Tetrahedron Vol. 47, No. 26, pp. 4591-4602, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
Pergamon Press plc

HIGHLY SELECTIVE TFAA-CLEAVAGE OF TERTIARY 2,4-DIMETHOXYBENZYLAMINES AND ITS USE IN THE SYNTHESIS OF SECONDARY AMINES

Peter Nussbaumer*, Karl Baumann, Thomas Dechat, Michael Harasek

Department of Dermatology, SANDOZ Forschungsinstitut Wien,
Brunnerstraße 59, A-1235 Wien, Austria

(*Received in Germany* 6 *March* 1991)

Summary: TFAA-treatment of allylic, propargylic, homopropargylic and some benzylic tert. 2,4-dimethoxybenzylamines leads to highly selective cleavage of their dimethoxybenzylic C-N bonds. The resultant trifluoroacetamides can then readily be converted to the corresponding secondary amines.

Introduction:

In the course of SAR-studies within the class of allylamine antimycotics[1,2], an efficient synthesis of pure (E)-N,6,6-trimethyl-2-hepten-4-yn-1-amine **1a** and structurally related secondary amines has been required. Usually **1a** has been synthesised by mono-alkylation of methylamine with 1-bromo-6,6-dimethyl-2-hepten-4-yne **5a** (E/Z=3/1) and then isolated from the resulting amine E/Z-mixture by selective crystallisation of its hydrochloride salt[2] in poor to moderate yields. Thus, a more convenient and improved synthetic method has been searched for. As E/Z-mixtures of tert. N-benzyl allylamine derivatives can be easily separated by chromatography, it was envisaged to make use of this benefit in developing a new access to **1a** and related compounds.

It is known that tert. benzylamines can be cleaved by anhydrides, but high temperatures (reflux, anhydride as solvent) and long reaction times are required[3,4]. The mechanism involves formation of an acylammonium salt, followed by heterolytic-type cleavage of the C-N-benzyl bond to yield a benzyl acetate and the corresponding N-acyl amine. This cleavage could be enhanced by

a) employing an aromatic fragment in which the developing benzyl cationic charge is stabilised by electron-donating groups, and

b) an anhydride with electron-withdrawing groups to stabilise the developing negative charge in the anionic-type fragment.

Thus, tertiary 2,4-dimethoxybenzylamines **2** were prepared to achieve stabilisation of the intermediate benzylic cationic charge by the two methoxy-substituents and the reaction of **2** with trifluoroacetic anhydride (TFAA) studied.

Results and Discussion:

Synthesis of trifluoroacetamides 3 from 2:

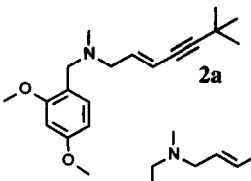
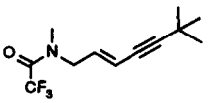
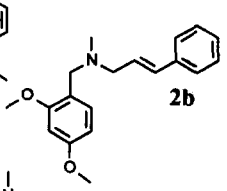
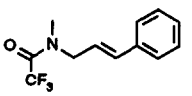
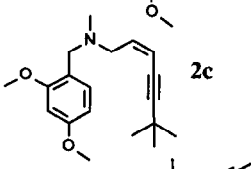
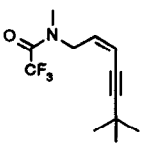
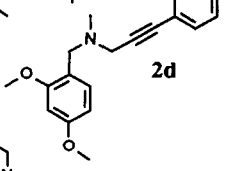
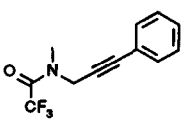
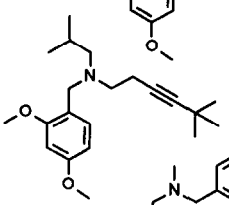
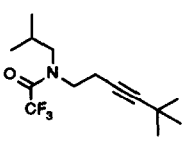
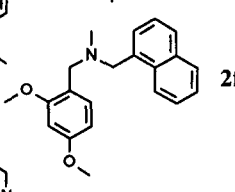
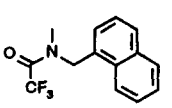
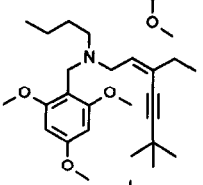
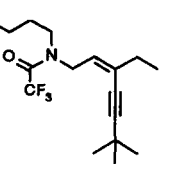
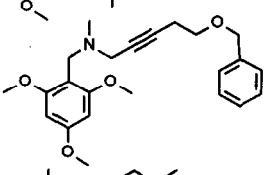
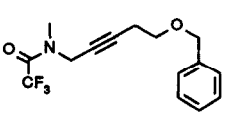
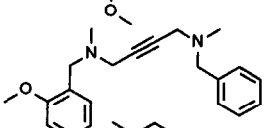
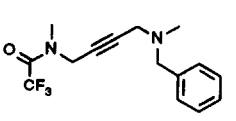
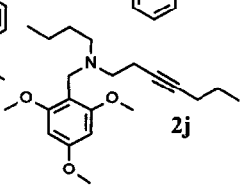
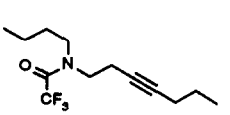
After treatment of **2a** with 1-2 equivalents of TFAA at 25° C for one hour in the presence of triethylamine (TEA) we observed completely regioselective cleavage of the benzylic C-N bond yielding trifluoroacetamide **3a** and dimethoxybenzyl trifluoroacetate, which were separated readily. The use of TFAA without TEA reduces yields, what is presumably due to partial hydrolysis of TFAA and subsequent formation of a salt **2**·TFA, which is resistent to further reaction.

