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# Hexafluoroacetone as a protecting and activating reagent: 5,5-difluoro- and *trans*-5-fluoropipecolic acids from glutamic acid

Alexander S. Golubev,[a,b] Hartmut Schedel,[a] Gabor Radics,[a] Marco Fioroni,[a,c] Sven Thust[a] and Klaus Burger[a,*]

[a]*Department of Organic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany*
[b]*Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov str. 28, GSP-1, V-334 Rus-117813 Moscow, Russia*
[c]*Department of Chemistry, Technical University of Eindhoven, Helix Building, Eindhoven, The Netherlands*

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Dedicated to Professor Dr. M. Lozinsky on the occasion of his 70th birthday

**Abstract**—Starting from hexafluoroacetone-protected (*S*)-glutamic acid, *trans*-5-fluoropipecolic and 5,5-difluoropipecolic acid have been synthesized. The piperidine ring was constructed by an intramolecular metal carbenoid NH insertion.


The application of substituted pipecolic acids as building blocks in drug design is steadily growing.[1,2] Furthermore, fluorine-containing proline[3] and pipecolic acid derivatives[4] represent valuable tools for the investigation of the *cis–trans* isomerization of the peptide bond[5] and for the investigation of peptide and protein folding.[6] Recently, we reported on the synthesis of 4-fluoro-substituted pipecolic acids.[4] In an extension of our studies we now disclose a preparatively simple route to the virtually unknown 5-fluoro-substituted pipecolic acids.

Based on recently published results, we thought that a suitably protected 5-oxopipecolic acid could serve as a key precursor in the synthesis of 5-hydroxy-, 5,5-difluoro- and 5-fluoropipecolic acids. Concise synthetic approaches to enantiomerically pure 5-oxo-[7] and 5-hydroxy-pipecolic[8] acids starting from suitably protected glutamic acid derivatives have been described. Construction[9] of the piperidine ring was achieved via ω-carboxy group activation and diazoketone formation, followed by a metal carbenoid NH insertion. This route attracted our interest, because it is preparatively simple, and both enantiomeric forms of glutamic acid are cheap and commercially available. We decided to combine the advantages of this strategy[7,8] with the advantages of the new hexafluoroacetone concept.

Glutamic acid **1** and hexafluoroacetone react at room temperature in DMSO or DMF to give 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one **2**.[10] In one-step, protection of the α-amino group and the adjacent carboxy group has been achieved, while the ω-carboxy group remains unaffected and can be derivatized regioselectively after separate activation.[11] When we tried to activate the ω-carboxy group of **2** by treatment with thionyl chloride we obtained the HFA-protected pGlu **3** in almost quantitative yield.[12] However, when milder activation strategies were applied, the intramolecular ring closure to give a lactam could be avoided. The mixed anhydride, formed on treatment of **2** with isobutyl chloroformate at −15 °C in the presence of *N*-methyl morpholine, was reacted directly with an excess of diazomethane (>3 equiv) at 0 °C to give diazoketone **4** in 61% yield (Scheme 1).

Compound **4** was subjected to a dirhodium tetraacetate catalyzed decomposition.[13] The reaction proceeds via an electrophilic Fischer-type carbene complex, surpressing the Wolff-type rearrangement completely in favour of an intramolecular metal carbenoid NH insertion.[14] The best yields (70–80%[15]) of the bicyclic compound **5** were obtained when a solution of **4** in chloroform was added dropwise to a vigorously stirred suspension of dirhodium tetraacetate in refluxing chloroform (Scheme 2).

*Keywords*: Glutamic acid; Hexafluoroacetone; Diazo ketones; Metal carbenoid NH insertion; DAST fluorination.
* Corresponding author. Tel.: +49-341-8622866; fax: +49-341-97365-99; e-mail: burger@organik.chemie.uni-leipzig.de

