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ORIGINAL ARTICLE

An improved protocol for the preparation of (*S*)-vinylglycine from (*S*)-methionine

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Abstract We present an optimized procedure for the synthesis of (*S*)-vinylglycine from (*S*)-methionine. The key step is a solvent free pyrolysis of an intermediate sulfoxide at high temperature. Using our optimized reaction conditions, Cbz-protected vinylglycine was obtained in high yield and with almost no side products. The protocol is scalable, fast and avoids the use of poisonous reagents.

Keywords Amino acids · Vinylglycine · Natural products · Pyrolysis

Introduction

β,γ-Unsaturated amino acids are common natural products and play a key role as mechanistic intermediates for several pyridoxal phosphate (PLP)-dependent enzymes involved in transaminations and eliminations (Berkowitz et al. 2006). Several applications of these compounds as herbicides and fungicides in plant protection and as food ripening inhibitors are known (Capitani et al. 2005; Rando 2002). The most prominent member of this amino acid family is vinylglycine, which has been intensively studied with respect to biological properties and as a building block for synthetic organic chemistry. (*R*)-Vinylglycine is a natural product produced by the mushroom *Rhodophyllus nidorosus*, whereas (*S*)-vinylglycine is generated in a variety of PLP-dependent enzymes as a mechanistic intermediate. Its broad-spectrum inhibiton properties make vinylglycine an extremely useful compound for the study of PLP-dependent enzymes.

In addition to interesting biological properties, vinylglycine has been intensively used as a building block in synthetic organic chemistry. Numerous applications in peptide chemistry (Chowdhury and Boons 2005; Howard-Jones et al. 2007; Marchand et al. 2008; Nolen et al. 2003; Xiao et al. 2008), the synthesis of amino acids (Wityak et al. 1987), peptide mimetics (Büchert et al. 2006; Chiou et al. 2007; Organ et al. 2002; Selvam et al. 2007), and in natural product syntheses (Aponick et al. 2008; Denmark et al. 2009; Kitamura et al. 2004) have been reported (recent selected examples are cited).

In consequence, a number of syntheses of this valuable amino acid have been reported. Some among these syntheses are racemic (Agouridas et al. 1985; Angst 1987; Baldwin et al. 1977; Ben-Ishahi et al. 1977; Bicknell et al. 1988; Castelhano et al. 1986; Chari and Wemple 1979; Fitzner et al. 1985; Greenlee 1984; Heinzer and Bellus 1981; Johnston et al. 1981; Vyas et al. 1984), diastereoselective (Hamon et al. 1992; Schöllkopf et al. 1984) and catalytic enantioselective approaches (Armstrong et al. 2007; Berkowitz and Maiti 2004; Trost et al. 2000), including enzymatic resolutions (Friis et al. 1974; Hallinan et al. 1994). In practice, ex-chiral pool strategies are the most frequently used because they combine a low number of steps with good enantiomeric purity of the product. Chiral educts are mannitol (Badorrey et al. 1997; Mulzer and Funk 1995), xylose (Chandrasekhar et al. 2002), glutamate (Barton et al. 1985; Hanessian and Sahoo 1984; Krol et al. 1991), serine (Beaulieu et al. 1991; Reginato et al. 2005; Rose et al. 2001), homoserine (Itaya et al. 1994; Pellicciari et al. 1988), and homoserine lactone (Berkowitz

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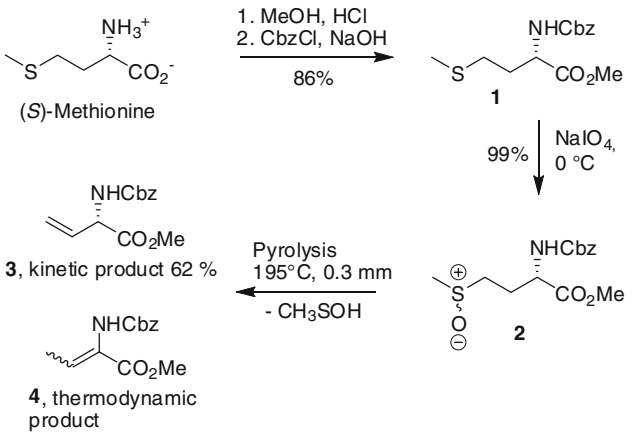