As shown in **Table 1**, this method is generally applicable for the synthesis of allylic (entry 1,2,3,7), propargylic (entry 4,8,9), homopropargylic (entry 5,10) and some benzylic[5] (entry 6) secondary trifluoroacetamides **3**. High yields of **3** are obtained from the appropriate di(tri)methoxy-benzylamines **2** under extremely mild and convenient conditions (room temperature, 0.75-2 hours).

In no case products resulting from non-regioselective cleavage of other C-N-bonds were observed. The introduction of the two methoxy-groups in ortho- and para-position of the benzyl moiety leads to complete regioselectivity (entry 6,9) of the reaction, even in the presence of such a notorious good leaving group as the naphthylmethyl function in the molecule (entry 6). As expected, under the reaction conditions a benzylic ether (entry 8) in the substrate remained intact.

The by-product di(tri)methoxybenzyl trifluoroacetate is removed either by chromatography or by treatment of the crude reaction product mixture with a few drops of acid (TFA, 1 N HCl) to induce polymerisation (comparable to the acid catalysed polymerisation of phenols or arenes with formaldehyde[6]) of the benzylic trifluoroacetate. The colourless polymer is then filtered off and the filtrate worked up as usual to obtain pure trifluoroacetamide **3**. Precipitation of this polymer from the reaction mixture is also observed during the end stage of the reaction, unless a base (e.g. triethylamine) is present, which is on the other hand necessary for complete conversion of the starting material.

Table 1: Cleavage of tert. 2,4-Dimethoxy- and 2,4,6-Trimethoxybenzylamines

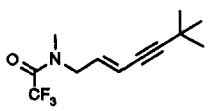
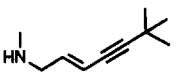
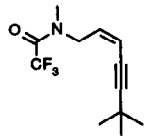
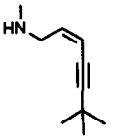
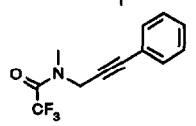
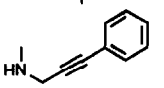
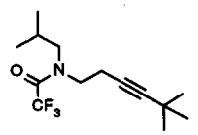
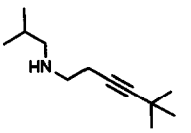
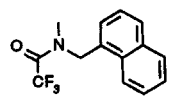
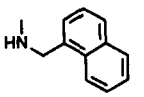
entry	precursor 2	time (hr)	product 3	yield [a]
1	 2a	1	3a 	95%
2	 2b	1.5	3b 	89%
3	 2c	0.75	3c 	92%
4	 2d	1	3d 	82%
5	 2e	2	3e 	83%
6	 2f	1.5	3f 	92%
7	 2g	0.75	3g 	94%
8	 2h	0.75	3h 	84%
9	 2i	2	3i 	75%
10	 2j	0.75	3j 	92%

[a] yields (not optimised) of isolated, analytically pure products

Synthesis of secondary amines 1 from 3:

A further advantage of the described process (in comparison with the cleavage reaction using acetic anhydride or methyl chloroformate) is that trifluoroacetamides can be easily converted to the corresponding amines by treatment with $NaBH_4$/ethanol[7] or mild alkaline hydrolysis[8]. This conversion of 3 to secondary amines 1 requires much milder reaction conditions in comparison with various other amine protecting groups (eg., alkaline hydrolysis can be achieved for trifluoroacetamides at pH ≥10, for acetamides and methyl carbamates at pH >12[9]) and can be achieved in almost quantitative yield. In **Table 2** some examples for the preparation of secondary amines 1 from trifluoroacetamides 3 are listed.

