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REGIOSPECIFIC ADDITIONS OF HYDRAZOIC ACID AND BENZYLAMINE TO 1-(ARYLSULFONYL)BICYCLO[1.1.0]BUTANES. APPLICATION TO THE SYNTHESIS OF CIS AND TRANS 2,7-METHANOGLUTAMIC ACIDS

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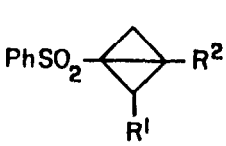
Addition of hydrazoic acid or benzylamine to 1-(arylsulfonyl) bicyclobutanes introduces the nitrogen nucleophile at position 3 of the derived cyclobutane, even when a carboxyl derivative is present at this position as a second activating group. Precursors of α-amino cyclobutane carboxylic acids may thus be obtained and these can be further transformed to the title diacids via carbonylation α to the sulfone and reduction.

The addition of nucleophiles across the central bond of bridgehead-activated bicyclo[1.1.0]butanes is a well documented reaction[1]. Addition of nitrogen nucleophiles to this system has, however, been limited until now to the addition of amines to 1-cyano bicyclobutanes, yielding stereospecifically[2], or stereoselectively[3], 1-amino-3-cyanocyclobutane derivatives.

It has now been found that by the use of N,N,N',N'-tetramethylguanidinium azide (TMGA) or of trimethylsilylazide (TMSA), 1-(arylsulfonyl)bicyclo[1.1.0]butanes of various substitution patterns (1, R^1 = H or *exo*-Me; R^2 = H, alkyl, hydroxyalkyl, carboxylic acid derivatives)[4] added the elements of hydrazoic acid to produce regiospecifically the addition products **2** in high yields. Azides **2** are useful precursors of cyclobutylamines of types **3** or **4**, obtainable from **2** by catalytic hydrogenation or by substitution α to the sulfone followed by reduction, including reductive elimination of the arylsulfonyl group.



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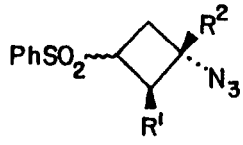

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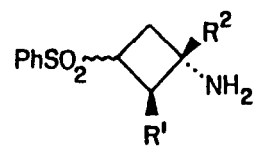

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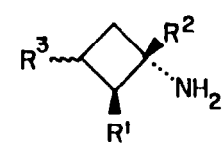

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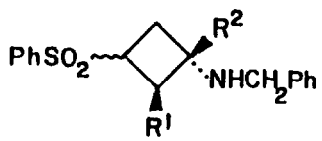
The reactions of **1** with TMGA or TMSA are carried out in N-methyl-2-pyrrolidone (NMP) or DMF at 80-90°C, producing **2** as a separable mixture of cis and trans isomers. The reactions with TMGA are relatively fast and provide **2** cleanly and readily from doubly activated **1** derivatives (R^2 = COOR, CONHR, $CONR_2$) as well as from 3-alkyl or 3-hydroxyalkyl derivatives (see Table 1).

Though reactions of **1** with TMSA are at least ten times slower, methoxycarbonyl groups are not solvolyzed (entries 4,5, Table 1) and ester products are obtained after 20 h, ratio 1.5, yield 92%.

A complementary approach to cyclobutylamine derivatives was based on the addition of benzylamine to **1**. Adducts **5** were again regiospecifically formed in good to high yields from singly or doubly activated **1** derivatives (Table 2). The reactions were carried out by warming **1** in excess benzylamine at 140°C under inert atmosphere until completion (2-4 h when R^1 = H, ca. 20 h when R^1 = Me; TLC monitoring).



