REDISCOVERED SYNTHESIS OF 3-CYANOQUINOLINE DERIVATIVES

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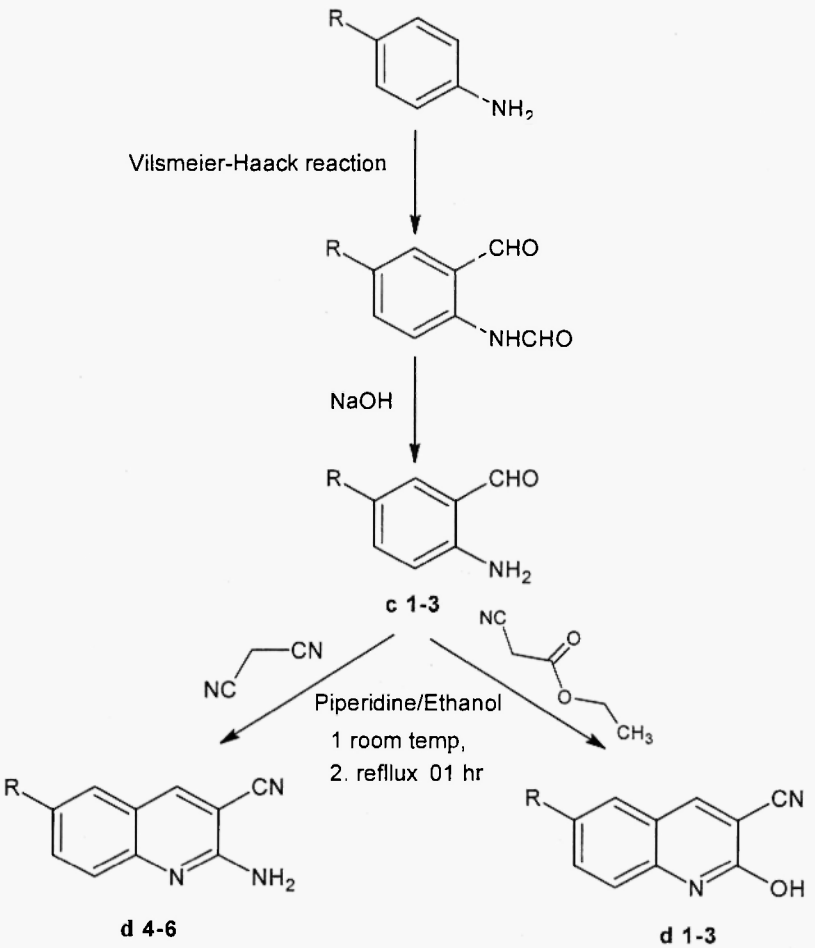
Abstract : The easy and rapid synthetic procedure for the synthesis of substituted 3-cyanoquinoline derivatives using available laboratory reagents is reported. Vilsmeier-Haack reaction is employed to the *p*-substituted aniline to yield formyl aniline. These on reaction with cyano ethylacetate and with malono nitrile in presence catalyst results in to 3-substituted quinolines.

Introduction

The synthesis of the quinoline and their derivatives has been of considerable interest to organic and medicinal chemists for many years as a large number of natural products[1] and drugs[2] contain this heterocyclic nucleus. Classical methods for the constructions of the quinoline ring involve the cyclization of substituted benzene derivatives. Such reactions include the Skraup, Debner-von Miller and Combes synthesis[3]. For an instance, the Skraup procedure involves the large amount of sulfuric acid at temperatures above 150^0C and the reaction is often violent. Since then many methods have been developed for the synthesis of quinolines;[4] but most of these methods are not fully satisfactory with regard to yield,[4a,c,e,g] reaction conditions,[4a,c,e,f] generality,[4b,d,e] and operational simplicity.[4a] Thus a simple, general and efficient procedure for the synthesis of this important heterocycle in demand.

Earlier methods of building the quinoline derivatives involve the reactions of the β-keto nitriles[5,6,7,8,9] with appropriately substituted *o*-amino benzaldehyde, which gives derivatives of 3-cyanoquinoline as a compound.[5] An alternative mode of condensation between *o*-amino benzaldehyde and β-keto ester is noted by Friedlander and Gohring.[10] Using this method, various derivatives of 3-cyanoquinoline are synthesized.[11,12,13,14,15,16]

Of the different method available in the literature for the synthesis of the quinoline ring, only few can be applied efficiently to the preparation of 3-cyanoquinoline derivative[17]. In this paper, we wish to report an efficient methodology for the synthesis of 3-cyanoquinoline derivatives $\mathbf{d}_{1\text{-}10}$ using various substituted *o*-amino benzaldehydes. $\mathbf{c}_{1\text{-}5}$ (Scheme-1)



