# Application of Stabase Protection in the α-Methylation of Alaproclate, an Alanine Ester of a Tertiary Phenethyl Alcohol

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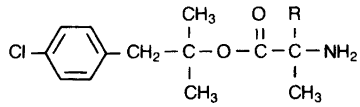
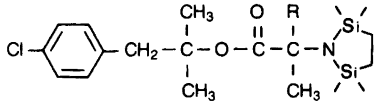
Alaproclate (*1*) is a selective inhibitor of the neuronal serotonin reuptake which is currently investigated as an antidepressive agent.[1] In the course of extending our studies we required the α-methyl analogue *4*, which preferably should be made from the readily available ester *1*.



*1* R = H
*4* R = $CH_3$

α-Alkylation of amino acid esters has been achieved through various protected forms including imine derivatives[2] and 2,2,5,5-tetramethyl-1-aza-2,5-disilolidine (stabase) adducts.[3] Recently, a mild method of preparing benzophenone Schiff bases of amino acid esters has been described.[4] However, we anticipated problems in selectively hydrolyzing imine protective groups after methylation without causing hydrolysis of the ester or elimination in the tertiary alcohol part. Therefore, the use of stabase appeared more attractive, even if examples of reactions of such a sterically hindered ester as *2* seem to be lacking.[3a] Electrophilic alkylation of a silyl ketene acetal was used successfully in one case when ordinary basic conditions was inappreciable.[3b]



*2* R = H
*3* R = $CH_3$

The stabase *2* was obtained in 79 % yield after reaction of *1* with 1,1,4,4,-tetramethyl-1,4-dichlorosilethylene in the presence of triethylamine followed by flash chromatography on alumina. The enolate of the stabase adduct of ethyl glycinate has been generated with lithium diisopropylamide (LDA) and alkylated at −78 °C,[3] which is in accordance with reactions of other esters having an α-hetero substituent such as aryloxy or alkoxy.[5] However, deprotonation of the stabase ester *2* required a higher temperature (−20 °C ) and the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, as revealed by $^1$H NMR examination of aliquouts taken at various temperatures and subjected to deuterolysis. The alkylation of the enolate with excess of iodomethane was carried out at −10 °C with a conversion of 72 %. Addition of 1,3-dimethyl-2-imidazolidinone (DMEU), a hexamethylphosphoric triamide substitute,[6] did not improve the degree of *C*-alkylation. The stabase mixture of *2* and *3* was hydrolyzed by a mild two-phase procedure ($Et_2O$/1 M HCl) which caused

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0302-4369/85 $2.50

instantaneous cleavage of the silyl group at room temperature. Finally, purification by flash chromatography gave the amine *4* in an overall yield of 53 % from *2*.

It can be concluded that stabase is a suitable protecting group also in the alkylation of the sterically demanding ester alaproclate. The stabase adduct is easily prepared and removed with no serious problems of ester hydrolysis or elimination in the tertiary alcohol moiety. The latter has been frequently observed in other reactions involving this tertiary phenethyl alcohol.

The amine *4* has been investigated as inhibitor of neuronal uptake of noradrenaline and serotonin in mouse brain slices. No effect was obtained after *in vivo* administration and only a very weak inhibition of serotonin uptake was observed *in vitro* ($IC_{50}$=9 $\mu$M),[7] *i.e.* *4* is ten-fold less active than alaproclate (*1*, $IC_{50}$=0.7 $\mu$M).[1]

*Experimental.* Melting points were obtained on a Mettler FP 61 apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Varian EM 360 A or a JEOL FX 200 spectrometer and $^{13}$C NMR on a JEOL FX 200 spectrometer using $Me_4Si$ as internal standard. Mass spectra (EI, 70 eV) were recorded on an LKB 9000 instrument. GLC's were run on an SE 30 capillary column and the amounts determined by a Hewlett-Packard 3390 A integrator. Preparative HPLC was conducted on a Waters LC 500 apparatus. Elemental analyses were performed by Analytische Laboratorium, Elbach, West Germany and are within ±0.4 % of the theoretical values.

