KINGDOM OF SAUDI ARABIA
AL-IMAM MOHAMMAD IBN SAUD ISLAMIC UNIVERSITY
COLLEGE OF SCIENCE
DEPARTMENT OF CHEMISTRY

المملكة العربية السعودية
جامعة الإمام محمد بن سعود الإسلامية
كلية العلوم
قسم الكيمياء

Synthesis of Fused Pyridines as Analgesic and Anti-inflammatory Profiles Expected

A graduation research project

Submitted

to the Department of Chemistry in partial fulfillment of the requirements

for the completion of the degree of Bachelor of Science in Chemistry

By
Abdulrhman Al-Omar

Under supervision

Of

Dr. Sami A. S. Al Hussin

First Semester, December 2015

Table of content

Abstract:

A simple, straightforward and efficient synthesis of a pharmaceutically interesting precursor with functionalized l,6-diamino-3,5-dicyano-4-phenyl-2-pyridones **3** has been achieved based on low-cost available commercially materials. Triazolo[l,5-*a*]pyridines and 1,8-naphthyridine derivatives **4**, **5**, **8** have been synthesized. All the synthesized compounds were fully characterized by spectroscopic, physical data and elemental analyses.

Acknowledgment:

My efforts bore fruit with the successful completion of this project. However, there are many others who share the reward of this effort simply because it would never have been this good without their help. I acknowledge the cooperation, encouragement and austerity of the Head of Department and the supervisor of my project, Dr. Sami Al- Hussin

Introduction

Triazolo[1,5-*a*]pyridines represent an important class of heterocyclic compounds. Several approaches have previously described the synthesis of triazolo[1,5-*a*]pyridines from pyridines or triazoles. Triazolo[l,5-a]pyridines are reported to be useful compounds as pharmaceuticals, fluorescent brighteners and complexing agents.

LITERATURE REVIEWS

Pyridines represent biologically interesting molecules [1-4] and one of precursors for the synthesis of triazolo[l,5-*a*]pyridines. Several approaches have previously described the synthesis of triazolo[1,5-*a*]pyridines from 1,6-damino pyridines [5-8]. Their synthetic usually involves several steps, either the pyridine ring or the triazole ring can be constructed first. Moreover, heterocyclic hydrazones or hydrazides are simple precursors and widely applicable methods for the synthesis of fused pyridines. However, these methods have some restrictions concerning the preparation of heterocyclic hydrazide or hydrazine in low yield via the reaction of 2-chloropyridine with hydrazine or carboxylic acid hydrazide. 2-Chloropyridine easily hydrolyzed to 2-pyridone, which might be an explanation for the low yield [Fig. 1]. In a particular, the heterocyclization of 2-hydrazino pyridine by subsequent incorporation of a one- carbon unit carrying an active functional group as carboxylic acid, ester or cyano group for example, afforded triazolo[4,3-*a*]pyridines which undergoes ring transformation to triazolo[1,5-*a*]pyridines. In order to overcome these limitation, with much convenient synthetic method, cyanoacetic acid hydrazide has been introduced to react with α,β- unsaturated nitriles as electron deficient alkenes affording excellent yield of triazolo[1,5-*a*]pyridines.

