ORIGINAL ARTICLE

A C G publications

Org. Commun. 11:3 (2018) 163-167

organic communications

Photooxygenation of 4-(5-methylfuran-2-yl)aminocyanopyridine derivatives

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(Received September 02, 2018; Revised September 27, 2018 ; Accepted September 28, 2018)

Abstract: One pot syntheses of six-, seven-membered cycloalkane and pyrane junctured aminocyanopyridines bearing furan unit were successfully prepared from the ketones, 2-((5-methylfuran-2-yl)methylene) malononitrile, and ammonium acetate. Photooxygenation of 2-(4-aminocyanopyridine) substituted 5-methylfurans gave 1,4-dicarbonyl functionalized aminocyanopyridine derivatives in good yield in one single operation.

Keywords: 4-Furyl-2-amino-3-cyanopyridines; singlet oxygene; 4-oxopent-2-enoylnicotinonitrile.

1. Introduction

Furans are useful precursors for a wide variety of building blocks and intermediates in organic synthesis.[1] The oxidation of furan generates the 1,4-enedione unit which can be found in several bioactive natural products.[2] The 1,4-enedione units are important intermediates in synthetic organic chemistry.[3] The oxidation of furan and its derivatives have been explored to access many biologically active compounds. [4] Usually, the oxidation of furan can be achieved by either chemical oxidation[5] or singlet oxygen.[6] Generally the chemical oxidation reagents are usually not compatible with the functional group which are commonly present in substrate. On the other hand, singlet oxygen is not only to be more functional group tolerant but also it is considered as higher yielding and nontoxic oxidizer as well.[7, 8]

Pyridines are important heterocyclic compounds that they serve as the main component to form the back bone of many natural products and bioactive molecules[9] with the several biological activities such as anti-microbial, cardiotonic, anti-Parkinson, anti HIV, antitumor, and anti-inflammatory. Multi-functionalized pyridines with amino- and cyano substituents (AmCyPys) also exhibit biological activity. In addition, further functionalization of the cyano and amino groups allow new biologically active compounds.[10, 11]

Aryl ketone moieties are widely found in drugs and medicinal intermediates as they have extraordinary biological and pharmaceutical properties.[12, 13] In addition, 4-acetylpyridine is an anticonvulsant and protects against hypothermic restraint stress-induced gastric ulceration in mice. 3-Acetylpyridine function as a neurotoxin and shows niacin-like activity.[14-17] The syntheses of aminocyanopyridine derivatives have been interest to unearth their potantials such as carbonic anhydrase inhibition[18, 19] and antimicrobial effects.[20]

Herein, we report the syntheses of furan-fused aminocyanopyridines; 2-amino-4-(5-methylfuran-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile **3a**, 2-amino-4-(5-methylfuran-2-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carbonitrile (**3b**) and 2-amino-4-(5-methylfuran-2-yl)-7,8-

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The article was published by ACG Publications
www.acgpubs.org/organic-communications July-September 2018 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.50.18.09.881

dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile (**3c**) and their photooxygenation to construct the α,β-unsaturated-1,4-enedione unit as the tunable functional group in addition to the present aminocyano functionality from simple starting material.

2. Experimental

2.1. Materials and apparatus

In the study all of commercial reagents and chromatography solvents were used as obtained if otherwise was not stated. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F254. Fluka Silica gel 60 (0.063-0.2 mm) was employed for column chromatography. NMR spectra were recorded by means of a Varian 400 MHz NMR instrument (1H NMR at 400 MHz, 13C NMR at 100 MHz) or a Bruker 400 MHz instrument (1H NMR at 400 MHz, 13C NMR at 100 MHz). 1H NMR data are stated as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, dd=doublet of doublets, ddd=doublet of doublets of doublets, brs=broad singlet, t=triplet, q=quartet, quint=quintet, m=multiplet or otherwise stated), integration, coupling constant (J, Hz). 13C NMR data are presented with reference to chemical shift (δ ppm).