Table 2: Synthesis of Secondary Amines from Trifluoroacetamides Using $NaBH_4$/EtOH

entry	precursor 3	product 1	yield [a,b]
1	3a 	1a 	99% (92%)
2	3c 	1c 	96%
3	3d 	1d 	98% (84%) [c]
4	3e 	1e 	93%
5	3f 	1f 	97% (91%)

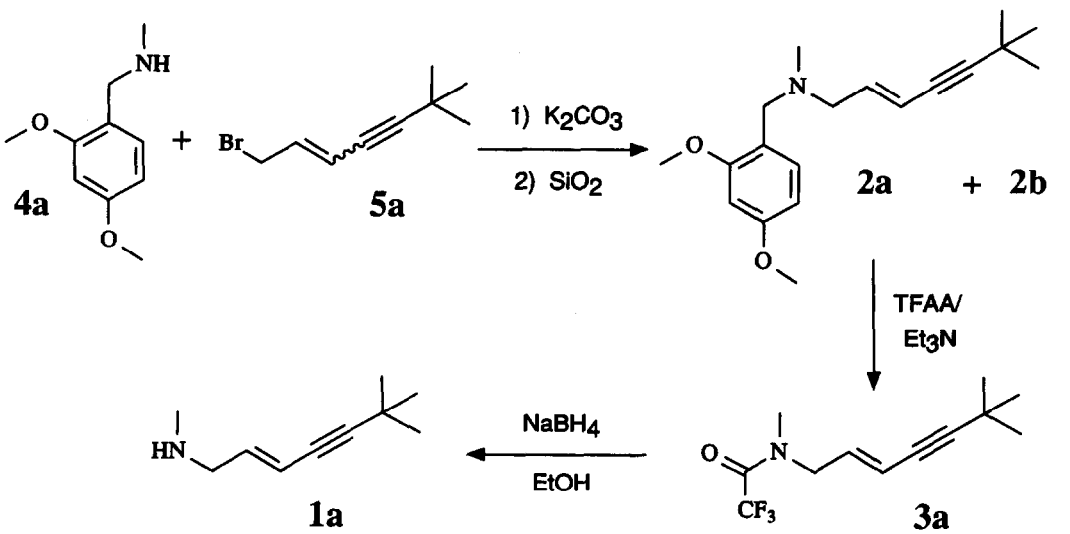
[a] yields of isolated, analytically pure products

[b] in parantheses: overall yields of sec. amines 1 starting from 2 without isolation of amides 3 (see experim. section, Method B)

[c] mp (hydrochloride): 166-167° C; lit[17]: 165-166° C

The two-step process for conversion of di(tri)methoxybenzylamines **2** to secondary amines **1** can be accomplished also without isolation of trifluoroacetamides **3** (**Table 2**; see experimental section, Method B): the crude reaction mixture of step one (TFAA/TEA) is treated with sodium borohydride in ethanol[7] and the secondary amines **1** are isolated by chromatography or via acidic aqueous extraction. This simplification of the process avoids difficulties arising from the volatility of trifluoroacetamides **3**, gives in some cases even higher yields of **1** and, therefore, enhances the attractiveness of this route for the application in the synthesis of secondary amines.

As the E/Z-mixtures of tert. N-benzyl allylamine derivatives can be easily separated (silica gel chromatography) before treatment with TFAA, the tedious fractional crystallisation is avoided, and pure E and Z-isomers of secondary allylamines can be obtained in good yields. The synthesis is summarised for **1a** in the following Scheme:



Conversion of N-methyl-2,4-dimethoxy-benzylamine **4a** with 1-bromo-6,6-dimethyl-2-hepten-4-yne (E/Z ≈ 3/1)[10] **5a** leads to an E/Z(≈3/1)-mixture of N-(2,4-dimethoxybenzyl)-N,6,6-trimethyl-2-hepten-4-ynamine, which is separated into the pure isomers **2a** (E) and **2b** (Z) by chromatography. Treatment of **2a** with TFAA/TEA produced trifluoroacetamide **3a** in almost quantitative yield. Deprotection of **3a** was accomplished using sodium borohydride in ethanol[7] to give **1a** in 92% overall yield, starting from **2a**.

The mild and high yielding conversion of **2** to secondary amines **1** suggested the further application of the 2,4-di(6-tri)methoxybenzyl function as a genuine protection group. For the protection step either a 2,4-di(6-tri)methoxybenzyl halide or a corresponding sulfonate was required. Surprisingly, only the 2,4-dimethoxybenzyl chloride has been mentioned in the literature[11] (excluding patents) so far, but without any experimental details of its synthesis. First experiments showed that those compounds were not stable under acidic conditions, but underwent polymerisation, as it was observed with 2,4-di(6-tri)methoxybenzyl trifluoroacetate, the by-product of the title reaction. This problem was overcome by preparing the appropriate benzyl methanesulfonate or tosylate from 2,4-di(6-tri)methoxybenzyl alcohol under definite basic conditions.

