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CERIC AMMONIUM NITRATE CATALYZED ONE-POT SYNTHESIS OF NOVEL ISOXAZOLYL-HEXAHYDROQUININDOLINONES

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ABSTRACT

The ceric ammonium nitrate (CAN) catalyzed synthesis of novel isoxazolyl-hexahydroquinindolinones **4** were simply achieved upon the reaction of isoxazolyl-2-indolinone **1** with 3-amino-5-methyl-isoxazole **2** and dimedone **3** in ethanol with good yields from commercially available materials.

Keywords: Isoxazolyl-2-indolinone, ceric ammonium nitrate, cyclization, isoxazolyl-hexa hydroquinindolinones

INTRODUCTION

Fused heterocycles have a wide variety of application in medicinal chemistry.[1,2] Despite several reports on fused heterocycles, there is a continuing demand for development of new methods for synthesis of novel fused heterocycles due to their plethora of medicinal applications.[3] Many derivatives of quinoline have been studied for the different biological activities such as antimicrobial,[4] anti-inflammatory,[5] antileishmanial,[6] antituberculosis,[7] antimalarial,[8] cytotoxicity[9] and HIV-1 integrase inhibitors.[10]

Indole, the potent basic pharmacodynamic nucleus has been reported to possess a wide variety of biological properties such as antiviral agents which inhibits of Herpes simplex virus replication,[11-13] fungicidal,[14] anti-inflammatory,[15] anticonvulsant,[16] and antibacterial.[17] Other compounds derived from 3-acetylindoles used in the treatment of gastrointestinal,[18] antiproliferative agent,[19,20] potential antiviral agents,[21] cardiovascular and central nervous system (CNS) disorders,[22] and also used as Herpes simplex type 1 (HIV-1) integrase inhibitors.[23]

Isoxazole derivatives are reported with diverse structural features and versatile biological properties such as antitumor,[24] CNS–active,[25] analgesic,[26] antimicrobial,[27] muscle relaxant,[28] for the treatment of hyper cholsteremia and hyperlipidemia,[29] as organic electrolytes for non-aqueous batteries[30] in photographic emulsions[31] as synthetic intermediates.[32] and as chemotherapeutic agents.[33]

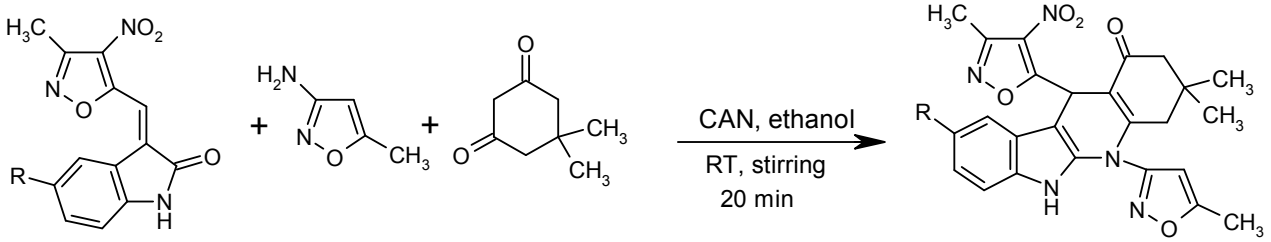
Ceric ammonium nitrate (CAN) is a convenient reagent for affecting a number of synthetic transformations due to its ready solubility in organic solvents, low toxicity, and high reactivity. The use of CAN as Lewis acid in C–C bond forming reactions has attracted synthetic chemists.[34] As a sequel to our study in exploring application of different reagents for the development of simple and efficient methods for the synthesis of isoxazole containing heterocyclic compounds[35], we, herein, report the synthesis of novel isoxazolyl-hexahydroquinindolinones, as potential drug candidates.

RESULTS AND DISCUSSION

Isoxazolyl-2-indolines[36] **1**, required for the synthesis of target compounds were obtained by Knoevenagel condensation of 3,5-dimethyl-4-nitroisoxazole with isatins.

The three-component reaction of isoxazolyl indolines **1**, 3-amino-5-methylisoxazole **2** and dimedone **3** in ethanol in the presence of 10 mol % ceric ammonium nitrate at ambient temperature for 20 min. resulted in the formation of 3,3-dimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydroquinindolinones **4** in good yields.

