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Synthesis of Novel 3-Aryl-isoxazolo[4,3-h]quinolines via Nucleophilic Substitution of Hydrogen (S_NH)

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ABSTRACT

A simple and efficient one-pot method for the synthesis of novel 3-aryl-isoxazolo[4,3-h]quinolines is described. The nucleophilic substitution of hydrogen is carried out by treating various arylacetonitriles with commercially available 8-nitroquinoline in basic methanol solution. The same synthetic approach has been used to obtain new isoxazolo[3,4-g]indazole and isoxazolophtalic anhydride.

Keywords: 8-Nitroquinoline, Nitroheteroaryle, Arylacetonitriles, Nucleophilic Substitution, Isoxazoloheteroaryle.

INTRODUCTION

Substituted heterocyclic compounds can offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. Among *N*-heterocyclic skeletons, fused quinolines have attracted the attention of chemists and biologists because they are key building blocks for the synthesis of biologically active natural products bearing quinoline skeletons [1]. In addition they are widely used in numerous commercial products, such as, pharmaceuticals, fragrances and dyes [2]. Molecules bearing quinoline skeletons have wide range of pharmaceutical activities, such as antitubercular [3a], antimalarial [3b], anti-inflammatory [4], anticancer [5], antibiotic [6], antihypertensive [7], platelet derived growth factor receptor tyrosine kinase (PDGF-RTK) inhibitory [8] and antihuman immunodeficiency virus (anti-HIV) [9]. In this regard, the development of new protocols for the synthesis of new quinoline incorporating heterocycles has attracted considerable interest in recent years [10].

On the other hand, isoxazoles represent an interesting class of heterocycles that display a range of biological properties, such as anti-inflammatory [11], antimicrobial [12], anticancer [13], antinociceptive and anti-invasive [14]. Combination of an isoxazole moiety with a quinoline nucleus may enhance pharmacological activities. From a synthetic point of view, to date, methods for obtaining isoxazoloquinoline derivatives are still limited [15].

In view of these important properties and searching for the synthesis of new isoxazoloquinolines, which are useful for biological screening, in the current paper, we report a novel one pot procedure for the construction of diverse isoxazoloquinolines based on the nucleophilic substitution of hydrogen of 8-nitroquinoline with different arylacetonitrile in basic methanol solution. The present work forms a part of our ongoing research programme on the development for the construction of important heterocyclic ring systems via nucleophilic substitution reactions of hydrogen in nitroheteroaryles [16-21].

MATERIALS AND METHODS

Melting points were determined using a Büchi-Tottoli apparatus. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6 and solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 300 (^1H)

or 75MHz (^{13}C) instruments. Chemical shifts are given in d parts per million (ppm) downfield from TMS. Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer Sciex API 3000 spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography (TLC) was carried out on SiO_2 (silica gel 60, F 254 Merck 0.063–0.200 mm), and the spots were located with UV light. Commercial reagents were used without further purification unless stated.

General procedure for the synthesis 3-aryl-isoxazolo[4,3-h]quinolines (**3a-e**).
Compound **1** (5 mmol) and arylacetonitrile (6 mmol) were added with stirring to a solution of 08 g KOH in 40 ml methanol. After the mixture was refluxed with stirring for 4 h, it was then poured into water. After neutralisation with dilute HCl solution, the precipitate was collected by filtration, washed with water, and air-dried to give **3a–e**.

3-(Phenyl)-isoxazolo[4,3-h]quinoline (**3a**). Yield: 72 %; mp 198-200 °C; ^1H NMR (DMSO-d_6): δ 7.22 (m, 1H), 7.38-7.42 (m, 4H), 7.46 (d, 1H, *J* = 9.4 Hz), 7.70 (dd, 1H, *J* = 4.5 and 7.8 Hz), 7.88 (d, 1H, *J* = 9.4 Hz), 8.29 (dd, 1H, *J* = 1.8 et 7.8 Hz), 8.82 (dd, 1H, *J* = 1.5 et 4.5 Hz), ^{13}C NMR (DMSO-d_6): δ 113.2 (C), 119.1 (CH), 125.0 (C), 125.3 (CH), 126.2 (CH), 127.4 (2CH), 129.8 (C), 129.0 (CH), 129.8 (2CH), 137.0 (CH), 141.8 (C), 150.4 (CH), 157.0 (C), 164.2 (C); EI-MS (m/z) = 247 $[M+1]^+$, Anal. Calcd for $C_{16}H_{10}N_2O$; C, 78.04; H, 4.09; N, 11.38. Found: C, 78.12; H, 4.02; N, 11.27.

