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# Note on the Esterification of Some *Z*-Amino Acids with Glyceraldehyde-diethylacetal

**Short Communication**

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The selective esterification of some *Z*-amino acids with glyceraldehyde-diethylacetal by using different OH-blocking groups is described.

*Notiz zur Veresterung einiger Z-Aminosäuren mit Glycerinaldehyddiethylacetal (Kurze Mitteilung)*

Es wird die selektive Veresterung einiger *Z*-Aminosäuren mit Glycerinaldehyd-diethylacetal unter Verwendung verschiedener OH-Schutzgruppen beschrieben.

*[Keywords: 2-O-(N-Benzyloxycarbonyl-amino acid)-3-O-(4-methoxyphenyl-diphenylmethyl)-DL-glyceraldehyde-diethylacetal; DL-Glyceraldehyde-diethylacetal-3-(4-methoxyphenyl-diphenylmethyl)-ether]*

In continuation of our research on defined compounds between amino acids and carbohydrates linked by an ester bridge we are now reporting some further products, which are formed by selective esterification of amino acids with glyceraldehyde-diethylacetal and glyceraldehyde-diethylacetal-3-triphenylmethylether[1] respectively (compounds **1** and **2**, see Table 1). The syntheses of these compounds were carried out in the presence of 1,1′-carbonyldiimidazole.

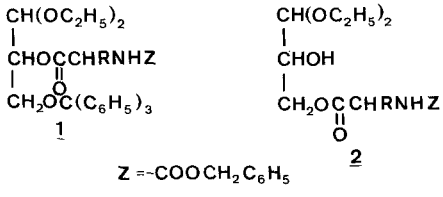


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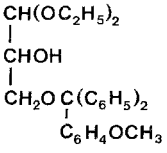
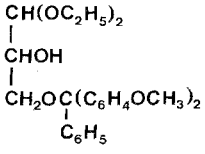
Table 1. *Preparation of 2-O-(N-Benzyloxycarbonyl-amino acid)-3-O-trityl-DL-glyceraldehyde-diethylacetal* (**1**) *and 3-O-(N-Benzyloxycarbonyl-amino acid)-DL-glyceraldehyde-diethylacetal* (**2**)

| Product | —*R* | Yield (%) | Molecular formula[a] |
|---|---|---|---|
| **1a** | $-CH_2SCH_2C_6H_5$ | 45 | $C_{44}H_{47}NO_7S$ (m. p. 146-148°) |
| **2a** | $-CH_2SCH_2C_6H_5$ | 7 | $C_{25}H_{33}NO_7S$ |
| **2b** | $-CH_2CH(CH_3)_2$ | 34 | $C_{21}H_{33}NO_7$ |

In a preceding paper[1] we have reported the difficulties of deblocking the trityl-group. In order to overcome this obstacle we proceeded as follows: i) Glyceraldehyde diethylacetal-3-(4-methoxyphenyl-diphenylmethyl)-ether (**3a**) and glyceraldehyde-diethylacetal-3-[bis(4-methoxyphenyl)-phenylmethyl]-ether (**3b**) were synthesized because it is known that the rate of acidic hydrolysis increases by approximately one order of magnitude for each *p*-methoxy-substituent introduced[2,3]. ii) Tetrahydropyranylether was used as the OH-protective group.



**3a**



**3b**

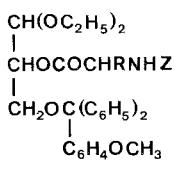
Compound **3b** is isolated only in poor yield, thus we tried to esterify some *Z*-amino acids with **3a** to obtain compounds **4** (see Table 2). Hydrolysis [$BF_3 \cdot (C_2H_5)_2O/CH_3OH$[4]] of **4a** leads to **5** which is also obtained from the correspondent tritylether[2]. No remarkable difference of the rate of acidic hydrolysis could be observed.

