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Synthesis of α-Trifluoromethyl Substituted α-Amino Acid Derivatives from Methyl 3,3,3-Trifluoro-2-diazopropionate

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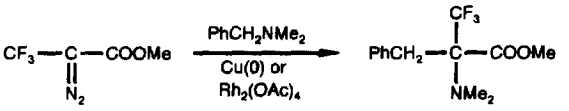
Abstract: New derivatives **2-7** of α-trifluoromethyl substituted amino acids are synthesized via transformation of ammonium ylides formed on reaction of methyl 3,3,3-trifluoro-2-diazopropionate with amines and amides, respectively.

Among various classes of fluorine containing biologically active compounds, fluorinated amino acids attract considerable attention. β-Fluorine containing α-amino acids exhibit promising properties as irreversible inhibitors of pyridoxalphosphate dependent enzymes[1] and as candidates for peptide modification. The search for new fluorinated building blocks represents an attractive strategy for amino acid synthesis. We developed a preparative method for the synthesis of α-trifluoromethyl substituted α-amino acids based on the amidoalkylation of carbon nucleophiles with highly electrophilic imines of methyl trifluoropyruvate.[2-4] Here we report on a new one-step procedure for α-CF_3-containing α-amino acids using methyl 3,3,3-trifluoro-2-diazopropionate (**1**),[5,6] which has not been utilized for this purpose earlier.

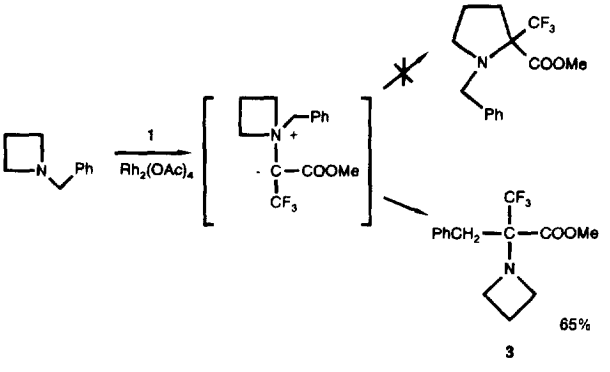
Ylides obtained on transition metal catalyzed decomposition of diazo carbonyl compounds which are capable to undergo [1.2]-Stevens rearrangement are becoming increasingly useful in synthetic chemistry.[7-9] We found that a [1.2]-shift of the benzyl group occurs on treatment of benzyl dimethyl amine with **1** in boiling benzene for 8-10 hours in the presence of catalytic amounts of copper.

This process is significantly accelerated (1-2 hours) when dirhodium tetraacetate is used for ylide formation yielding α-trifluoromethyl phenylalanine **2**.[10]



1 **2** 65-71%

The readily available N-benzyl azetidine[11] does not undergo ring enlargement on reaction with **1** to give the corresponding N-benzyl α-trifluoromethyl proline methyl ester as postulated earlier.[9] Instead, a [1.2]-benzyl migration occurs and the α-trifluorophenylalanine derivative **3** is obtained. Its structure was unambiguously proved by ^{13}C NMR spectroscopy[12].



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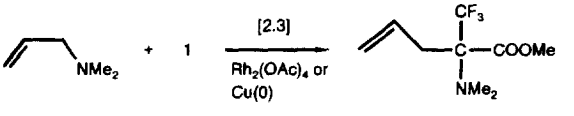
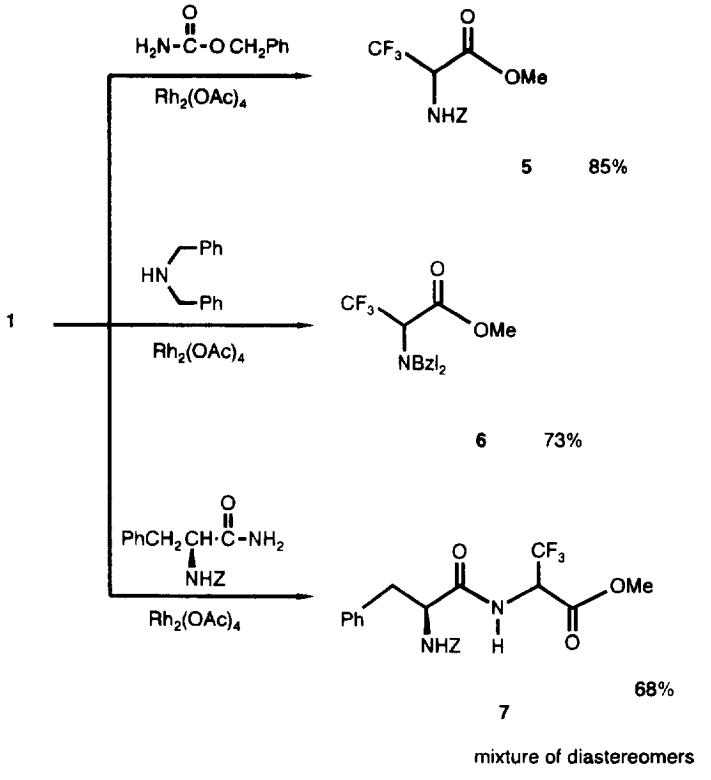
The formal [1.2]-Stevens shift involving a symmetry allowed [2.3]-sigmatropic rearrangement is a facile bond reorganization process for some catalytically generated ylides.[13,14] We also applied **1** in this type of transformation.



