SYNTHESIS, STEREOCHEMISTRY AND SYNTHETIC POTENTIAL OF 6-(BENZOTRIAZOL-1-YL)-6-(MORPHOLIN-4-YL)BICYCLO[3.1.0]HEXANE

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Abstract - Reaction of 4-(cyclohexen-1-yl)morpholine with 1-chlorobenzotriazole in the presence of triethylamine gave 6-(benzotriazol-1-yl)-6-(morpholin-4-yl)-bicyclo[3.1.0]hexane (**1e**) (70%) as confirmed by X-ray crystallography. Treatment of **1e** with Grignard reagents substituted the benzotriazolyl moiety with a phenyl (**7a**, 91%) or a benzyl (**7b**, 98%) group.

Introduction

Three general methods are known for the preparation of carbonyl derivatives of bicyclo[3.1.0]hexan-6-one (**1a**). The first involves cyclocondensation of derivatives of adipic aldehyde; thus, treatment of 1,1,6,6-tetrakis(phenylthio)hexane with methyllithium in THF in the presence of TMEDA gave thioketal (**1b**) in 40% yield.[1] The second method is the ring closure of enamines derived from 2-bromocyclohexanone; thus, reaction of 3-bromo-2-dimethylaminocyclohexene with dimethylamine in the presence of silver tetrafluoroborate gave aminal (**1c**) in 95 % yield.[2] According to the third method, succinimido derivative (**1d**) was obtained in 60% yield by the reaction of (morpholin-4-yl)cyclohexene with *S,S*-dimethyl-succinimidosulfonium fluorosulfonate.[3] We now report a simple preparative method for a derivative of benzotriazole (**1e**) structurally similar to compound (**1d**) but with considerable synthetic potential brought by the benzotriazolyl substituent.[4]

1a, XY = O

1b, X = Y = SPh

1c, X = Y = $N(CH_3)_2$

1d, X = $N(CH_2CH_2)_2O$, Y = $N(COCH_2)_2$

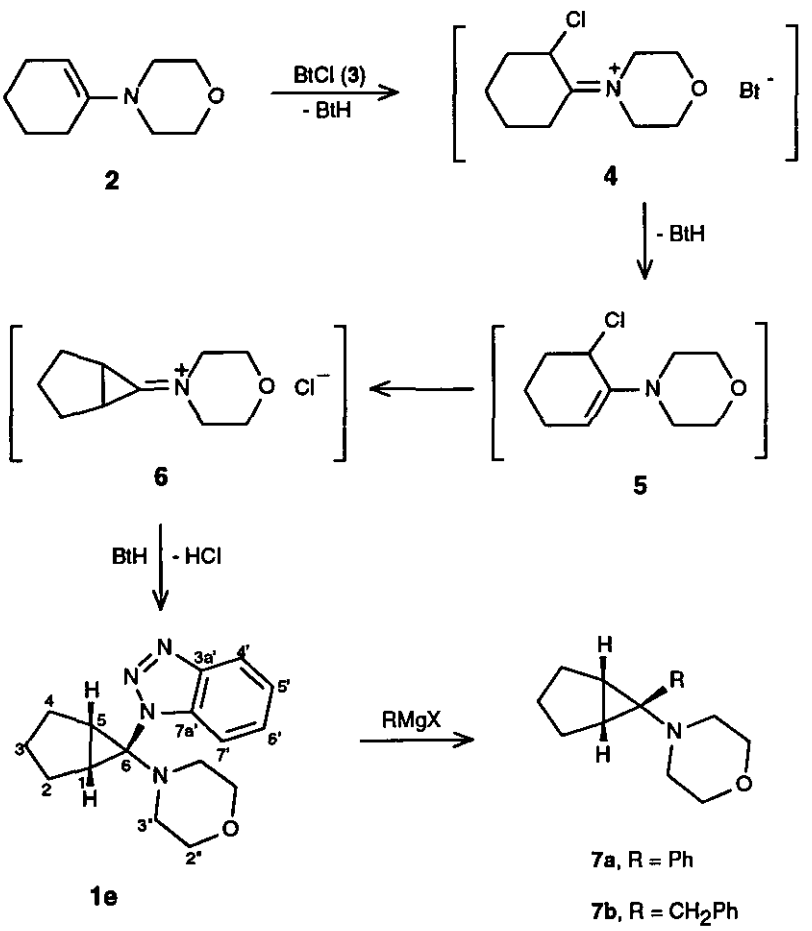
1e, X = $N(CH_2CH_2)_2O$, Y = benzotriazol-1-yl