As example, **2f** was additionally synthesised following this procedure: 2,4-dimethoxybenzyl alcohol was reacted with methanesulfonyl chloride in dichloromethane in the presence of 3 equivalents of N,N-diisopropylethylamine. After complete conversion of the alcohol, the whole reaction mixture was added to a solution of N-methyl-1-naphthalenemethanamine **1f** in dimethylformamide. **2f** was isolated in 82% yield and subsequently deprotected to give **1f** (91% yield) by treatment with TFAA/TEA, followed by $NaBH_4$ in ethanol (Table 2, entry 5). The conversion of **2f** to **3f** (Table 1, entry 6) was an important experiment to verify the selectivity of the cleavage reaction.

In summary, treatment of tert. allylic, propargylic, homopropargylic and some benzylic di(tri)methoxybenzylamines with TFAA leads to highly selective cleavage at their di(tri)methoxybenzylic C-N bond yielding the corresponding trifluoroacetamides, which can be readily converted to secondary amines. Therefore, the decribed method

- represents a valuable additional method for the synthesis of secondary amines and
- demonstrates the potential usefulness of the 2,4-di(6-tri)methoxybenzyl function as protection group for secondary amines (using 2,4-di(6-tri) methoxybenzyl sulfonates or chlorides),

in particular for those containing acetylenic groups, where debenzylation cannot be achieved by hydrogenation.

Experimental Section:

^{1}H-NMR spectra were recorded at 90 MHz (Bruker WH 90) or 250 MHz (Bruker WM 250) in $CDCl_3$ with $(CH_3)_4Si$ as internal standard. Chemical shifts are given as δ units. Mass spectra (intensive ions are given) were recorded on a MAT 311A instrument with EI ion source (70 eV and 250° C) and direct inlet system by Dr. A. Nikiforov at the Institute of Organic Chemistry, University of Vienna. Elemental analyses were performed by Mag. J. Theiner, microanalytical laboratory at the University of Vienna, Institute of Organic Chemistry.

Synthesis of Di(tri)methoxybenzylamines 2:

1. N-Alkylation:

N-(2,4-dimethoxybenzyl)-N,6,6-trimethyl-2-hepten-4-ynamine (2a + 2c):

To a solution of 2 g (11 mmol) N-methyl-2,4-dimethoxybenzylamine **4a** and 2.14 g (16.5 mmol) N-ethyl-diisopropylamine in 35 ml abs. DMF 2.22 g (11 mmol) 1-bromo-6,6-dimethyl-2-hepten-4-yne (E/Z ~ 3/1)[10] **5a** are added slowly. After stirring overnight at room temperature the solvent is distilled off in vacuo and the residue partitioned between water/ether. The organic layer is dried over sodium sulfate and evaporated in vacuo. Chromatography over silica gel (hexane/ethyl acetate = 2.5/1) yields pure **2a** (E-isomer) and **2c** (Z-isomer) as colourless oils.

2a: NMR δ 7.13-7.28 (m,1H); 6.38-6.55 (m,2H); 6.14 (dt,J=16+6Hz,1H); 5.64 (dt,J=16+1.5Hz,1H); 3.81 (s,6H); 3.46 (s,2H); 3.07 (dd,J=6+1.5Hz,2H); 2.21 (s,3H); 1.25 (s,9H).

$C_{19}H_{27}NO_2$ (301.43): calc. 75.71%C, 9.03%H, 4.65%N; found 75.57%C, 9.09%H, 4.58%N.

2c: NMR δ 7.16-7.23 (m,1H); 6.42-6.49 (m,2H); 6.0 (dt,J=10.5+6.5Hz,1H); 5.61 (dt,J=10.5+1.5Hz,1H); 3.81 (s,6H); 3.49 (s,2H); 3.3 (dd,J=6.5+1.5Hz, 2H); 2.24 (s,3H); 1.25 (s,9H).

$C_{19}H_{27}NO_2$ (301.43): calc. 75.71%C, 9.03%H, 4.65%N; found 75.49%C, 8.97%H, 4.50%N.

The following tertiary amines were prepared as described for **2a**:

2b (starting with **4a** and (E)-1-bromo-3-phenyl-2-propene):

NMR δ 7.17-7.43 (m,6H); 6.54 (d,J=16Hz,1H); 6.43-6.5 (m,2H); 6.35 (dt,J= 16+6.5Hz,1H); 3.81 (s,6H); 3.52 (s,2H); 3.22 (dd, J= 6.5+1Hz;2H); 2.26 (s,3H).