In a typical reaction, a mixture of isoxazolyl indoline **1a**, 3-amino-5-methylisoxazole **2** and dimedone **3** and ceric ammonium nitrate (10 mol%) were taken in ethanol (5 mL) and stirred at ambient temperature for 20 min. The termination of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on to crushed ice and the resulted precipitate was filtered and washed with cold alcohol. The crude product was purified by recrystallization from benzene. The product was identified as 3,3-dimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydroquinindolinones **4a** (Scheme 1)



1 **2** **3** **4**

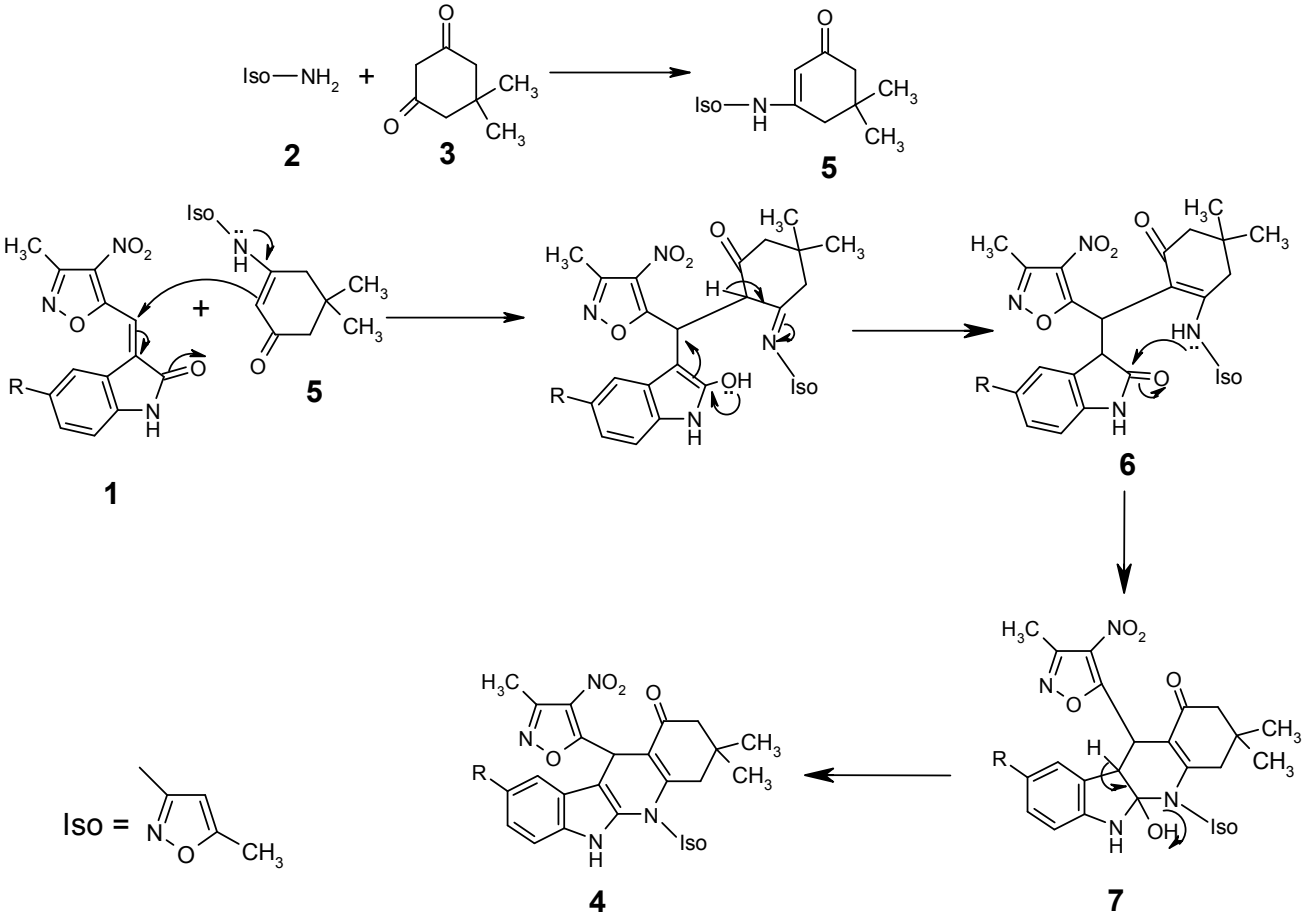
1 a, 4a, R=H
1 b, 4b, R=Cl
1 c, 4c, R=Br
1 d, 4d, R=CH_3
1e, 4e, R=OCH_3
1 f, 4f, R=F