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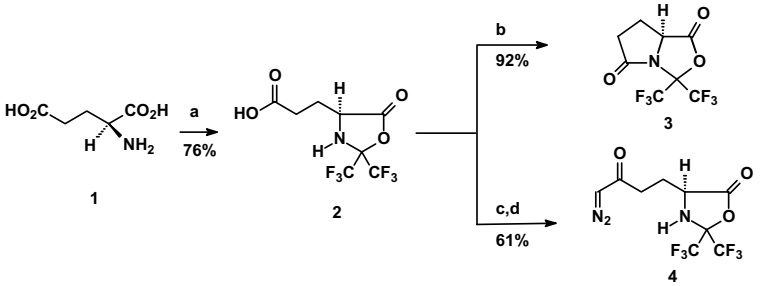
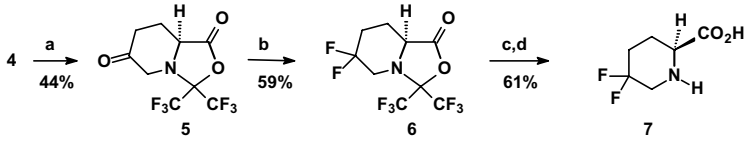
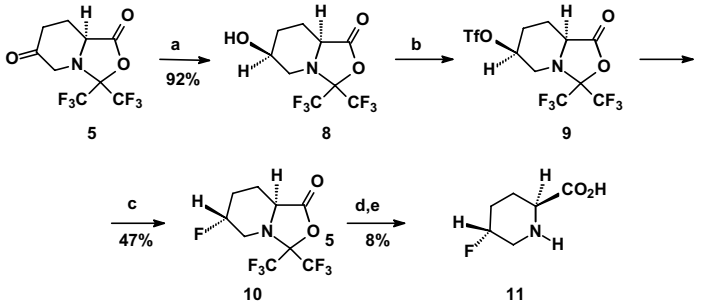


**Scheme 1.** Reagents and conditions: (a) hexafluoroacetone, DMSO; (b) $SOCl_2$; (c) ClOCO-*i*-Bu, *N*-methyl morpholine; (d) $CH_2N_2$.



**Scheme 2.** Reagents and conditions: (a) $Rh_2(O_2CCH_3)_4$, $CHCl_3$; (b) DAST in $CH_2Cl_2$; (c) aq HCl in dioxane; (d) propene oxide.



**Scheme 3.** Reagents and conditions: (a) $BH_3$·THF; (b) $(CF_3SO_2)_2O$; (c) 3HF·$Et_3N$, 3′ MS (d) aq HCl in dioxane; (e) propene oxide.

Next, DAST (diethylaminosulfur trifluoride) fluorodeoxygenation[16] of compound **5** was performed in solution in methylene chloride on adding 2 equiv of DAST at −78 °C to give the HFA-protected difluoropipecolic acid **6**. Transformation of **6** into the unprotected 5,5-difluoro-L-pipecolic acid **7**[17] was achieved on stirring with aqueous HCl in dioxane (1:1) at room temperature followed by treatment with propene oxide to trap the HCl.

Reduction of the carbonyl group of **5** to give a hydroxy group was achieved on reaction with $BH_3$·THF at −78 °C[18] with excellent regio- and stereo-selectivity in 92% yield. The reason for the high selectivity is the concave geometry of the bicyclic system,[19] which favours *exo*-attack of the hydride ion to the carbonyl group to give exclusively the *cis*-hydroxy derivative **8** (Scheme 3).

Fluorodehydroxylation of **8** with DAST gave an inseparable mixture of compounds. Therefore, we transformed the hydroxy group into the triflate **9**. The latter was converted into HFA-protected *trans*-fluoropipecolic acid **10** on treatment with 3HF·$Et_3N$ in the presence of molecular sieves (3 Å)[20] in 60% yield.[21] Transformation of **10** into the unprotected *trans*-5-fluoro-L-pipecolic acid **11** was achieved on stirring with HCl in dioxane (1:1) at room temperature followed by treatment with propene oxide. Compounds **6** and **10** are carboxy-activated species and can be directly applied to peptide coupling.