Results and Discussion

Treatment of 1-(morpholin-4-yl)cyclohexene (**2**) with 1-chlorobenzotriazole (**3**) in the presence of triethylamine gave 6-(benzotriazol-1-yl)-6-(morpholin-4-yl)bicyclo[3.1.0]hexane (**1e**) in 70% yield. A reasonable reaction sequence starts with electrophilic attack of **3** on the enamine C-2 atom giving chloroiminium salt (**4**). The Cl-N bond of chlorobenzotriazole is polarized to give the chlorine atom a positive charge;[5] thus, electrophilic attack of **3** on 9-ethylcarbazole results in the formation of 3-chloro-9-ethylcarbazole (94%).[6] Elimination of the H-6 proton from cation (**4**) then gives chloroenamine (**5**) and benzotriazole. In a similar manner, 3-chloro-[3*H*]-indole systems and benzotriazole were obtained from reactions of indole alkaloids with **3**;[7] and chloroenamines of type (**5**) were isolated intermediates in the synthesis of 6,6-bis(dialkylamino)bicyclo[3.1.0]hexanes (**1c**).[2] Interaction of the electron pair on C-6 with the chlorine bearing atom (C-2) in **5** eliminates chloride and gives iminium cation (**6**). Addition of benzotriazole to the C=N bond of **6** then produces the final product (**1e**). A route similar to this was proposed before for a reaction of 1-(morpholin-4-yl)cyclohexene with *S,S*-dimethylsuccinimidosulfonium fluorosulfonate proceeding in the presence of tertiary amines.[3] In our case, triethylamine (or excess of enamine (**2**)) played the role of a base accepting the hydrogen chloride eliminated during the reaction.

High resolution nmr spectra and 2D proton-carbon correlations [HETCOR] allowed assignment of all the proton and carbon resonances. Irradiation of the H-1 and H-5 multiplets in the Nuclear Overhauser Experiment gave 6% enhancement of the benzotriazole H-7' resonance and proved the configuration of the benzotriazolyl substituent to be *exo*. Such a stereochemistry is rationalized in terms of the attack of benzotriazole on the iminium cation from the less hindered side.

The morpholine proton resonances of **1e** exhibited an ABXY pattern in accordance with the previous data for similar compounds,[3,8] although the four proton resonances of the H-2 and H-4 atoms formed a slightly broadened singlet.



Any doubts about the molecular structure were resolved by the X-ray crystallographic data. Figure 1 shows a perspective view and atom labelling of the crystal structure, confirming the presence of the bicyclo[3.1.0]hexane skeleton and the 6-*exo*-(1-benzotriazolyl) and 6-*endo*-(N-morpholinyl) substituent stereochemistry. Atom coordinates, bond lengths and bond angles are given in Tables 1 and 2. The cyclopentane ring exists in an envelope conformation with C-3 displaced 0.339(2) Å in the *endo* direction out of the plane described by C-1, C-2, C-4 and C-5. The benzotriazole ring is planar to within 0.004 Å and is oriented so as to minimize interactions with the other substituents. The morpholine ring exists in that chair conformation which minimizes steric interactions with the methylene groups of the bicyclo[3.1.0]hexane skeleton. There are no unusually short (<3.3 Å) intermolecular contacts between non-hydrogen atoms.