Scheme 1 Rapoport's synthesis of Cbz-vinylglycine methyl ester **3**

and Smith 1996). In addition, methionine has been frequently used as an educt for the synthesis of vinylglycine. A short four-step procedure to Cbz-protected vinylglycine methylester **3** (Scheme 1) has been reported by Rapoport (Afzaliardakani and Rapoport 1980; Carrasco et al.1992). This protocol has later been used by several groups (including ours) for the preparation of vinylglycine. The key step of this sequence is the thermolytic elimination of methyl sulfenic acid from sulfoxide **2** to give the desired double bond in **3** along with a mixture of *E/Z*-isomers **4**. This step has been optimized earlier by Meffre, who used *o*-dichlorobenzene as a solvent for elimination (Meffre et al. 1989), and Griesbeck by a photochemical elimination (Griesbeck and Hirt 1995). Meffre's method is readily scalable and overcomes many of the problems associated with other protocols, but gives a somewhat lower yield (48%), whereas Griesbecks protocol is not suitable for large-scale preparations. Thermal eliminations of sulfoxides have been shown to be dependent on the nature of substituents attached to sulfur and may be performed at relatively low temperature (80°C) in solution (Patel and Long 2009). However, the preparation of the required precursors adds to the overall number of synthetic steps, making this approach less attractive.

Materials and methods

General

TLC was performed on silica gel aluminum sheets. Flash column chromatography was performed on silica gel (0.04–0.063 mm; 230–400 mesh ASTM). ^{1}H chemical shifts are referenced to residual non-deuterated solvent ($CHCl_3$, $\delta_H = 7.26$ ppm). ^{13}C chemical shifts are referenced to the solvent signal ($CDCl_3$, $\delta_C = 77.16$ ppm). NMR spectra were recorded on a 400-MHz instrument. Optical rotations are reported at 589 nm. The following compounds were prepared according to literature procedures: Cbz-(*S*)-methionine methylester **1**, (*S*)-methyl-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate **2** (Carrasco et al. 1992).

Cbz-(*S*)-vinylglycine methyl ester **3**. 10.0 g sulfoxide **2** (32.0 mmol) were distilled in a Kugelrohr apparatus at 205°C and 0.012 mbar. A small tube, directly after the evaporation vessel, was preheated to about 600°C by a pyrolysis oven or a heat gun. The distillate was collected in an ice-cooled bulb to give 7.77 g of a slightly yellow oil, which slowly crystallizes upon cooling. This crude product has a purity of ~95% according to ^{1}H-NMR and can be further purified by column chromatography (Hexane/EtOAc 6:1) to give 6.26 g (25.1 mmol, 79%) of the title compound as a colorless solid. $[\alpha]_D^{26} = -8.04$ (c 7.1; MeOH); Mp.: 35−36°C; $R_f = 0.35$ (Hexane/EtOAc, 2:1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44–7.27 (m, 5H, Ar–H), 6.00−5.81 (m, 1H, C**H**=CH_2), 5.50 (br d, 1H, NH), 5.36 (dd, 1H, $^{2}J = 1.3$ Hz, $^{3}J = 17.1$ Hz, CH=C**H**$_{trans}$), 5.28 (dd, 1H, $^{2}J = 1.3$ Hz, $^{3}J = 10.3$ Hz, CH=**CH**$_{cis}$), 5.13 (s, 2H, C**H**$_2$Ph), 4.89−5.01 (m, 1H, α-H), 3.77 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.0 (MeO-***C***O), 155.7 (NH***C***O), 136.3 (***C***$_q$-Ar), 132.4 (***C***H=CH_2), 128.7 (Ar), 128.3 (Ar), 128.3 (Ar), 117.9 (CH=***C***H_2), 67.3 (O***C***H_2-Ar), 56.2 (NH***C***H), 52.9 (O***C***H_3); Elemental analysis: calcd. C 62.64%, H 6.07%, N 5.62%; found C 62.42%, H 6.13%, N 5.34%; IR (KBr) [v^{-1}]: 3295, 3067, 3032, 2954, 2894, 1747, 1691, 1641, 1548, 1467, 1455, 1437, 1409, 1377, 1339, 1274, 1256, 1218, 1178, 1092, 1028, 995, 944, 917, 903, 841, 792, 777, 759, 736, 695.