Scheme I

The scope and generality of this one-pot three-component synthesis of isoxazolyl-hexahydroquinindolinones is illustrated by conducting the reaction with substituted isoxazolyl indolines. The desired product was obtained in each case with good yields. Finally, the results

indicate that this synthetic strategy permits the introduction of diverse array of substituents on the isatin and the approach proved to be of general applicability. Our results demonstrate that CAN is an efficient, environmentally friendly catalyst for the one-pot three-component condensation of isoxazolyl indolines, isoxazole amine and dimedone to prepare isoxazolyl hexahydroquinindolinones in good yields in short reaction times.

The formation of **4** could be explained by the following plausible mechanism. The reaction occurs *via.,* an initial formation of **5** from the condensation of isoxazole amine **2** with dimedone **3**, which makes a nucleophilic attack on isoxazolyl indoline **1** to give the intermediate **6**, which subsequently undergoes cyclization with elimination of water to afford the title compounds **4**.



Scheme II

The IR spectra of isoxazolylhexahydroquinindolinones **4** exhibited characteristic absorption bands at 3252 and 1732 cm^{-1} due to NH and C=O functional groups respectively. ^1H NMR spectra of **4** displayed two prominent signals at δ 4.74 and 8.21 due to quinoline ring proton and indole NH proton respectively. The mass spectrum of **4a** showed a molecular ion $[M+H]^+$ peak at m/z 474 supporting the product formation.

In conclusion, we report a convenient and a facile ceric ammonium nitrate catalyzed synthesis of novel isoxazolyl-hexahydroquinindolinones (**4**) from commercially available materials. This synthesis benefits from a simple method of purification, which does not require

chromatography. This ease of purification compliments this synthetic technology practical, easy to perform and facile. In view of the potential biological activity of isatin and isoxazole nuclei, we predict that the newly synthesized compounds may be drug candidates.

EXPERIMENTAL SECTION

Melting points are determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra was recorded in KBr on Perkin Elmer spectrum BX series FT-IR spectrometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using tetramethyl silane as internal standard and mass spectra on a Jeol JMC-300 spectrometer. C, H and N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for the synthesis of 3,3-dimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydro quinindolinones 4a-f

A mixture of isoxazolyl indoline-2-one (**1)** (1 mmol), 3-amino-5-methyl-isoxazole (**2)** (1 mmol), dimedone (**3)** (1 mmol), and ceric ammonium nitrate 10 mol% in ethanol (5 mL) were stirred at ambient temperature for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was poured on to crushed ice and the resulted precipitate was filtered and washed with cold alcohol and recrystallized from benzene.

3,3-Dimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydro quinindolinones (4a)

Yield **7**8%, orange solid. mp 211-213^{0}C. IR (KBr) cm^{-1}: 3252, 1732, 1556, 1362.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.71 (s, 6H, $2CH_3$), 1.84 (m, 2H, CH_2), 2.12 (m, 2H, CH_2), 2.25 (s, 3H, isoxazole-CH_3), 2.34 (s, 3H, isoxazole-CH_3), 4.74 (s, 1H, quinoline-H), 6.14 (s, 1H, isoxazole-H), 7.10 – 7.68 (m, 4H, Ar-H), 8.01 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 474 $(M+H)^+$. Anal. Calcd for $C_{25}H_{23}N_5O_5$: C, 63.42; H, 4.90; N, 14.79. Found. C, 63.39; H, 4.94; N, 14.83%.