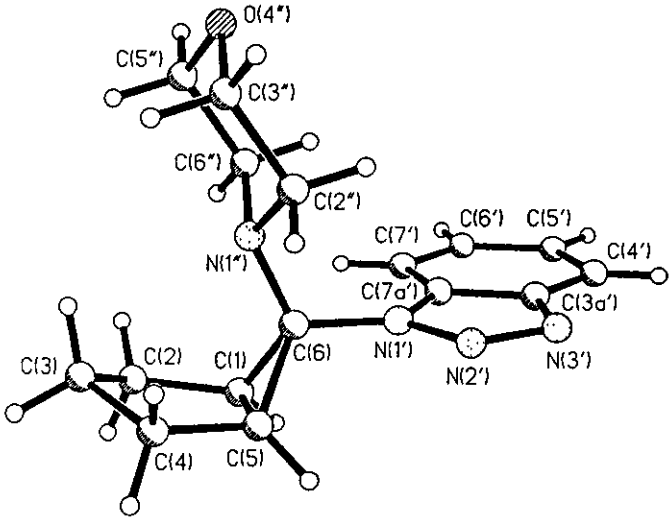


Figure 1. Perspective view and atom labelling of X-ray structure.

The unusually high stability of compound (**1e**) in comparison with other geminal benzotriazol-1-yl, morpholin-4-yl derivatives deserves comment. Thus, compound (**1e**) was purified by column chromatography and was inert to atmospheric moisture over several months, whereas, e.g., 1-(benzotriazol-1-yl)-1-(morpholino-4-yl)cyclopentane is very sensitive to water.[9] The hydrolysis of compounds of this type starts by ionization into the iminium cation and benzotriazolide anion, and is followed by an attack of water on the iminium carbon atom. Such ionic dissociation of **1e** is energetically disfavored due to the additional strain imposed on the cyclopropane system by the sp^2 carbon atom formed. However, the benzotriazolyl moiety in **1e** is mobile enough to allow its substitution by nucleophiles. Grignard reagents are frequently used for such substitution of the benzotriazolyl group:[4] reaction of **1e** with phenylmagnesium bromide proceeded smoothly at room temperature in THF giving compound (**7a**) in 91% yield. A compound similar to **7a**, having pyrrolidinyl instead of the morpholinyl group, was previously obtained in 49% yield from a reaction of 3-chloro-2-(pyrrolidin-1-yl)cyclohexene with phenylmagnesium bromide.[10] Reaction of **1e** with benzylmagnesium chloride gave compound (**7b**) in 98% yield.

The ^1H and ^{13}C nmr patterns of the bicyclo[3.1.0]hexane system of compounds (**7**) differed remarkably from

those of compound (**1e**). Application of the proton-proton selective decoupling and 2D proton-carbon correlation (HETCOR) techniques allowed complete assignment of the ^{1}H and ^{13}C nmr spectra of compounds (**7**). A NOE experiment carried out on compound (**7a**) proved the *exo* location of the phenyl group; thus, irradiation of the H-1 and H-5 doublet at δ 1.71 caused a 9% enhancement of the phenyl *ortho* proton multiplet at δ 7.20. This indicates that the difference in the nmr patterns of compounds (**1e**) (four protons singlet from H-2 and H-4) and (**7**) (wide range multiplet from the same protons) was caused simply by differences in diamagnetic anisotrophy of the benzotriazol-1-yl (**1e**) and phenyl (**7a**) or benzyl (**7b**) groups.

In conclusion, the above experiments demonstrate a versatile and regioselective method for preparation of 6-aminobicyclo[3.1.0]hexanes.

EXPERIMENTAL

Melting points (°C) were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded on a Varian VXR 300 spectrometer using $CDCl_3$ as the solvent and TMS as the reference. 1-(Morpholin-4-yl)-1-cyclohexene was prepared according to the literature method.[11]

6-(Benzotriazol-1-yl)-6-(morpholin-4-yl)bicyclo[3.1.0]hexane (1e).

