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New route for the synthesis of 2-chloroquinoline-3-carbonitriles

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Abstract: A group of cyanoacetanilides prepared by the reaction of aniline and its derivatives with ethylcyanoacetate. In an efficient route, the latter compounds underwent formylation and cyclocondensation to convert to 2-chloroquinoline-3-carbonitrile derivatives in the Vilsmeier's reagent.

Keywords:2-Chloroquinoline-3- carbonitrile, Ethylcyanoacetate, Vilsmeier's reagent.

Introduction

Quinoline derivatives represent the most known class of heterocycles, and a number of synthetic route have been exhibited since their discovery. Various natural products were created on the quinoline skeleton, especially in biologically active alkaloids. This heterocyclic system is often used for the design of many valuable compounds with diverse pharmacological properties. An exhaustive review has recently reported several cases of biological applications due to naturally occurred quinoline derivatives [1]. Artificial quinoline derivatives also played an important role in current medicinal chemistry. A huge number of phosphodiesterase 3 inhibitors were designed, prepared and biologically evaluated upon the 2- quinolone structure [2]. In a previous communication, the synthesis of an antimicrobial group of novel pyrazolo[3,4-b]quinolines was reported by starting from 2-chloroquinoline-3-carbonitrile, which was prepared in a 4 steps synthetic route from 2-chloroquinoline-3- carboxaldehyde [3] as shown in Scheme **1.** The precursor of this long route was also prepared according to a published procedure [4].

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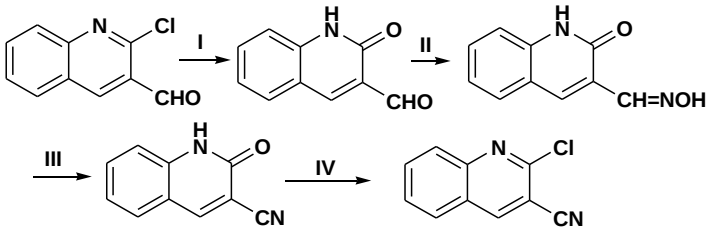
Pursuing of our research for the synthesis of privilege heterocycles [5], we exhibit an efficient route for the preparation of 2-chloroquinoline-3- carbonitriles.

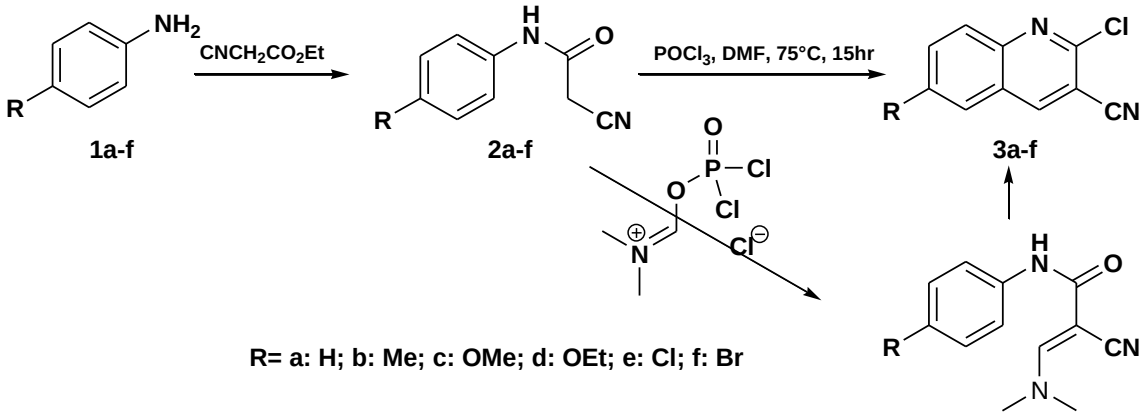


Scheme 1: Previous route for the synthesis of 2-chloroquinoline-3- carbonitrile

Results and Discussion

The present research for synthesis of 2-chloroquinoline-3- carbonitriles **3a-f**, was based upon the cyclization of cyanoacetanilides **2a-f** under reflux condition with Vilsmeier's reagent as shown in Scheme **2**. Cyanoacetanilides **2a-f** also prepared by the reaction of substituted anilines **1a-f** with ethylcyanoacetate according to the previous reports [6-9].

