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SYNTHESIS OF SOME NEW QUINOLINE DERIVATIVES FROM O-NITRO TOLUENE

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ABSTRACT: Quinolines have become important compounds because of their variety of applications in medicinal, synthetic organic chemistry as well as in the field of industrial chemistry. In recent years there are greater societal expectations that chemists should produce greener and more sustainable chemical processes. In this article, we have reported an attempt of the synthesis of derivative compounds 1-5 by sequence of reactions. The starting compound o-nitro toluene 1 was converted into substituted o-amino benzylcyanide viz the starting compound o-nitro toluene 1 was reacted with N-bromosuccinamide in CCl_4 gives bromoderivative 2 in good yield. Bromoderivative 2 on cynation by using NaCN in DMSO/DMF gives cyanoderivative 3 in moderate yield. This compound on reduction gives amino derivative 4 good yields. The amino derivative 4 on reaction with maleic anhydride gives acid derivative 5 in good yields. Furthermore, the acid derivative 5 on reaction with ethyl alcohol in presence of sulfuric acid at reflux temperature offered 3-(2-cyanomethyl-phenylcarbamoyl)-acrylic acid ethyl ester 6. Further a ester derivative 3- (2-cyanomethyl-phenylcarbamoyl)-acrylic acid ethyl ester 6 on reaction with potassium hydroxide in ethyl alcohol at reflux temperature gave (4-cyano-2-oxo-1,2,3,4-tetrahydro -quinolin-3-yl)-acetic acid ethyl ester 7 derivative with excellent yield. All the synthesized compounds were characterized by spectral and analytical methods by IR, ^{1}H and ^{13}C NMR and elemental analysis.

KEYWORDS: Quinoline, Oxadiazole, Thiadiazole, Triazole, Hydrazide.

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1.INTRODUCTION

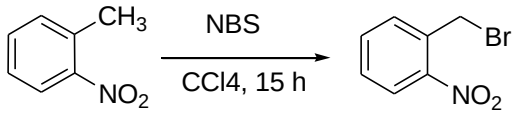
Quinoline derivatives are important nitrogen containing heterocyclic compounds and widely used as 'parental' compounds to synthesize molecules with medical benefits especially with antimalarial[1], antimicrobial[2] activities. Some quinoline derivatives also show effective anticancer[4] activity. Quinoline derivatives have also shows antiseptic, antipyretics, antimicrobial[3], antimycobacterial[5],antibacterial[6,7], anticonvulsant, anti-inflammatory and cardiovascular activities. The presence of quinoline ring and ancillary aromatic ring by functionalized spacers such as amides, hydrazides, urea, and 1-hydroxy prop-1-en-3-one moiety in HIV-1 integrase inhibitors[8] showed biological activity. Oxadiazole derivatives are an important group of heterocyclic compounds have been subject of extensive study in the recent past. Numerous reports have highlighted their chemistry and use[9-11]. In literature certain compounds bearing 1, 3, 4-oxadiazole/thiadiazole and 1, 2, 4 triazole nucleus possess significant anti-inflammatory activity[12-15], 4-thaiazolidinone derivatives are also possess antibacterial[16-18], antifungal[19-21], antiviral[22-24] and antituberculosis[27-29] properties. 4-Thaizolidinones have been reported as novel inhibitors of the bacterial enzyme[30].The evidence of tuberculosis is increasing worldwide, partly due to poverty and inequity and partly due to the HIV/AIDS pandemic, which greatly increase the risk of infectious proceeding to overt disease.

2. MATERIALS AND METHODS

The synthetic strategy adopted to obtain the target compounds are depicted in following Scheme. The starting compound o-nitro toluene **1** was reacted with N-bromosuccinamide in CCl_4 gives bromoderivative **2** in good yield. It was also observed that very poor yield in the bromination of compound **1** with molecular bromine in different solvent. Bromoderivative **2** on cynation by using NaCN in DMSO/DMF gives cyano derivative **3** in moderate yield. This compound on reduction gives amino derivative **4** in 60% yields. The amino derivative **4** on reaction with maleic anhydride gives acid derivative **5** in 50% yields.

