ELSEVIER

Journal of Fluorine Chemistry 86 (1997) 77–80

JOURNAL OF FLUORINE CHEMISTRY

Reaction between alkyl isocyanides and 1,1,1,5,5,5-hexafluoropentane-2,4-dione. Synthesis and structure of 1-alkyl-3,5-bis(trifluoromethyl)-5-hydroxy-1*H*-pyrrol-2(5*H*)-ones

Issa Yavari [a,*], Ahmad Shaabani [a], Sakineh Asghari [a], Marilyn M. Olmstead [b], Nasser Safari [c]

[a] *Department of Chemistry, University of Tarbiat Modarres, P.O. Box 14155-4838, Tehran, Iran*
[b] *Department of Chemistry, University of California, Davis, CA 95616, USA*
[c] *Department of Chemistry, University of Shahid Beheshti, Evin, Tehran, Iran*

Received 5 December 1995; accepted 24 June 1997

Abstract

Alkyl isocyanides undergo a complex reaction with 1,1,1,5,5,5-hexafluoropentane-2,4-dione to afford 1-alkyl-3,5-bis(trifluoromethyl)-5-hydroxy-1*H*-pyrrol-2(5*H*)-ones (**3**) in fairly high yields. The products were characterized by ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry and elemental analysis. The structure of compound **3b** (cyclohexyl) was confirmed by single-crystal X-ray analysis. © 1997 Elsevier Science S.A.

Keywords: 1-Cyclohexyl-3,5-bis(trifluoromethyl)-5-hydroxy-1*H*-pyrrol-2(5*H*)-one; Dihydropyrrole derivatives; Fluorinated lactams; Nuclear magnetic resonance spectroscopy

1. Introduction

Isocyanides, by virtue of their carbenic character, react readily with most common multiple bonds to give three-, four- and five-membered cycloadducts derived by formal 1:1, 1:2 and 2:1 substrate–isocyanide interactions [1–3]. Cycloaddition of this type is unique to isocyanides. The reaction of isocyanides with carbon-centred double bonds tends to occur in a stepwise manner and is initiated by a zwitterionic intermediate whose ultimate fate appears to be dictated by the nature of the original double-bonded substrate [4,5]. Isocyanides insert preferentially into the carbon–oxygen double bond of electron-deficient ketones, such as hexafluoroacetone, to afford imino-1,3-dioxolanes in high yield [6,7]. Activated α,β-unsaturated carbonyl compounds, which are capable of assuming a cisoid configuration, generally lead to five-membered 1:1 adducts [8,9]. 1,1,1,5,5,5-Hexafluoropentane-2,4-dione (**1**) is apparently completely enolized in the gas phase [10] and in the liquid phase [11], thus providing an electron-deficient hetero-1,3-diene. The work reported here was undertaken in order to study the possibility of reaction between **1** and alkyl isocyanides, such as tert-butyl isocyanide or cyclohexyl isocyanide.

2. Results and discussion

The two-component condensation reactions produce the hithero unknown fluorinated dihydropyrroles (**3**) in fairly high yields. The structures of compounds **3a** and **3b** were deduced from elemental analysis, ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectroscopy and IR spectroscopy. The nature of these compounds (1:1 adducts) was also apparent from the mass spectra which displayed molecular ion peaks at $m/z=291$ and $m/z=317$ for **3a** and **3b** respectively. Initial fragmentations involve loss from or of the side-chains and the RNCO moiety.

The structure of compound **3b** was determined by X-ray crystallography. The general view of the molecular structure is shown in Fig. 1. There are two nearly identical molecules in the asymmetric unit. The only significant difference between the two is in the torsion angles of the CF_3 groups, which differ by 11°. There is hydrogen bonding between the two molecules, as shown in Fig. 2. Final atomic coordinates are presented in Table 1, with derived bond lengths and angles in Table 2. Other bond distances and angles within the molecules are normal and agree well with representative molecules in the Cambridge Structural Database.

---

* Corresponding author. Fax: 0098-800-6544.