This is worthy of noting that distillation of phosphoroxychloride and drying of dimethylformamide significantly increased the yield and purity of the target products. Possible mechanism of the conversion illustrated in Scheme **2**. We also found that ortho- substituted cyanoacetanilides could not undergo such cyclocondensation, maybe because of the steric effects.



Scheme 2: Present route for the synthesis of 2-chloroquinoline-3- carbonitrile

IR spectra of these compounds confirmed devoid of stretching vibration bands at 1690 and 3380 cm^{-1} belonging to CO and NH groups due to precursors, but showed a new vibration band at around 1050cm^{-1} for C-Cl bond. These results also were strongly verified by observation of two molecular ion peaks M and M+2 with the ratio 3 to 1 according to isotopic pattern of a chlorine atom in the cases **3a-d**. In the cases **3e** and **3f**, the ratio of molecular ion peaks M, M+2 and M+4 were observed according to the expected pattern.

Conclusion

In conclusion, sequential treatment of aniline and para substituted anilines with ethylcyanoacetate and Vilsmeier's reagent is a general and efficient route for the synthesis of 2-chloroquinoline-3- carbonitrile derivatives.

Experimental

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. 1H NMR (300 MHz) and 13C NMR (75 MHz) spectra of products were carried out on Bruker Avance spectrometer in Chloroform-d ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. The purity of all new compounds synthesized was tested by TLC using chloroform as mobile phase.

General procedure for the preparation of cyanoacetanilides 2a-f:

A solution of each aniline (10 mmol) and triethylamine (10 mmol) in chloroform (20ml) cooled in an ice bath. 2-Cyanoacetylchloride (10 mmol) was added and stirred for 5 minutes. The solvent was removed in reduced pressure and the residue was recrystallized from ethanol-water to obtain cyanoacetanilides **2a-f**.

*2-Cyano-N-phenylacetamide (**2a**):*

Yield 1.3 g (81%), white powder, mp193°C.IR spectrum, ν, cm^{-1}: 1690 (C=O), 2230 (CN), 3310 (NH); ^{1}H NMR spectrum, δ, ppm: 3.62 (s, 2H, CH_2), 7.1-7.5 (5H, m, H Ph), 7.9 (broad, 1H, NH); ^{13}C NMR spectrum, δ, ppm: 26.5 (CH_2), 117.1 (CN), 120.5 ($C_{2,6}$), 124.4 (C_4), 128.9 ($C_{3,5}$), 138.3 (C_1), 169.7 (CO); Mass spectrum, *m*/*z* (*I*rel, %): 160 $[M]^+$ (35), 93 $[PhNH_2]^{+\cdot}$ (100). Elemental Analysis; Found: C, 67.74; H, 5.24; N, 17.26. Calculated for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49.

*2-Cyano-N-(4-methylphenyl)acetamide (**2b**):*

Yield 1.3 g (85%), white powder, mp178 – 180°C.IR spectrum, ν, cm^{-1}: 1680 (C=O), 2230 (CN), 3320 (NH); ^{1}H NMR spectrum, δ, ppm: 2.33 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 6.40 (2H, d, J = 7.1, H Ar); 6.80 (2H, d, J = 7.1, H Ar), 7.9 (broad, 1H, NH); ^{13}C NMR

spectrum, δ, ppm: 19 (CH_3), 26.5 (CH_2), 117.1 (CN), 120.5 ($C_{2,6}$), 125.4 (C_4), 128.9 ($C_{3,5}$), 138.3 (C_1), 169.7 (CO); Mass spectrum, *m*/*z* (*I*rel, %): 174 $[M]^+$ (40), 107 $[4\text{-Me-PhNH}_2]^{+\cdot}$ (100). Elemental Analysis; Found: C, 69.21; H, 5.93; N, 15.86. Calculated for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08.