Results and discussion

For a project in cancer cell imaging (Humblet et al. 2009; Misra et al. 2007) we needed multigram quantities of **3**, which is a valuable precursor for cancer-specific carboxypeptidase ligands (Feng and Coward 2006; Zhou et al. 2005). The Rapoport protocol was our first choice because it is short, efficient, and most importantly, for biological applications, it avoids the use of poisonous reagents like selenium species and heavy metal salts. However, the pyrolysis did not give the desired vinylglycine **3** in reproducibly high yields in our hands. In most cases we obtained mixtures of the desired product **3** (as the major component) and substantial amounts of the more stable isomer **4** along with starting material **2** [similar observations have also been made by Miller (Rajendra and Miller 1987)]. From these mixtures pure **3** can only be obtained by repeated chromatography [all products have similar retention factors on silica gel: R_f (kinetic product **3**): 0.35; R_f

Table 1 Experimental parameter for the thermal elimination of methyl sulfenic acid from sulfoxide **2** in a Kugelrohr apparatus according to Scheme 1

Entry	*T* (°C)	*P* (mbar)	*t* (h)	**3** (%)[a]	**4** (%)[a]	**2** (%)[a]
1[b]	195	0.3	3	60	8	32
2[d]	195	0.03	3	30	–	70
3[c]	210	0.3	3	52	26	22
4[d]	210	0.03	3	45	–	55

[a] Percentage of crude product, determined by ^{1}H-NMR

[b] Conditions according to Carrasco et al. (1992); approximately 60% of sulfoxide **2** remained undistilled in the evaporation vessel

[c] Approximately 40% of sulfoxide **2** remained undistilled in the evaporation vessel

[d] Complete distillation

(thermodynamic products (*E*/*Z*)-**4**): 0.42 and 0.25 (Hexane:EtOAc 2:1)] which is time-consuming and causes diminished yields, especially for large-scale preparations. Rapoport has noted in his early paper that the outcome of the pyrolysis is highly dependent on the pressure and temperature of the reaction and we have therefore performed a set of experiments under different conditions (Table 1).

From this data it became evident that temperature, time, and pressure of the reaction need to be carefully controlled. If the reaction is performed according to entry 1 in Table 1 at relatively low temperature (195°C) and 0.3 mbar, the distillation is not complete within 3 h, leaving a substantial portion of the educt **2** unchanged in the distillation vessel. The distillate contains the product **3** along with the isomerized derivative **4** and some educt **2**. Rising the temperature to 210°C (entry 3) while leaving the pressure constant (0.3 mbar) accelerates the distillation and leaves less educt **2** in the distillation vessel. The distillate contains in this case more of the unwanted isomer **4** but less of the educt **2** compared to entry 1, corresponding to a higher rate of elimination. Lowering the pressure to 0.03 mbar brings the distillation to completion within three hours (entries 2 and 4). In these two cases, the resulting distillate does not contain any isomerized material **4**. However, a large amount of sulfoxide **2** distills without elimination.

We concluded that an ideal protocol for the thermal elimination should have the following features: (a) high vacuum for a rapid distillation (less unwanted side products), (b) a moderate temperature in the evaporation vessel (less side reactions), and (c) a short exposure to high temperature in the gas phase (complete pyrolysis of sulfoxide **2** to alkene **3**). To achieve these conditions, we have included a second oven into a standard Kugelrohr apparatus according to Fig. 1. It should be noted that this pyrolysis oven might also be substituted by a standard laboratory heat gun.