Compound	R
c_1, d_1, d_4	NO_2
c_2, d_2, d_5	Cl
c_3, d_4, d_6	Br

Scheme-1

Results and Discussions

First, we prepared the substituted *o*-amino benzaldehyde $\mathbf{c}_{1\text{-}3}$ through Vilsmeier-Haack reaction. The Vilsmeier-Haack reaction is a convenient method for the formylation of activated and heteroaromatic compounds. The required starting compounds $\mathbf{c}_{1\text{-}3}$ are prepared by the reaction of *p*-substituted aniline with phosphoryl chloride using dimethyl formamide. *p*-Substituted aniline is treated with the salt derived from $POCl_3$ and DMF for half an hour at 5^0C. The reaction mixture is heated at 80^0C for two hours. Subsequent treatment with aq NaOH solution afforded substituted *o*-amino benzaldehydes $\mathbf{c}_{1\text{-}3}$ in yield 78-85%. The anticipated 3-cyanoquinoline derivatives $\mathbf{d}_{1\text{-}6}$ are synthesized from appropriately substituted *o*-amino benzaldehydes with cyano ethylacetate, and malanonitrile, in presence of piperidine as a catalyst. The ethanolic solution of cyano ethylacetate and catalytic amount of piperdine is kept for stirring at the room temperature for ten to twenty minutes. To this solution, substituted *o*-amino benzaldehydes $\mathbf{c}_{1\text{-}5}$ is added with constant stirring. At the end of the addition, the desired product gets precipitates out, gave product $\mathbf{d}_{1\text{-}3}$. In order to ensure the ring cyclization, it is further refluxed on water bath about one hour. On cooling, the solid obtained is filtered and dried, with the yield 80%. The structures of compounds $\mathbf{d}_{1\text{-}3}$ are confirmed by spectral studies. Similarly, the compounds $\mathbf{d}_{4\text{-}6}$ are prepared and characterized by spectral data.

Experimental

Melting points in open capillary on a Cintex melting point apparatus, Shimadzu IR-470 spectrometer Bruker AC 300F NMR Spectrophotometer (300 MHz) using TMS as internal standard, automatic Finnigan-MAT 1020C Mass spectrometer with ionization energy 70eV are used to characterize the compounds.

Reactions of p-substituted aniline with Vilsmeier reagent: Synthesis of Substituted o-amino benzaldehyde $c_{1\text{-}3}$
Vilsmeier reagent is prepared by mixing ice-cold, dry DMF (0.1 mol, 7.3 g, 7.69 ml) and $POCl_3$ (0.1 mol, 15.34 g, 9.0948 ml). The mixture was then stirred for 15 minutes at 5^0C in the ice-salt mixture bath. The *p*-substituted aniline is dissolved in dry DMF and added over about 20-30 minutes at 0-5^0C. The reaction mixture is stirred for 30 minutes at room temperature and heated to 80^0C with constant stirring. After the heating, cold and aq NaOH solution is added to the reaction mixture. The product gets precipitates out. The precipitate is collected by filtration and recrystalized in absolute alcohol to give $\mathbf{c_{1\text{-}3}}$.

Reactions of substituted o-amino benzaldehyde $c_{1\text{-}3}$ *with cyano ethylacetate: Synthesis of 3-cyanoquinolin-2-one.* $d_{1\text{-}3}$
To the ethanolic solution of the cyano ethylacetate 2-3 drops of piperidine is added. The solution is kept stirring for about 30 minutes. To this substituted *o*-amino benzaldehyde $\mathbf{c_{1\text{-}5}}$ in ethanol is added drop wise by maintaining room temperature. There itself the product gets precipitates out, to ensure the ring cyclization the reaction mixture is refluxed for 2 hr on heating mantle. On cooling, the product get re-precipitates which is insoluble in ethanol. The solid separated is collected by filtration, washed with ethanol and dried in an oven. Obtained product $\mathbf{d_{1\text{-}3}}$ is pure and the further recrystalized by absolute alcohol.

6-Nitro-3-cyanoquinolin-2-one: d_1
Prepared by the reaction of 2-amino-5-nitrobenzaldehyde $\mathbf{c_1}$.
Light yellow spongy solid. (1.82 g, 85 %); mp 215^0C; IR (KBr,v, cm^{-1}): 1687.6 (CO), 2212.2 (CN), 3369 - 3483.2 (-NH, -OH); ^{1}H NMR (δ, DMSO-d6): 7.6 - 8.8 (m, 4H, Ar-H), 11 (s, 1H, -OH, D2O exchangeable); Mass: *m/z*: 215 (M^+); Analysis: $C_{10}H_5N_3O_3$ Cal; C 55.85%; H 2.34 %; N 19.53 %; Found; C 55.72 %; H 2.83 %; N 19.00 %.