2.2. Methods

*2.2.1. General method for preparation of **2***

α-Cyano-β-aryl crotonitriles **2** were prepared starting from 5-methylfuran-2-carbaldehyde in accordance with the procedure described in the literature.[11, 18]

*2.2.2. General method for preparation of **3a–c***

Compound **2** (5 mmol) was suspended in toluene (10 mL), and then ammonium acetate (7,5 mmol) and cycloalkanone derivatives (5 mmol) (cylohexanone, cyloheptanone, tetrahydro-4H-pyran-4-one) were added to the mixture. The flask was fitted with a reflux condenser and a water separator, and the mixture was refluxed for 6 h. Then, the solvent was evaporated, and the mixture was re-dissolved in chloroform (150 mL) and washed with water (2x50 mL). The organic phase was dried with $MgSO_4$, filtered off and recrystallized from ethyl acetate. All aminocyanopyridines (**3a–c**) were prepared by using this procedure[18-20] (Scheme 1).

2-Amino-4-(5-methylfuran-2-yl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile (**3c**): Yield 72%; m.p.: 183-185 °C; IR (cm^{-1}) 3433-3307 (NH_2), 3161 (CH Aryl), 2965 (CH Alkyl), 2203 (CN). ^{1}H-NMR (DMSO-d_6, δ, ppm), 2.39 (s, 3H, CH_3), 2.75 (t, *J*= 5.8 Hz, 2H, -CH_2-), 3.93 (t, *J*= 5.8 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.66 (s, 2H, NH_2), 6.36 (d, *J*= 3.6Hz, 1H, CH_{furan}), 6.93 (d, *J*= 3.6 Hz, 1H, CH_{furan}).^{13}C (DMSO-d_6, δ, ppm), 15.1, 33.7, 65.8, 67.5, 85.2, 110.2, 117.5, 118.8, 139.8, 146.7, 155.7, 156.1, 159.9, 161.0.

*2.2.3. General procedure for photooxygenation of 2-amino-3-cyanopyridine derivatives **3a-c** with TPP*

The solution of **3a-c** (1 equiv) in DCM (10 mL) was illuminated at 0 °C by using a halogen lamp (500 Watt) in the presence of TPP (0.4 mol%) while oxygen was being bubbled in the solution. The reaction was kept at the same temperature during the process. The reaction was monitored with TLC. When the starting material consumed, the reaction was treated with Me_2S (10 equiv) at 0 °C and allowed to warm to RT. Solvent was removed in vacuo. The residue was purified by radial chromatography or column chromatography (EtOAc/hexanes)**.**

*(E,Z)-2-amino-4-(4-oxopent-2-enoyl)-5, 6,7,8-tetraahydroquinoline-3-carbonitrile (**4a**)*: Yield 88%; IR (cm^{-1}) 3412-3314 (NH_2), 3184 (CH Aryl), 2823 (CH Alkyl), 2218 (CN), 1766 and 1714 (C=O).^{1}H-NMR ($CDCl_3$, δ, ppm) 1.71-1.80 (m, 4H), 2.39 (s, 3H, CH_3), 2.72 (t, J= 10.9 Hz, 2H, -CH_2-), 2.86 (t, *J*= 10.9

Hz, 2H, CH_2), 5.27 (s, 2H, NH_2), 6.55; 6.56 (d, J_E= 5.5 Hz, 1H, CH_{olefin}), 6.57; 6.60 (d, J_z= 12.0 Hz, 1H, CH_{olefin}), 6.63; 6.66 (d, J_z= 12.0 Hz, 1H, CH_{olefin}), 6.70; 6.72 (d, J_E= 5.5 Hz, 1H, CH_{olefin}).