9-Chloro-3,3-dimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydro quinindolinones (4b)

Yield 80%, orange solid. mp 222-224^{0}C. IR (KBr) cm^{-1}: 3251, 1722, 1546, 1352.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.76 (s, 6H, $2CH_3$), 1.90 (m, 2H, CH_2), 2.10 (m, 2H, CH_2), 2.21 (s, 3H, isoxazole-CH_3), 2.34 (s, 3H, isoxazole-CH_3), 4.71 (s, 1H, quinoline-H), 6.17 (s, 1H, isoxazole-H), 7.01 – 7.71 (m, 3H, Ar-H), 8.01 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 508 $(M+H)^+$. Anal. Calcd for $C_{25}H_{22}N_5O_5Cl$: C, 59.12; H, 4.37; N, 13.79. Found. C, 59.17; H, 4.40; N, 13.77%.

9-Bromo-3,3-dimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydro quinindolinones (4c)

Yield 79%, orange solid. mp 227-229^{0}C. IR (KBr) cm^{-1}: 3255, 1721, 1540, 1345.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.74 (s, 6H, $2CH_3$), 1.88 (m, 2H, CH_2), 2.11 (m, 2H, CH_2), 2.23 (s, 3H, isoxazole-CH_3), 2.31 (s, 3H, isoxazole-CH_3), 4.69 (s, 1H, quinoline-H), 6.10 (s, 1H, isoxazole-H), 7.00– 7.61 (m, 3H, Ar-H), 8.21 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 552

$(M+H)^+$. Anal. Calcd for $C_{25}H_{22}N_5O_5Br$: C, 54.36; H, 4.01; N, 4.47. Found. C, 54.32; H, 4.06; N, 4.51%.

3,3,9-Trimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydro quinindolinones (4d)

Yield 76%, orange solid. mp 217-219^{0}C. IR (KBr) cm^{-1}: 3245, 1730, 1536, 1326.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.71 (s, 6H, $2CH_3$), 1.86 (m, 2H, CH_2), 2.10 (m, 2H, CH_2), 2.22 (s, 3H, isoxazole-CH_3), 2.31 (s, 3H, isoxazole-CH_3), 2.52 (s, 3H, Ar-CH_3), 4.70 (s, 1H, quinoline-H), 6.11 (s, 1H, isoxazole-H), 7.02– 7.71 (m, 3H, Ar-H), 8.00 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 488 $(M+H)^+$. Anal. Calcd for $C_{26}H_{25}N_5O_6$: C, 64.06; H, 5.17; N, 14.37. Found. C, 64.02; H, 5.20; N, 14.41%.

9-Methoxy-3,3-dimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydro quinindolinones (4e)

Yield 77%, orange solid. mp 213-215^{0}C. IR (KBr) cm^{-1}: 3235, 1721, 1532, 1323.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.73 (s, 6H, $2CH_3$), 1.90 (m, 2H, CH_2), 2.10 (m, 2H, CH_2), 2.22 (s, 3H, isoxazole-CH_3), 2.30 (s, 3H, isoxazole-CH_3), 3.63 (s, 3H, OCH_3), 4.69 (s, 1H, quinoline-H), 6.14 (s, 1H, isoxazole-H), 7.00– 7.69 (m, 3H, Ar-H), 8.11 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 504 $(M+H)^+$. Anal. Calcd for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91. Found. C, 62.06; H, 5.06; N, 13.87%.

9-Fluoro-3,3-dimethyl-5-(5-methyl-3-isoxazolyl)-11-(3-methyl-4-nitro-5-isoxazolyl)-2,3,4,5,6,11-hexahydro quinindolinones (4f)

Yield 80%, orange solid. mp 209-211^{0}C. IR (KBr) cm^{-1}: 3251, 1727, 1542, 1345.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.74 (s, 6H, $2CH_3$), 1.85 (m, 2H, CH_2), 2.12 (m, 2H, CH_2), 2.20 (s, 3H, isoxazole-CH_3), 2.32 (s, 3H, isoxazole-CH_3), 4.72 (s, 1H, quinoline-H), 6.13 (s, 1H, isoxazole-H), 7.00 – 7.85 (m, 3H, Ar-H), 8.23 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 492 $(M+H)^+$. Anal. Calcd for $C_{25}H_{22}N_5O_5F$: C, 61.10; H, 4.51; N, 14.25. Found. C, 61.07; H, 4.48; N, 14.27%.

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