Table 2. *Preparation of 2-O-(N-Benzyloxycarbonyl-amino acid)-3-O-(4-methoxyphenyl-diphenylmethyl)-DL-glyceraldehyde-diethylacetal* (**4**)

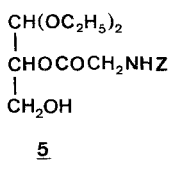
| Product | —*R* | Yield (%) | Molecular formula[a] |
|---|---|---|---|
| **4a** | —H | 11 | $C_{37}H_{41}NO_8$ |
| **4b** | $-CH_3$ | 5 | $C_{38}H_{43}NO_8$ |
| **4c** | $-CH_2C_6H_5$ | 5 | $C_{44}H_{47}NO_8$ |

[a] All compounds gave satisfactory elemental analyses.

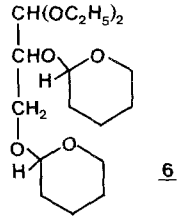
The reaction of glyceraldehyde-diethylacetal and dihydropyran was carried out in ether and $BF_3 \cdot (C_2H_5)_2O$ as catalyst[5]. Only the bis-protected product **6** could be isolated.



**4**



**5**



**6**

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## Experimental

**1**, **2** and **4** were prepared according to Ref.[1].

*DL-Glyceraldehyde-diethylacetal-3-(4-methoxyphenyl-diphenylmethyl)-ether* (**3 a**)

A solution of 0.05 mol *DL*-glyceraldehyde-diethylacetal and an equimolar amount of *p*-anisyldiphenylmethyl chloride in dry pyridine (50 ml) was kept at 50° for 48 h. It was then poured into 150 ml of water and extracted with ether. The organic layer was washed with diluted citric acid, $H_2O$, $NaHCO_3$-solution and $H_2O$ and dried over $K_2CO_3$. Chromatography of the residue on silica gel (toluene/ethyl acetate 3:1) gave a yield of 74%. The oil could not be crystallized. Calcd. for $C_{27}H_{32}O_5$ (436.6): C 74.29 H 7.40. Found: C 74.80 H 7.44. $^1$H-NMR ($CDCl_3$): $\delta = 1.19$ (6 H, dtc, $CH_3$), 2.49 (1 H, d, OH), 3.32 (2 H, part of an ABM-system, H-3), 3.48-3.78 (5 H, m, $OCH_2$ and H-2), 3.81 (3 H, s, $OCH_3$), 4.66 [1 H, d, $HC(OR)_2$], 6.88 (2 H, d, *o-ar*H), 7.22-7.54 (12 H, m, *ar*H).

*DL-Glyceraldehyde-diethylacetal-3-(bis(4-methoxyphenyl)-phenylmethyl)-ether* (**3 b**)

Reaction of equimolar amounts of *DL*-glyceraldehyde-diethylacetal and *p*-dianisyl-phenylmethyl chloride as described above afforded 5% of **3 b**. Calcd. for $C_{28}H_{34}O_6$ (466.6): C 72.08 H 7.35. Found: C 71.80 H 7.24. $^1$H-NMR ($CCl_4$): $\delta = 1.19$ (6 H, mc, $CH_3$), 2.48 (1 H, s, OH), 3.06-3.68 (7 H, m, $OCH_2$, H-2 and H-3), 3.71 (6 H, s, $OCH_3$), 4.54 [1 H, d, $HC(OR)_2$], 6.73 (4 H, d, *o-ar*H), 7.04-7.48 (9 H, m, *ar*H).

*2-O-(N-Benzyloxycarbonyl-glycyl)-DL-glyceraldehyde-diethylacetal* (**5**)

Treatment of **4 a** with $BF_3/(C_2H_5)_2O$ in methanol as described[1] gave **5** in quantitative yield.

*2,3-Di-O-tetrahydropyranyl-DL-glyceraldehyde-diethylacetal* (**6**)

A mixture of 1.64 g (0.01 mol) *DL*-glyceraldehyde-diethylacetal, 3.36 g (0.04 mol) 3,4-dihydro-2*H*-pyran and some drops of $BF_3 \cdot (C_2H_5)_2O$ in 20 ml dry ether was stirred at room temperature for 2 h. Evaporation under reduced pressure provided 1.3 g (38%) of **6**. Calcd. for $C_{17}H_{32}O_6$ (332.4): C 61.42 H 9.70. Found: C 61.70 H 9.12.

