CHEMISTRY LETTERS, pp. 1425−1428, 1991.

Synthesis of 2-Bis(trifluoromethyl)hydroxymethyl Substituted Cyclic Amines through Novel Intramolecular Substitution of an Arylsulfonyl Group

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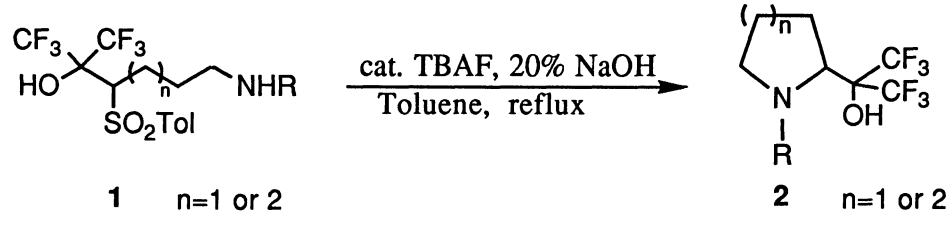
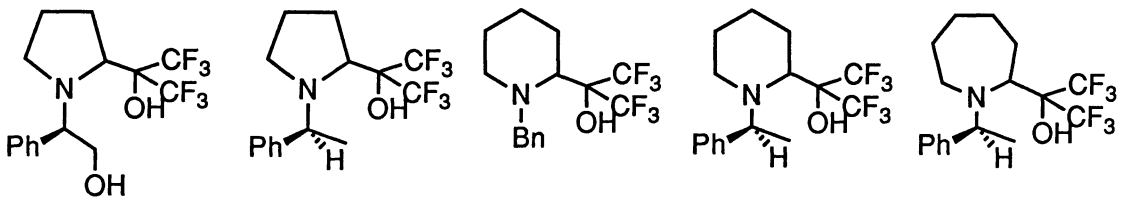
ω-Amino-1,1-bis(trifluoromethyl)-2-sulfonyl-1-pentanol or -hexanol provided the corresponding pyrrolidine or piperidine having BTHM group at the 2-position via intermediary epoxide by treating with NaOH in the presense of phase-transfer catalyst.

Fluorinated compounds have been attracting interest owing to the characteristic features of fluorine atom and fluorinated molecules, particularly in the field of medicinal chemistry, material science as well as organic synthesis.[1,2] From the recent advances in development of asymmetric reactions using cyclic amino alcohols such as pyrrolidine derivatives,[3,4] it may be of interest to prepare the cyclic amines having a bis(trifluoromethyl)hydroxymethyl (1,1,1,3,3,3-hexafluoro-2-hydroxy-2-propyl; abbreviated as BTHM) group, which is expected to have unique properties on the basis of its steric bulkiness,[5] enhanced acidity of the hydroxyl group,[6] and its chemical stability.[7] For the synthesis of such geminally bistrifluoromethylated cyclic amino alcohols, we have explored an efficient method, which involves a novel sulfone chemistry.[8]

In this paper, we report a facile preparation of 2-BTHM pyrrolidines **2a, 2b** and piperidines **2c, 2d** from ω-amino-1,1-bis(trifluoromethyl)-2-arylsulfonyl-1-alkanols **1** via intramolecular displacement of an arylsulfonyl group to the intermediary epoxide followed by nucleophilic attack by the ω-amino group. Furthermore, the determination of the absolute configuration of each diastereomer of the pyrrolidine derivative **2a** and its conversion into the homochiral pyrrolidines **2i-2k** are also described.



1 n=1 or 2 **2** n=1 or 2



2a 2b 2c 2d 2e

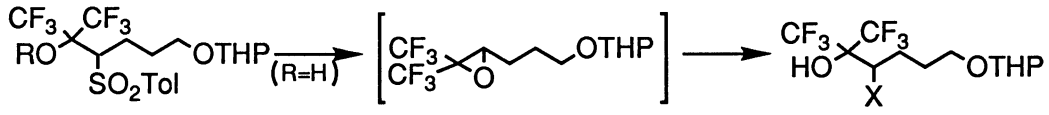
It is known that an arylsulfonyl group acts as a leaving group in some cases through the intramolecular nucleophilic attack of carbanion giving the cyclopropane derivative, while epoxide can be hardly obtained by treating β-hydroxysulfone with base due to the preferential retro aldol type reaction.[9] In contrast, it was found that in the case of 1,1-bis(trifluoromethyl) derivative **1**, formal nucleophilic displacement of the arylsulfonyl group by the ω-amino group smoothly proceeds to give the cyclic amines **2a-2d** without the retro aldol type reaction. Thus, reaction of **1a** with 20% NaOH in toluene in the presence of 10 mol% of tetrabutylammonium fluoride (TBAF) under reflux for 5 h provided a diastereomeric mixture of the pyrrolidine derivative **2a** in 90% yield. In a similar manner, both the pyrrolidine **2b** and the piperidines **2c, 2d** were obtained in good yields, while with **1e** this reaction was not effective to prepare the seven membered ring compound **2e** (Table 1).