3-(4-Methylphenyl)-isoxazolo[4,3-h]quinoline (**3b**). Yield: 76 %; mp 167-169 °C; ^1H NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.42 (d, 2H, *J* = 8.1 Hz), 7.47 (d, 1H, *J* = 9.4 Hz), 7.73 (dd, 1H, *J* = 4.5 and 7.8 Hz), 7.91 (d, 1H, *J* = 9.4 Hz), 7.98 (d, 2H, *J* = 8.1 Hz), 8.33 (dd, 1H, *J* = 1.8 et 7.8 Hz), 8.88 (dd, 1H, *J* = 1.5 et 4.5 Hz), ^{13}C NMR (DMSO-d_6): δ 21.5 (CH_3), 113.6 (C), 119.3 (CH), 124.9 (C), 125.5 (CH), 126.4 (CH), 127.0 (2CH), 129.8 (C), 130.6 (2CH), 136.9 (CH), 140.2 (C), 141.4 (C), 150.3 (CH), 156.9 (C), 164.5 (C); EI-MS (m/z) = 261 $[M+1]^+$, Anal. Calcd for $C_{17}H_{12}N_2O$; C, 78.44; H, 4.65; N, 10.76. Found: C, 78.56; H, 4.60; N, 10.85.

3-(4-Methoxyphenyl)-isoxazolo[4,3-h]quinoline (**3c**). Yield: 86 %; mp 174-176 °C; ^1H NMR (DMSO-d_6): δ 3.85 (s, 3H, CH_3O), 7.16 (d, 2H, *J* = 9.0 Hz), 7.44 (d, 1H, *J* = 9.4 Hz), 7.73 (dd, 1H, *J* = 4.5 and 8.1 Hz), 7.90 (d, 1H, *J* = 9.4 Hz), 8.05 (d, 2H, *J* = 9.0 Hz), 8.33 (dd, 1H, *J* = 1.5 et 8.1 Hz), 8.88 (dd, 1H, *J* = 1.5 et 4.5 Hz), ^{13}C NMR (DMSO-d_6): δ 55.9 (CH_3O), 113.0 (C), 115.5 (2CH), 119.4 (CH), 120.3 (C), 125.5 (CH), 126.0 (CH), 128.8 (2CH), 129.8 (C), 136.8 (CH), 140.2 (C), 150.2 (CH), 156.8 (C), 161.6 (C), 164.5 (C); EI-MS (m/z) = 277 $[M+1]^+$, Anal. Calcd for $C_{17}H_{12}N_2O_2$; C, 73.90; H, 4.38; N, 10.14. Found: C, 73.78; H, 4.46; N, 10.25.

3-(4-Chlorophenyl)isoxazolo[4,3-h]quinoline (3d). Yield: 78 %; mp 225-227 °C; ^1H NMR ($CDCl_3$): δ 7.32 (d, 1H, *J* = 9.4 Hz), 7.55 (d, 2H, *J* = 8.7 Hz), 7.61 (dd, 1H, *J* = 4.5 and 7.8 Hz), 7.68 (d, 1H, *J* = 9.4 Hz), 7.97 (d, 2H, *J* = 8.7 Hz), 8.33 (dd, 1H, *J* = 1.5 et 7.8 Hz), 8.98 (dd, 1H, *J* = 1.5 et 4.5 Hz), ^{13}C NMR ($CDCl_3$): δ 114.0 (C), 118.6 (CH), 124.6 (CH), 126.0 (CH), 126.5 (C), 128.0 (2CH), 129.7 (2CH), 136.3 (CH), 137.5 (C),140.4 (C), 149.7 (CH), 151.7 (C), 156.7 (C), 163.6 (C); EI-MS (m/z) = 281 (^{35}Cl) $[M+1]^+$, 283 (^{37}Cl) $[M+3]^+$, Anal. Calcd for $C_{16}H_9ClN_2O$; C, 68.46; H, 3.23; N, 9.98. Found: C, 68.54; H, 3.11; N, 10.08.