a) 1-(Morpholin-4-yl)-1-cyclohexene (3.34 g, 0.02 mol) was added dropwise to a stirred solution of 1-chlorobenzotriazole (1.53 g, 0.01 mol) in methylene chloride (20 ml) under nitrogen at -40 °C. The obtained yellow solution was warmed up to ambient temperature over 1 h and stirred for an additional 7 h. The solvent was evaporated *in vacuo* and the resulting brown oil was subjected to column chromatography (silica gel/$CHCl_3$) to give **1e** as colorless prisms (1.28 g, 45%), mp 160 - 161 °C. Purification by recrystallization from benzene gave an analytical sample. ^{1}H Nmr δ 1.87 (m, 1 H, H-3), 2.11 (m, 5 H, H-2 (2 H) + H-3 (1 H) + H-4 (2 H)), 2.28 (m, 2 H, H-1 + H-5), 2.38 (td, J = 11.5 and 3.2 Hz, 2 H, Ha-3" + Ha-5"), 2.98 (d, J = 11.9 Hz, 2 H, He-3" + He-5"), 3.56 (td, J = 11.5 and 2.4 Hz, 2 H, Ha-2" + Ha-6"), 3.71-3.76 (m, 2 H, He-2" + He-6"), 7.35 (ddd, J = 8.3, 7.0 and 1.0 Hz, 1 H, H-5′), 7.47 (ddd, J = 8.3, 7.0 and 1.0 Hz, 1 H, H-6′), 7.64 (dt, J = 8.3 and 1.0 Hz, 1 H, H-7′), 8.05 (dt, J = 8.3 and 1.0 Hz, 1 H, H-4′). ^{13}C Nmr δ 26.3 (2 C, C-2 + C-4), 26.4 (C-3), 33.3 (2 C, C-1 + C-5), 50.2 (2 C, C-3" + C-5"), 64.3 (C-6), 67.0 (2 , C-2" + C-6"), 110.7 (C-7′), 120.1 (C-4′), 123.7 (C-5′), 127.4 (C-6′), 133.8 (C-7a′), 145.4 (C-3a′). *Anal.* Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.58; H, 7.12; N, 19.90.

b) To a stirred solution of 1-chlorobenzotriazole (1.53g, 0.01 mol) in methylene chloride (20 ml) was added

dropwise 1-(morpholin-4-yl)-1-cyclohexene (1.67 g, 0.01 mol) and then triethylamine (1.01 g, 0.01 mol) under nitrogen at -5 °C. After the addition, the mixture was warmed up to ambient temperature and stirred for 24 h. The solvent was evaporated *in vacuo* and the residue was dissolved in chloroform. The chloroform solution was washed with 5 % $NaHCO_3$ solution, water and dried ($MgSO_4$). The solvent was evaporated to give 2.0 g (70%) of pure **1e**.

6-(Morpholin-4-yl)-6-phenylbicyclo[3.1.0]hexane (7a)

Phenylmagnesium bromide (5.25 ml, 2.0 M in ether, 0.015 mol) was added dropwise to a stirred solution of **1e** (1.0 g, 0.0035 mol) in THF (20 ml) under nitrogen at room temperature. The reaction mixture was stirred for 6 h, then poured into water and extracted with ether (4 x 20 ml). The combined organic layers were washed with water (3 x 20 ml), dried ($MgSO_4$), evaporated *in vacuo* and the resulting yellow oil was subjected to column chromatography (silica gel/toluene) to give **7a** as colorless prisms (0.77 g, 91%) mp 70 °C. Analytical sample was recrystallized from hexane. ^{1}H Nmr: δ 1.71 (d, J = 4.7 Hz, 2 H, H-1 + H-5), 1.79-2.10 (m, 6 H, H-2 + H-3 + H-4), 2.27 (dt, J = 11.5 and 2.5 Hz, 2 H, Ha-3′ + Ha-5′), 2.59 (d, J = 11.3 Hz, 2 H, He-3′ + He-5′), 3.54 (t, J = 11.9 Hz, 2 H, Ha-2′ + Ha-6′), 3.70 (d, J = 9.6 Hz, 2 H, He-2′ + He-6′), 7.17-7.31 (m, 5 H). ^{13}C Nmr: δ 26.4 (2 C), 28.6, 32.7 (2 C), 50.6 (2 C), 56.3, 67.5 (2), 126.8, 127.6 (2 C), 130.7 (2 C), 138.4. *Anal.* Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.01; H, 8.80; N, 5.72.