Table 1. Conversion of ω-Aminosulfone **1** into Cyclic Amine **2**

Entry	1	n	-NHR	2	Yield/%[a]
1	**1a**	n=1	NHCH(Ph)CH_2OH[b]	**2a**[d]	90
2	**1b**	n=1	NHCH(Ph)CH_3[c]	**2b**[d]	80
3	**1c**	n=2	NHBn	**2c**	91
4	**1d**	n=2	NHCH(Ph)CH_3[c]	**2d**[d]	50
5	**1e**	n=3	NHCH(Ph)CH_3[c]	**2e**	0

a) Isolated yield. b) *R*-configuration. c) *S*-configuration. d) Diastereomer ratio was ca. 1:1. e) The starting material **1e** was completely consumed.

The present reaction may involve the intermediary epoxide, since the reaction of hydroxyl free compound **5a** with NaOH in the presence of TBAF provided the 1,2-diol **7**, while the methoxymethyl derivative **5b** was unchanged under the similar reaction conditions. Moreover, in the case of **5a** intermolecular displacement of the sulfonyl group by benzylamine occurred under the similar reaction conditions as above to give the amino alcohol **8** in 75% yield. Thus, the present desulfonylative substitution reaction via intermediary epoxide **6** followed by the nucleophilic ring-opening of the epoxide is specific reaction for the geminally bistrifluoromethylated β-hydroxysulfone derivatives.[10, 11]



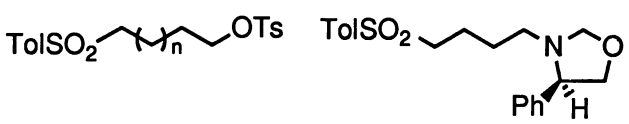
5a R=H
5b R=MOM

6

7 X=OH
8 X=NHBn

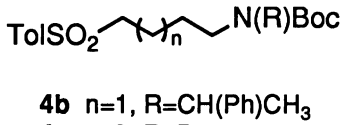
The starting ω-aminosulfone derivatives **1a-1e** (Table 1) were prepared as follows: Reaction of the tosylate **3** with the primary amine (RNH_2, Et_3N, DMF) followed by *N,O*-acetalization ($MeOCH_2Cl$, *i*-Pr_2NEt, THF) gave **4a** or *N*-*t*-butoxycarbonylation [$(Boc)_2O$, Et_3N, CH_2Cl_2] gave **4b-4e**. Deprotonation of the *N*-protected ω-aminosulfone **4a** with *n*-butyllithium (THF, -78 °C, 15 min) or **4b-4e** with LDA (THF, -78 °C,

1 h) and the subsequent introduction of hexafluoroactone gas provided the hexafluorocarbinols (85-95% yield), which were quantitatively deprotected by acid treatment with 10%-HCl in methanol to give **1a** or with trifluoroacetic acid to give **1b-1e**.



3a n=1
3b n=2

4a



4b n=1, R=CH(Ph)CH_3
4c n=2, R=Bn
4d n=2, R=CH(Ph)CH_3
4e n=3, R=CH(Ph)CH_3

A diastereomeric mixture of the pyrrolidine **2a** [TLC (Merck precoated plate #5715; solvent system, CH_2Cl_2/Et_2O=40/1 v/v), (2R,1'R)-**2a**: Rf=0.56, (2S,1'R)-**2a**: Rf=0.47] was found to be readily separated by silica gel column chromatography.[12] The absolute stereochemistry was unambiguously confirmed by X-ray crystallographic analysis of the picrate of one of the diasteromers [picrate of (2S,1'R)-**2a** : mp 153-156 °C] (Fig. 1).