6-Chloro-3-cyanoquinolin-2-one: d_2
Prepared by the reaction of 2-amino-5-chlorobenzaldehyde $\mathbf{c_2}$.
Solid. (1.4 g, 70 %); mp: 195^0C; IR (KBr,v, cm^{-1}): 1682.1 (CO), 2218.72 (CN), 3367.5 - 3479.3 (-NH, -OH); ^{1}H NMR (δ, DMSO-d6): 7.8-8.9 (m, 4H, Ar-H), 11.1 (s, 1H, -OH, D2O exchangeable); MS: *m/z* :204 (M^+); Analysis: $C_{10}H_5ClN_2O$ Cal; C 58.70 %; H 2.46 %; N 13.69 %; Found; C 57.42 %; H 2.70 %; N 12.94 %.

6-Bromo-3-cyanoquinolin-2-one: d_3
Prepared by the reaction of 2-amino-5-bromobenzaldehyde $\mathbf{c_3}$.
solid. (1.79 g, 72 %); mp: 220^0C; IR (KBr,v, cm^{-1}): 1686.7 (CO), 2220.21 (CN), 3369.3 – 3478.5 (-NH, -OH); ^{1}H NMR (δ, DMSO-d6): 7.4 - 8.7 (m, 4H, Ar-H), 10.9 (s, 1H, -OH, D2O exchangeable), MS: *m/z*: 249 (M^+); Analysis: $C_{10}H_5BrN_2O$ Cal; C 48.22 %; H 2.02 %; N 11.25 %; Found; C 48.12 %; H 1.78 %; N 11.78 %.

Reactions of substituted o-amino benzaldehyde $c_{1\text{-}3}$ *with malanonitrile: Synthesis of 2-amino-3-cyanoquinoline* $d_{4\text{-}6}$
To the ethanolic solution of the malanonitrile 2-3 drops of piperidine is added and the solution is kept stirring for about 30 minutes. To this substituted *o*-amino benzaldehyde $\mathbf{c_{1\text{-}3}}$ in ethanol is added drop wise by maintaining room temperature. There itself the product get precipitates out, to ensure the ring cyclization the reaction mixture is refluxed for 2 hr on heating mantle. On cooling the product get re-precipitates, the precipitate is collected by filtration and recrystalized in ethanol to give $\mathbf{d_{3\text{-}6}}$

2-Amino-6-nitro-3-cyanoquinoline: d_4
Prepared by the reaction of 2-amino-5-nitrobenzaldehyde $\mathbf{c_1}$.
Brownish yellow solid (1.75 g, 82%); mp: 260^0C; IR (KBr,v, cm^{-1}): 1682.1(CO), 2218.72 (CN), 3367.5 - 3479.3 ($-NH_2$); ^{1}H NMR (δ, DMSO-d6): 7.5 - 8.6 (m, 4H, Ar-H), 6.2 (s, 2H, NH_2); MS: *m/z* :214 (M^+); Analysis: $C_{10}H_6N_4O_2$ Cal; C 56.08 %; H 2.82 %; N 26.16 %; Found; C 56.45 %; H 2.49 %; N 26.67 %.

2-Amino-6-chloro-3-cyanoquinoline: d_5
Prepared by the reaction of 2-amino-5-chlorobenzaldehyde **c_2**.
Solid. (1.44 g, 73 %); mp: 225^{0}C; IR (KBr, ν, cm^{-1}): 1683.1(CO), 2225.54 (CN), 3361.5 - 3477.6 (-NH_2); ^{1}H NMR (δ, DMSO-d6): 7.3 - 8.8 (m, 4H, Ar-H), 6.1 (s, 2H, NH_2); MS: *m/z:* 203 (M^+); Analysis: $C_{10}H_6ClN_3$ Cal; C 58.98 %; H 2.97 %; N 20.64 %; Found; C 58.79 %; H 2.83 % N 20.83%.

2-Amino-6-bromo-3-cyanoquinoline: d_6
Prepared by the reaction of 2-amino-5-bromobenzaldehyde **c_3**.
Solid (1.71 g, 69 %); mp: 250^{0}C; IR (KBr,ν, cm^{-1}): 1685.4 (CO), 2217.3 (CN), 3363.1 - 3474.3 (-NH_2); ^{1}H NMR (δ, DMSO-d6): 7.6- 8.6 (m, 4H, Ar-H), 6.2 (s, 2H, NH_2); MS: *m/z:* 248 (M^+); Analysis: $C_{10}H_6BrN_3$ Cal; C 48.41 %; H 2.44 %; N 16.94 %; Found; C 47.96 %; H 2.83 %; N 16.14 %.

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