http://www.e-journals.net

ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
Vol. 4, No. 3, pp. 372-375, July 2007

Synthesis and Characterization of 9-Phenyl-9*H*-purin-6-amines from 5-Amino-1-phenyl-1*H*-imidazole-4-carbonitriles

ASIEH YAHYAZADEH* and FATEMAH HABIBI

Department of Chemistry,
University of Guilan, P.O. Box 1914, Rasht, Iran.

yahyazadehphd@yahoo.com

Received 13 December 2006; Accepted 10 January 2007

Abstract: 9-Phenyl-9*H*-purin-6-amine derivatives have been synthesized in high yields by reaction between 5-amino-1-phenyl-1*H*-imidazole-4-carbonitrile with $HC(OEt)_3$ and Ac_2O followed by reaction with ammonia.

Keywords : Imidazole , 9-Phenyl-9*H*-purin-6-amine, Purine, Formimidate, Formamidine

Introduction

Purines are a class of heterocyclic compounds which play an important role in many biological processes[1-5]. The most important natural occurrence of purines is in the nucleotides and nucleic acids; compounds which perform some of the most crucial functions in fundamental metabolism. The chemotherapeutic uses of purines and purine analogues have prompted tremendous efforts towards their synthesis, both in academia and in the pharmaceutical industry[6-9].

As the purine ring system is a fusion of two aromatic heterocyclces, pyrimidine and imidazole, a logical starting point for ring synthesis is an appropriately substituted pyrimidine or imidazole from which the second ring can be constructed by a cyclization process[10,11].

Experimental

All solvents purified and dried using established procedures. The ^1H NMR spectra were recorded on Hitachi-Perkin-Elmer R24B (60 MHz) or Bruker XL 300 (500 MHz) instruments

(with J-values given in Hz), ^{13}C NMR spectra either on a Bruker WP 80 or XL300 instrument, and IR spectra on a Shimadzu IR-435 spectrophotometer. Mass spectra were recorded on a Kratos Concept instrument. The melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

General procedure for the preparation of 1-aryl-4-cyano-5-[(ethoxy-methylene)amino]imidazoles ***(4a-b)***

A mixture of 5-amino-1-aryl-4-cyanoimidazole (0.5 g), triethyl orthoformate (12.0 M equivalent), and acetic anhydride (6.0 M equivalent) was heated gently at 70-80 ^{0}C under an argon atmosphere for several hours. After TLC showed that no starting material remained the resulting yellow-brown solution was evaporated under vacuum to give a residue which, upon treatment with a mixture of dry diethyl ether / hexane (1:1) afforded a precipitate which was filtered off, washed with the same mixture and dried under vacuum to give the products **4a-b.**

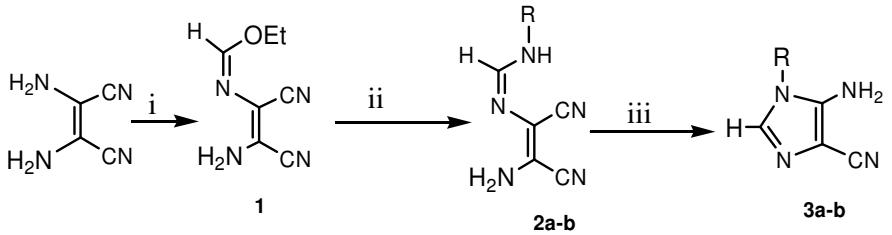
General procedure for the preparation of 9-aryl-6-aminopurines ***(5a-b)***

To a stirred solution of the 1-aryl-4-cyano-5-[(ethoxymethylene)amino]imidazole (**4a-b)** (0.3 g) in dry methanol (8-10 cm^3) under an argon atmosphere at room temperature was added amonnia (1M equivalent). After 15-20 minutes, the separated precipitate was filtered off, washed with a mixture of dry diethyl ether/hexane (1:1), and dried under vacuum to give **5a-b**.

Results and Discussion

5-amino-4-cyanoimidazoles are useful intermediates for purine synthesis[12]. There are few reports of 9-aminopurine derivatives and most of the routes described are from 5-amino-4-hydrazinopyrimidine precursors, substituted in the 2- and 6-position[13-17].

We therefore decided to investigate the reactions of 9-phenyl-9H-purin-6-amines **5a-b** were prepared via a multistep synthesis from ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (**1**), by treatment with a phenyl-amine in a 1:1 molar ratio in ethanol in the presence of a catalytic amount of aniline hydrochloride to give the corresponding formamidine[16, 17] (Scheme 1). Cyclisation of the formamidines in the presence of a strong base, aqueous KOH solution, provided the corresponding 5-amino-1-phenyl-1*H*-imidazole-4-carbonitriles (**3a-b)**,[9,10] which are readily converted to 9-phenyl-9H-purin-6-amines (**5a-b)** by treatment with $HC(OEt)_3$ and Ac_2O followed by reaction with ammonia (Scheme 2).



1 **2a-b** **3a-b**

a : R=4-BrC_6H_4-

b : R=4-FC_6H_4-

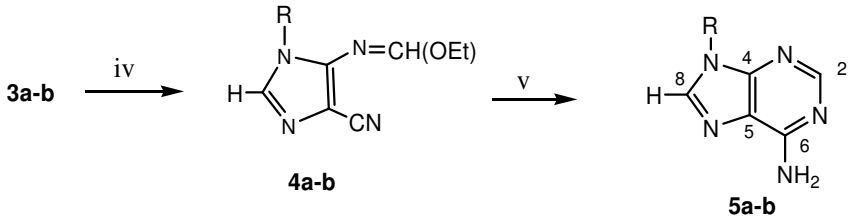
Scheme 1. Reagents and conditions: (i) $HC(OEt)_3$, dioxane, heat; (ii) RNH_2, $PhNH_3^+Cl^-$, room temp., 3-4h; (iii) 1mol KOH aq. room temp.