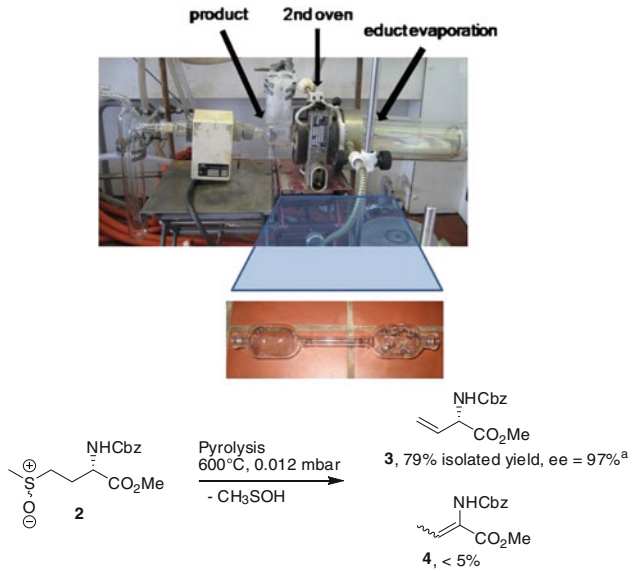

Fig. 1 Modified Kugelrohr apparatus and improved reaction scheme for the synthesis of Cbz-protected vinylglycine **3**. [a]The enantiomeric purity of **3** was determined by HPLC analysis of the crude product on a chiral stationary phase (see supporting information)

Table 2 Experimental parameter for the thermal elimination of methyl sulfenic acid from sulfoxide **2** in a modified Kugelrohr apparatus according to Fig. 1

Entry	*T*1 (°C)[a]	*T*2 (°C)[b]	*P* (mbar)	*t* (h)	**3** (%)[c]	**4** (%)[d]	**2** (%)[e]
1	230	380	0.011	1	70	–	30
2	240	410	0.018	1	66	–	34
3	215	500	0.016	1.5	74	–	26
4	215	600	0.010	1.5	89	–	11
5	205	600	0.012	2	>95	–	–

[a] Temperature in Kugelrohr apparatus

[b] Temperature of second oven ±20°C

[c] Percentage of vinylglycine **3** in the crude product, determined by ^{1}H-NMR

[d] Percentage of thermodynamic product **4** in the crude product, determined by ^{1}H-NMR

[e] Percentage of sulfoxid **2** in the crude product, determined by ^{1}H-NMR

As depicted in Table 2, we have used a relatively high vacuum of ~0.01−0.02 mbar to ensure a rapid distillation process, which is essential to avoid unwanted side reactions in the evaporation vessel. In consequence, none of the unwanted isomers **4** were detected in all cases. However, significant amounts of educt are observed in the distillate if the temperature in the evaporation vessel is too high or the temperature in the second oven is too low (entries 1−4).

According to Table 2 (entry 5), the best results were obtained with a modest evaporation temperature (205°C) and a high temperature of the second oven (600°C) leading