## Acknowledgements

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15. Compound **6**: colourless crystals; mp 34–35 °C; $[\alpha]_D^{22} = -14.9$ (*c* 1, $CH_2Cl_2$); IR (KBr): *v* 1842 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 1.84 (1H, br m, C$H_2$CHN), 1.90 (1H, m, C$H_2$CH$_2$CHN), 2.20 (1H, br m, C$H_2$CHN), 2.41 (1H, m, C$H_2$CH$_2$CHN), 3.11 (1H, br dd, $^3J_{HF} = 26.1$ Hz, $^2J = 12.4$ Hz, C$H_2$N), 3.62 (1H, br d, $^3J = 10.5$ Hz, CHN), 3.68 (1H, br t, $J_{HF,HH} = 11.6$ Hz, C$H_2$N); $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ 23.75 (d, $^3J_{CF} = 10.3$ Hz, *C*H$_2$CHN), 31.81 (dd, $^2J_{CF} = 25.9$ Hz, $^2J_{CF} = 23.9$ Hz, *C*H$_2$CH$_2$CHN), 50.77 (dd, $^2J_{CF} = 38.8$ Hz, $^2J_{CF} = 27.1$ Hz, *C*H$_2$N), 55.14 (*C*HN), 88.06 (dqq, $^2J_{CF} = 34.4$ Hz, $^2J_{CF} = 32.4$ Hz, $^4J_{CF} = 2.0$ Hz, *C*(CF$_3$)$_2$), 117.62 (ddq, $^1J_{CF} = 247.9$ Hz, $^1J_{CF} = 241.9$ Hz, $^5J_{CF} = 1$ Hz, *C*F$_2$), 120.20 (qq, $^1J_{CF} = 287.1$ Hz, $^3J_{CF} = 1$ Hz, *C*F$_3$), 121.65 (q, $^1J_{CF} = 293.7$ Hz, *C*F$_3$), 166.90 (d, $^5J_{CF} = 1.8$ Hz, C=O); $^{19}F$ NMR (376 MHz, $CDCl_3$ without $^1H$ decoupling): $\delta$ −75.62 (q, $^4J_{FF} = 8.4$ Hz, CF$_3$), −78.73 (dq, $^4J_{FF} = 8.4$ Hz, $^6J_{FF} = 1.2$ Hz, CF$_3$), −102.86 (d, $^2J_{FF} = 244.6$ Hz, CF$_2$), −104.40 (dq, $^2J_{FF} = 244.6$ Hz, $^6J_{FF} = 1.2$ Hz, CF$_2$); MS (EI) *m*/*z* (%): 313 $[M]^+$ (6), 266 (9), 244 (20), 216 (100), 196 (13), 176 (7), 100 (10), 69 (20).
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17. 5,5-Difluoro-(*S*)-pipecolic acid **7**: white powder; mp 250 °C (sealed tube); $[\alpha]_D^{22} = -9$ (*c* 1, $H_2O$); $^1H$ NMR (300 MHz, $D_2O$): $\delta$ 1.85–2.32 (m, 4H), 3.38 (ddd, $J = 23.5$, 13.5, 5.5 Hz, 1H), 3.58 (m, 1H), 3.72 (dd, $J = 10.7$, 2.8 Hz, 1H); $^{13}C$ NMR (50.3 MHz, $D_2O$): $\delta$ 25.30 (t, $J = 5$ Hz), 32.38 (t, $J = 23$ Hz), 48.55 (t, $J = 32$ Hz), 59.86, 120.92 (t, $J = 242$ Hz), 174.88 (t, $J = 5$ Hz).
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21. Compound **10**: colourless crystals; mp 51 °C, $[\alpha]_D^{22} = -9$ (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 1.62 (1H, m, C$H_2$CH$_2$CHN), 1.92 (1H, m, C$H_2$CHN), 2.04 (1H, m, C$H_2$CH$_2$CHN), 2.33 (1H, m, C$H_2$CH$_2$CHN), 3.03 (1H, br dd, $J = 13.4$ Hz, $J_{HF} = 35.5$ Hz, CH$_2$N), 3.54 (1H, br d, $J = 11.5$ Hz, CHN), 3.72 (1H, br t, $J = 12.7$ Hz, CH$_2$N), 4.78 (1H, br d, $J_{HF} = 45.9$ Hz, CHF); $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ 22.02 (*C*H$_2$CHN), 28.18 (d, $^2J_{CF} = 22.2$ Hz, *C*H$_2$CH$_2$CHN), 49.02 (d, $^2J_{CF} = 20.8$ Hz, CH$_2$N), 55.55 (CHN), 83.65 (d, $^1J_{CF} = 179.2$ Hz, CHF), 88.78 (qq, $^2J_{CF} = 33.5$ Hz, $^2J_{CF} = 31.3$ Hz, *C*(CF$_3$)$_2$), 120.28 (qq, $^1J_{CF} = 287.1$ Hz, CF$_3$), 121.83 (q, $^1J_{CF} = 294.2$ Hz, CF$_3$), 168.27 (C=O); $^{19}F$ NMR (376 MHz, $CDCl_3$ without $^1H$ decoupling): $\delta$ −75.28 (br q, $^4J_{FF} = 8$ Hz, CF$_3$), −78.68 (br dq, $^4J_{FF} = 8.4$ Hz, $^6J_{FF} = 1.3$ Hz, CF$_3$), −187.24 (br dttq, $^2J_{HF} = 45.3$ Hz, $^3J_{HF} = 34.3$ Hz, $^3J_{HF} = 11.0$ Hz, $^6J_{FF} = 1.3$ Hz, CHF); MS (EI) *m*/*z* (%): 295 (7) $[M]^+$, 198 (25) $[M-CF_3CO]^+$, 169 (15), 149 (14), 102 (82), 82 (36), 69 (62).