The initial step involved conversion of the 5-amino-4-cyanoimidazoles **(3)** to the corresponding ethoxyimidates **(4)**. These were prepared by heating the appropriate cyanoamine with triethyl orthoformate and acetic anhydride on a water bath at 60-80 ^{o}C for several hours (Scheme 2).

Once TLC confirmed complete consumption of the starting material, the result in solution were evaporated under vacuum to give a residue that upon treatment with a mixture of dry diethyl ether and hexane (1:1), gave the required imidates **4a** and **4b** as a solid in 81-87% respectively yield. The products were recrystallised from a mixture of dry diethyl ether and hexane (1:1). In the infrared spectra the presence of the cyano and C=N stretching vibrations were observed in the range of 2210-2220 and 1630-1650 cm^{-1} respectively.

The ^{1}H NMR spectra of the isolated ethoxyimidates (**4a-b**) showed the presence of the H-2 proton of the imidazole ring in the range of δ7.26-8.28 ppm. The *H*-7 proton appeared in the range δ8.28-8.66 ppm. The CH_2 and CH_3 of the ethoxy group had clear quartet and triplet patterns as expected in the regions of δ1.32-1.55 and δ4.31-4.5 ppm respectively. The other bands were in agreement with expected structures. The ^{13}C NMR spectra of the imidazoles had the expected number of bands with the C-2 carbon of the imidazole ring in the region of δ135.4-140.9, the C-7 carbon at δ159.9-165.5 and the C-4 carbon within the region of δ98.9-103.0 ppm.

The imidates (**4a-b)** were converted to the corresponding 9-phenyl-9*H*-purin-6-amines (**5a-b)** by treatment with ammonia in the minimum amount of methanol. The reaction was carried out under an argon atmosphere at room temperature. During the first 20 minutes a white precipitate started to form. After 2-3 h TLC showed no staring material, and filtration of the reaction mixture gave the purines as a powder in 67-83% yield. The purines (**5a-b)** were fully characterized by microanalysis and spectroscopic methods.



a : R=4-Br$C_6H_4^-$
b : R=4F$C_6H_4^-$

Scheme 2. Reagents and conditions:(iv) $HC(OEt)_3$, $(CH_3CO)_2O$, heat, (v) NH_3, MeOH, heat.

The elemental analysis and mass spectra of isolated 9-phenyl-9*H*-purin-6-amines (**5a-b)** were satisfactory. In the infrared spectra, the NH stretching vibrations were observed as 2-3 bands in the range of 3300-3150 and C=N absorption band in the range 1650-1660 cm^{-1}. The NH_2 protons were observed in the range δ5.70-5.93 ppm, the proton at position *H*-2 of the purines system appeared in the regions of δ8.12-8.26 ppm and the proton at position H-8 were seen as a singlet in the range of δ8.08-8.22 ppm. The ^{13}C NMR spectra of the compounds (**5a-b)** had the expected number of peaks. The C-8 carbon of the imidazoles ring appeared in the region of 143.5-144.0 ppm. The carbon at positions C-2 and C-6 of the purines system appeared at δ152.0-152.6 and 158.2-158.4 ppm respectively.

Acknowledgments

We are thankful to the Guilan University Research Council for the partial support of this work.

References

1 Booth B L, Dias A D and Proenca M F, *J. Chem. Soc. Perkin. Trans. 1*, 1992, 2119.
2 Booth B L, Freitas A P, Fernanda M and Proenca J R P, *J. Chem. Research (S),* 1993, 260.
3 Huryn D M and Okabe M, Aids-Driven nucleoside Chemistry, 1992, **92**, 1745.
4 Erian A W, *Chem. Rev*. 1993, **93,** 1991.
5 Asano S, Itano K, Yamagata Y and Kohda K, *Nucleosides & Nucleotides.* 1994, **13**, 1453.
6 Birkett P R and King H, *Tetrahedron*, 1993, **49**, 11029.
7 Ohtsuka Y, *J. Org. Chem*. 1979, **44**, 827.
8 Moriya O, *Synth. Commun*. 1984, 1057.
9 Yahyazadeh A, *Russ. J. Org. Chem*. 2003, **39**, 1649.
10 Yahyazadeh A, Pourrostam B and Rabiee M, *Bull. Korean. Chem. Soc*. 2003, **24**, 1723.
11 Booth B L, Alves M J, Carvalho A, Eastwood P R and Nezhat L, *J. Chem. Soc. Perkin. Trans.* 1994, **2**, 1949.
12 Yahyazadeh A and Booth B L, *Synth. Commun*. 2001, **31**, 3225.
13 Yahyazadeh A and Sharifi Z, *Phosphorus, Sulfur, and Silico*n. 2006, **6**, 1339.
14 Yahyazadeh A and Booth B L, *Synth. Commun*. 2002, **21**, 3241.
15 Booth B L, Alves M J, Proenca J R P and Fernanda M, *J. Chem. Soc. Perkin. Trans. 1*, 1990, 1705.
16 Al-Azmi A, Elassar A A and Booth B L, *Tetrahedron,*.2003, **59**, 2749.
17 Al-Azmi A, Elassar A A, Booth B L, Carpenter A R, Carvalho A and Marrelec E, *J. Chem. Soc. Perkin. 1*, 2001, 2532.