*2-Cyano-N-(4-methoxyphenyl)acetamide (**2c**):*

Yield 1.7 g (90%), white powder, mp135 – 137°C.IR spectrum, ν, cm^{-1}: 1690 (C=O), 2230 (CN), 3320 (NH); ^{1}H NMR spectrum, δ, ppm: 3.63 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 6.30 (2H, d, *J* = 7.1, H Ar); 6.70 (2H, d, *J* = 7.1, H Ar), 7.93 (broad, 1H, NH); ^{13}C NMR spectrum, δ, ppm: 26.5 (CH_2), 55.8 (OCH_3), 117.1 (CN), 120.5 ($C_{2,6}$), 128.9 ($C_{3,5}$), 138.3 (C_1), 159.1 (C_4), 169.7 (CO); Mass spectrum, *m*/*z* (*I*rel, %): 190 $[M]^+$ (35), 123 $[4\text{-MeO-PhNH}_2]^{+\cdot}$ (100). Elemental Analysis; Found: C, 63.21; H, 5.51; N, 14.57. Calculated for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73.

*2-Cyano-N-(4-ethoxyphenyl)acetamide (**2d**):*

Yield 1.82 g (90%), white powder, mp178 - 180°C.IR spectrum, ν, cm^{-1}: 1690 (C=O), 2230 (CN), 3320 (NH); ^{1}H NMR spectrum, δ, ppm: 1.41 (t, 3H, $OCH_2\underline{CH_3}$), 3.60 (s, 2H, CH_2), 4.11 (q, 2H, $O\underline{CH_2}CH_3$), 6.33 (2H, d, *J* = 7.1, H Ar); 6.71 (2H, d, *J* = 7.1, H Ar), 7.90 (broad, 1H, NH); ^{13}C NMR spectrum, δ, ppm: 15.1 ($OCH_2\underline{CH_3}$), 26.5 (CH_2), 63.3 ($O\underline{CH_2}CH_3$), 117.1 (CN), 120.5 ($C_{2,6}$), 128.9 ($C_{3,5}$), 138.3 (C_1), 159.7 (C_4), 169.7 (CO); Mass spectrum, *m*/*z* (*I*rel, %): 204 $[M]^+$ (30), 137 $[4\text{-EtO-PhNH}_2]^{+\cdot}$ (100). Elemental Analysis; Found: C, 64.41; H, 6.15; N, 13.48. Calculated for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72.

*N-(4-Chlorophenyl)-2-cyanoacetamide (**2e**):*

Yield 1.57 g (80%), white powder, mp201 – 203°C.IR spectrum, ν, cm^{-1}: 1690 (C=O), 2230 (CN), 3320 (NH); ^{1}H NMR spectrum, δ, ppm: 3.65 (s, 2H, CH_2), 6.53 (2H, d, *J* = 7.1, H Ar); 6.95 (2H, d, *J* = 7.1, H Ar), 7.95 (broad, 1H, NH); ^{13}C NMR spectrum, δ, ppm: 26.5 (CH_2), 117.1 (CN), 120.7 ($C_{2,6}$), 134.5 (C_4), 125.1 ($C_{3,5}$), 138.3 (C_1), 169.7 (CO); Mass spectrum, *m*/*z* (*I*rel, %): 196 $[M(^{37}Cl)]^+$ (10), 194 $[M(^{35}Cl)]^+$ (30)(35), 27 127 $[4\text{-Cl-PhNH}_2]^{+\cdot}$ (100). Elemental Analysis; Found: C, 55.73; H, 3.85; N, 14.17. Calculated for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; N, 14.39.

