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Crystal and Molecular Structure of 6-Methyl-2-(trifluoromethyl)-(6*H*)-imidazo[1,2-*c*]pyrimidin-5-one

The title compound (C₈H₆F₃N₃O) crystallizes as colorless plates, triclinic, $a = 10.916(2)$ Å, $b = 11.140(1)$ Å, $c = 8.368(1)$ Å, $\alpha = 95.938(9)^\circ$, $\beta = 105.24(1)^\circ$, $\gamma = 64.843(9)^\circ$, $V = 888.6(2)$ Å³, $Z = 4$, $D_{\text{calc}} = 1.623\text{g/cm}^3$, space group $P\bar{1}$. The structure was solved by direct methods and refined by the full-matrix least-squares method ($R_w = 0.047$).

Keywords: crystal structure, imidazo[1,2-*c*]pyrimidine, trifluoromethyl, cycloaddition, cytosine, bromoacetoxime

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1. Introduction

The facile reactions of chloroacetaldehyde and bromoacetaldehyde with adenine and cytosine moieties produce etheno adducts that are highly fluorescent. Such etheno adducts often retain the biological activities of the parent systems. The ready formation of these adducts, their highly fluorescent nature, and the biological importance of adenine and cytosine residues, including their presence in nucleic acids, have combined to make etheno adduct formation an important tool in many facets of nucleotide and polynucleotide research (LEONARD, 1984).

The use of ¹⁹F-NMR to probe the structure and function of macromolecules is well-documented, with particularly important contributions having been made in the area of protein biochemistry. As an approach to labeling polynucleotides with fluorine for potential ¹⁹F-NMR studies, we have initiated a program to develop procedures to synthesize fluorinated etheno adducts. Toward this end, we have attempted condensations of 1,1,1-trifluoro-3-bromoacetone and its derivatives with cytosine and its derivatives. As shown in Fig. 1, the reaction of 1-methylcytosine and 1-bromo-3,3,3-trifluoroacetoxime (ZIMMER et al., 1992) yielded a single addition product. Depending upon the regiochemistry of the initial condensation reaction, two regioisomers, I and II, could be formed. No obvious methods such as NMR for unequivocal elucidation of the structure were apparent. We therefore carried out an X-ray single crystal determination to solve this structural problem.

2. Experimental

Reaction of 1-methylcytosine with 1-bromo-3,3,3-trifluoroacetoxime in dimethylformamide produced a major product. Recrystallization of the product from ethanol gave a single crystal suitable for the X-ray analysis. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Mo-K α which is radiated from a rotating anode

generator. Cell constants and an orientation matrix for data collections were determined from least-squares refinement of carefully centered 20 reflections of $22.0 < 2\theta < 24.9^\circ$. The reflection data were collected at a temperature of $23 \pm 1^\circ\text{C}$ using the $\omega - 2\theta$ scan technique to maximum 2θ value of 55° . Of the 4291 reflections measured, 4076 were unique ($R_{\text{int}} = 0.013$). During the data collection, the intensities of three representative reflections which were measured after every 150 reflections showed no significant variation demonstrating stability of the crystal and the molecule under X-ray irradiation. Correction for Lorentz and polarization factors were applied. The crystal data and experimental details are summarized in Table 1. Estimated standard deviations in the least significant figure are given in parentheses in the Tables.

3. Structure analysis

On the basis of 2114 observed reflections ($I > 3.00\sigma(I)$), the structure was solved by direct methods (Burla et al, 1989) and expanded using Fourier techniques (BEURSKENS et al, 1994), and then refined by full-matrix least-squares methods. The non-H atoms were refined with anisotropic thermal parameters, and the H atoms were refined with the isotropic ones. The H atoms were assigned based on the expected bonding geometry and included in the final cycles of the refinement. The maximum and minimum peaks in the final difference Fourier map were $+0.20\text{e}^- \text{\AA}^{-3}$ and $-0.23\text{e}^- \text{\AA}^{-3}$, respectively. All calculations were performed using the TEXAN crystallographic software package (MOLECULAR STRUCTURE CORPORATION, 1985 & 1992).

