Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4881-4884, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01018-6

Generation of Doubly Trifluoromethylsubstituted Carbocations: Synthesis of α,α-Bis(trifluoromethyl)benzylamines

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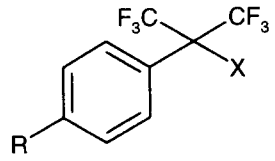
Abstract: α,α-Bis(trifluoromethylbenzyl)triflates offer a convenient access to the corresponding amines through S_N1 type reactions. © 1997 Elsevier Science Ltd.

In recent years, the introduction of fluorine-containing groups such as a trifluoromethyl into organic compounds has been widely investigated because of the unique biological activities and physical properties that fluoro-substitution can impart to a molecule.[1] As part of our structure-activity studies on the inhibition of testosterone 5α-reductase by 4-azasteroids, we were interested in the preparation of α,α-bis(trifluoromethy)benzylamines of type **1**.[2]

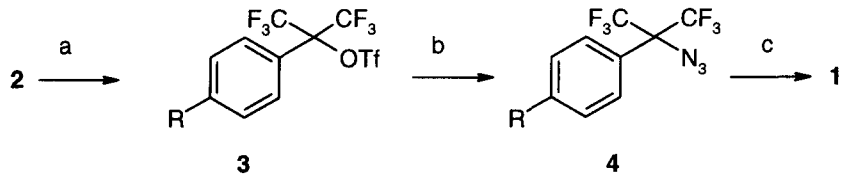


1 X = NH_2
2 X = OH

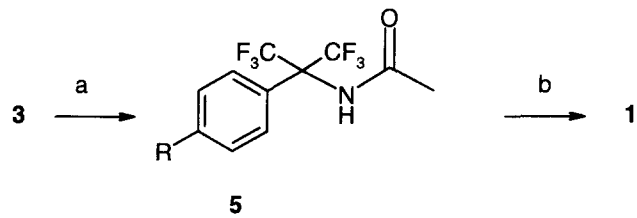
As far as our knowledge is concerned only one synthesis of these compounds has been described up to now.[3] Such synthesis is based on the reaction of hexafluoroisopropylidenimine with an aromatic hydrocarbon under extremely vigorous Friedel-Crafts conditions with moderate yields only when strongly electron-donating substituents are present on the aromatic ring (R=OMe y: 56%; R=H y: 12%). Herein we wish to describe a novel procedure which furnishes these compounds with reasonable yields starting from ready available alcohols of type **2**.[4]

In order to perform the conversion of alcohol to amine two procedures used in the case of tertiary alcohols have been taken into account: the use of sodium azide in trifluoroacetic acid followed by reduction of the azide[5] and the Ritter reaction via hydrolysis of the initially formed amides.[6] Since the trifluoromethyl group is one of the most potent electron-withdrawing groups, as reflected by its Hammet substituent constants (σ^+_p for CF_3 equals 0.596) in both cases the generation of a highly destabilized carbocation that undergoes nucleophilic attack either by the azide ion or by a nitrile is required. Numerous groups have carried out extensive studies related to destabilized carbocations and many α-CF_3 cations are quite viable in synthetic and mechanistic

studies despite the electronic demand of the CF_3 group but as far as we know no synthetic application has been discribed in which reactivity of a doubly trifluoromethylsubstituted carbocation is involved.[7] As alcohol **2** itself failed to react either by azide desplacement in acidic media or in conditions usually employed in the Ritter reaction , the hydroxy group has been converted into a sulfonate in order to take advantage of a better leaving group. As neither a tosylate nor a mesylate were sufficiently reactive for our purposes we tried activation by means of a trifluoromethanesulfonate which belongs to the most activating functional groups for nucleophilic substitution in organic chemistry, documented by well known solvolytic data, as well as by many mechanistic and preparative applications.[8] Eventually activation as triflate[9] furnished under mild conditions both the azide and the amide. Typical procedures are reported.[10]



(a) MeOK, $(CF_3SO_2)_2O$, Toluene; (b) NaN_3, TFA, r.t.; (c) Raney-Ni.