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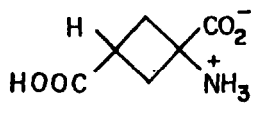
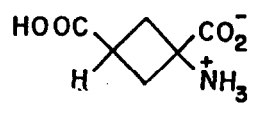
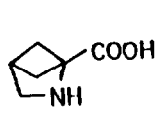


trans - **6**



cis- **6**



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The geometry of addition of the azide and amine was specific relative to a 2-methyl group[5], but only moderatly selective relative to the sulfone group. Stereoselectivity was, however, much higher in the case of benzylamine

Table 1. Reaction conditions, ratio of isomers and yields for 1 + TMGA → 2.[a,b]

Entry	Substituents (1,2)	Solvent	Reaction time (h)	Product ratio trans-S,N/cis-S,N	Yield (%)
1.	$R^1=H, R^2=H$	NMP	1	1.1	96
2.	$R^1=H, R^2=CH_3$	NMP	2	0.32	89
3.	$R^1=H, R^2=CH_2OTHP$[c]	NMP	4	0.25	85
4.	$R^1=H, R^2=CO_2CH_3$	$CHCl_3$-NMP 7:1[d]	20	1.6	85
5.	$R^1=H, R^2=CO_2CH_3$	DMF[d]	2	1.5	86
6.	$R^1=H, R^2=CONH_2Ph$	NMP	2	4.7	93
7.	$R^1=H, R^2=CON$⟨⟩	NMP	3	5.6	95
8.	$R^1=CH_3, R^2=H$	NMP	2	1.6	96
9.	$R^1=CH_3, R^2=CON$⟨⟩	NMP	20	2.0	93

a. A molar ratio of 1.2 of TMGA to 1 was used. b. Correct analytical and spectral data were obtained for all new compounds. c. Tetrahydropyranyl ether. d. Partial solvolysis to the acids occurred in $CHCl_3$-NMP and total solvolysis in DMF.

Table 2. Reaction conditions, ratio of isomers and yields for 1 + $PhCH_2NH_2$ → 5.[a]

Substituents 1	5	Reaction time (h)	Product ratio trans-S,N/cis-S,N	Yield (%)
$R^1=H, R^2=CH_3$	$R^1=H, R^2=CH_3$	4	b	79
$R^1=H, R^2=CH_2OH$	$R^1=H, R^2=CH_2OH$	2	b,c	77
$R^1=H, R^2=CH_2OTHP$[d]	$R^1=H, R^2=CH_2OTHP$[d]	3	b	83
$R^1=CH_3, R^2=CH_3$	$R^1=CH_3, R^2=CH_3$	20	b	68
$R^1=CH_3, R^2=CH_2OTHP$[d]	$R^1=CH_3, R^2=CH_2OTHP$[d]	20	b	93
$R^1=H, R^2=CONHCH_2Ph$	$R^1=H, R^2=CONHCH_2Ph$	3	0.61	90
$R^1=H, R^2=CO_2CH_3$	$R^1=H, R^2=CONHCH_2Ph$[e]	4	0.57	90
$R^1=H, R^2=CO_2C_2H_5$	$R^1=H, R^2=CO_2C_2H_5$	4	5.0	83
$R^1=H, R^2=CON$⟨⟩	$R^1=H, R^2=CON$⟨⟩	20	b	56
$R^1=CH_3, R^2=CO_2CH_3$	$R^1=CH_3, R^2=CONHCH_2Ph$	20	f	50
$R^1=CH_3, R^2=CO_2C_2H_5$	$R^1=CH_3, R^2=CO_2C_2H_5$	20	g	49
	$R^1=CH_3, R^2=CONHCH_2Ph$			11

a. After completion of the reaction, excess benzylamine was evaporated and products were isolated by chromatography on silica gel. b. Only the trans-S,N product was isolated but the presence of some cis-S,N product was detected by NMR in late chromatography fractions. c. The same trans-S,N product was obtained by lithium aluminium hydride reduction of the corresponding ethyl ester product. d. Tetrahydropyranyl ether (a diastereomeric mixture in the case of $R^2=CH_3$). e. The products were obtained as the benzylamides. f. The cis-S,N benzylamide isomer was the only isolated product. g. A mixture of the trans-S,N ester and the cis-S,N benzylamide was obtained.