The final atomic parameters are given in Table 2; the bond lengths and angles are listed in Table 3. The ORTEP drawing and the atomic numbering system of the molecule are shown in Fig. 2.

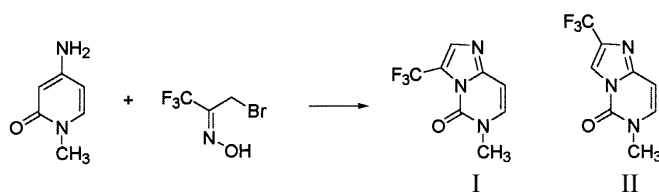


Fig. 1: Possible chemical structures of the product

4. Discussion

Single-crystal X-ray analysis confirms the structure of the product obtained from the reaction of 1-methylcytosine with 1-bromo-3,3,3-trifluoroacetoxime to be 6-methyl-2-(trifluoromethyl)-(6*H*)-imidazo[1,2-*c*]pyrimidin-5-one (II).

Although two crystallographically different kinds of molecules are found in the unit cell, we arbitrarily discuss the structure of one representative molecule, because the other one is essentially the same. Their corresponding bond lengths and angles fit within the standard deviations.

The 5-membered imidazole ring is quite planar with a mean deviation of 0.0004 \AA from the least-squares plane. The pyrimidinone ring is also planar with a deviation of 0.0029 \AA . The dihedral angle between the least-squares planes is 0.55° . The bicyclic ring system is totally planar with the following deviations from the least-squares plane: C1 $0.0023(37) \text{ \AA}$, N1 $0.0061(32) \text{ \AA}$, C2 $-0.0033(44) \text{ \AA}$, C3 $-0.0022(46) \text{ \AA}$, C4 $-0.0024(39) \text{ \AA}$, N3 $0.0036(34) \text{ \AA}$, C6 $0.0053(38) \text{ \AA}$, C5 $-0.0019(37) \text{ \AA}$ and N2 $-0.0076(30) \text{ \AA}$. The methyl and the trifluoromethyl carbon atoms, C7 and C8, deviate 0.022 \AA and 0.021 \AA from the least-

w	$1/\sigma^2(F_0)$
R_w	0.047
No. of reflections used	2114 ($I > 3.00\sigma(I)$)
No. of parameters	271
Measurement	Rigaku AFC5R
Program system	TEXSAN
Structure determination	direct method
Refinement	full matrix (F^2)

Table 1: Crystal and experimental data

atom	x	y	z	B_{eq}
F1	0.9095(3)	0.4325(3)	0.0593(4)	6.62(8)
F2	0.6927(3)	0.5603(2)	0.0235(4)	6.30(7)
F3	0.8276(3)	0.5254(3)	0.2673(4)	6.98(9)
F4	0.8848(3)	-0.2912(2)	0.5879(4)	5.86(7)
F5	0.6634(3)	-0.2280(3)	0.5343(4)	6.19(7)
F6	0.7832(3)	-0.2652(3)	0.7837(3)	6.44(8)
O1	0.9113(3)	-0.0565(3)	0.0809(4)	4.80(7)
O2	0.9112(3)	0.1801(3)	0.5527(4)	4.93(8)
N1	0.7186(3)	-0.0174(3)	0.1747(4)	3.79(8)
N2	0.7754(3)	0.1551(3)	0.1422(4)	3.16(7)
N3	0.6576(3)	0.3683(3)	0.1975(4)	4.00(8)
N4	0.7304(3)	0.3315(3)	0.6555(4)	4.11(8)
N5	0.7728(3)	0.1100(3)	0.6443(4)	3.10(7)
N6	0.6448(3)	0.0212(3)	0.7128(4)	3.88(8)
C1	0.8104(4)	0.0193(4)	0.1289(5)	3.46(9)
C2	0.6034(4)	0.0730(5)	0.2280(5)	4.5(1)
C3	0.5728(4)	0.2016(4)	0.2408(6)	4.6(1)
C4	0.6613(4)	0.2490(4)	0.1969(5)	3.62(9)
C5	0.8462(4)	0.2220(4)	0.1074(5)	3.34(8)
C6	0.7725(4)	0.3504(4)	0.1421(5)	3.51(9)
C7	0.7486(5)	-0.1587(4)	0.1662(6)	5.6(1)
C8	0.8012(5)	0.4656(4)	0.1242(6)	4.7(1)
C9	0.8131(4)	0.2064(4)	0.6128(5)	3.76(9)
C10	0.6149(4)	0.3583(4)	0.7176(5)	4.41(10)
C11	0.5773(4)	0.2648(4)	0.7427(5)	4.20(10)
C12	0.6577(3)	0.1317(4)	0.7045(5)	3.44(8)
C13	0.8336(4)	-0.0236(4)	0.6118(5)	3.41(8)
C14	0.7547(4)	-0.0747(4)	0.6550(5)	3.36(8)
C15	0.7650(5)	0.4399(4)	0.6259(6)	5.7(1)
C16	0.7720(4)	-0.2132(4)	0.6413(5)	4.2(1)