PII S0022-1139(97)00093-6

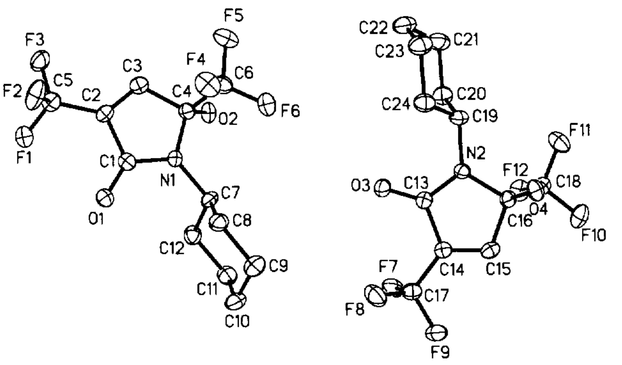
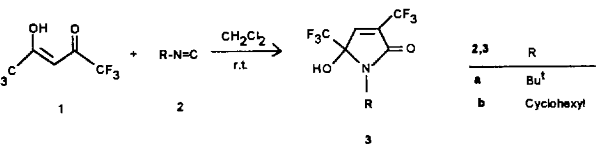
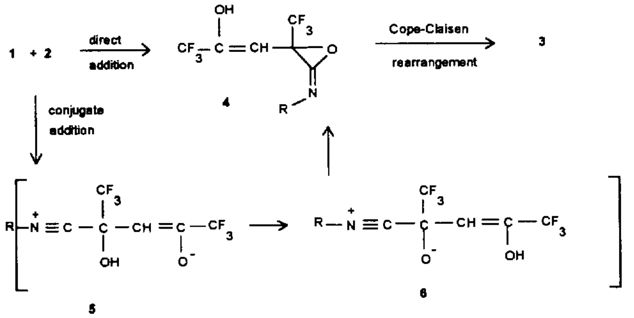


Fig. 1. General view and atom numbering scheme of two molecules of **3b** in the asymmetric unit (50% probability ellipsoids). Hydrogen atoms are omitted for clarity.



The dihydropyrrole (**3**) apparently results from initial conjugate (or direct) attack of alkyl isocyanide on the β-carbon (or carbonyl carbon) atom of **1** to give the imino-oxirane **4**, which undergoes a Cope–Claisen-type rearrangement [12] to form the corresponding fluorinated unsaturated lactam **3** as the final product.



The ^{1}H NMR spectrum of **3a** exhibits two single lines, readily recognizable as arising from tert-butyl ($\delta = 1.58$) and hydroxyl ($\delta = 4.12$) groups, together with a fairly broad quartet ($\delta = 7.21$) for the vinyl proton which shows $^4J_{FH} = 1.5$ Hz with the allylic trifluoromethyl group. The proton-decoupled ^{13}C NMR spectrum of **3a** displays three single lines, together with five quartets. The single lines are assigned to the tert-butyl group and the imine carbon atom. The multiplets are readily recognizable from their respective $^nJ_{FC}$ values (Section 3). The ^{19}F NMR spectrum of **3a** exhibits two resonances at $\delta = -71.4$ and $\delta = -66.4$ for the two different trifluoromethyl groups [13].

The ^{1}H and ^{13}C NMR spectra of **3b** are similar to those of **3a**, except for the cyclohexyl group. The cyclohexyl group in **3b** is attached to a ring system bearing an asymmetric carbon atom. Thus the proton-decoupled ^{13}C NMR spectrum of this compound shows six diastereotopic carbon atoms for the six-membered ring [14]. The methine group of the cyclohexyl moiety appears as a triple triplet ($^3J_{HH} = 11.2$ and 3.1 Hz) indicating the axial position of this hydrogen atom. The ^{19}F NMR spectrum of **3b** exhibits two signals ($\delta = -78.8$ and $\delta = -66.5$) for the CF_3 groups.

