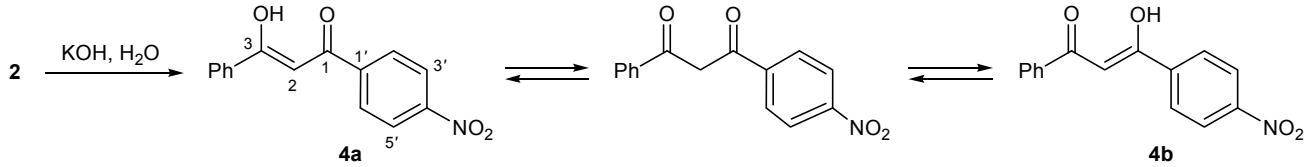
Scheme 1.



Scheme 2.



Scheme 3.



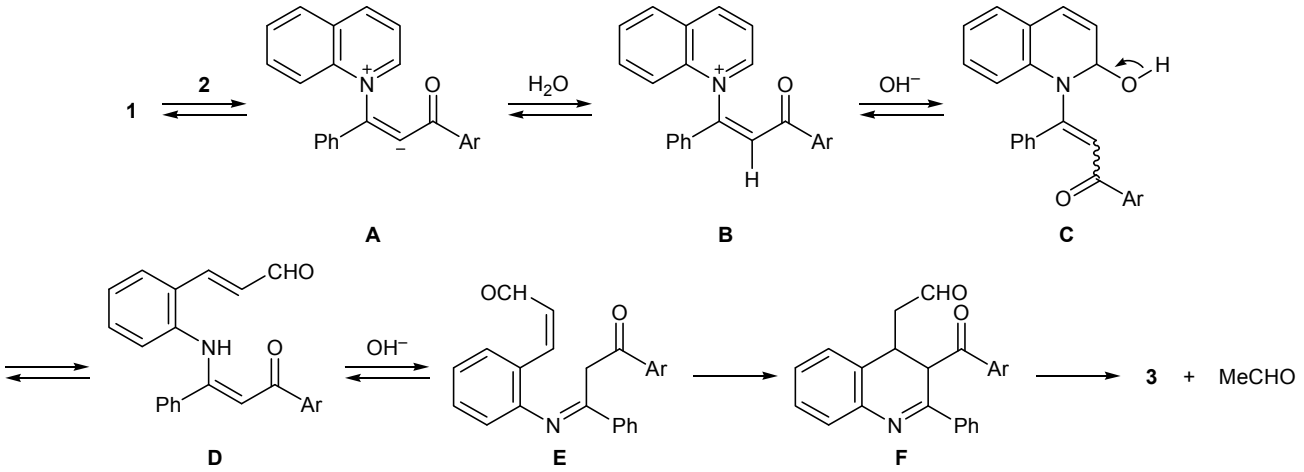
acetylene traces were detected in the reaction mixture. Obviously, the reaction is a complex tandem process initiated by 1,3-dipolar adduct **A** derived from quinoline and electron-deficient acetylene **2** (Scheme 4). After neutralization of the carbanionic center by proton from a water molecule, quinolinium hydroxide **B** in its covalent form **C** undergoes rearrangement with opening of the pyridine ring by analogy with [1, 2]. Base-catalyzed prototropic shift in intermediate *N*-vinyl aldehyde **D** gives imine **E**, and intramolecular Michael addition of the activated methylene group in the latter to the α,β-unsaturated aldehyde fragment closes dihydroquinoline ring to form intermediate **F**. Elimination of acetaldehyde molecule from **F** yields substituted quinoline **3**. The proposed scheme was confirmed by the detection of acetaldehyde in the reaction mixture by mass spectrometry.

The expected high reactivity of intermediates **A**–**E** could favor their other transformations, which would reduce the yield of final product **3**.

The described one-pot synthesis of quinoline **3** is the first example of simultaneous double C^2/C^3 functionalization of the pyridine fragment of quinoline molecule with *p*-nitrobenzoyl(phenyl)acetylene. It cannot be ruled out that the observed cascade process may be general for some quinolines and electron-deficient acetylenes. We hope to answer this question in the course of further study of this reaction.