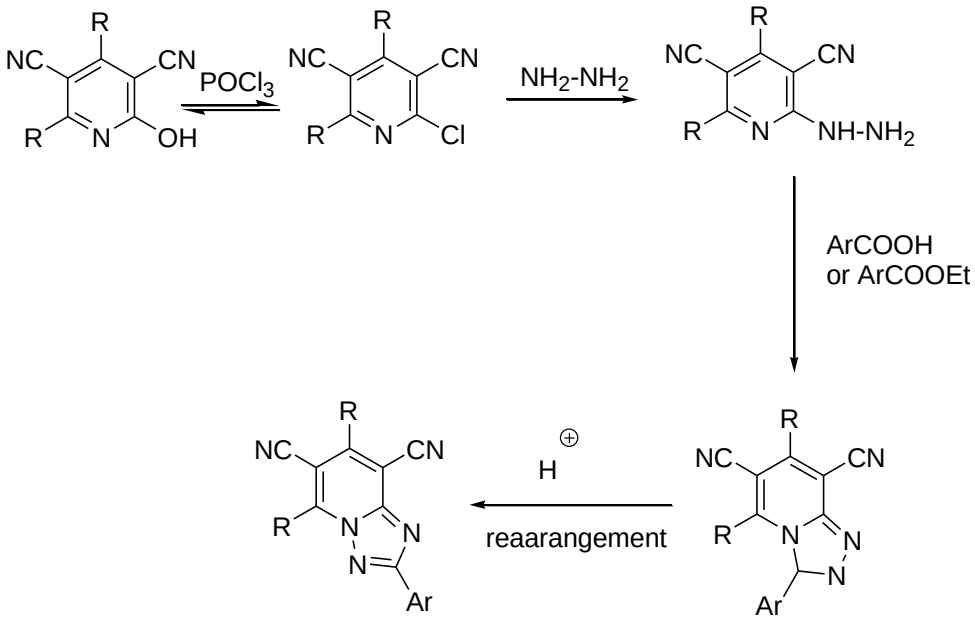
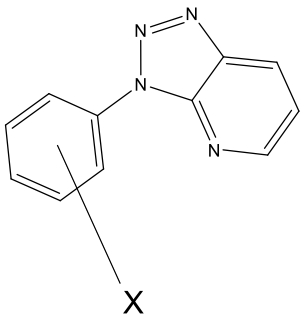


Figure 1

Triazolo[l,5-*a*]pyridines are reported to be useful compounds as pharmaceuticals (9), fluorescent brighteners (l 0) and complexing agents (I1).

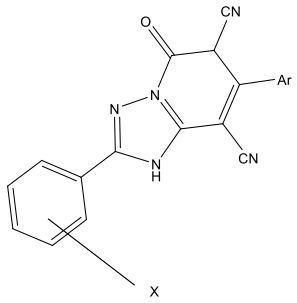
The analgesic activity of many 3-(substituted phenyl)triazolo[4,5-*b*]pyridines (I) was reported by researchers in *Merck Sharp & Dohme Laboratories* [12].



(I)

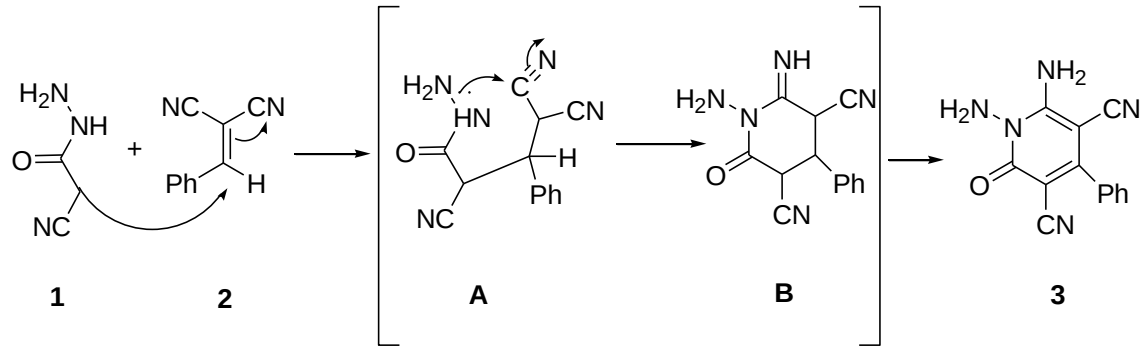
Some of the prepared compounds were reported to be superior in analgesic activity to codeine and *d*-propoxyphene without showing any narcotic characteristics. Some of the compounds also possessed activity against Carrageenan-induced foot edema in the rat.

In the present research project, the synthesis of an example of triazolo[1,5-a]pyridines and their related derivatives was attempted. The prepared compounds, which have some structural similarity to the above mentioned triazolopyridines (I), are expected to have analgesic and anti-inflammatory activity.



Results and Discussion:

1,6-diamino-3,5-dicyano-4-phenyl-2-pyridone **(3)**, the key starting material of the present investigation, was prepared in a good yield by reacting the benzylidene malononitrile **(2**) as electron deficient alkenes with cyanoacetic acid hydrazide **(1)**. The reaction is easily performed in ethanol at room temperature by stirring a mixture of **1** and **2** for 1 hours in the presence of a catalytic amount of triethyl amine (Scheme 1).