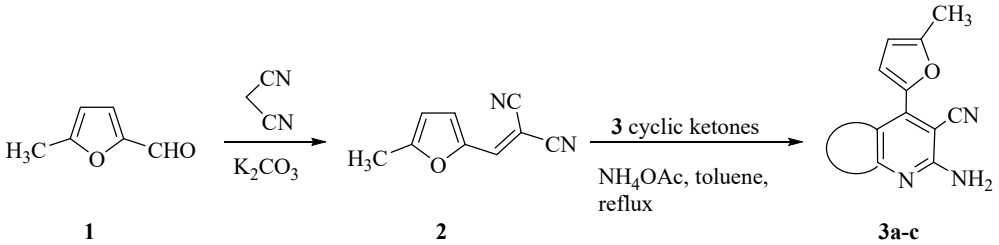
(Z)-2-amino-4-(4-oxopent-2-enoyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carbonitrile ***(4b)****:* Yield: 85%; IR (cm^{-1}) 3472-3359 (NH_2), 3184 (CH Aryl), 2859 (CH Alkyl), 2218 (CN), 1766 and 1709 (C=O). ^{1}H-NMR ($CDCl_3$, δ, ppm) 1.60-1.86 (m, 6H), 2.37 (s, 3H, CH_3), 2.71(t, *J*= 10.9 Hz, 2H, -CH_2-), 2.91 (t, *J*= 10.9 Hz, 2H, CH_2), 5.12 (s, 2H, NH_2), 6.55; 6.56 (d, J_E= 5.5 Hz, 1H, CH_{olefin}), 6.57; 6.60 (d, J_z= 12.0 Hz, 1H, CH_{olefin}), 6.55 (d, J_z= 5.49 Hz, 1H, CH_{olefin}), 6.60 (d, J_E= 5.49 Hz, 1H, CH_{olefin}). ^{13}C-NMR ($CDCl_3$, ppm) 13.7, 26.2, 28.0, 29.2, 31.7, 39.5,112.6, 113.1, 126.8, 127.2, 134.7, 135.0, 135.1, 138.2, 158.9, 169.3.

(*E,Z*)-2-amino-4-(4-oxopent-2-enoyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridine-3-carbonitrile (***4c***): Yield: 89%; IR (cm^{-1}) 3415-3340 (NH_2), 3189 (CH Aryl), 2854 (CH Alkyl), 2218 (CN), 1728 and 1709 (C=O). ^{1}H-NMR ($CDCl_3$, δ, ppm) 2.39 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 2.91 (m, 4H, CH_2), 4.01 (t, *J*= 6.0 Hz, 2H, CH_2), 4.05 (t, *J*= 6.0 Hz, 2H, CH_2), 4.78 (b, 2H, -CH_2-), 4.90 (b, 2H, -CH_2-), 5.20 and 5.29 (s, 2H, NH_2), 6.57 (d, J_Z= 5.49 Hz, 1H, CH_{olefin}), 6.67; (d, J_E= 11.8 Hz, 1H, CH_{olefin}), 6.76 (d, J_E= 11.8 Hz, 1H, CH_{olefin}), 6.78 (d, J_z= 5.49 Hz, 1H, CH_{olefin}).