(4-Nitrophenyl)(2-phenylquinolin-3-yl)methanone (3). *a*. A solution of 0.006 g (20 mol %) of potassium hydroxide in 0.5 mL of water was added to a mixture of 0.064 g (0.500 mmol) of quinoline (**1**) and 0.126 g (0.500 mmol) of acetylene **2**. The mixture was stirred for 24 h at 55–60°C, water was removed under reduced pressure, and the residue was subjected to column chromatography to isolate 0.043 g (24%) of quinoline **3** as light brown powder, mp 184–186°C (from Et_2O). IR spectrum, ν, cm^{-1}: 1665 (C=O), 1524 (NO_2). ^1H NMR spectrum, δ, ppm: 7.24 m (3H, *m*-H, *p*-H), 7.64 m (1H, 6-H), 7.54 m (2H, *o*-H), 7.72 m (2H,

Scheme 4.



Ar = 4-$O_2NC_6H_4$.

2′-H, 6′-H), 7.86 m (1H, 7-H), 7.94 m (1H, 5-H), 8.05 m (2H, 3′-H, 5′-H), 8.25 m (1H, 8-H), 8.44 s (1H, 4-H). ^{13}C NMR spectrum, δ_C, ppm: 126.0 (C^{4a}), 127.8 (C^6), 128.4 (C^5), 123.5 ($C^{3'}$, $C^{5'}$), 128.8 (C^m), 129.4 (C^p), 129.5 (C^o), 129.9 (C^8), 130.6 ($C^{2'}$, $C^{6'}$), 131.9 (C^7), 131.8 (C^3), 138.6 (C^4), 139.6 (C^i), 141.9 ($C^{1'}$), 148.8 (C^{8a}), 150.1 ($C^{4'}$), 157.1 (C^2), 195.6 (C=O). Found, %: C 74.87; H 3.93; N 7.52. $C_{22}H_{14}N_2O_3$. Calculated, %: C 74.57; H 3.98; N 7.91.

b. A solution of 0.006 g (20 mol %) of potassium hydroxide in 0.5 mL of water was added to a solution of 0.064 g (0.500 mmol) of quinoline (**1**) and 0.126 g (0.500 mmol) of acetylene **2** in 1 mL of acetonitrile. The mixture was stirred for 48 h at 55–60°C. We isolated 0.033 g (19%) of quinoline **3** and 0.015 g (11%) of hydroxy enone **4**.

(*Z*)-3-Hydroxy-1(3)-(4-nitrophenyl)-3(1)-phenylprop-2-en-1-one (4). White powder, mp 160–162°C (from Et_2O); published data [11]: mp 166–167°C; compound **4** exists as a mixture of two enol tautomers due to strong intramolecular hydrogen bond O–H···O [12]. IR spectrum, ν, cm^{-1}: 3371 (OH), 1654 (C=O), 1726 (NO_2), 1523, 1344. ^1H NMR spectrum, δ, ppm: 6.88 s (1H, 2-H), 7.50 m (2H, *m*-H), 7.60 m (1H, *p*-H), 7.99 m (2H, *o*-H), 8.12 m (2H, 2′-H, 6′-H), 8.32 m (2H, 3′-H, 5′-H), 16.65 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 93.4 (C^2), 123.0 ($C^{3'}$, $C^{5'}$), 126.6 (C^o), 127.2 (C^m), 128.0 ($C^{2'}$, $C^{6'}$), 132.3 (C^p), 134.3 (C^i), 140.1 ($C^{1'}$), 149.0 ($C^{4'}$), 180.8 (C^3), 186.9 (C^1). The ^1H NMR and IR spectra of **4** were similar to those given in [11].

The IR spectra were recorded from films on a Bruker IFS 25 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.1 and 100.6 MHz, respectively, using $CDCl_3$ as solvent and hexamethyldisiloxane as internal standard. The mass spectrum of the reaction mixture was recorded on a Shimadzu GCMS-QP5050A instrument. The elemental analysis was performed on a Flash EA 1112 Series analyzer. The melting points were measured on a Kofler hot stage. The progress of the reactions was monitored by IR spectroscopy, following the disappearance of the C≡C stretching band at 2198 cm^{-1}. Quinoline (**1**) was commercial product, and *p*-nitrobenzoyl(phenyl)acetylene (**2**) was synthesized as described in [13]. Column chromatography was performed on Silica gel 60 (0.060–0.200 mm) using chloroform–benzene–ethanol (20:4:1) as eluent.

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