$^1$H-NMR ($\delta$ in ppm); Bruker WH 270; due to the use of *L*-amino acids and *DL*-glyceraldehyde-diethylacetal the $^1$H-NMR-spectra contain the superimposed signals of the diastereomers and diastereotopic groups.

**1a**: (acetone-$d_6$); 1.0 (6 H, mc, $CH_3$), 2.91 (2 H, mc, C**H**$_2$SCH$_2$*ar*), 3.22–3.81 (6 H, m, $OCH_2$), 3.74 (2 H, d, $SCH_2$*ar*), 4.61 (1 H, mc, OCOC**H**$_2$NH), 4.66 (1 H, d, H of C-1), 5.02–5.13 (3 H, m, $COOCH_2$*ar* and H of C-2), 6.73 (1 H, dd, NH), 7.06–7.55 (25 H, m, *ar*H).

**2a**: ($CDCl_3$); 1.2 (6 H, mc, $CH_3$), 2.76 (3 H, mc, C**H**$_2$SCH$_2$*ar*), 3.53 (4 H, mc, $OCH_2R$), 3.66 (2 H, s, —SC**H**$_2$*ar*), 3.80 (1 H, mc, C**H**OH), 4.14–4.41 [3 H, mc, $CH_2OCO$ and $CH(OR')_2$], 4.57 (1 H, mc, COC**H**NH), 5.05 (2 H, s, $COOCH_2$*ar*), 5.81 (1 H, d, NH), 7.17–7.34 (1 OH, m, *ar*H).

**2b**: (acetone-$d_6$); 0.93 [6 H, d, $CH(CH_3)_2$], 1.2 (6 H, mc, $CH_3$), 1.50–1.84 [3 H, m, $CHCH_2CH(CH_3)_2$ and OH], 1.94 [1 H, mc, C**H**$(CH_3)_2$], 3.42–3.96 (6 H, m, $OCH_2$, C**H**OH and part of $CH_2OCO$), 4.14–4.49 [3 H, m, part of $CH_2OCO$ and $CH(OR)_2$], 5.09 (2 H, s, $CH_2$*ar*), 5.94 (1 H, d, NH), 7.32 (5 H, s, *ar*H).

**4a**: ($CDCl_3$); 1.11 (6 H, dtc, $CH_3$), 3.26–3.72 (7 H, m, $OCH_2$ and H of C-2), 3.77 (3 H, s, $OCH_3$), 4.07 (2 H, d, CO—C**H**$_2$—NH), 4.74 [1 H, d, $CH(OR)_2$], 5.13 (2 H, s, COOC**H**$_2$-*ar*H), 5.3 (1 H, broad, NH), 6.84 (2 H, d, *o-ar*H), 7.16–7.49 (17 H, m, *ar*H).

**4b**: ($CDCl_3$); 1.1 (6 H, dtc, $CH_3$), 1.42 (3 H, dd, alanine —$CH_3$), 3.21–3.71 (6 H, m, $OCH_2$), 3.75 (3 H, s, $OCH_3$), 4.48 (1 H, m, NH—C**H***R*—CO), 4.73 [1 H, dd, $HC(OR)_2$], 5.04–5.18 (3 H, m, H of C-2 and O—C**H**$_2$-*ar*H), 5.44 (1 H, broad, NH), 6.81 (2 H, d, *o-ar*H), 7.13–7.46 (17 H, m, *ar*H).

**4c**: ($CDCl_3$); 1.04–1.26 (6 H, m, $CH_3$), 2.94–3.77 (8 H, m, $OCH_2$ and $CH_2$ of phenylalanine), 3.78 (3 H, s, $OCH_3$), 4.51–4.78 [2 H, m, C**H**—NH and $CH(OR)_2$], 5.04–5.16 (3 H, m, OC**H**-*ar*H and H of C-2), 5.28 (1 H, broad, NH), 6.84 (2 H, d, *o-ar*H), 7.16–7.41 (22 H, m, *ar*H).

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