(a) CH_3CN, TFA, TFAA; (b) 98% H_2SO_4, reflux.

Table 1.

ENTRY	TRIFLATE	R	CONDITIONS	PRODUCT	YIELD
1	3a	H	NaN_3,,TFA, r.t., 6 h	4a	65%
2	3b	Me	NaN_3,,TFA, r.t., 50'	4b	71%
3	3d	CF_3	NaN_3,,TFA, r.t.- 100° C, several hours	--	N. R.
4	3a	H	CH_3CN, TFA, TFAA, 60° C, 50'	5a	75%
5	3b	Me	CH_3CN, TFA, TFAA, r.t., 5'	5b	80%
6	3c	F	CH_3CN, TFA, TFAA, 50° C, 25'	5c	77%
7	3d	CF_3	CH_3CN, TFA, TFAA, 50-100° C, several hours	5d	N. R.

Various solvents have been tested but best reactivity was observed only when highly ionizing solvents such as trifluoroethanol or trifluoroacetic acid were employed suggesting that, in order to achieve carbocationic reactivity, solvolytic conditions are required even though strong activation is present.

It is well established that destabilized carbocations give rise to extensive charge delocalization into the aromatic ring thus showing high electronic demand on the aryl group substituent. In accordance to this observation we have noticed that reactions are dramatically accelerated by electron-donating substituents while an electron-withdrawing group such as a trifluoromethyl in the para position totally prevents reaction. Moreover, in spite of our efforts, we didn't succeed in preparing the p-OMe substituted triflate and this failure may be due to the extremely high reactivity of such activated derivative.

In conclusion, the methods described and particularly the one based on the Ritter reaction offer a convenient access to α,α-bis(trifluoromethyl)benzylamines and represent the first example of functional group transformation of α,α-bistrifluoromethylated alcohols achieved by means of S_N1 type reactions of their triflates.[11]

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9. Preparation of triflates is carried out by activating the corresponding alcohol through its potassium salt. Activation is most conveniently performed either by means of MeOK in Toluene followed by distillation of MeOH or with KH in Et_2O. The potassium salt is then reacted with triflic anhydride.

10. Preparation of amines by N_3^- displacement: triflate **3a** (14.2 g,37.8 mmol) was mixed with sodium azide (4.9 g,75.6 mmol) and treated dropwise with trifluoroacetic acid (15.2 mL) over a 10 minutes period. After stirring at room temperature for 6 hours, 32% ammonium hydroxide (100 mL) was added slowly at 0°C. The organic layer was separated and the aqueous one was washed thoroughly with water, dried over sodium sulphate and the solvent removed under vacuum. The crude product was purified by flash chromatography (pentane) to give azide **4a** which was then dissolved in isopropanol (125 mL), treated with activated Raney-Nickel in portions and stirred at room temperature until no more foaming occured. The mixture was filtered and the isopropanolic solution was treated with gaseous hydrochloric acid. After evaporating the solvent, 6.89 g. of white solid 1,1,1,3,3,3-hexafluorophenylpropylamine hydrochloride were obtained.

Preparation of amines by Ritter reaction: triflate **3b** (390 mg, 1 mmol) is treated first with acetonitrile (78 mL, 1.5 mmol) and then with TFA (1.5 mL) and TFAA (0.5 mL), at room temperature, with stirring, under a nitrogen atmosphere. The reaction immediately becomes dark yellow and after 5' water is added dropwise till precipitation of a white solid occurs. The solid is filtered with suction, washed with water, affording, after drying, 240 mg of acetamide (yield:80%). Acetamides are hydrolized by refluxing in 95% sulfuric acid for several hours. Extraction with Et_2O of the acidic phase furnishes amine **1b** in quantitative yield.

11. For S_N2 type reactions of α–trifluoromethylated alcohols: Hagiwara, T.; Tanaka, K. and Fuchikami, T. *Tetrahedron Lett.* **1996**, 37, 8187-8190.

(*Received in UK* 12 *May* 1997; *accepted* 23 *May* 1997)