3-(4-Bromophenyl)-isoxazolo[4,3-h]quinoline (3e). Yield: 74 %; mp 232-234 °C; ^1H NMR ($CDCl_3$): δ 7.40 (d, 1H, *J* = 9.4 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.60 (dd, 1H, *J* = 4.5 and 7.8 Hz), 7.67 (d, 1H, *J* = 9.4 Hz), 7.84 (d, 2H, *J* = 8.4 Hz), 8.31 (dd, 1H, *J* = 1.5 et 7.8 Hz), 8.96 (dd, 1H, *J* = 1.5 et 4.5 Hz), ^{13}C NMR ($CDCl_3$): δ 116.7 (C), 118.4 (CH), 124.5 (C), 124.9 (CH), 126.3 (CH), 129.1 (2CH), 131.1 (2CH), 136.0 (CH), 137.2 (C),141.0 (C), 149.5 (CH), 151.4 (C), 156.6 (C), 163.2 (C); EI-MS (m/z) = 326 (^{79}Br) $[M+1]^+$, 328 (^{81}Br) $[M+3]^+$, Anal. Calcd for $C_{16}H_9BrN_2O$; C, 59.10; H, 2.79; N, 8.62. Found: C, 59.18; H, 2.84; N, 8.73.

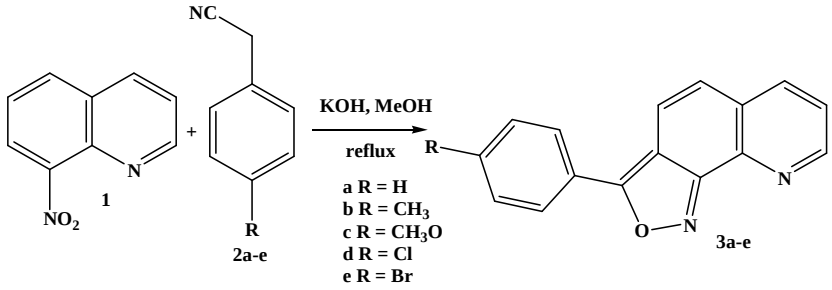
Synthesis of compounds (5) and **(7)**. These compounds were prepared from 1-methyl-6-nitroindazole **4** and 3-nitrophthalic anhydride **6** using the same procedure applied to 8-nitroquinoline **1**.

8-(4-Chlorophényl)-1-methyl-1H-isoxazolo[3,4-g] indazole (5). Yield: 78 %; mp 146-148 °C; ^1H NMR ($CDCl_3$): δ 3.69 (s, 3H, NCH_3), 7.23 (d, 1H, *J* = 9.6 Hz), 7.53 (d, 1H, *J* = 9.6 Hz), 7.57 (d, 2H, *J* = 8.4 Hz), 7.64 (d, 2H, *J*= 8.4 Hz), 7.87 (s, 1H)., ^{13}C NMR ($CDCl_3$): δ 40.8 (NCH_3), 105.0 (C), 109.4 (CH), 119.4 (C), 126.2 (CH), 127.4 (C), 130.0 (C), 129.1 (2CH), 131.3 (2CH), 135.5 (CH), 137.5 (C), 158.9 (C), 162.2 (C).

3-(4-Methoxyphenyl)isoxbenzofuro[4,5-c]isoxazole-6,8-dione (7). Yield: 64 %; mp 275-276 °C; ^1H NMR (DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 7.17 (d, 2H, *J* = 9.0 Hz), 7.41 (d, 1H, *J* = 9.0 Hz), 8.07 (d, 2H, *J*= 9.0 Hz), 8.18 (d, 1H, *J* = 9.0 Hz), ^{13}C NMR (DMSO-d_6): δ 56.0 (OCH_3), 114.2 (C), 115.7 (2CH), 119.9 (C), 123.4 (CH), 123.8 (CH), 124.1 (C), 128.9 (2CH), 131.7 (C), 155.1 (C), 162.0 (C), 166.1 (C), 166.8 (C), 167.1 (C); EI-MS (m/z) = 296 $[M+1]^+$, Anal. Calcd for $C_{16}H_9NO_5$; C, 65.09; H, 3.07; N, 4.74. Found: C, 65.16; H, 3.15; N, 4.64.

RESULTS AND DISCUSSION

The new 3-aryl-isoxazolo[4,3-h]quinolines **3a-e** were synthesized via the nucleophilic substitution of hydrogen of 8-nitroquinoline **1** with arylacetonitriles **2a-e** in basic methanol solution in good yields (72-86%, scheme 1). The simple work-up procedure was performed by filtration of the precipitated product after the mixture was concentrated at reduced pressure.



Scheme 1 : Synthesis of new 3-aryl-isoxazolo[4,3-h]quinolines 3a-e

The structure of products **3a–e** was confirmed by ^{1}HNMR, ^{13}CNMR and DEPT spectroscopy in addition to mass spectral and elemental analysis data. The spectral details of all these are given in experimental section. For example, the expanded ^{1}H NMR spectrum of compound **3c**, revealed in particular the presence of two doublet signals at 7.44 (d, 1H, *J* = 9.4 Hz) and 7.90 (d, 1H, *J* = 9.4 Hz) ppm attributed to two protons of aromatic rings (H-5, H-6) in **3c** (Figure 1).