*N-(4-Bromophenyl)-2-cyanoacetamide (**2f**):*

Yield 1.57 g (80%), white powder, mp198 - 200°C.IR spectrum, ν, cm^{-1}: 1690 (C=O), 2230 (CN), 3320 (NH); ^{1}H NMR spectrum, δ, ppm: 3.61 (s, 2H, CH_2), 6.42 (2H, d, *J* = 7.1, H Ar); 6.80 (2H, d, *J* = 7.1, H Ar), 7.90 (broad, 1H, NH); ^{13}C NMR spectrum, δ, ppm: 26.3 (CH_2), 117.2 (CN), 120.7 ($C_{2,6}$), 122.5 (C_4), 125.1 ($C_{3,5}$), 138.3 (C_1), 169.7 (CO); Mass spectrum, *m*/*z* (*I*rel, %): 240 $[M(^{81}Br)]^+$ (28), 238 $[M(^{79}Br)]^+$ (28), 173 $[4\text{-Br-PhNH}_2]^{+\cdot}$ (100). Elemental Analysis; Found: C, 45.44; H, 3.08; N, 11.87. Calculated for $C_9H_7BrN_2O$: C, 45.22; H, 2.95; N, 11.72.

General procedure for the preparation of 2-chloroquinoline-3- carbonitriles 3a-f:

To an ice bath cooled phosphoroxychloride (30 mmol), dimethylformamide (10 mmol) was added drop wisely and stirred for 5 minutes. Cyanoacetanilides **2a-f** was added to the solution and the reaction mixture was heated on 75^0C for 15 hours. The reaction mixture was poured to crude ice and the precipitate was air dried after filtration. The residue was recrystallized from ethanole to obtain 2-chloroquinoline-3-carbonitriles **3a-f**.

*2-Chloroquinoline-3-carbonitrile (**3a**):*

Yield 1.51 g (80%), yellow powder, mp188–189 °C according to the previous report[3].

*2-Chloro-6-methylquinoline-3-carbonitrile (**3b**):*

Yield 1.51 g (75%), yellow powder,mp 175–177 °C. IR spectrum, ν, cm^{-1}: 2231 (CN), 1614 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.40 (S, 3H, CH_3), 7.23 (dd, 1H, *J* = 7, C_7-H); 7.5 (dd, 1H, *J* = 5, C_8-H); 7.90 (d,1H, J= 2, C_5-H); 8.55 (s, 1H, C_4-H). ^{13}C NMR spectrum, δ, ppm: 24.8 (CH_3), 117.2 (CN), 120 (C_8), 121.5 (C_3), 126.8 (C_6), 127.8 (C_5), 129.4 (C_7), 135.9 (C_4), 148.2 (C_{4a}), 151.4 (C_2), 164 (C_{8a}); Mass spectrum, *m*/*z* (*I*rel, %): 202 $[M]^+$ (100), 204 $[M+2]^+$ (32). Elemental Analysis; Found: C, 65.33; H, 3.59; N, 13.66. Calculated for $C_{11}H_7ClN_2$: C, 65.20; H, 3.48; N, 13.82.

*2-Chloro-6-methoxyquinoline-3-carbonitrile (**3c**):*

Yield 1.75 g (80%), yellow powder,mp 180–182 °C. IR spectrum, ν, cm^{-1}: 2231 (CN), 1614 (C=N). ^{1}H NMR spectrum, δ, ppm: 3.95 (s, 3H, OCH_3), 7.20 (dd, 1H, *J* = 7, C_7-H); 7.42 (dd, 1H, *J* = 5, C_8-H); 7.87 (d,1H, *J*= 2, C_5-H); 8.53 (s, 1H, C_4-H). ^{13}C NMR spectrum, δ, ppm: 56.1 (OCH_3), 117.2 (CN), 120 (C_8), 121.5 (C_3), 127.8 (C_5), 129.4 (C_7), 135.9 (C_4), 148.2 (C_{4a}), 151.4 (C_2), 160.3 (C_6), 164 (C_{8a}); Mass spectrum, *m*/*z* (*I*rel, %): 218 $[M]^+$(100), 220 $[M+2]^+$ (32). Elemental Analysis; Found: C, 60.64; H, 3.45; N,