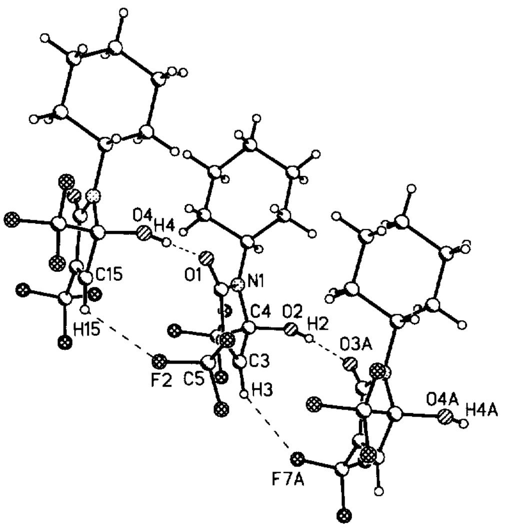


Fig. 2. View of a linear chain of **3b** molecules that associate by means of intermolecular contacts through hydrogen bonds (broken lines).

The structural assignments made on the basis of the NMR spectra of compounds **3a** and **3b** were supported by the measurement of the IR spectra. Of special interest is the hydroxyl absorption at 3338 and 3350 cm^{-1} for **3a** and **3b** respectively. The C–F stretching absorption appears at about 1145–1195 cm^{-1} [15].

In summary, the major synthetic advantages of these reactions are the mild reaction conditions, easy synthesis of isocyanides, excellent yields, experimental simplicity and commercial availability of 1,1,1,5,5,5-hexafluoropentane-2,4-dione.

3. Experimental details

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analysis was performed using a Heraeus CHN-O-Rapid Analyser. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a JEOL EX-90A spectrometer at 90 and 22.6 MHz respectively. ^{19}F NMR spectra were recorded at 376.6 MHz using a Varian Unity Plus NMR spectrometer.

3.1. Preparation of 1-tert-butyl-3,5-bis(trifluoromethyl)-5-hydroxy-1H-pyrrol-2(5H)-one (3a)

To a magnetically stirred solution of **1** (0.412 g, 1.98 mmol) in dichloromethane (5 ml) at −10 °C was added dropwise a mixture of tert-butyl isocyanide (0.162 g, 1.95 mmol) in dichloromethane (1 ml) over a period of 10 min.

Table 1
Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2×10^3) for compound **3b**

Atom	x	y	z	U(eq) [a]
F(1)	−82(2)	2183(2)	554(1)	40(1)
F(2)	748(2)	613(2)	912(1)	43(1)
F(3)	−1600(2)	371(2)	954(1)	36(1)
F(4)	1513(2)	1632(2)	3935(1)	38(1)
F(5)	−700(2)	1136(2)	4412(1)	39(1)
F(6)	1054(2)	3086(2)	5053(1)	36(1)
O(1)	2439(2)	4003(2)	1965(1)	28(1)
O(2)	−940(2)	3634(2)	4059(1)	26(1)
N(1)	1303(2)	3915(2)	3295(1)	23(1)
C(1)	1432(3)	3456(3)	2410(2)	22(1)
C(2)	83(3)	2150(2)	2074(2)	23(1)
C(3)	−745(3)	1858(3)	2744(2)	24(1)
C(4)	−16(3)	2952(2)	3601(2)	22(1)
C(5)	−216(3)	1339(3)	1124(2)	27(1)
C(6)	472(3)	2202(3)	4262(2)	28(1)
C(7)	2279(3)	5286(2)	3872(2)	23(1)
C(8)	3911(3)	5322(3)	3953(2)	28(1)
C(9)	4911(3)	6749(3)	4538(2)	36(1)
C(10)	4775(3)	8001(3)	4192(2)	36(1)
C(11)	3144(3)	7952(3)	4140(2)	33(1)
C(12)	2133(3)	6547(3)	3538(2)	29(1)
F(7)	4408(2)	9759(2)	7358(1)	35(1)
F(8)	5911(2)	8707(2)	6740(1)	41(1)
F(9)	6718(2)	10456(2)	7897(1)	36(1)
F(10)	5300(2)	8484(2)	10753(1)	36(1)
F(11)	3588(2)	6406(2)	10487(1)	37(1)
F(12)	3229(2)	8089(2)	9968(1)	33(1)
O(3)	3077(2)	6398(2)	7151(1)	28(1)
O(4)	5982(2)	6428(2)	9514(1)	25(1)
N(2)	3869(2)	6202(2)	8540(1)	22(1)
C(13)	3893(3)	6871(3)	7859(2)	22(1)
C(14)	5130(3)	8275(2)	8124(2)	21(1)
C(15)	5757(3)	8415(2)	8924(2)	23(1)
C(16)	5010(3)	7095(3)	9274(2)	22(1)
C(17)	5546(3)	9295(3)	7530(2)	26(1)
C(18)	4268(3)	7504(3)	10129(2)	26(1)
C(19)	2893(3)	4724(2)	8521(2)	24(1)
C(20)	1224(3)	4594(3)	8496(2)	29(1)
C(21)	232(3)	3061(3)	8463(2)	36(1)
C(22)	534(3)	2021(3)	7684(2)	36(1)
C(23)	2199(3)	2138(3)	7731(2)	34(1)
C(24)	3212(3)	3660(3)	7750(2)	28(1)