Synthetic procedures

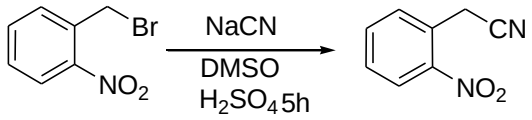
1-(Bromomethyl)-2-nitrobenzene



1 2

A mixture of o-nitrotoluene **1** (6.85 g, 0.05 mol) and N-bromosuccinamide (0.06 mol) in chloroform (50 mL) was refluxed for 15 h. After cooling down to room temperature, chloroform (50 mL) was evaporated under vacuum, the crude product obtained was collected by suction filtration, dried and recrystallized from 50% ethanol to yield title compound **2** (7.49 g) as brown colored prisms.

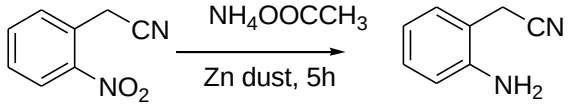
2-(2-nitrophenyl)acetonitrile



2 3

A mixture of bromo derivative **2**, sodium chloride and catalytic amount of H_2SO_4 in DMSO or DMF at 50 ºC was stirred for 5h furnish 2-(2-nitrophenyl)acetonitrile. The progress of the reaction was monitored by TLC (toluene/ethyl acetate 8:2) till the reactant was consumed. After completion, the reaction mixture was poured in cold water (100 mL). The obtained solid was filtered washed with water, dried and purified by column chromatography gave title compound **3**.

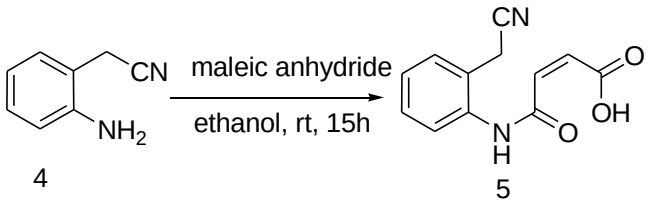
2-(2-aminophenyl)acetonitrile



3 4

The 2-(2-nitrophenyl)acetonitrile 3 was reaction with ammonium acetate, zic dust at 130 ºC temperature for 5h offered amino derivatives **4** in 60% yield 2-(2-minophenyl) acetonitrile. The reaction mixture was cooled to room temperature, and then poured in ice cold water. The crude product separated was collected by suction filtration, dried and recrystallized from ethanol/DMF (8:2) gave title compound **4** as yellow colored prism.

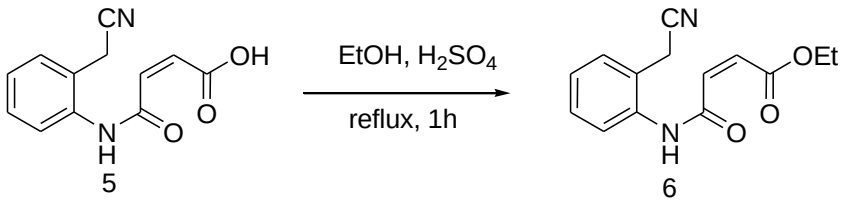
(Z)-3-(2-(cyanomethyl)phenyl carbamoyl) acrylic acid



4 5

The 2-(2-aminophenyl)acetonitrile **4** maleic anhydride in ethanol at room temperature was stirred for 15 h furnish acid derivative **5** in 83% yield. The progress of the reaction was monitored by TLC (toluene/ethyl acetate 8:2) till the reactant was consumed. After completion, the solvent removed under vacuum and the reaction mixture was poured in cold water (500 mL). The obtained solid was filtered washed with water, dried and recrystallized from ethanol/DMF (8:2) to yield title compound **5** as yellow needles