$C_{19}H_{23}NO_2$ (297.40): calc. 76.73%C, 7.80%H, 4.71%N; found 76.32%C, 7.75%H, 4.60%N.

2e (starting with N-isobutyl-2,4-dimethoxybenzylamine[12] and 5,5-dimethyl-3-hexynyl methansulfonate[13]):

NMR δ 7.4 (d,J=7.5Hz,1H); 6.48 (dd,J=7.5+2.5Hz,1H); 6.43 (d,J=2.5Hz, 1H); 3.81 (s,3H); 3.79 (s,3H); 3.53 (s,2H); 2.58 (tr,J=7.5Hz,2H); 2.29 (tr,J=7.5 Hz,2H); 2.21 (d,J=7.5Hz,2H); 1.76 (non,J=7.5Hz,1H); 1.18 (s,9H); 0.87 (d,J=7.5Hz, 6H).

$C_{21}H_{33}NO_2$ (331.50): calc. 76.09%C, 10.03%H, 4.23%N; found 76.14%C, 10.16 %H, 4.34%N.

2f (starting with **4a** and 1-chloromethylnaphthalene or **1f** and 2,4-dimethoxybenzyl alcohol via the mesylate):

NMR δ 8.17-8.38 (m,1H); 7.70-7.94 (m,2H); 7.22-7.58 (m,5H); 6.40-6.55 (m, 2H); 3.95 (s,2H); 3.82 (s,3H); 3.79 (s,3H); 3.62 (s,2H); 2.20 (s,3H).

$C_{21}H_{23}NO_2$ (321.42): calc. 78.47%C, 7.21%H, 4.36%N; found 78.48%C, 7.11%H, 4.16%N.

2g (starting with N-butyl-2,4,6-trimethoxybenzylamine[14] and 1-bromo-6,6-dimethyl-3-ethyl-2-hepten-4-yne[15]):

NMR δ 6.12 (s,2H); 5.84 (tr,J=7Hz,1H); 3.82 (s,3H); 3.8 (s,6H); 3.6 (s, 2H); 3.32 (d,J=7Hz,2H); 2.46 (tr,J=7.5Hz,2H); 2.11 (dqua,J=1.2+7.5Hz,2H); 1.45-1.63 (m,2H); 1.2-1.36 (m,2H); 1.25 (s,9H); 1.06 (tr,J=7.5HZ,3H); 0.9 (tr,J=7.5Hz,3H).

$C_{25}H_{39}NO_3$ (401.60): calc. 74.77%C, 9.79%H, 3.49%N; found 74.72%C, 9.73%H, 3.51%N.

2j (starting with N-butyl-2,4,6-trimethoxybenzylamine[14] and 1-bromo-3-heptyne[16]):

NMR δ 6.14 (s,2H); 3.83 (s,3H); 3.81 (s,6H); 3.61 (s,2H); 2.02-2.82 (m,8H); 1.08-1.8 (m,6H); 0.9 (tr,J=7Hz,6H).

$C_{21}H_{33}NO_3$ (347.50): calc. 72.58%C, 9.57%H, 4.03%N; found 72.94%C, 9.56%H, 4.21%N.

2. Mannich reaction:

N-(2,4-dimethoxybenzyl)-N-methyl-3-phenyl-2-propynamine (2d):

620 mg (3.4 mmol) N-methyl-2,4-dimethoxybenzylamine **4a**, 103 mg (3.4 mmol) p-formaldehyde and 350 mg (3.4 mmol) phenylacetylene are mixed with 55 mg (0.4 mmol) zinc chloride in 15 ml abs. dioxane and refluxed for 2.5 h. The solvent is distilled off in vacuo and the residue treated with aqueous sodium bicarbonate/dichloromethane. The organic layer is dried over magnesium sulfate and concentrated in vacuo. The crude product is purified by chromatography over silica gel (hexane/ethyl acetate = 2/1) yielding 750 mg (74%) **2d** as a colourless oil: NMR δ 7.45-7.56 (m,2H); 7.28-7.36 (m,3H); 7.24 (d,J=9Hz,1H); 6.63-6.75 (m,2H); 3.83 (s,3H); 3.82 (s,3H); 3.62 (s, 2H); 3.56 (s,2H); 2.43 (s,3H).

$C_{19}H_{21}NO_2$ (295.38): calc. 77.26%C, 7.17%H, 4.74%N; found 76.99%C, 7.20%H, 4.59%N.