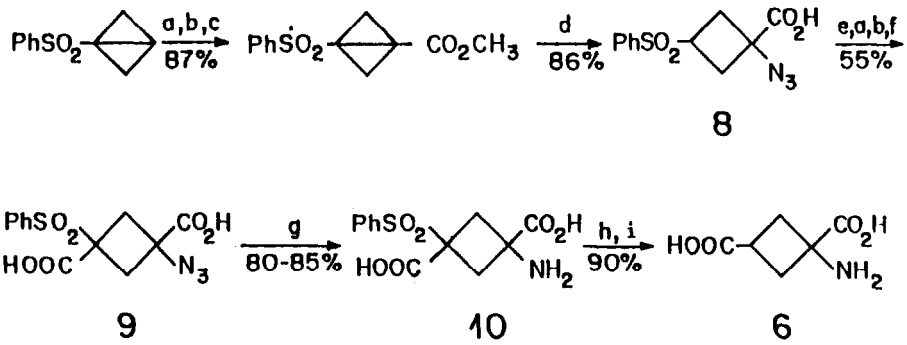
which produced preponderantly the trans-S,N isomers. When a secondary process occurred, such as attack of an ester group by the amine to form an amide, or when the starting material was a secondary amide, a reversal of selectivity was observed.

The trans-S,N 5 isomers were also preponderantly formed when a 2-exo-methyl was present in 1, the sulfone group being thus placed cis to this methyl in 2. An indication as to the sulfone-methyl relationship is given by the chemical shift of the 2-methyl protons, the doublet being shifted upfield by ca. 0.5 ppm in the case of the trans-1,2 isomer (cis-S,N).

The sequence of reactions which leads from 1 to 3, 5 and 4 may provide a facile access to α-amino cyclobutane mono and dicarboxylic acids and their derivatives. These compounds belong to a group of alicyclic, or α-substituted, non-natural amino acids of which numerous examples have been recently synthesized and tested for potential biological activities.[6] Two natural cyclobutane amino acids, namely trans-2,4-methanoglutamic acid (trans-6) and 2,4-methanoproline (7), isolated from the seeds of *Ateleia herbert smithii* have also been described recently.[7] Interest in the possible role of these acids in protecting the seeds from insect predation has led to the synthesis of methanoproline,[8,9] but no synthesis of methanoglutamic acid has as yet been published.

The present synthesis of 6 is based on the carboxylation of 8 (entry 5, Table 1), followed by reduction of the azide and reductive elimination of the sulfone (Scheme). The overall yield of cis and trans-6 from 1 ($R^1 = R^2 = H$) is of 25-30%.

Scheme



(a) BuLi, hexane, THF, -78°C; (b) CO_2; (c) MeI; (d) TMGA, DMF; (e) NaH, THF, 0°C; (f) H_3O^+; (g) 5% Pd on C, EtOH, H_2; (h) Li, NH_3; (i) Dowex 50x8, H^+ form.

Isomers 8 could be separated by their great difference of solubility in benzene. Both gave, however, on carboxylation, almost exclusively one and the same trans diacid isomer 9. By reducing 9 in ethanol, the major part of the amino diacid 10 was deposited on the catalyst. It was extracted with boiling water and crystallized with two molecules of water as one pure isomer. More of 10 was recovered from the ethanol solution, bringing the total yield to that indicated. The molecular structure of 10 was determined by X-ray analysis to be the trans-S,N structure shown in Figure 1.[10,11]

The mixture of cis- and trans- 6 recovered from the ion exchange column after reduction of 10 could be separated column chromatography on cellulose powder. The structure of the first-eluted, major isomer was determined by X-ray analysis to be cis-6 (Figure 2).[10,11] It crystallizes in the monoclinic crystal class with one molecule of water.

Identity of the second isomer with the natural trans- 6 was also established by X-ray analysis, besides comparison of analytical and spectral data with those published.[7]

Because of practical difficulties in the isolation of the 6 isomers by the above method, an alternative approach was adopted which involved reduction of the ester of 8 to the amine, benzoylation of the amine and carboxylation. Separation of the 6 isomers as their N-benzoyl dimethyl ester was then possible by chromatography on silica gel. Hydrolysis with 6N HCl at 100°C provided pure cis or trans-6. A detailed description will be given in a full account of this work.