6-(Benzyl)-6-(morpholin-4-yl)bicyclo[3.1.0]hexane (7b)

Similarly to **7a**, this compound was obtained from **1e** (0.75 g, 0.0026 mol) and benzylmagnesium chloride (6.5 ml, 1.2 M in ether, 0.0078 mol) in THF (20 ml). The reaction mixture was stirred for 12 h to give **7b** as colorless prisms (0.66 g, 98%), mp 66 - 67 °C. ^{1}H Nmr: δ 1.27 (m, 2 H, H-1 + H-5), 1.61-1.97 (m, 6 H, H-2 + H-3 + H-4), 2.51 (d, J = 11.5 Hz, 2 H, He-3′ + He-5′), 2.79 (dt, J = 11.4 and 2.1 Hz, 2 H, Ha-3′ + Ha-5′), 2.85 (s, 2 H), 3.49 (t, J = 10.8 Hz, 2 H, Ha-2′ + Ha-6′), 3.73 (d, J = 9.6 Hz, 2 H, He-2′ + He-6′), 7.14-7.27 (m, 5 H). ^{13}C Nmr: δ 26.1(2 C), 28.5, 31.4(2 C), 35.9, 50.0(2 C), 50.7, 67.7 (2 C), 125.8, 127.9 (2 C), 130.1 (2 C), 139.8. *Anal.* Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44; Found: C, 79.18; H, 9.03; N, 5.34.

Crystallography

Crystal data at -150 °C: $C_{16}H_{20}N_4O$), Mr = 284.36, orthorombic, space group Pbcn, a = 22.753(7), b = 7.673(3), c = 16.718(9) Å, U = 2919(2) Å^3, F(000) = 1216, Z = 8, D_c = 1.29 g cm^{-3}, μ(Mo-Kα) = 0.84 cm^{-1}, ω scans, $2\theta_{max}$ = 52 °C, N = 2870, 191 parameters, S = 0.96, wR(F^2) = 0.117 for all data, R = 0.044 for 2233 reflections with $1 > 2\sigma(1)$.

Intensity data were collected at -150 °C with a Nicolet R3m four-circle diffractometer by using monochromatized Mo Kα (λ = 0.7107 Å) radiation. Cell parameters were determined by least squares refinement, the setting angles of 24 accurately centered reflections (2θ > 20°) being used. Throughout data collection the intensities of three standard reflections (800, 220, 004) were monitored at regular intervals and this indicated no significant crystal decomposition. The space group followed from systematic absences. The intensities were corrected for Lorentz and polarization effects but not for absorption.

The structure was solved by direct methods using SHELXTL PC,[12] and refined on F^2 using SHELXL92.[13] All non-hydrogen atoms were refined with anisotopic thermal parameters. Hydrogen atoms were included in calculated positions with isotropic thermal parameters 1.3 times the isotropic equivalent of their carrier carbons. The function minimized was $\Sigma w (F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + 0.0851P^2]^{-1}$ where $P = [\max(F_o^2) + 2F_c^2]/3$. Final atom coordinates and bonding geometries are listed in Tables 1 and 2, respectively. Tabulations of hydrogen atom coordinates, anisotropic thermal parameters, structure factors and equations of meanplanes are available from one of the authors (*P. J. S.*).

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic thermal parameters ($Å^2x10^3$).