The following tert. amines were prepared as described for **2d** starting with N-methyl-2,4-dimethoxybenzylamine (**4a**) or N-methyl-2,4,6-trimethoxybenzylamine and the corresponding acetylene:

2h: NMR δ 7.23-7.42 (m,5H); 6.13 (s,2H); 4.58 (s,2H); 3.82 (s,3H); 3.80 (s,6H); 3.63 (tr,J=7.5Hz,2H); 3.57 (s,2H); 3.32 (tr,J=2Hz,2H); 2.56 (trtr,J=7.5+2Hz,2H); 2.3 (s,3H).
$C_{23}H_{29}NO_4$ (383.49): calc. 72.03%C, 7.62%H, 3.65%N; found 72.41%C, 7.40%H, 3.58%N.

2i: NMR δ 7.2-7.45 (m,6H); 6.42-6.50 (m,2H); 3.82 (s,6H); 3.64 (s,2H); 3.60 (s,2H); 3.43 (tr,J=1.6Hz,2H); 3.39 (tr.J=1.6Hz,2H); 2.39 (s,6H).

Synthesis of trifluoroacetamides 3:

(E)-N-trifluoroacetyl-N,6,6-trimethyl-2-hepten-4-ynamine (**3a**):
0.58 g (1.9 mmol) **2a** are dissolved in 20 ml abs. CH_2Cl_2 and treated consecutively with 0.43 g (4.2 mmol) TEA and 0.8 g (3.8 mmol) TFAA under ice cooling. After stirring for one hour at room temperature the mixture is poured into 10 ml 2M aqueous pH 7 buffer with vigorous stirring. Extraction with CH_2Cl_2, followed by silica gel chromatography (hexane/ethyl acetate = 5/1) yields 451 mg (95%) of pure **3a** as a colourless oil.

Instead of chromatographic purification, the crude extract can be treated with a few drops of 1 N HCl, stirred for some minutes and extracted again with ether. The organic layer is washed with diluted aqueous $NaHCO_3$ solution, dried and the solvent evaporated. Kugelrohrdistillation (120°C/12 mmbar) of the residue affords pure **3a** (93% yield).
NMR (2 rotamers, ratio ≈ 2/1) δ 5.74-6.12 (2xdt,J=16+6Hz,1H); 5.62 (d,J=16Hz,1H); 3.92-4.12 (m,2H); 3.07 (qua,J=1.8Hz,N-CH_3 of major rotamer); 2.97 (qua,J=1Hz,N-CH_3 of minor rotamer); 1.23 (s,9H).
MS (m/e): 247, 232, 178, 152, 150, 140, 136, 135, 122, 120, 110, 105.
$C_{12}H_{16}F_3NO$ (247.26): calc. 58.29%C, 6.52%H, 5.66%N; found 58.30%C, 6.48%H, 5.51%N.

The following trifluoroacetamides were prepared as described for **3a** starting from the corresponding tert. amines **2b-2j**:

3b: NMR (2 rotamers, ratio ≈ 1.4/1) δ 7.23-7.44 (m,5H); 6.53-6.64 (m,1H); 6.02-6.21 (m,1H); 4.14-4.24 (m,2H); 3.14 (qua,J=1.3Hz,N-CH_3 of major rotamer); 3.04 (s,N-CH_3 of minor rotamer).

MS (m/e): 243, 174, 152, 117, 115.

$C_{12}H_{12}F_3NO$ (243.23): calc. 59.26%N, 4.97%H, 5.76%N; found 59.12%C, 5.17%H, 5.65%N.

3c: NMR (2 rotamers, ratio ≈ 1/1) δ 5.66-5.86 (m,2H); 4.18-4.35 (m,2H); 3.1 (qua,J=1.8Hz,N-CH_3 of rotamer I); 3.01 (qua,J=1Hz,N-CH_3 of rotamer II); 1.27 (s,9H).

$C_{12}H_{16}F_3NO$ (247.26): calc. 58.29%C, 6.52%H, 5.66%N; found 58.21%C, 6.67%H, 5.60%N.

3d: NMR (2 rotamers, ratio ≈ 2.3/1) δ 7.41-7.49 (m,2H); 7.27-7.38 (m,3H); 4.52 (s,N-CH_2- of major rotamer); 4.43 (s,N-CH_2- of minor rotamer); 3.28 (qua,J=1.3Hz,N-CH_3 of major rotamer); 3.19 (s,N-CH_3 of minor rotamer).

MS (m/e): 241, 226, 172, 115.

$C_{12}H_{10}F_3NO$ (241.22): calc. 59.75%C, 4.18%H, 5.81%N; found 59.47%C, 4.39%H, 5.60%N.

3e: NMR (2 rotamers) δ 3.45-3.58 (m,2H); 3.26-3.38 (m,2H); 2.38-2.52 (m, 2H); 1.94-2.18 (m, 1H); 1.18 (s,9H); 0.93 (d,J=7.5Hz,6H).

MS (m/e): 277, 234, 220, 182, 126, 93, 57.

