



Synthesis, crystallographic and theoretical investigation of 7-benzyl-3*h*-[1,2,4]triazolo[3,1-*i*]purine

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ABSTRACT

The title compound has been prepared in high yield from 9-benzyl-purine derivative by reaction with diethoxymethyl acetate (DEMA). The structure of the tricyclic compound, 7-(2-chlorobenzyl-3*H*-[1,2,4]triazolo[3,1-*i*]purine 2, was confirmed by X-ray analysis. Semiempirical calculations for predicting geometrical parameters are in excellent agreement with the X-ray crystal structure.

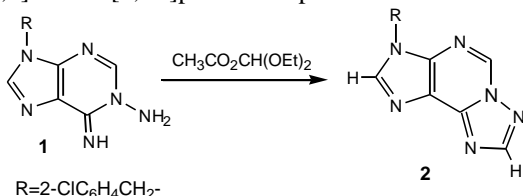
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Introduction

Fused triazoles have been found to exhibit a wide range of biological activities [1-3]. Most of these compounds show significant *in vivo* antitumor and antiviral activity and, in addition, possess fluorescent properties which makes them of interest as biological probes [4-7].

As a class of compounds the *s*-triazolo[3,1-*i*]purines have been prepared from the corresponding 6-hydrazinopurines by reaction with diethoxymethyl acetate (DEMA) [8-11]. As part of our ongoing study of the use of diaminomaleonitrile as a cheap starting material for a range of imidazole, purine, dihydropurine and pyrimidine derivatives. We have previously described the synthesis of some derivatives of 1-amino-9-aryl- (or benzyl)-6-iminopurines [5-9]. We decided to investigate the reaction of 1-amino-9-benzyl-6-iminopurine 1 with cyclizing agent diethoxymethyl acetate to see

whether this might provide a route to 7-(2-chlorobenzyl)-3*H*-[1,2,4]triazolo[3,1-*i*]purine compound.



Results and Discussion

1-Amino-9-(2-chlorobenzyl)-6-iminopurine 1 was prepared via a multistep synthesis from ethyl (Z)-N-(2-amino-1,2-dicyanovinyl)formimidate [6-10], by treatment with a benzylamine in a 1:1 molar ratio in ethanol in the presence of a catalytic amount of anilinium hydrochloride to give the corresponding formamidine. Cyclisation of the formamidine in the presence of a strong base, aqueous KOH solution, provided the corresponding 5-amino-1-benzyl-4-cyanoimidazole, which are readily converted to 1-amino-9-benzyl-6-iminopurine by treatment with HC(OEt)₃ and Ac₂O followed by reaction with hydrazine hydrate [11,12].

On heating 1 with an excess of diethoxymethyl acetate (DEMA), 7-benzyl-3*H*-[1,2,4]triazolo[3,1-*i*]purine 2 is obtained in good yield. Compound 2 was refluxed in diethoxymethyl acetate for 4-5 hours, after which time TLC showed that all starting material had been consumed. Removal of the solvent and addition of water to the residue followed by extraction with chloroform gave pure compound 2 in 87% yield as pale yellow crystal and after recrystallization from chloroform-hexane that was characterized fully.

The microanalysis and mass spectra of the isolated triazolo-purine 2 was satisfactory. The ¹H NMR spectra had some interesting features. The H-8 of the imidazole ring shifted to higher field at 8.78, with H-2 of the purine ring at 8.90 ppm and H-5 at 9.82 ppm. The ¹³C NMR spectra of the compound 2 had the expected number of bands, with the C-8 carbon having a chemical shift at δ 141.8, C-5 at □147.7 and C-2 at □ 158.9 ppm. The infrared spectrum confirmed the presence of the C=N stretching vibration in the region of 1600-1680 cm⁻¹.

Crystals of compound 2 suitable for a single crystal X-ray structure determination was obtained and the results (Fig. 1) confirmed the expected structure. As far as we are aware the X-ray structure of a 2 has not been reported previously. However, the structure is almost analogous to that established for 3-methyl-3*H*-[1,2,4]-triazolo[5,1-*i*]purine reported by Asano et al [13].

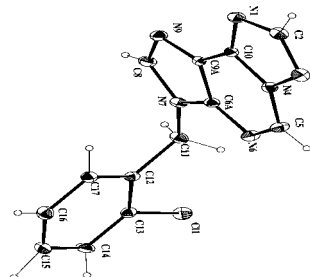


Fig. 1 X-ray structure of 7-(2-Chlorobenzyl)-3*H*-[1,2,4]triazolo[3,1-*i*]purine 2 with atomic numberings

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Table 1 : X-ray structure data, AM1 and PM3 computational studies of 7-(2-chlorobenzyl-3H-[1,2,4]triazolo[3,1-i]purine 2.