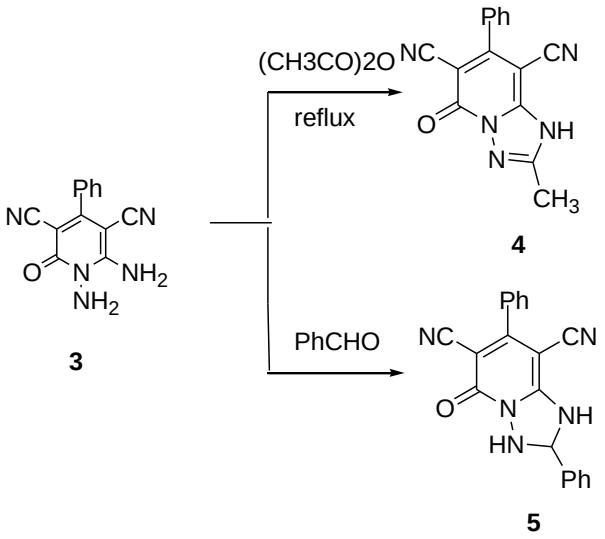
Scheme (1)

Mechanistically, the reaction occurs via initial nucleophilic addition of a carbon acid **1** to electon deficient alkene **2** affording an adduct **A,** followed by the intramolecular cyclization yielding **B**. Autoxidation occurred affording the titled compound **3.**

We reported in this research project a simple route to the formation of triazolo[1,5-*a*] pyridines **4** by the reaction of acetic anhydride with **3** under reflux for 5 hours. ^{1}H-NMR data of the resulting triazolo[1,5-*a*]pyridines **4** revealed the disappearance of NH_2 protons signals and appearance of NH proton signal at δ 11.5 ppm. On the other hand, the IR spectrum of **4** revealed the presence of two signals at 2230 and 1650 corrsponding to CN and CO group. The appearance of one cyano group in its IR reported previously as the presence of a carbonyl group might be act as a masking for the appearance of the cyano group.

To the best of our knowledge, there is only one precedent in the literature in which a condensation of *N*-aminopyridone with aromatic aldehyde in dioxane containing piperidine as a catalyst formed piperidinium salt of the corresponding triazolopyridine [8].

Unexpectedly, upon reacting the pyridine derivative **3** with aromatic aldehydes in absence of piperidine under reflux, the dihydrotriazolopyridine derivatives **5** were smoothly isolated, rather than the expected products (piperidinium salts). ^{1}H-NMR spectrum of **5** revealed the coupling of triazole protons, and the presence of two signals at δ 8.5 ppm and δ10.9 ppm corresponding to the two NH.

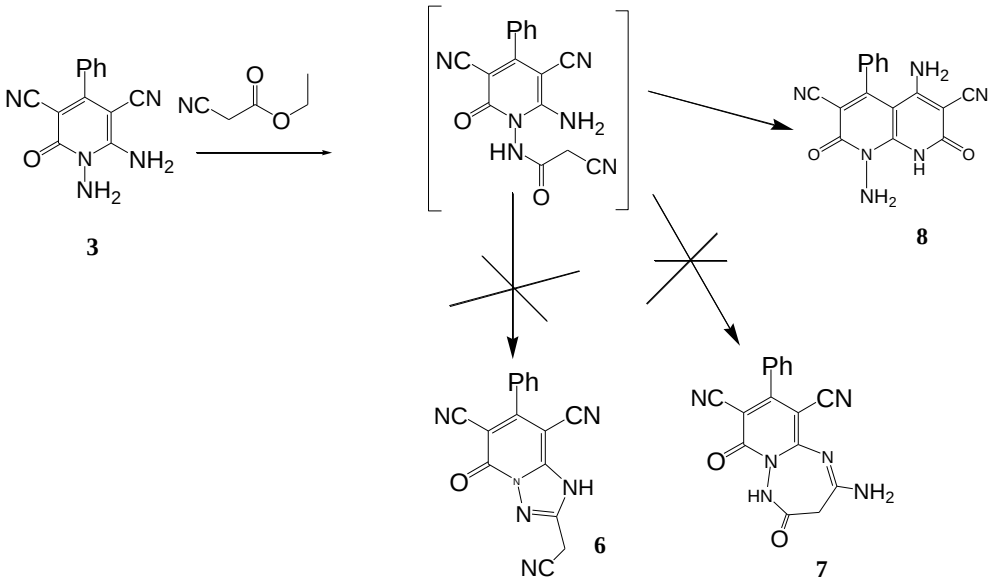


Scheme (2)