$C_{14}H_{22}F_3NO$ (277.33: calc. 60.63%C, 8.0%H, 5.05%N; found 60.79%C, 8.05%H, 5.04%N.

3f: NMR δ 7.25-8.10 (m,7H); 5.17 (s,2H); 3.0 (qua,J=1.8Hz,3H).

$C_{14}H_{12}F_3NO$ (267.25): calc. 62.92%C, 4.53%H, 5.24%N; found 62.72%C, 4.48%H, 5.08%N.

3g: NMR (2 rotamers) δ 5.4-5.7 (m,1H); 4.12-4.32 (m,2H); 3.24-3.48 (m,2H); 2.16 (qua,J=7.5Hz,2H); 1.2-1.7 (m,4H); 1.29 (s,9H); 1.09 (tr,J=7.5Hz,3H); 0.95 (tr,J=7.5Hz,3H).

$C_{17}H_{26}F_3NO$ (316.40): calc. 64.54%C, 8.28%H, 4.43%N; found 64.75%C, 8.36%H, 4.45%N.

3h: NMR (2 rotamers, ratio ≈ 2/1) δ 7.27-7.44 (m,5H); 4.57 (s,2H); 4.26 (tr,J=2Hz,N-CH_2- of major rotamer); 4.18 (br.s,N-CH_2- of minor rotamer); 3.59 (tr,J=7Hz,O-$\underline{CH_2}$-CH_2- of major rotamer); 3.58 (tr,J=6.5Hz,O-$\underline{CH_2}$-CH_2- of minor rotamer); 3.18 (qua,J=1Hz,N-CH_3 of major rotamer); 3.09 (br.s, N-CH_3 of minor rotamer); 2.53 (trtr,J=7+2Hz,2H).

MS (m/e): 299, 268, 178, 172, 171, 159.

$C_{15}H_{16}F_3NO_2$ (299.30): calc. 60.19%C, 5.39%H, 4.68%N; found 60,10%C, 5.50%H, 4.55%N.

3i: NMR (2 rotamers, ratio ~ 2/1) δ 7.22-7.39 (m,5H); 4.34 (tr,J=2Hz, CF_3-CON-CH_2- of major rotamer); 4.26 (br.s,CF_3CON-CH_2- of minor rotamer); 3.56 (s,Ph-CH_2- of major rotamer); 3.54 (s,Ph-CH_2- of minor rotamer); 3.32 (tr, J=2Hz,2H); 3.24 (qua,J=1.7Hz,N-CH_3 of major rotamer); 3.15 (s,N-CH_3 of minor rotamer); 2.33 (s,3H).
MS (m/e): 298, 283, 229, 207, 201.
$C_{15}H_{17}F_3N_2O$ (298.31): calc. 60.40%C, 5.74%H, 9.39%N; found 60.08%C, 5.88%H, 9.19%N.

3j: NMR (2 rotamers) δ 3.4-3.56 (m,4H); 2.42-2.55 (m,2H); 2.1-2.21 (m,2H); 1.25-1.7 (m,6H); 0.87-1.02 (m,6H).
$C_{13}H_{20}F_3NO$ (263.31): calc. 59.30%C, 7.65%H, 5.32%N; found 59.39%C, 7.54%H, 5.10%N.

Synthesis of secondary amines 1:

(E)-N,6,6-trimethyl-2-hepten-4-yn-1-amine (1a):
Method A: 1.1 g (4.4 mmol) **3a** are dissolved in 15 ml abs. ethanol and 660 mg (17.5 mmol) sodium borohydride are added at room temperature. After stirring for 1.5 h the mixture is concentrated in vacuo. The residue is taken up in 10 ml 1 N HCl and washed three times with ether. The acidic aqueous phase is made alkaline with 2 N NaOH and extracted with ether. The ether layer is dried over magnesium sulfate and carefully concentrated in vacuo to give 666 mg (99%) of pure **1a**.
Method B: The crude reaction product mixture, obtained according to the procedure described for the synthesis of **3a**, starting with 1.89 g (6.27 mmol) **2a**, is dissolved in 20 ml abs. ethanol and treated with 1.1 g (29 mmol) sodium borohydride in portions. Following the work up description of Method A, 1.43 g (92% from **2a**) pure **1a** are isolated: mp (hydrochloride) 163-166° C (ethanol/ether), NMR ($CDCl_3$) δ 6.07 (dt, J=16+6.25 Hz,1H), 5.62 (dt,J=16+1Hz,1H), 3.22 (dd,J=6.25+1Hz,2H), 2.41 (s,3H), 1.23 (s,9H), 1.15 (s,1H).