3. Result and Discussion

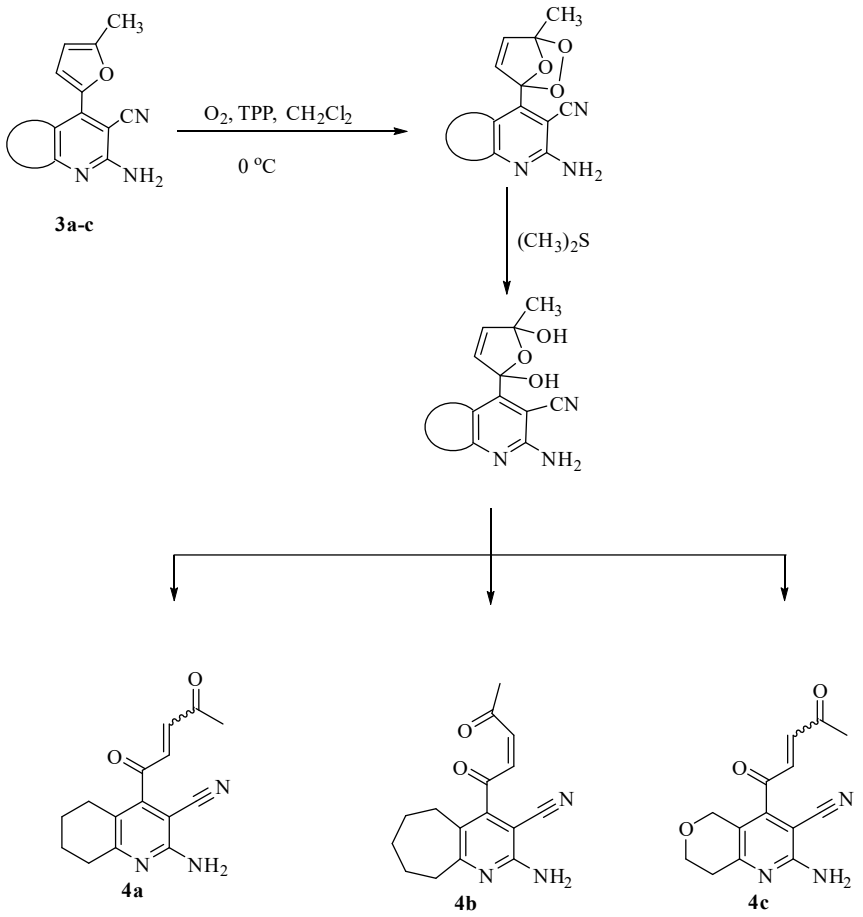
We commenced with the methylfurfural **1** and malononitrile to furnish **2**. In our previous study[11,18-20], three aminocyano pyridines; 2-amino-4-(5-methylfuran-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile, 2-amino-4-(5-methylfuran-2-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carbonitrile and 2-amino-4-(5-methylfuran-2-yl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile (**3a-c**) were obtained in 75, 73 and 72% yields respectively as seen Scheme 1.

When starting materials in hand, we began to establish the best photooxygenation condition for every substrate by using different sensitizer, solvent and reaction temperature. For this purposes, **3a** was subjected to the RB (Rose Bengal) sensitized photooxygenation by carrying out in MeOH at -78 °C using a 500 W halogen lamp while oxygen was passed through the solution. After the consumption of aminocyanopyridines judged by TLC, the reaction was quenched with excess Me_2S to cleavage the peroxide bond. ^{1}H NMR of crude mixtures showed unpromising result. For this reason, the photooxygenation of **3a** was repeated under the TPP-sensitized condition in DCM at 0 °C by monitoring the reaction with TLC. After the reaction was completed, the crude material was purified on silica gel column to obtain **4a** 88% conversion in yield. Encouraging this pleasing result, **3b** and **3c** were also oxidized under the similar photooxidation condition to give **4b** and **4c,** respectively (Scheme 2).



Scheme 1. Synthesis of 4-furyl-2-amino-3-cyanopyridine derivatives (**3** cyclic ketones: cyclohexanone; cycloheptanone; tetrahydro-4H-pyran-4-one).

Asta et al.[21] synthesized of (*E*)/(*Z*) 3-alkene-2,4-diones from 2,5-dialkylfurans via laccase-catalyzed ring opening. They reported $^3J_{3\text{-H},4\text{-H}}$ = 11.8 Hz for (Z)-3-octene-2,5-dione and $^3J_{3\text{-H},4\text{-H}}$ = 11.9 Hz for (Z)-3-nonene-2,5-dione. In our study, the coupling constant of vinylic protons in enedione units of **4b** was ^3J =5.5 Hz, which is also indicating its *Z* configuration.



Scheme 2. Photooxygenation of 4-furyl-2-amino-3-cyanopyridine derivatives

4. Conclusion

Photooxyganation of aminocyanopyridines **3a-c** gave the corresponding 2-amino-3-cyanopyridine bearing α,β-unsaturated-1,4-dicarbonyl unit that otherwise can not be constructed in one single operation. To the best of our knowledge, these compounds are not known in the literature and can be taken for further structural manipulation to prepare a new series of structurally polyfunctional compunds for drug discovery research.

Acknowledgements

The authors would like to thank R. Altundas (Gebze Technical University) for helpful discussions and his critical linguistic editing of the manuscript.

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