Moreover, the ^{13}C NMR and DEPT spectra of **3c** (Figure 2) exhibited the presence of 17 carbon resonances, containing seven quaternary aromatic carbons, nine aromatic methines and one mehyl group. These spectroscopic data obtained agrees with the expected structure of **3c**.

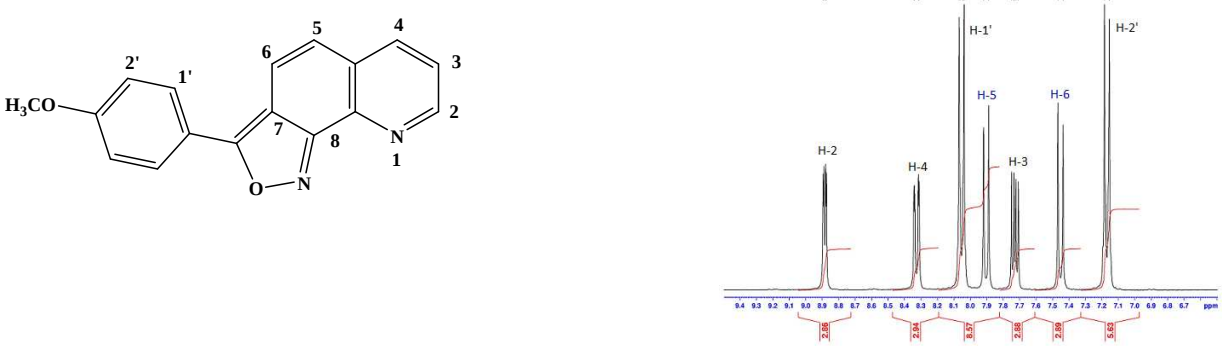


Figure 1: The expanded view of ^{1}H NMR spectrum of compound 3c in downfield region

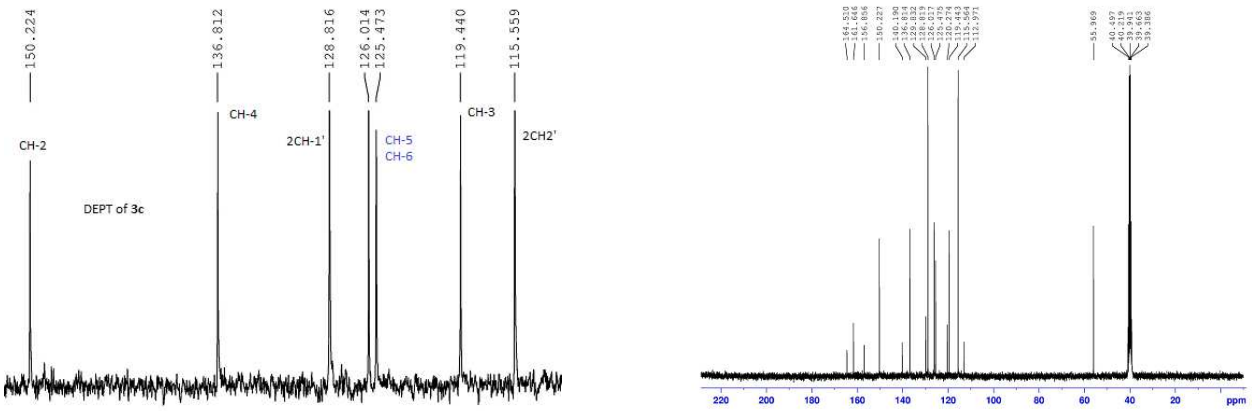
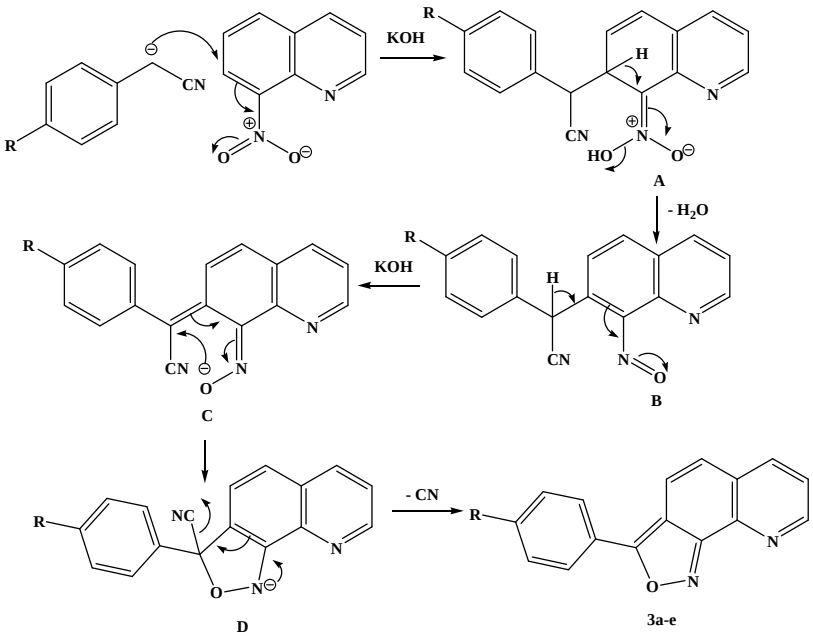