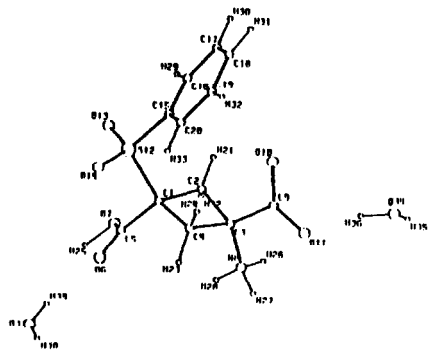


Figure 1. Structure of **10**

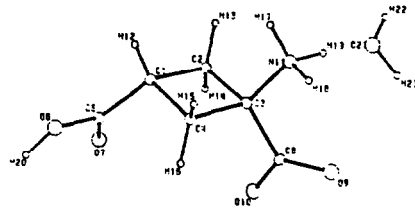
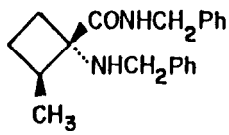


Figure 2. Structure of cis-**6**

The addition of benzylamine to bicyclic sulfones **1** provides another approach to cyclobutane amino acid derivatives. Various methano analogs of natural proteinogenic amino acids or derivatives thereof, may be obtained from the primary adducts by reductive elimination of the sulfone and standard functional group modifications. A straight-forward example is the preparation of racemic benzylamides of N-benzyl-methanovaline (**11**) and N-benzyl-methanoisoleucine (**12**) by addition of benzylamine to **1** (R^1 = *exo*-CH_3, R^2 = $CONHCH_2Ph$) and reduction with sodium amalgam, before or after methylation α to the sulfone.



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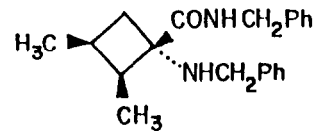

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One pure isomer was obtained in each case, in 70-75% yield in the reduction step. The structure of **11** is dictated by the direction of addition of the amine. It was further confirmed by X-ray structure determination of **12**[10,11] which established the cis relationship of the two methyls and their trans geometry relative to the benzylamino residue.

REFERENCES AND NOTES

1. Y. Gaoni, A. Tomažič, *J. Org. Chem.*, 1985, **50**, 2948-2957, and references therein.
2. E.P. Blanchard, A. Cairncross, *J. Am. Chem. Soc.*, 1966, **88**, 487-495.
3. V.V. Razin, V.A. Vasin, K.A. Ogloblin, *Zh. Org. Khim.*, 1980, **16**, 1780-1781.
4. Newly prepared bicyclobutanes will be described in a separate publication.
5. Y. Gaoni, A. Tomažič, E. Potgieter, *J. Org. Chem.*, 1985, **50**, 2943-2947.
6. See among others: M. Joucla, M. El Goumzili, *Tetrahedron Letters*, 1986, **27**, 1681-1684; D. Kalvin, K. Ramalingham, R. Woodard , *Synth. Comm.* 1985, **15**, 267-272; M.J. O'Donnell, W.A. Bruder, T.A. Eckrich, D.F. Schullenberger, G.S. Staten, *Synthesis*, 1984, 127-128; M. Rodriguez, J.M. Bland, J.W. Tsang, M. Goodman, *J. Med. Chem.* 1985, **28**, 1527-1529; J.B. Lombardini, J.R. Surfin, *Biochem. Pharmacol.* 1983, **32**, 489-495.
7. E.A. Bell, M.Y. Qureshi, R.J. Pryce, D.H. Janzen, P. Lemke, J. Clardy, *J. Am. Chem. Soc.* 1980, **102**, 1409-1412.
8. M.C. Pirrung, *Tetrahedron Letters*, 1980, 4577-4578.
9. P. Hughes, M. Martin, J. Clardy, *Tetrahedron Letters*, 1980, 4579-4580.

10. The determination of X-ray structures was performed by Dr. Felix Frolow of this institute, and is here gratefully acknowledged.

11. Atomic coordinates for this structure can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

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