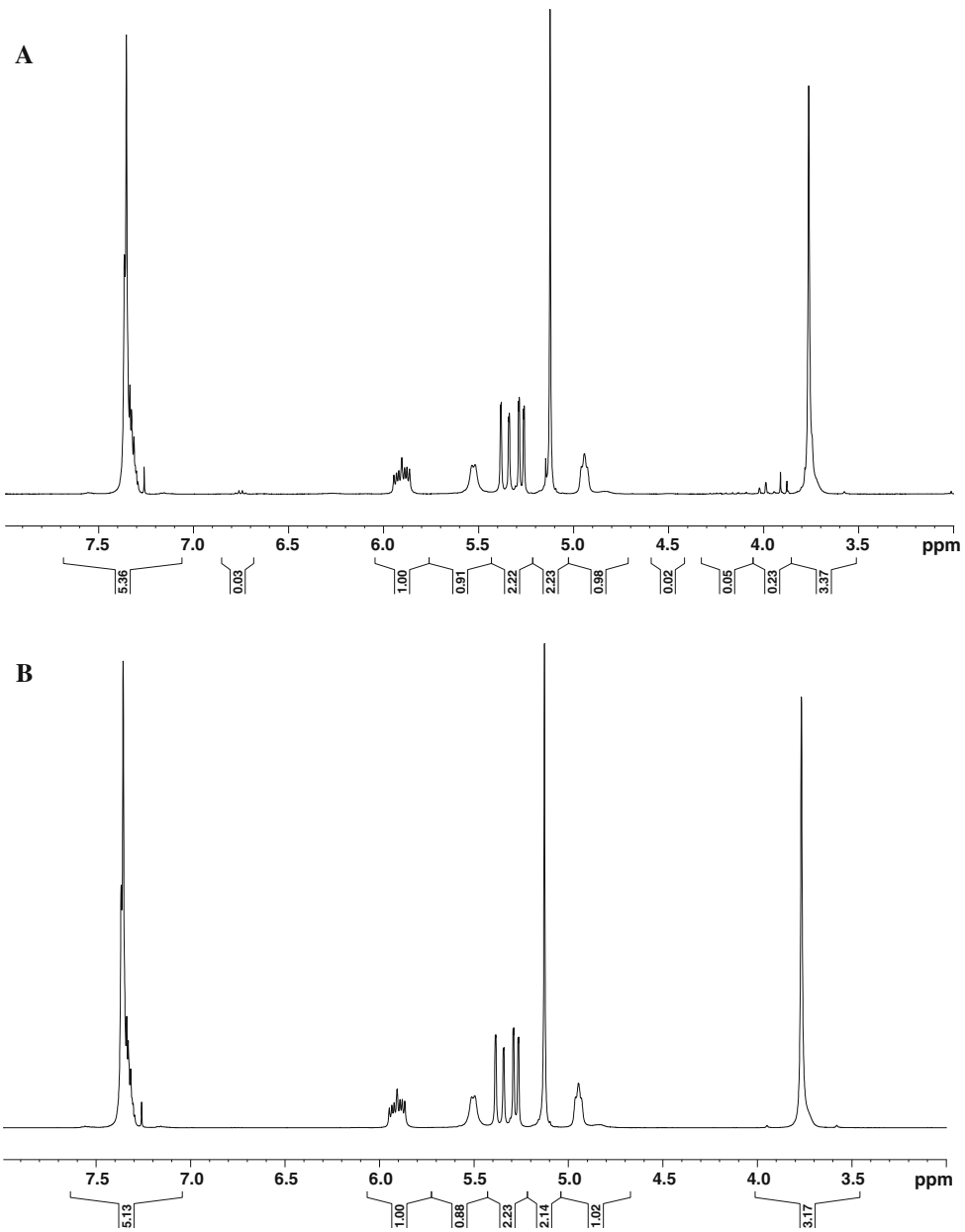

Fig. 2 **a** ^{1}H-NMR-spectrum of the distillate (crude product **3**) obtained according to entry 5, Table 2; **b** ^{1}H-NMR-spectrum of pure **3** after column chromatography for comparison

to a complete conversion of sulfoxide **2** in the gas phase to give almost pure **3** after 2 h without any remaining educt.

Using these optimized conditions a complete distillation and an almost quantitative conversion of sulfoxide **2** to alkene **3** is observed in the crude NMR spectrum of the distillate (Fig. 2). For most applications the purity of this crude product will be sufficient. However, complete removal of impurities can be achieved by a single-column chromatography to give vinylglycine derivative **3** in 79% isolated yield. It should be noted that the high-temperature conditions do not lead to epimerization: the product **3** was obtained with excellent enantiomeric purity after pyrolysis (97% ee, see supporting information for details).

In conclusion, we have developed an improved protocol for the thermal elimination of sulfoxide **2** to Cbz-protected vinylglycine **3**. This method relies on standard laboratory equipment and gives essentially pure protected vinylglycine **3** in excellent yield without chromatographic purification. It should be noted that the reported protocol is suitable for multigram synthesis of vinylglycine **3** and is thus a significant improvement compared to known methods for the preparation of this extremely valuable amino acid.

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