1c: NMR ($CDCl_3$) δ 5.92 (dt,J=10+6.25 Hz,1H), 5.58 (dt,J=10+1Hz,1H), 3.44 (dd,J=6.25+1Hz,2H), 2.44 (s,3H), 1.25 (s,9H), 1.1 (s,1H).

1e: mp (1,5-naphthalene disulfonate) 200-202° C (2-propanol)
NMR ($CDCl_3$) δ 2.69 (tr,J=6.5Hz,2H); 2.42 (d,J=6.7Hz,2H); 2.34 (tr,J=6.5 Hz,2H); 1.76 (non,J=6.7Hz,1H); 1.5 (br.s.,1H); 1.19 (s,9H); 0.91 (d,J=6.7 Hz,6H).
$C_{12}H_{23}N \cdot \frac{1}{2}C_{10}H_8S_2O_6$ (325.41): calc. 62.75%C, 8.36%H, 4.30%N; found 62.68%C, 8.44%H, 4.30%N.

References and notes:

1. a) Stütz, A. in "Antifungal Drugs" (ed. Georgiev, V.St.) **1988**, Vol. 544 of "The Annals of the New York Academy of Sciences", 46-62; b) Stütz, A., Angew. Chem. Int. Ed. Engl. **1987**, 26, 320-328.

2. Nussbaumer, P.; Petranyi, G.; Stütz, A., J. Med. Chem. **1991**, 34, 65-73.

3. a) Tiffeneau, M., Bull. Soc. Chim. Fr. **1911**, 9, 819-825; b) Tiffeneau, M.; Fuhrer, K.Bull. Soc. Chim. Fr. **1914**, 15, 162-175; c) Drefahl, G.; Lückert, H.; Köhler, W., J. prakt. Chem. **1960**, 11, 341-344; d) Khai, B.T.; Arcelli, A., J. Organomet. Chem. 1983 (252), C9-C13.

4. Mechanistic studies: a) Mariella, R.P.; Brown, K.H., Can. J. Chem. **1971**, 49, 3348-3351 and ibid. **1973**, 51, 2177-2179; b) Gol'dfarb, Ya. L.; Belen'kii, L.I., Can. J. Chem. **1973**, 51, 2174-2176.

5. The benzyl group must not be substituted by strong electrondonating groups for efficient synthesis of sec. N-benzyl trifluoroacetamides.

6. Adolphs, P.; Giebeler, E.; Stäglich, P., Houben-Weyl **E20**, 3, 1795, 1800 (1987).

7. Weygand, F.; Frauendorfer, E., Chem. Ber. **1970**, 103, 2437-2449.

8. a) Schwartz, M.A.; Rose, B.F.; Vishnuvajjala, B., J. Am. Chem. Soc. **1973**, 95, 612-613; b) Weygand, F.; Swodenk,W., Chem. Ber. **1957**, 90, 639-645; c) Imazawa, M.; Eckstein, F., J. Org. Chem. **1979**, 44, 2039-2041.

9. Greene, T.W. in "Protective Groups in Organic Synthesis", Wiley-Interscience, New York (1981).

10. Stütz, A.; Petranyi, G., J. Med. Chem. **1984**, 27, 1539-1543.

11. Nicoletti, T.M.; Raston, C.L.; Sargent, M.V., J. Chem. Soc., Chem. Comm. **1988**, 1491-1493.

12. prepared from 2,4-dimethoxybenzaldehyde and 2-methyl-propylamine by reduction of the corresponding Schiff base with sodium borohydride: NMR δ 7.13 (d,J=7.8Hz,1H); 6.4-6.46 (m,2H); 3.81 (s,3H); 3.8 (s,3H); 3.71 (s,2H); 2.38 (d,J=6.7Hz,2H); 1.77 (non,J=6.7Hz,1H); 1.68 (br.s, 1H); 0.89 (d,J=6.7Hz,3H).

13. Stütz, A., Ger. Offen. DE 3,442,529 (CA **1986**, 105, 114765v).

14. prepared from 2,4,6-trimethoxybenzaldehyde and n-butylamine by reduction of the corresponding Schiff base with sodium borohydride: NMR δ 6.12 (s,2H); 3.8 (s,9H); 3.75 (s,2H); 2.54 (tr,J=7Hz,2H); 1.79 (br.s,1H); 1.24-1.53 (m,4H); 0.89 (tr,J=7Hz,3H).

15. prepared from 3,3-dimethyl-1-butyne and 1-penten-3-one according to the synthesis of **5a** (ref. 10) and used without further purification.

16. Newman, M.S.; Wotiz, J.H., J. Am. Chem. Soc. **1949**, 71, 1292-1297.

17. Simon, D.Z.; Salvador, R.L.; Champagne, G., J. Med. Chem. **1970**, 13, 1249-1250.