Figure 2: The ^{13}C NMR spectrum and an expanded of DEPT spectra of compound 3c

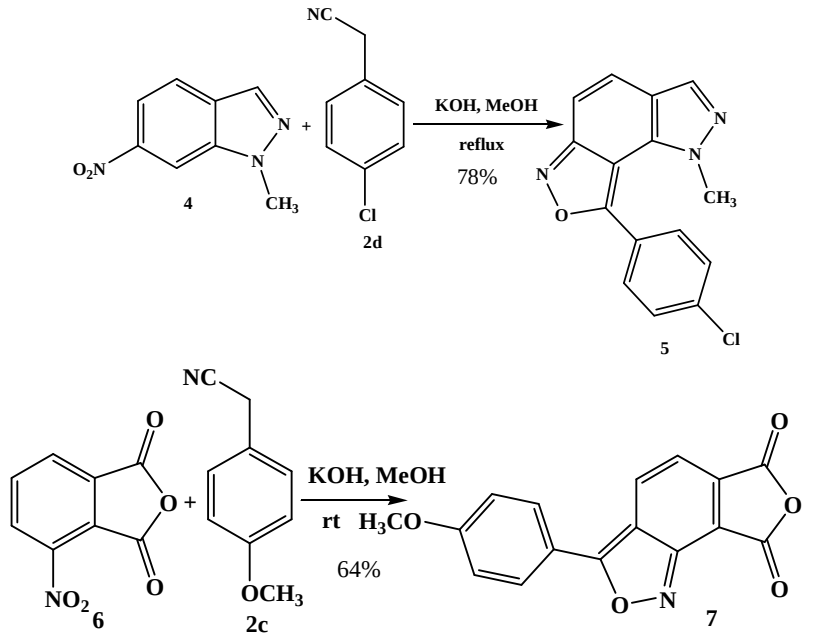
The formation of 3-aryl-isoxazolo[4,3-h]quinolines **3a–e** can be explained by the mechanism shown in Scheme 2. Attack of the carbanion of arylacetonitrile on 8-nitroquinoline **1** affords intermediate **A**, whereby intermediate **A** is

converted to **B** followed by elimination of H_2O, to afford **C**, which in turn undergoes an intramolecular cyclisation, followed by elimination of CN to give D and thus **3a-e**.



Scheme 2. Proposed reaction mechanism for the formation of compounds 3a-e

Encouraged by this excellent result, we decided to enlarge the scope of this methodology to the synthesis of other isoxazoloheteroaryls by analyzing the preliminary reactivity of 1-methyl-6-nitroindazole **4** and 3-nitrophthalic anhydride **6** with arylacetonitrile using the optimized reaction conditions (scheme 3). As expected, we obtained exclusively the corresponding isoxazolo[3,4-g]indazole **5** and 3-(4-méthoxyphenyl)isobenzofuro[4,5-c]isoxasole-6,8-dione **7** in 78 and 64% yields, respectively.



Scheme 3. Synthesis of new isoxazoloheteroaryls 5 and 7

CONCLUSION

In conclusion, we have synthesized some novel derivatives of isoxazolo[4,3-h]quinoline, isoxazolo[3,4-g]indazole and isoxazolophtalic anhydride by nucleophilic substitution of hydrogen of nitroheteroaryl with different arylacetonitrile in basic media. This methodology offers several advantages, such as good yields, short reaction

times, simple procedure, and mild conditions. This appears to be a general method to prepare new building blocks of possible interest in medicinal chemistry.

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