12.72. Calculated for $C_{11}H_7ClN_2O$: C, 60.43; H, 3.23; N, 12.81.

*2-Chloro-6-ethoxyquinoline-3-carbonitrile (**3d**):*

Yield 1.62 g (70%), yellow powder,mp 172–174 °C. IR spectrum, ν, cm^{-1}: 2231 (CN), 1614 (C=N). ^1H NMR spectrum, δ, ppm: 1.43 (t, 3H, $OCH_2\underline{CH_3}$), 4.25 (q, 2H, $O\underline{CH_2}CH_3$), 7.20 (dd, 1H, *J* = 7, C_7-H); 7.42 (dd, 1H, *J* = 5, C_8-H); 7.87 (d, 1H, *J*= 2, C_5-H); 8.53 (s, 1H, C_4-H). ^{13}C NMR spectrum, δ, ppm: 15.3 ($OCH_2\underline{CH_3}$), 63.5 ($O\underline{CH_2}CH_3$), 117.2 (CN), 120 (C_8), 121.5 (C_3), 127.8 (C_5), 129.4 (C_7), 135.9 (C_4), 148.2 (C_{4a}), 151.4 (C_2), 160.3 (C_6), 164 (C_{8a}); Mass spectrum, *m*/*z* (*I*rel, %): 232 $[M]^+$ (100), 234 $[M+2]^+$ (32). Elemental Analysis; Found: C, 62.18; H, 4.05; N, 11.91. Calculated for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04.

*2, 6-Dichloroquinoline-3-carbonitrile (**3e**):*

Yield 1.8 g (80%), brown powder,mp 193–195 °C. IR spectrum, ν, cm^{-1}: 2231 (CN), 1614 (C=N). ^1H NMR spectrum, δ, ppm: 7.23 (dd, 1H, *J* = 7, C_7-H); 7.46 (dd, 1H, *J* = 5, C_8-H); 7.89 (d, 1H, *J*= 2, C_5-H); 8.54 (s, 1H, C_4-H). ^{13}C NMR spectrum, δ, ppm: 117.2 (CN), 120 (C_8), 121.5 (C_3), 127.8 (C_5), 129.4 (C_7), 135.9 (C_4), 136.3 (C_6), 148.2 (C_{4a}), 151.4 (C_2), 164 (C_{8a}); Mass spectrum, *m*/*z* (*I*rel, %): 222 $[M]^+$ (100), 224 $[M+2]^+$ (32), 226 $[M+4]^+$ (10). Elemental Analysis; Found: C, 54.07; H, 1.95; N, 12.73. Calculated for $C_{10}H_4Cl_2N_2$: C, 53.85; H, 1.81; N, 12.56.

*6-Bromo-2-chloroquinoline-3-carbonitrile (**3f**):*

Yield 1.8 g (80%), brown powder,mp 193–195 °C. IR spectrum, ν, cm^{-1}: 2231 (CN), 1614 (C=N). ^1H NMR spectrum, δ, ppm: 7.23 (dd, 1H, *J* = 7, C_7-H); 7.46 (dd, 1H, *J* = 5, C_8-H); 7.89 (d, 1H, *J*= 2, C_5-H); 8.54 (s, 1H, C_4-H). ^{13}C NMR spectrum, δ, ppm: 117.2 (CN), 120 (C_8), 121.5 (C_3), 127.8 (C_5), 129.4 (C_7), 135.9 (C_4), 124.2 (C_6), 148.2 (C_{4a}), 151.4 (C_2), 164 (C_{8a}); Mass spectrum, *m*/*z* (*I*rel, %): 266 $[M]^+$ (77), 268 $[M+2]^+$ (100), 270 $[M+4]^+$ (24). Elemental Analysis; Found: C, 45.05; H, 1.62; N, 10.64. Calculated for $C_{10}H_4BrClN_2$: C, 44.90; H, 1.51; N, 10.47.

Acknowledgements

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