	x	y	z	U_{eq} [a]
C(1)	3690(1)	-2318(2)	978(1)	25(1)
C(2)	3291(1)	-3621(2)	1399(1)	28(1)
C(3)	3622(1)	-4207(2)	2164(1)	31(1)
C(4)	4281(1)	-3824(2)	2011(1)	32(1)
C(5)	4305(1)	-2459(2)	1344(1)	26(1)
C(6)	3947(1)	-818(2)	1455(1)	22(1)
N(1')	4136(1)	643(2)	951(1)	23(1)
N(2')	4708(1)	1216(2)	973(1)	28(1)
N(3')	4761(1)	2587(2)	510(1)	30(1)
C(3A')	4213(1)	2942(2)	175(1)	25(1)
C(4')	4037(1)	4271(2)	-358(1)	30(1)
C(5')	3451(1)	4291(2)	-587(1)	30(1)
C(6')	3046(1)	3032(2)	-300(1)	28(1)
C(7')	3213(1)	1714(2)	223(1)	25(1)
C(7A')	3807(1)	1703(2)	459(1)	23(1)
N(1")	3720(1)	-365(2)	2229(1)	21(1)
C(2")	4138(1)	578(2)	2749(1)	25(1)
C(3")	3877(1)	736(2)	3584(1)	29(1)
O(4")	3314(1)	1602(1)	3572(1)	30(1)
C(5")	2915(1)	660(2)	3070(1)	27(1)
C(6")	3146(1)	522(2)	2216(1)	23(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

Table 2. Bond lengths (Å) and angles (°).

C(1)-C(6)	1.517(2)	C(1)-C(2)	1.523(2)	C(1)-C(5)	1.530(2)
C(2)-C(3)	1.549(2)	C(3)-C(4)	1.550(2)	C(4)-C(5)	1.531(2)
C(5)-C(6)	1.512(2)	C(6)-N(1')	1.436(2)	C(6)-N(1')	1.466(2)
N(1')-N(2')	1.376(2)	N(1')-C(7A')	1.378(2)	N(2')-N(3')	1.311(2)
N(3')-C(3A')	1.395(2)	C(3A')-C(7A')	1.408(2)	C(3A')-C(4')	1.411(2)
C(4')-C(5')	1.388(2)	C(5')-C(6')	1.419(2)	C(6')-C(7')	1.389(2)
C(7')-C(7A')	1.408(2)	N(1")-C(6")	1.472(2)	N(1")-C(2")	1.478(2)
C(2")-C(3")	1.522(2)	C(3")-O(4")	1.443(2)	O(4")-C(5")	1.433(2)
C(5")-C(6")	1.525(2)				

C(6)-C(1)-C(2)	119.0(1)	C(6)-C(1)-C(5)	59.5(1)
C(2)-C(1)-C(5)	108.3(1)	C(1)-C(2)-C(3)	106.4(1)
C(2)-C(3)-C(4)	106.2(1)	C(5)-C(4)-C(3)	106.5(1)
C(6)-C(5)-C(1)	59.8(1)	C(6)-C(5)-C(4)	117.5(1)
C(1)-C(5)-C(4)	107.9(1)	N(1")-C(6)-N(1')	116.0(1)
N(1")-C(6)-C(5)	120.4(1)	N(1')-C(6)-C(5)	114.1(1)
N(1")-C(6)-C(1)	121.3(1)	N(1')-C(6)-C(1)	113.1(1)
C(5)-C(6)-C(1)	60.7(1)	N(2')-N(1')-C(7A')	110.0(1)
N(2')-N(1')-C(6)	120.5(1)	C(7A')-N(1')-C(6)	129.4(1)
N(3')-N(2')-N(1')	109.1(1)	N(2')-N(3')-C(3A')	108.2(1)
N(3')-C(3A')-C(7A')	108.7(1)	N(3')-C(3A')-C(4')	130.4(1)
C(7A')-C(3A')-C(4')	121.0(1)	C(5')-C(4')-C(3A')	117.1(1)
C(4')-C(5')-C(6')	121.5(1)	C(7')-C(6')-C(5')	122.1(1)
C(6')-C(7')-C(7A')	116.3(1)	N(1')-C(7A')-C(7')	133.8(1)
N(1')-C(7A')-C(3A')	104.1(1)	C(7')-C(7A')-C(3A')	122.1(1)
C(6)-N(1")-C(6")	114.6(1)	C(6)-N(1")-C(2")	114.7(1)
C(6")-N(1")-C(2")	110.7(1)	N(1")-C(2")-C(3")	109.1(1)
O(4")-C(3")-C(2")	111.7(1)	C(5")-O(4")-C(3")	109.8(1)
O(4")-C(5")-C(6")	111.3(1)	N(1")-C(6")-C(5")	109.0(1)

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