[a] U(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

Table 2
Selected bond lengths (Å) and angles (°) for compound **3b**

Bond lengths (Å)			
F(1)–C(5)	1.330(3)	F(2)–C(5)	1.345(3)
F(3)–C(5)	1.337(3)	F(4)–C(6)	1.340(3)
F(5)–C(6)	1.336(3)	F(6)–C(6)	1.332(3)
O(1)–C(1)	1.228(3)	O(2)–C(4)	1.386(3)
N(1)–C(1)	1.355(3)	N(1)–C(4)	1.464(3)
N(1)–C(7)	1.480(3)	C(1)–C(2)	1.497(3)
C(2)–C(3)	1.320(3)	C(2)–C(5)	1.484(3)
C(3)–C(4)	1.513(3)	C(4)–C(6)	1.537(3)
C(7)–C(12)	1.523(3)	C(7)–C(8)	1.527(3)
C(8)–C(9)	1.528(3)	C(9)–C(10)	1.520(4)
C(10)–C(11)	1.520(4)	C(11)–C(12)	1.527(3)
F(7)–C(17)	1.346(3)	F(8)–C(17)	1.329(3)
F(9)–C(17)	1.336(3)	F(10)–C(18)	1.339(3)
F(11)–C(18)	1.329(3)	F(12)–C(18)	1.342(3)
O(3)–C(13)	1.230(3)	O(4)–C(16)	1.389(3)
N(2)–C(13)	1.359(3)	N(2)–C(16)	1.465(3)
N(2)–C(19)	1.481(3)	C(13)–C(14)	1.491(3)
C(14)–C(15)	1.313(3)	C(14)–C(17)	1.486(3)
C(15)–C(16)	1.513(3)	C(16)–C(18)	1.532(3)
C(19)–C(24)	1.523(3)	C(19)–C(20)	1.532(4)
C(20)–C(21)	1.526(3)	C(21)–C(22)	1.515(4)
C(22)–C(23)	1.529(4)	C(23)–C(24)	1.527(3)
Bond angles (°)			
C(1)–N(1)–C(4)	111.7(2)	C(1)–N(1)–C(7)	124.8(2)
C(4)–N(1)–C(7)	123.3(2)	O(1)–C(1)–N(1)	127.3(2)
O(1)–C(1)–C(2)	126.5(2)	N(1)–C(1)–C(2)	106.2(2)
C(3)–C(2)–C(5)	127.1(2)	C(3)–C(2)–C(1)	109.8(2)
C(5)–C(2)–C(1)	123.1(2)	C(2)–C(3)–C(4)	109.5(2)
O(2)–C(4)–N(1)	113.9(2)	O(2)–C(4)–C(3)	115.3(2)
N(1)–C(4)–C(3)	102.7(2)	O(2)–C(4)–C(6)	105.4(2)
N(1)–C(4)–C(6)	110.6(2)	C(3)–C(4)–C(6)	109.0(2)