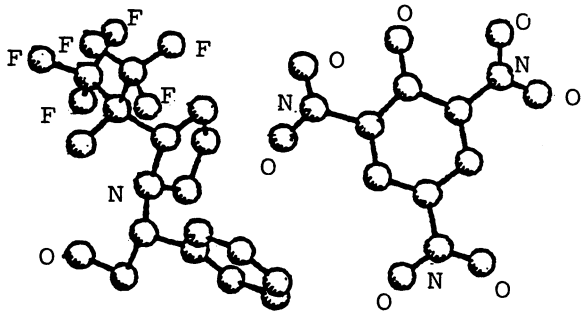
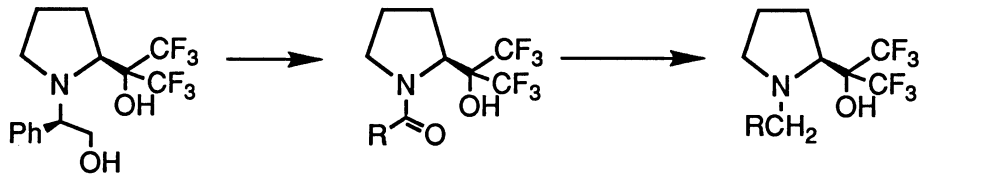


Fig. 1. Molecular structure of picrate of (2S,1'R)-**2a.**

Conversion of diastereomerically pure **2a** into the *N*-substituted pyrrolidines **2i-2k** was achieved as follows: Hydrogenolysis of (2S,1'R)-**2a** (10% Pd-C, HCOOH-MeOH, rt, 30 min) followed by *N*-acylation (RCOCl, Et_3N, CH_2Cl_2) gave *N*-acylated pyrrolidines **2f-2h,** which were reduced to **2i-2k** ($LiAlH_4$, THF, reflux).[13]



(2S,1'R)-**2a**

2f R=Ph (65%)
2g R=Me_2NCH_2 (82%)
2h R=EtO (52%)

2i R=Ph (85%)
2j R=Me_2NCH_2 (63%)
2k R=H (58%)

In this paper, we achieved a facile preparation of 2-BTHM pyrrolidines and piperidines through a unique sulfone chemistry based on the BTHM group. Further applications to asymmetric reactions using the fluorinated amino alcohols are currently carried out.

We are grateful to Central Glass Company for providing hexafluoroacetone and to Tokuyama Science Foundation for financial support.

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6) The pKa values of alcohols are as follws: $(CF_3)_2CHOH$ 9.3, CF_3CH_2OH 12.8, EtOH 15.9, and $(CH_3)_2CHOH$ 17.1.

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10) In the case of β-monotrifluoromethyl-β-hydroxysulfone derivative, retro aldol type reaction easily occurred when treated with base.

11) While the phase-transfer catalyzed condition was effective for desulfonylative substitution reaction, **1a** was unchanged when treated with potassium hydride in THF-HMPA under reflux condition.

12) (2S, 1'R)-**2a**: $[\alpha]_D^{25}$ -38.9° (*c* 2.03, $CHCl_3$), ^{1}H-NMR($CDCl_3$)δ: 7.40-7.23(5H, m), 4.18-4.09(2H, m), 3.95(1H, dd, J=10.3 and 3.4 Hz), 3.85(1H, d, J=5.6 Hz), 3.12(1H, m), 2.89(1H, m), 2.08(1H, m), 1.68(2H, m), 1.38(1H, m); ^{19}F-NMR($CDCl_3$, relative to benzotrifluoride)δ: -8.67(q, J=11 Hz), 13.07 (q, J=11 Hz); (2R, 1'R)-**2a**: $[\alpha]_D^{25}$ -11.68° (*c* 1.49, $CHCl_3$), ^{1}H-NMR ($CDCl_3$)δ: 7.39-7.20(5H, m), 4.22(1H, dd, J=10.7 and 9.3 Hz), 4.12(1H, dd, J=4.9 and 9.3 Hz), 4.00(1H, m), 3.99(1H, dd, J=10.7 and 4.9 Hz), 3.05(2H, m), 2.07(1H, m), 1.77(3H, m); ^{19}F-NMR ($CDCl_3$)δ: -8.87(q, J=11.2 Hz), -13.4(q, J=11.2 Hz).

13) (S)-(-)-**2i**; $[\alpha]_D^{25}$ -12.71° (*c* 0.80, $CHCl_3$), ^{1}H-NMR($CDCl_3$)δ: 7.38-7.29(5H, m), 7.04(1H, s, OH), 3.86(2H, ABq, J=12.96 Hz, NCH_2Ph), 3.54(1H, dd, J=9.08 and 2.00 Hz, 2-H), 2.96(1H, ddd, J=10.4, 6.44 and 4.12 Hz, 5-H), 2.61(1H, m, 5-H), 2.10-1.70(4H, m, 3-H, 4-H); ^{19}F-NMR($CDCl_3$)δ: -8.87(q, J=11.0 Hz), -14.27(q, J=11.0 Hz).

(Received May 29, 1991)