Synthesis of 3-(2-cyanomethyl-phenyl carbamoyl)-acrylic acid ethyl ester, 6

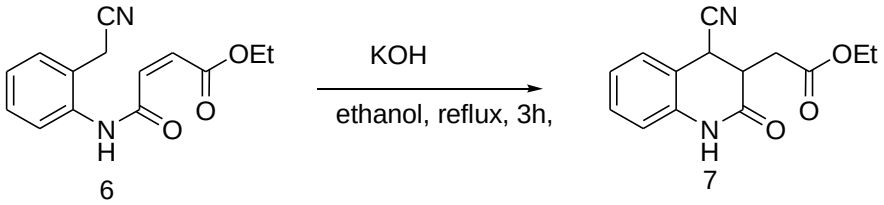


5 6

A (Z)-3-(2-(cyanomethyl)phenyl carbamoyl) acrylic acid **6** (3.45 g, 0.015 mol) and 1ml H_2SO_4

reflux in ethanol (100ml). The resulting reaction mixture was kept stirring for 1 h. The progress of the reaction was monitored by TLC (toluene/ethyl acetate 8:2) till the reactant was consumed. After completion, the solvent was evaporated under reduced pressure. The reaction mixture was poured in cold water (500 mL). The obtained solid was filtered washed with water, dried and recrystallized from ethanol to yield title compound **6.**

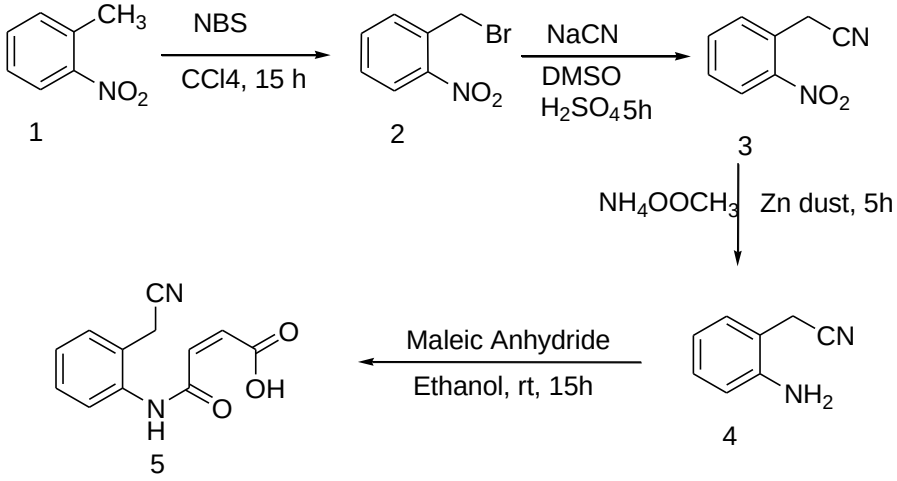
Synthesis of (4-cyano-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester, 7



The compound **6** (0.258 g, 0.001 mol) was reflux with KOH (0.112 g, 0.002 mol) in dry ethanol (20 mL) for 3 h. The progress of the reaction was monitored by TLC (toluene/ethyl acetate 2:8) till the reactant was consumed. After completion of the reaction, the reaction mixture was cooled to room temperature, the solid obtained was filtered, washed with water, dried and recrystallized from DMF to furnished compound **7** in good yield.

3. RESULTS AND DISCUSSION

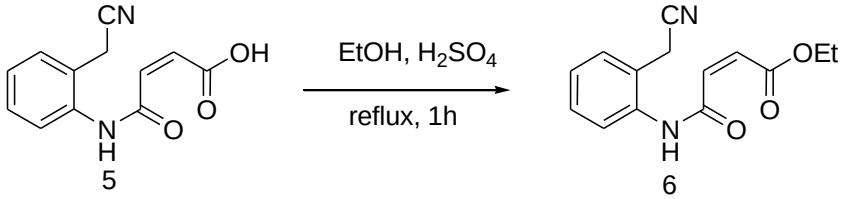
The structure of compound **2** was assigned using spectroscopic and analytical methods. The mass spectrum of **2** showed base peaks at 215 (M+). The structure of compound **3** was assigned using spectroscopic method. The instance IR of compound **3** showed cyanide stretching frequency at 2170 cm^{-1}. The o-nitrobenzyl cyanide on reduction with Sn/HCl or ammonium formate / zinc dust furnish amino derivatives **4** in 60% yield. The obtained crude product was purified by dissolving in 1:1 HCl, and then neutralizing with NaOH gave pure compound **4** which was further purified by crystallization in ethanol. The structure of pure compound **4** was assigned using spectroscopic and analytical methods. For instance IR of **4** showed cyanide stretching frequency at 2180 cm^{-1}; NH stretching frequency at 3354-3390 cm^{-1}. The ^1H NMR spectrum of **4** in $CDCl_3$ showed the resonance singlet at 4.00 δ for -CH_2- methylene. The up field singlet resonance at 5.14 δ was assignable for NH_2 protons and the remaining aromatic protons resonance at expected chemical shifts and splitting pattern.