F(1)–C(5)–F(3)	107.3(2)	F(1)–C(5)–F(2)	107.2(2)
F(3)–C(5)–F(2)	106.3(2)	F(1)–C(5)–C(2)	112.4(2)
F(3)–C(5)–C(2)	112.0(2)	F(2)–C(5)–C(2)	111.3(2)
F(6)–C(6)–F(5)	107.6(2)	F(6)–C(6)–F(4)	107.4(2)
F(5)–C(6)–F(4)	107.1(2)	F(6)–C(6)–C(4)	112.5(2)
F(5)–C(6)–C(4)	110.7(2)	F(4)–C(6)–C(4)	111.3(2)
N(1)–C(7)–C(12)	111.0(2)	N(1)–C(7)–C(8)	110.9(2)
C(12)–C(7)–C(8)	112.3(2)	C(7)–C(8)–C(9)	110.5(2)
C(10)–C(9)–C(8)	111.5(2)	C(11)–C(10)–C(9)	110.5(2)
C(10)–C(11)–C(12)	111.0(2)	C(7)–C(12)–C(11)	110.4(2)
C(13)–N(2)–C(16)	111.2(2)	C(13)–N(2)–C(19)	124.6(2)
C(16)–N(2)–C(19)	124.0(2)	O(3)–C(13)–N(2)	126.7(2)
O(3)–C(13)–C(14)	126.6(2)	N(2)–C(13)–C(14)	106.7(2)
C(15)–C(14)–C(17)	127.8(2)	C(15)–C(14)–C(13)	109.6(2)
C(17)–C(14)–C(13)	122.6(2)	C(14)–C(15)–C(16)	110.1(2)
O(4)–C(16)–N(2)	113.8(2)	O(4)–C(16)–C(15)	115.0(2)
N(2)–C(16)–C(15)	102.5(2)	O(4)–C(16)–C(18)	105.5(2)
N(2)–C(16)–C(18)	110.8(2)	C(15)–C(16)–C(18)	109.4(2)
F(8)–C(17)–F(9)	107.5(2)	F(8)–C(17)–F(7)	106.7(2)
F(9)–C(17)–F(7)	106.5(2)	F(8)–C(17)–C(14)	111.9(2)
F(9)–C(17)–C(14)	111.9(2)	F(7)–C(17)–C(14)	112.1(2)
F(11)–C(18)–F(10)	107.7(2)	F(11)–C(18)–F(12)	107.2(2)
F(10)–C(18)–F(12)	106.9(2)	F(11)–C(18)–F(16)	113.5(2)
F(10)–C(18)–C(16)	110.2(2)	F(12)–C(18)–C(16)	111.1(2)
N(2)–C(19)–C(24)	111.0(2)	N(2)–C(19)–C(20)	111.3(2)
C(24)–C(19)–C(20)	112.3(2)	C(21)–C(20)–C(19)	110.7(2)
C(22)–C(21)–C(20)	111.7(2)	C(21)–C(22)–C(23)	110.8(2)
C(24)–C(23)–C(22)	111.2(2)	C(19)–C(24)–C(23)	110.8(2)