As a continuation for our approach to synthesize new derivatives of triazolopyridines using simple bifunctional reagent, the reaction of **3** with ethyl cyanoacetate took place affording unexpected product. The ^{1}H-NMR spectrum showed two amino groups in 4-6 and 8.5 ppm region respectively.

These results didn't coincide with the proposed structure **6** and at the same time, it cannot fit with the formation of a diazepine ring **7** which is more unlikely. However, this result agrees with the structure **8** as a result of 1,2 shift. On the other hand, formation of structure

6 occurred as a result of the reaction of cyanoacetic acid and **3a** in $POCl_3$ under reflux, reported previously [13].



(Scheme 3)

Conclusion:

1,6-diamino-3,5-dicyano-4-phenyl-2-pyridone **(3)**, is a simple precursor for fused triazolopuridine and 1,8-naphthyridine derivatives.

Experimental:

General:

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded at 300 MHz for. Deuterated DMSO was used as solvent. The chemical constants (*J*) in Hertz (Hz). IR spectra were recorded on a FT-IR using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography (TLC) using silica gel. The melting points were determined on a melting point apparatus and are uncorrected.

1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (**3):**

A mixture of **1** (0.02 mole) and **2** (0.01 mole) in absolute ethanol (25 ml) containing catalytic amount of triethyl amine was allowed to stir for 1 hour at room temperature. The resulting precipitate was filtered off, washed several times with ethanol and crystallized to afford compounds **3**.

1,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile derivative (4):

A mixture of equimolar amounts of **3** and acetic anhydride was refluxed for 5 hours. The resulting dark brown solid was filtered off and crystallized from acetic acid to afford **4**. Yield 82%. Mp: 259-260 ^{o}C. IR (Nujol mull), cm^{-1} 3300 (NH), 2218 (CN), 1710 (C=O), 1670 (C=C)); 1HNMR (300 MHz, DMSO-*d6*, δ,ppm): 2.2 (3H, s, CH_3), 7.1-7.6 (5H, m, Ar-H), and 11.5 (1H, s, NH exchangeable with D_2O).

2-phenyl-5-oxo-7-(3-phenyl -1,2,3,5- tetrahydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitriles (5):

A mixture of equimolar amounts of **3** and benzaldehyde in ethanol was allowed to reflux for eleven hours. The resulting precipitate was filtered off, washed several times with ethanol and crystallized from glacial acetic acid to afford **5**. Yield 78%. Mp: 289-290 ^{o}C. IR (Nujol mull), cm^{-1} 3300(NH), 3320(NH), 2216(CN), 1713 (C=O), 1683(C=C); 1HNMR (300 MHz, DMSO-*d6*, δ,ppm): 6.3 (1H, d, benzylic proton of the triazole ring) 7.3-8 (10H, m), 8.5 (1H, s, NH exchangeable with D_2O) and 10.9 (1H,s, NH exchangeable with D_2O).

1,5-Diamino-4-(3-phenyl)-2,7-dioxo-1,2,7,8-tetrahydro-1,8-naphthyridine-3,6-dicarbonitrile (8)

Compound **3** (0.01 mole) was allowed to reflux in the presence of ethyl cyanoacetate (20 ml) for 6 hours. The resulting precipitate was filtered off and crystallized from glacial acetic acid to afford 80% of **8**. Yield 71%. Mp: 289-290 ^{o}C. IR (Nujol mull), cm^{-1} 3300(NH), 3250(NH_2), 3200(NH_2), 2210 (CN), 1670 (C=O), 1700 (C=O), 1660 (C=C); ^{1}HNMR (300 MHz, DMSO-*d6*, δ,ppm): 4.4 (2H, s, NH_2), 5.6 (2H, s, NH_2), 7.4-7.7 (5H, m, Ar), 8.9 (1H, s, NH).