X-ray crystal structure		Theoretical data		X-ray crystal structure		Theoretical data	
Bond	Angle (o)	AM1	PM3	Bond	Angle (o)	AM1	PM3
C10-N1-C2	101.9(4)	103.22	103.4	N9-C9a-C10	132.9(4)	132.3	133.0
N3-C2-N1	118.1(4)	114.6	110.8	C6a-C9a-C10	116.0(4)	117.2	116.9
C2-N3-N4	100.8(4)	104.2	105.9	N1-C10-N4	109.8(4)	108.5	106.6
C5-N4-N3	124.9(4)	129.6	127.6	N1-C10-C9a	136.4(4)	135.5	137.1
C5-N4-C10	125.5.6(4)	121.0	123.3	N4-C10-C9a	113.7(4)	115.8	116.1
N3-N4-C10	109.4(4)	109.2	108.9	N7-C11-C12	114.5(4)	117.1	115.7
N6-C5-N4	121.3(4)	121.3(4)	120.4	C17-C12-C13	117.7(4)	118.5	118.5
C5-N6-C6a	115.5(4)	116.0	117.9	C17-C12-C11	122.2(4)	123.1	123.7
N6-C6a-N7	127.0(4)	129.3	128.7	C13-C12-C11	120.0(4)	119.2	120.1
N6-C6a-C9a	127.8(5)	125.2	125.1	C14-C13-C12	121.6(5)	120.8	121.1
N7-C6a-C9a	105.2(4)	105.4	106.0	C14-C13-C11	119.4(4)	118.3	118.6
C6a-N7-C8	106.2(4)	105.8	107.1	C12-C13-C11	118.9(4)	120.8	120.2
C6a-N7-C11	127.0(4)	126.9	127.2	C15-C14-C13	120.4(5)	119.7	119.5
C8-N7-C11	126.7(5)	127.0	126.5	C14-C15-C16	119.4(5)	119.9	119.8
N9-C8-N7	113.4(5)	113.5	112.9	C15-C16-C17	120.8(5)	120.2	120.4
C8-N9-C9a	104.3(4)	104.8	107.7	C12-C17-C16	120.0(5)	120.7	120.4
N9-C9a-C6a	110.9(4)	110.3	109.0	N9-C9a-C10	132.9(4)	132.3	133.0

Table 2 : X-ray structure data, AM1 and PM3 computational studies of 7-(2-chlorobenzyl-3H-[1,2,4]triazolo[3,1-i]purine 2

X-ray crystal structure		Theoretical data		X-ray crystal structure		Theoretical Data	
Bond	Length (Å)	AM1	PM3	Bond	Length (Å)	AM1	PM3
C11-C13	1.754(5)	1.703	1.687	N7-C11	1.461(6)	1.432	1.467
N1-C10	1.326(6)	1.354	1.352	C8-N9	1.305(7)	1.339	1.392
N1-C2	1.357(7)	1.407	1.391	N9-C9A	1.370(6)	1.393	1.392
C2-N3	1.314(7)	1.364	1.340	C9A-C10	1.419(6)	1.426	1.422
N3-N4	1.378(6)	1.347	1.377	C11-C12	1.513(7)	1.503	1.499
N4-C5	1.368(7)	1.402	1.415	C12-C17	1.390(7)	1.397	1.394
N4-C10	1.384(6)	1.457	1.422	C12-C13	1.393(6)	1.406	1.400
C5-N6	1.292(7)	1.319	1.318	C13-C14	1.373(7)	1.397	1.391
N6-C6a	1.351(6)	1.387	1.388	C14-C15	1.366(8)	1.393	1.389
C6a-N7	1.366(6)	1.402	1.403	C15-C16	1.375(9)	1.393	1.390
C6a-C9a	1.387(6)	1.451	1.413	C16-C17	1.395(8)	1.394	1.391
N7-C8	1.371(7)	1.412	1.409				

It can be seen from this that the C-N double bonds are localised between C8-N9, C9a-C6a, N6-C5 and N3-C2. The three rings from a plane with the 2-chlorobenzyl group bent out of the plane as anticipated. From an examination of the ¹H nmr chemical shifts of the three ring protons it is clear that the proton on C5 is the most highly deshielded (9.65 ppm) followed by the proton on C2 (8.72 ppm) with the proton on C8 being least deshield (8.61 ppm).

Computational studies

The most promising semiempirical SCF-MO methods for predicting geometries and electronic properties were AM1 and PM3, as implemented in MOPAC program [14]. MOPAC 6.0 was used exclusively for the work presented herein. The geometry of the 7-(2-Chlorobenzyl)-3H-[1,2,4] triazolo[3,1-i]purine 2 has been studied with using semiempirical molecular orbital methods. This compound has C1 point group and ΔH formation 194.489 kcal/mol with dipolment 4.289 Debye.

All calculations were performed using AM1 and PM3 at high precision, and then the geometrical predictions have been

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