The reaction mixture was then allowed to warm to room temperature and stirred for 12 h. After 24 h in a refrigerator at 5 °C, white crystals (0.48 g, m.p. 120–122 °C, 85%) were collected by filtration. Recrystallization from dichloromethane yielded colourless crystals (0.42 g), m.p. 123–124 °C. IR (KBr) (cm^{-1}): 3338 (OH); 3105 (=CH); 1714 (C=N); 1670 (C=C); 1150–1190 (CF$_3$). ^{1}H NMR (CDCl$_3$, Me$_4$Si): δ 1.58 (9H, s, ^{t}Bu); 4.12 (s, 1H, OH); 7.21 (br q, $^4J_{FH}=1.5$ Hz, =CH). ^{13}C NMR (CDCl$_3$, Me$_4$Si): δ 29.32 (CH$_3$); 55.25 (CMe$_3$); 91.97 (q, $^2J_{FC}=33.52$ Hz, C–OH); 121.62 (q, $^1J_{FC}=266.50$ Hz, CF$_3$); 124.44 (q, $^1J_{FC}=284.62$ Hz, CF$_3$); 133.24 (q, $^2J_{FC}=34.44$ Hz, =C–CF$_3$); 146.94 (q, $^3J_{FC}=2.72$ Hz, CH); 165.37 (C=N). ^{19}F NMR (CDCl$_3$, CFCl$_3$): $\delta=-71.4$ and $\delta=-66.4$ (2CF$_3$). Mass (m/z, %): 291 (M$^+$, 22); 276 (M$^+$ −CH$_3$, 100); 236 (M$^+$ −C$_4$H$_7$, 95); 192 (M$^+$ −C$_4$H$_9$NCO, 50); 99 (C$_4$H$_7$NCO$^+$, 12); 57 (C$_4$H$_9^+$, 94); 42 (NCO$^+$, 94). Analysis: calculated for C$_{10}$H$_{11}$NO$_2$F$_6$ (291.2): C, 41.24%; H, 3.81%; N, 4.81%; found: C, 41.3%; H, 3.7%; N, 4.7%.

*3.2. Preparation of 1-cyclohexyl-3,5-bis(trifluoromethyl)-5-hydroxy-1H-pyrrol-2(5H)-one (**3b**)*

A similar reaction, but using cyclohexyl isocyanide, yielded a white powder (0.56 g, 80%), m.p. 147–150 °C. Recrystallization from dichloromethane yielded **3b** as colourless crystals (0.50 g), m.p. 150–152 °C. IR (KBr) (cm^{-1}): 3350 (OH); 3130 (=CH); 1716 (C=N); 1666 (C=C); 1147–1195 (CF_3). ^1H NMR ($CDCl_3$, Me_4Si): δ 1.2–2.2 (10H, m, $5CH_2$); 3.50 (1H, tt, $J = 11.2$ and 3.1 Hz, axial CH); 4.16 (1H, s, OH); 7.24 (1H, br q, $^4J_{FH} = 1.8$ Hz, =CH). ^{13}C NMR ($CDCl_3$, Me_4Si): δ 26.32, 27.25, 27.33, 30.91 and 31.16 ($5CH_2$); 54.57 (CH); 88.78 (q, $^2J_{FC} = 33.13$ Hz, C–OH); 121.39 (q, $^1J_{FC} = 266.52$ Hz, CF_3); 124.10 (q, $^1J_{FC} = 283.70$ Hz, CF_3); 134.28 (q, $^2J_{FC} = 35.35$ Hz, =C–CF_3); 145.15 (q, $^3J_{FC} = 4.6$ Hz, =CH); 163.86 (C=N). ^{19}F NMR ($CDCl_3$, $CFCl_3$): $\delta = -78.8$ and $\delta = -66.5$ ($2CF_3$). Mass (*m/z*, %): 317 (M^+, 5); 274 ($M^+ - HNCO$, 30); 236 ($M^+ - C_6H_9$, 100); 192 ($M^+ - C_6H_{11}NCO$, 8); 125 ($C_6H_{11}NCO^+$, 6); 83 ($C_6H_{11}^+$, 22); 82 ($C_6H_{10}^+$, 90). Analysis: calculated for $C_{12}H_{13}NO_2F_6$ (317.2): C, 45.43%; H, 4.13%; N, 4.42%; found: C, 45.1%; H, 4.2%; N, 4.5%.

