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Synthesis and Characteristics of 2-Bromophenyl-6-iminopurine from 2-Bromophenyl-4-cyanoimidazole

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Abstract: It has been demonstrated that the 5-amino-1-(2-bromophenyl)-4-cyanoimidazole can be converted to 1-amino-9-(2-bromophenyl)-6-iminopurine by first forming the imidate by treatment with $HC(OEt)_3$ and Ac_2O followed by reaction with hydrazine monohydrate. 5-amino-1-(2-bromophenyl)-4-cyanoimidazole has prepared from diaminomaleonitrile by moltistep synthesis.

Keywords : Diaminomaleodinitrile, Purine, Imino-purine, Imidazole

Introduction

Purines and fused purines, being an integral part of DNA and RNA, play an essential role in several biological processes and have considerable chemical and pharmacological importance. Particularly, the purine ring can be found in the nucleoside antibiotics, antibacterial, antitumor, as well as veterinary products[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 the pharmaceutical industry and academia[6-9].

Experimental

All solvents were 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.

1-(2-Bromophenyl)-4-cyano-5-[(ethoxy-methylene)amino]imidazole(2)[6-7]

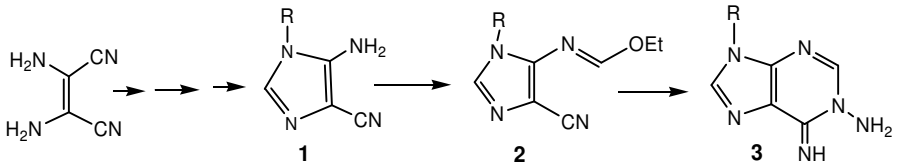
A mixture of 5-amino-1-(2-bromophenyl)-4-cyanoimidazole (0.5 g), triethyl orthoformate (12.0 M equivalent), and acetic anhydride (6.0 M equivalent) was heated gently at 70-80 ^{o}C under an argon atmosphere for several hours. After TLC showed that no starting material remains, the resulting yellow-brown solution was evaporated under vacuum to give the product **2** as oil. This was used without further purification in the next stage.

1-Amino-9-(2-bromophenyl)-6-iminopurine(3)

To a stirred solution of the 1-(2-bromophenyl)-4-cyano-5-(ethoxymethylene)amino]-imidazole **2** (0.4 g) in dry methanol (10-12 cm^3) under an argon atmosphere at room temperature was added to hydrazine monohydrate (IM 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 **3** as a white crystalline solid (0.34g, 1.16 m mol, 70%). Melting point is 194-196 ^{o}C. [Found : C, 45.4; H, 3.2; N, 29.0; Br, 27.5 . $C_{12}H_9N_6Br$ requires C, 45.0; H, 3.0; N, 28.7, Br, 27.3%]; m/z (FAB) 294 $(M+1)^+$ 24.0, 293 $(M)^+$ 100%, 213 $[(M+1)-Br]^+$ 64.8%, 197 (55.3%), 182 (17.4%) ; δ_H (500 MHz, d_6-DMSO) 5.90 (s, 2H, NH_2), 7.26 (dd, 1H, $^3J_{14,15}$ 7Hz, H15), 7.64-7.72 (m, 2H, H13 & H14), 7.86 (d, 1H, $^3J_{12,13}$ 7Hz, H12), 8.10 (s, 1H, H8), 8.16 (s, 1H, H2) ppm; δ_C (75 MHz, d_6-DMSO) 126.2 (C5), 131.8 (C15), 133.1 (C10), 133.7 (C14), 133.8 (C13), 136.5 (C12), 138.0 (C11), 143.7(C8), 145.9 (C4), 152.0 (C2), 158.2 (C6) ppm ; ν_{max} (Nujol mull) 3300 m, 3280 s, 3140 m, 3140 s, 3090 s, (NH str.), 3040 s, 2970 m, 1650s, (C=N str.), 1600 m, (N-H bend), 1560 s, 1550 s, 1500 m, 1480 m, 1450 m, 1380 m, 1350 m, 1220s, 1205 m, 1180 s, 1145 s, 1075 s, 1045 m, 940 s, 860 m, 820 s, 760 s cm^{-1}.

Results and Discussion

1-Amino-6-iminopurines are potential chemotherapeutic agents that have been little explored[10,11]. In order to synthesize the desired 9-arylpurines, we undertook the following reactions.

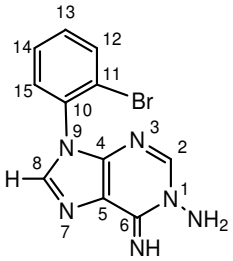


R=2-BrC_6H_4-

1-Amino-9-(2-bromophenyl)-6-iminopurine **3** was prepared *via* a multistep synthesis from ethyl(*Z*)-N-(2-amino-1,2-dicyanovinyl)formimidate.[12] Cyclization of the formamidine in the presence of a strong base, aqueous KOH solution, provided the corresponding 5-amino-1-(2-bromophenyl)-4-cyanoimidazole **1**.[13-15] The initial step involved conversion of the 5-amino-4-cyanoimidazole **1** to the corresponding ethoxyimidates **2**. These were achieved by a modification of the procedure used by Taylor and Loeffler[16] and also by Ried and Laoutidis.[17] In general, it was prepared by heating the appropriate cyanoamine with triethyl orthoformate and acetic anhydride on a water-bath at 60-80 ^{o}C for several hours. The resulting yellow-brown solution was evaporated under vacuum to give the product **2** as an oil. This was used without further purification in the next stage.

The ethoxyimidates **2** was cyclized to the corresponding 1-amino-9-(2-chlorobenzyl)-6-iminopurine **3** by treatment with hydrazine monohydrate in the minimum amount of methanol. The reaction was carried out under an argon atmosphere at room temperature and after 10-20 minutes a precipitate separated out. This was filtered and washed with a mixture of dry diethyl ether and hexane (1:1), followed by a small amount of ethanol. The elemental analysis and mass spectra of all isolated 1-amino-9-(2-bromophenyl)-6-iminopurine **3** was satisfactory.

In the infrared spectra, the NH stretching vibrations were observed as 3-4 bands in the range of 3300-3010 and C=N absorption band at 1660 cm^{-1}. The imine hydrogen was not observed in ^{1}H nmr spectra, possibly because it was too broad and could not be distinguished from the line. The NH_2 protons were observed at δ5.94 ppm, the proton at position H-2 of the purine system appeared at δ8.26 ppm and the proton at position H-8 was seen as a singlet at δ8.22 ppm.



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