*Stabase adduct of alaproclate* (*2*). A solution of 1,1,4,4-tetramethyl-1,4-dichlorosilethylene (8.61 g, 0.02 mol) in 10 ml dry $CH_2Cl_2$ was added to a stirred solution of alaproclate[1] (*1*, base, 5.1 g, 0.02 mol) and triethylamine (11.1 ml, 0.08 mol) in 50 ml $CH_2Cl_2$ under $N_2$ at room temperature. After stirring overnight 200 ml hexane were added and the hydrochloride was filtered off. Evaporation of the solvent gave 7.9 g crude product, which was flash chromatographed on alumina (neutral, 400 g) with $Et_2O$/hexane 1:2 as eluent to give 6.3 g (79 %) pure stabase *2*. $^1$H NMR ($CDCl_3$): $\delta$ 7.25 (AA'BB', 4, $C_6H_4$), 3.66 (q, 1, $CHCH_3$), 3.09 (s, 2, benzylic), 1.43 (s, 6, $C(CH_3)_2$), 1.30 (d, 3, $CHCH_3$), 0.70 (s, 4, $CH_2CH_2$), 0.13 (s, 12, $Si(CH_3)_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ 175.2, 135.8, 132.5, 131.9, 128,2, 81.8, 52.8, 45.7, 26.1, 25.9, 21.9, 8.4, 1.6, 0.5; MS (EI, 70 eV): *m/z* (relative intensity) 231 ($M-ClC_6H_4CH=CMe_2$, 100), 202 (8.3), 186 (MeCH=N=Stabase, 98), 169/167 (1.3/3.6), 127/125 ($ClC_6H_4CH_2$, 5.9/16), 73 ($SiMe_3$, 14); Anal. Calcd for $C_{19}H_{32}ClNO_2Si_2$: C, 57.33; H, 8.10; Cl, 8.91; N, 3.52. Found: C, 57.24; H, 7.94; Cl, 8.89; N, 3.44.

*Methylation of stabase adduct.* To a solution of lithium diisopropylamide, prepared from i-$Pr_2NH$ (1.12 ml, 7.9 mmol) and BuLi (7.9 mmol in hexane) in 20 ml THF, and N,N,N',N'-tetramethylethylenediamine (1.19 ml, 7.9 mmol) was injected a solution of alaproclate stabase (*2*, 2.5 g, 6.3 mmol) in 15 ml THF at −20 °C under $N_2$ over 0.5 h. The mixture was stirred for 1.5 h and $^1$H NMR examination of a sample quenched with $D_2O$ showed complete lithiation. Iodomethane (1.57 ml, 25 mmol) was added at −10 °C and the mixture was stirred for 2.5 h at −10 °C. Conc. ammonia (5 ml) and 100 ml $H_2O$ were added to quench excess of iodomethane. The mixture was extracted twice with hexane, dried ($Na_2SO_4$) and evaporated to afford 2.6 g containing 72 % of *3* according to GC. A sample of this crude material was partially purified by filtration through a silica plug with hexane/$Et_2O$ 1:2 as eluent to give a mixture of stabase adducts *2* and *3* in a ratio of 13:87. $^1$H NMR ($CDCl_3$): $\delta$ 7.24 (AA'BB', 4, $C_6H_4$), 3.08 (s, 2, benzylic), 1.43 (s, 12, $C(CH_3)_2$), 0.68 (s, 4, $CH_2CH_2$), 0.13 (s, 12, $Si(CH_3)_2$); MS (EI, 70 eV): *m/z* (relative intensity) 245 ($M-ClC_6H_4CH=CMe_2$, 11), 230 (20), 217 (4.7), 216 (3.7), 200 ($Me_2C=N=$Stabase, 100), 169/167 (0.8/3.3), 127/125 ($ClC_6H_4CH_2$, 3.6/9.7), 73 ($SiMe_3$, 13).

*1-(4-Chlorophenyl)-2-methyl-2-propyl 2-amino-2-methylpropionate (4).* The bulk (2.5 g) of the crude stabase *3* was dissolved in $Et_2O$ and rapidly hydrolyzed by extraction twice with 1 M HCl. The aqueous phase was immediately made alkaline and extracted twice with $Et_2O$. Drying ($MgSO_4$) and evaporation afforded 1.5 g of crude amine, which was purified by preparative HPLC on $SiO_2$ with hexane/$Et_2O$/EtOAc 5:2:3 saturated with ammonia as eluent to give 0.9 g (53 %) of *4*. A tartrate salt was precipitated from hot EtOH/$Et_2O$ in a yield of 1.4 g, mp 136–139 °C. $^1$H NMR ($CDCl_3$, base): $\delta$ 7.26 and 7.11 (AA'BB', 4, J=8.3 Hz, $C_6H_4$), 3.03 (s, 2, benzylic), 1.75 (br s, 2, $NH_2$), 1.46 (s, 6, $OC(CH_3)_2$), 1.26 (s, 6, $NC(CH_3)_2$); $^{13}$C NMR ($CDCl_3$, base): $\delta$ 177.4, 135.4, 132.5, 131.8, 128.0, 82.0, 55.0, 46.0, 27.6, 25.7; MS (EI, 70 eV): *m/z* (relative intensity) 169/167 (0.31/0.97), 168/166 ($ClC_6H_4CH=CMe_2$, 0.80/2.3), 153/151 (0.46/1.4), 131 (3.2), 127/125 ($ClC_6H_4CH_2$, 1.8/5.3),

58 ($Me_2C{=}NH_2$, 100); Anal. Calcd for $C_{18}H_{26}ClNO_8 \cdot 0.5\ H_2O$:C, 50.41; H, 6.35; Cl, 8.27; N, 3.27; O, 31.71. Found: C, 50.33; H, 6.26; Cl, 8.19; N, 3.24; O, 31.43.

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Received December 10, 1984.