*3.3. X-Ray structure determination of compound **3b***

3.3.1. Crystal data

$C_{12}H_{13}F_6NO_2$, $M = 317.23$, triclinic, space group $P\bar{1}$, $a = 9.4069(12)$ Å, $b = 10.167(2)$ Å, $c = 15.308(3)$ Å, $\alpha = 102.43(2)°$, $\beta = 90.617(11)°$, $\gamma = 108.836(13)°$, $V = 1348.0(4)$ Å^3, $Z = 4$, $D_x = 1.563$ mg m^{-3}, λ(CuKα) = 1.54178 Å, $\mu = 1.441$ mm^{-1}, $T = 130(2)$ K.

3.3.2. Data collection and reduction

A colourless needle (0.20 mm × 0.08 mm × 0.04 mm) was mounted in an inert oil. Data were collected to $2\theta_{max} = 56.5°$. The radiation employed was Ni-filtered CuKα from a Siemens P4 diffractometer equipped with a rotating anode source operating at 15 kW. A 3.4% decay in the intensities of two standard reflections was observed during the data collection. The data were scaled to adjust for this decay. An absorption correction based on XABS2 [16] gave a maximum and minimum transmission of 0.956 and 0.903. Of 7145 measured data, 3571 were unique ($R_{int} = 0.0476$).

3.3.3. Structure solution and refinement

The structure was solved by direct methods and refined anisotropically on F^2 (program SHELXTL 5.03, XL, G.E. Sheldrick, University of Göttingen, 1994). Hydrogen atoms were included using a riding model with isotropic U equal to 1.2 times that of the bonded carbon. Hydrogen atoms bonded to the two hydroxyl groups were located on a difference map and allowed to refine freely. Refinement was by full-matrix least-squares methods, based on F^2, using all data and with anisotropic thermal parameters for non-hydrogen atoms. The largest peaks in the final difference map were less than 0.20 e Å^{-3}.

Acknowledgements

We gratefully acknowledge financial support from the Research Council of the University of Tarbiat Modarres.

References

[1] I. Ugi, Angew. Chem. Int. Ed. Engl. 21 (1982) 810.
[2] H.M. Walborsky, M.P. Persiasamy, in: S. Patai, Z. Rappoport (Eds.), The Chemistry of Functional Groups, Supplement C, Wiley, New York, 1983, Chapter 20, pp. 835–887.
[3] S. Marcaccini, T. Torroba, Org. Prep. Proced. Int. 25 (1993) 141.
[4] Y. Ito, H. Kato, T. Saegusa, J. Org. Chem. 47 (1982) 741.
[5] N. Obata, T. Takizawa, Tetrahedron Lett. (1969) 3403.
[6] W.J. Middleton, D.C. England, C.G. Krespan, J. Org. Chem. 32 (1967) 948.
[7] B. Zeeh, Synthesis (1969) 65.
[8] G. Morel, E. Marchand, A. Foucaud, L. Toupet, J. Org. Chem. 55 (1990) 1721.
[9] D. Moderhack, Synthesis (1985) 1083.
[10] R.L. Lintvedt, H.F. Holtzclaw Jr., J. Am. Chem. Soc. 88 (1966) 2713.
[11] U. Kucklander, U. Herweg-Wahl, W. Massa, G. Baum, Chem. Ber. 120 (1987) 1791.
[12] J. March, Advanced Organic Chemistry, Reaction, Mechanisms and Structures, 4th ed., Wiley, New York, 1992, pp. 1130–1141.
[13] A.A. Kadyrov, I. Neda, T. Kaukorat, A. Fischer, P.G. Jones, R. Schmutzler, J. Fluor. Chem. 72 (1995) 29.
[14] E.E. Eliel, S.H. Wilen, Stereochemistry of Organic Compounds, Wiley, New York, 1994, Chapter 8, pp. 465–538.
[15] R.M. Silverstein, G.C. Bassler, T.C. Morril, Spectrometric Identification of Organic Compounds, 5th ed., Wiley, New York, 1991, p. 130.
[16] S. Parkin, B. Moezzi, H. Hope, XABS2: an empirical absorption correction program, J. Appl. Crystallogr. 28 (1995) 53.