The amino derivative **4** on reaction with maleic anhydride in glacial acetic acid at room temperature gives 83% yield. The crude product was purified by column chromatography on silica gel eluting with toluene, yields title compound **5**. The instance IR of compound **5** showed amide stretching frequency at 1687 cm-1; cyanide stretching frequency at 2180 cm-1: -NH at 3350 cm-1 and –OH stretching frequency at 3430 cm-1. The ^{1}H NMR spectrum of **5** in DMSO-*d6* showed the resonance singlet at 4.10 δ for -CH_2- methylene. The up field doublet resonance at 6.38 δ and 6.87 δ with J = 15 Hz were assignable for CH=CH protons and the remaining protons resonance at expected chemical shifts and splitting pattern.

Synthesis of 3-(2-cyanomethyl-phenylcarbamoyl)-acrylic acid ethyl ester, 6

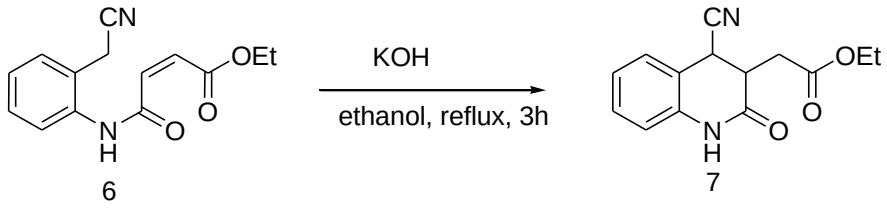
The acid derivative **5** on reaction with ethyl alcohol in presence of sulfuric acid at reflux temperature offered ester derivative 6 in 85% yield. The crude product was purified by column chromatography on silica gel eluting with toluene and ethyl acetate, yields title compound **6**. The instance IR of compound **6** showed ester stretching frequency at 1748 cm-1; cyanide stretching frequency at 2190 cm-1: -NH at 3320 cm-1. The ^{1}H NMR spectrum of **5** in $CDCl_3$ showed the resonance singlet at 4.00 δ for -CH_2- methylene. The quartet triplet signal of ethyl group show stretching frequency at 3.40 δ for –CH_2- and 1.30 δ for –CH_3 proton respectively. The up field doublet resonance at 6.33 δ and 6.89 δ with J = 14 Hz were assignable for CH=CH protons and the remaining protons resonance at expected chemical shifts and splitting pattern.



Synthesis of (4-cyano-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester, 7

A ester derivative 3-(2-cyanomethyl-phenylcarbamoyl)-acrylic acid ethyl ester **6** on reaction with potassium hydroxide in ethyl alcohol at reflux temperature gave hydroquinoline derivative **7** in 65% yield. The crude product was purified by recrystallization in ethyl alcohol yields title compound **7**.

The instance IR of compound **7** showed ester stretching frequency at 1730 cm-1; cyanide stretching frequency at 2185 cm-1: -NH at 3443 cm-1. The ^{1}H NMR spectrum of **5** in $CDCl_3$ showed the resonance multiplet at 3.56 δ for -CH_2- methylene and two –CH- protons. The doublet of –CH2- protons showed stretching frequency at 4.27 δ. The up field doublet resonance at 6.33 δ and 6.89 δ with J = 14 Hz were disappear for CH=CH protons and the remaining protons resonance at expected chemical shifts and splitting pattern.



4. CONCLUSION

We have synthesized various Quinoline derivatives. The synthetic utility of the methods used is very much applicable for other syntheses. The remarkable advantages of this method are ease of isolation, excellent yields of product.

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CONFLICT OF INTEREST

I am declaring here that there is no any financial interest or any conflict of interest exists.

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