$$B_{ov} = 8/3 \cdot \pi^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos \gamma + 2U_{13}aa^*cc^* \cos \beta + 2U_{23}bb^*cc^* \cos \alpha)$$

Table 2: Final parameters of non-H atoms

Molecule A		Molecule B	
atom-atom	distance	atom-atom	distance
F1-C8	1.325(5)	F4-C16	1.331(4)
F2-C8	1.350(5)	F5-C16	1.346(5)
F3-C8	1.334(5)	F6-C16	1.333(4)
O1-C1	1.208(4)	O2-C9	1.212(4)
N1-C1	1.379(4)	N4-C9	1.372(4)
N1-C2	1.386(5)	N4-C10	1.393(5)
N1-C7	1.463(5)	N4-C15	1.469(5)
N2-C1	1.394(4)	N5-C9	1.393(5)
N2-C4	1.395(4)	N5-C12	1.392(4)
N2-C5	1.376(4)	N5-C13	1.379(4)
N3-C4	1.312(5)	N6-C12	1.308(5)
N3-C6	1.379(4)	N6-C14	1.387(4)
C2-C3	1.326(6)	C10-C11	1.324(6)
C3-C4	1.417(5)	C11-C12	1.419(5)
C5-C6	1.355(5)	C13-C14	1.349(5)
C6-C8	1.474(6)	C14-C16	1.468(5)

Table 3: Bond distances (Å)

Molecule A		Molecule B	
atom-atom-atom	angle	atom-atom-atom	angle
C1-N1-C2	122.7(3)	C9-N4-C10	122.7(3)
C1-N1-C7	116.8(3)	C9-N4-C15	116.9(3)
C2-N1-C7	120.5(3)	C10-N4-C15	120.4(3)
C1-N2-C4	125.8(3)	C9-N5-C12	126.3(3)
C1-N2-C5	127.3(3)	C9-N5-C13	126.5(3)
C4-N2-C5	106.9(3)	C12-N5-C13	107.1(3)
C4-N3-C6	104.4(3)	C12-N6-C14	104.5(3)
O1-C1-N1	124.6(4)	O2-C9-N4	124.6(4)
O1-C1-N2	122.2(3)	O2-C9-N5	122.3(3)
N1-C1-N2	113.2(3)	N4-C9-N5	113.1(3)
N1-C2-C3	122.9(4)	N4-C10-C11	122.8(3)
C2-C3-C4	118.6(3)	C10-C11-C12	118.7(3)
N2-C4-N3	111.3(3)	N5-C12-N6	111.3(3)
N2-C4-C3	116.7(3)	N5-C12-C11	116.4(3)
N3-C4-C3	131.9(3)	N6-C12-C11	132.3(3)
N2-C5-C6	104.7(3)	N5-C13-C14	104.8(3)
N3-C6-C5	112.6(3)	N6-C14-C13	112.3(3)
N3-C6-C8	119.8(3)	N6-C14-C16	120.3(3)
C5-C6-C8	127.6(3)	C13-C14-C16	127.3(3)
F1-C8-C6	112.0(3)	F4-C16-C14	111.8(3)
F2-C8-C6	112.3(4)	F5-C16-C14	112.6(3)
F3-C8-C6	113.2(4)	F6-C16-C14	113.5(3)

Table 4: Bond angles (°)

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