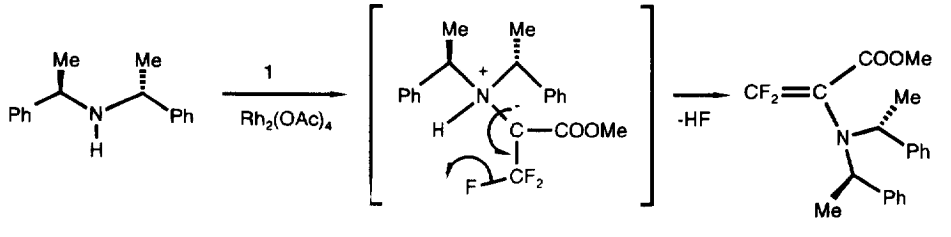
4 70-72%

The reaction of **1** with allyl dimethyl amine is complete within 6-8 hours when heated in benzene or excess of amine in the presence of Cu (0) or $Rh_2(OAc)_4$ as catalysts giving the allyl glycine derivative **4**.

Reactions involving N-H insertion have been investigated under copper or rhodium catalyzed conditions.[15,16] However, they have received nearly no attention as synthetic route to alanine derivatives,[16] including peptides. Interaction of **1** with amides and secondary amines takes place already at the room temperature in dichloromethane affording α-trifluoroalanine derivatives.[17]



Our attempt to induce stereoselectivity on reaction of **1** with bis[(*R*)-1-phenylethyl]amine was unsuccessful, the fluorinated enamine **9**[18] was isolated in 30% yield. Probably, the HF elimination can be explained by the steric effects which prevent rapid proton transfer from nitrogen to carbon in the initially formed ylide **8**.



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Acknowledgement

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10. **2:** ^{1}H NMR (d_6-acetone) δ 2.50 (m, 6H, NMe_2); 3.27 (d, $^{2}J_{HH}$ = 15.2 Hz, 1H, CH_2); 3.37 (d, $^{2}J_{HH}$ = 15.2 Hz, 1H, CH_2); 3.69 (s, 3H, OMe); 7.23 (m, 5H, Ph). ^{13}C NMR (d_6-acetone) δ 38.7 (CH_2); 40.8 (NMe_2); 52.6 (OMe); 74.8 (q, $^{2}J_{CF}$ = 22.5 Hz, -$\underline{C}$-CF_3); 126.5 (q, $^{1}J_{CF}$ = 294.7 Hz, CF_3); 128.0, 129.0, 131.2, 135.8 (Ph); 168.7 (C=O). ^{19}F NMR (d_6-acetone) δ 13.4 (s, 3F, CF_3).
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12. **3:** ^{1}H NMR ($CDCl_3$) δ 2.09 (m, 2H, CH_2); 2.97 (d, $^{2}J_{HH}$ = 13.5 Hz, 1H, CH_2Ph); 3.27 (d, $^{2}J_{HH}$ = 13.5 Hz, 1H, CH_2Ph); 3.47 (m, 2H, CH_2); 3.73 (m, 2H, CH_2N); 3.80 (s, 3H, OMe); 7.24 (m, 5H, Ph). ^{13}C NMR ($CDCI_3$) δ 17.2 (CH_2); 36.8 (NCH_2Ph); 51.7 (2 NCH_2); 52.2 (OMe); 72.9 (q, $^{2}J_{CF}$ = 24.5 Hz, -$\underline{C}$-CF_3); 122.8 (q, $^{1}J_{CF}$ = 288.5 Hz, CF_3); 127.6, 128.3, 130.7, 134.7 (Ph); 167.8 (C=O). ^{19}F NMR ($CDCl_3$) δ 9.3 (s, 3F, CF_3).
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17. **5:** ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, OMe); 5.08 (m, 1H, CH); 5.17 (s, 2H, OCH_2); 5.62 (br.s, 1H, NH); 7.37 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$) δ 4.73 (d, $^{2}J_{FH}$ = 6.9 Hz, 3F, CF_3).
18. **9:** ^{1}H NMR (d_6-acetone) δ 1.15 (d, $^{2}J_{HH}$ = 6.7 Hz, 6H, 2 $CHMe$); 3.35 (s, 3H, OMe); 4.22 (q, $^{2}J_{HH}$ = 6.7 Hz, 2H, 2 $CHMe$); 7.31 (m, 10H, 2 Ph). ^{19}F NMR (d_6-acetone) δ 0.54 (d, $^{2}J_{FF}$ = 9.1 Hz, 1F, $=CF_2$); 5.42 (d, $^{2}J_{FF}$ = 9.1 Hz, 1F, $=CF_2$).

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