References:

1. Bategeri, R.; Beaulieu, P. L.; Llinas-Brunet, M.; Ferland, J. M.; Cardozo, M.; Moss, N.; Batel, U.; Proudfoot, J. R.; ***PCT Int. Appl. WO***, 99 31, 066, 1999; ***Chem. Abstr***., 1999, 131, 59136a.

2. Abadi, A.; Al-Deeb, O.; Al-Afify, A.; El-Kashef, H.; ***Farmaco***, 1999, 54, 195-201.

3. Dube, D.; Brideau, C.; Deschenes, D.; Fortin, R.; Friesen, R. W.; Gordon, R.; Girard, Y.; Reindaeu, D.; Savoei,C.; Chan, C. ***Bioorg. Med. Chem. Lett.*** 1999, 9, 1715-1720.

4. Lee, K.; Glenn, C.; Connoly, D. T.; Corley, D. G.; Flynn, D. L.; Hamme, A.; Hegde, S. G.; Melton, M. A.; Schilling, R. J.; Sikorski, J. A.; Wall, N. N.; Zablocki; J. A; ***PCT Int. Appl. WO***, 99, 41, 237, 1999; ***Chem. Abstr***. 1999, 131, 157711d.

A) Al-Omran, F.; Abdel Khalik, M. M.; EL-Nagdi, M. H.; ***Heteroatom Chemistry*** 1995, 6, 545-552. b) Yamada, Y.; Yasuda, H.; Takayama, A.; ***Heterocycles***, 1998, 48, 1185-1192.

5. Phadke, R. C.; Rangnekar, D. W.; ***Synthesis***, 1986, 860-862

6. Molina, P.; Tarraga, A.; Garcia, C.; ***Heterocycles***, 1988, 27, 733-743.

7. Waheed M. B., ***Acta Chem. Slov***. 2003, 50, 223.

8. As immune adjuvants, stomach secretion inhibitors, antivirals, and antihypertensives. Kyorin Pharmaceuticals Co., Kabo, K.; Itoh, N.; Sohzu, I.; Isomura, Y.; and Honma. H.; ***Fr. Pat***. 2450259, 1980; ***Chem. Abstr***., 1982, 97, 72373z; *Jap. Pat.* 7905996, 1979 ***Chem. Abstr***. 1979, 91, 570071; F. Busseran, J. C. Chermann, E. Declearq, and C. Hannoun. ***Ann. Virol.,*** 1983, 134E, 127; L. Carey, M. Martin-Smith, B. J. Price, P. Blatcher, J. W. Clinherow, D. E. Bays, and J. Bradshaw, **Eur. Pat. Appl. EP** 48855S, 1982 ***Chem. Abstr.*** 1982, 97, 55814b.

9. Buell, B. G. ;and R. S. Long, US Patent, 3272831, 1966 *Chem. Abstr*., 1967, 66, 19832g; K. Weber, ***Eur. Pat. Appl***., EP 67792, 1982 ***Chem. Abstr***., 1983, 98, 127689K.

10. S. B. Sann, H. Behm, P. T. Beurkens, J. Conrnelissen, J. P. Hassnoot, and A. T.

Leustra, *J. Cryst. Spect. Res.*, **1987**, 17, 81.

11. J. L. Soto, C. Seoane, P. Zamorano, F. J. Guardado, *Synthesis*, **1981**, 529.

12. Mohamed, M. S.; Zaki, M. E. A.; Khalifa, N. M., Zohny, Y. M., Heterocyclic Communicatioms, 2008, 14, 345- 356.

13. Zaki, M. E. A., Current Organic Syntheis, submitted.

CV

Name: Abdulrhman Mohammad Alomar

College: College of Sciences

Department: Chemistry

University: Imam Muhammad bin Saud University

Date of Birth: 11/1/1413

Place of Birth: AL-Zulfi

E-mail: a.m.a.al3omar@gmail.com

Mobile: 0560013345

Phone: 0112333929

Post address: 3642

Postal Code: 14224