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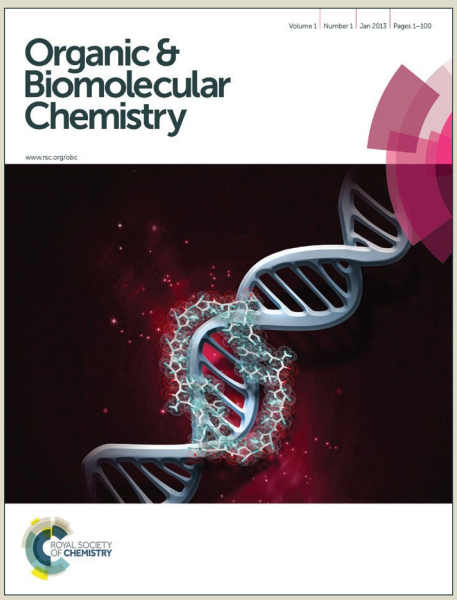

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COMMUNICATION

Continuous-Flow Thermolysis for the Preparation of Vinylglycine Derivatives

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***Syn* sulfoxide elimination was carried out under continuous-flow conditions in a mesofluidic thermolysis reactor. The design of the reactor enabled accurate control of reaction time and conditions, affording a convenient scale-independent procedure for the production of *N*,*C*-protected vinylglycine derivatives. Thermolysis at 270 °C under 1000 psi of pressure in superheated toluene enabled typical daily outputs ranging from 11 to 46 g day^{-1} with excellent selectivities and ee (> 97%). The various competitive reaction pathways were studied and rationalized according to a computational study.**

Introduction

Vinylglycine (VG) is the simplest but the most widely studied natural non-proteinogenic β,γ-unsaturated amino acid.[1] D-VG is produced by the mushroom *Rhodophyllus nidorosus*, while L-VG is a common metabolite or mechanistic intermediate produced in a variety of pyridoxal phosphate enzymatic processes.[1] VG displays a wide range of biological activities such as transaminase inhibition and antibacterial properties.[1] Consequently, VG and its derivatives have attracted a considerable attention from synthetic chemists. A plethora of synthetic strategies to produce VG have flourished since 1977[2] starting from methionine,[3] serine,[4] homoserine,[5] homocysteine,[6] mannitol,[7] xylose,[8] aspartic acid,[9] glutamic acid,[10] or other building blocks.[11] Either stereoselective or racemic strategies, possibly followed by enzymatic resolution, have been reported and reviewed.[1,3d,6] VG and derivatives have also found utility as chiral building blocks for accessing diverse and complex molecular architectures.[1,12]

Among the wide variety of strategies developed for the synthesis of VG derivatives, the most straightforward one involves the thermolysis of methionine sulfoxide (MetO) derivatives. This strategy, however, usually requires high temperatures and vacuum, and is hampered by extensive isomerization and degradation. Quintard *et al* reported a scalable process for the large-scale thermolysis of sulfoxides derived from *N*-Cbz-L-methionine methyl ester in batch.[3d] They reproduced the original procedure reported by Rapoport in a Kugelrhor distillation apparatus,[3a] but faced significant amounts of dehydrobutyrine isomers among other side products; after optimization, the thermolysis was performed in batch in refluxing mesitylene. Typically, 48 h were required to process 16.5 g of *N*-Cbz-L-methionine sulfoxide methyl ester (77%). The control of the temperature and the reaction time are paramount for achieving high conversion and selectivity for this reaction, but other parameters have also a significant impact on the reaction outcome such as additives and solvent nature.[3a,3b,3d,6] Long *et al* studied the impact of the nature of the sulfoxide on the thermolysis step by considering various alkyl and aryl homocysteine sulfoxides. The 2-nitrophenyl analog underwent *syn* elimination in refluxing toluene for 18 h.[6] Longer reaction times, or higher boiling point solvents increased the isomerisation of vinylglycine towards its dehydrobutyrine isomers. Despite promising results, this method suffers from long reaction time and requires less common homocysteine derivatives.

Continuous-flow chemical processing, *i.e.* chemical processes carried out in continuous-flow micro- and mesostructured reactors (μFRs), has emerged over the last decade as an economically viable alternative to batch reactors for a wide variety of synthetic applications.[13] They enable the continuous production of commodity and specialty chemicals according to a more reliable, reproducible, efficient and flexible manufacturing strategy.[14] μFRs offer a wide range of advantages for performing organic transformations, even under intensified[15] or extreme conditions (temperature, pressure):[16] precise control over local temperature conditions, fast mixing, inherent safety and homogeneity of the production are amongst the most important.[17]

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In this work, we report a scale-independent continuous-flow process for the stereoeselective thermolysis of MetO derivatives. The *syn* sulfoxide elimination required less than 2 min to reach 99% conversion in a mesofluidic continuous-flow device at 270 °C under 1000 psi of pressure (69 bar), using superheated toluene and in the presence of a methylsulfenic acid scavenger. The procedure conveniently sustains the production of up to 46 g day^{-1} of VG derivatives, and is compatible with a variety of *N*,*C*-protecting groups. We also provide a computational rationalization of the competitive reaction pathways leading to the formation of the main impurities, *i.e.* the *E*,*Z*-dehydrobutyrine isomers.

Results and discussion

N,*C*-Protected L- or D-methionine derivatives were prepared from commercial L- or D-methionine, and then oxidized towards the corresponding MetO derivatives **1a-g** using $NaIO_4$ according to litterature procedures.[3a,3b,3d,6] Common protecting groups were selected for this library of MetO derivatives: Cbz (L-,D-**1a** and L-**1e**), Boc (L-**1b**), Fmoc (L-**1c** and L-**1f**), NBOC (L-**1d** and L-**1g**) and methyl (**1a-d**) or benzyl (**1e-g**) esters for *N*- and *C*-termini protection, respectively (Scheme 1).

Flash thermolysis was carried out in a mesofluidic device consisting of a temperature-regulated oven embedded with a SS coil reactor (OD 1/16", ID 500 µm, V_{int} = 1.7 mL) (Scheme 1). The reactor setup enabled fast reaction parameters screening, *i.e.* temperature and residence time. The pressure was set at 1000 psi (69 bar) to enable superheated conditions inside the reactor. The reactor effluent was cooled to 10 °C, collected and then analyzed (off-line HPLC). The operational parameters were optimized on compound L-**1a** (feed concentration 10 g L^{-1}). Various solvents were tested, but the best results were obtained from experiments carried out in toluene;[6] besides, toluene eased downstream purification (see below).

The impact of both the temperature and the residence time (ranging from 34 s to 1.7 min) inside the thermolysis reactor are summarized in Figure 1 (entries 1-3, 10-12, 19-21). Higher temperatures and longer residence times increased the conversion of compound L-**1a** (calculated on the residual amount of L-**1a** in the crude mixture). The conversion with a 5 mL min^{-1} flow rate was 46, 86 and 98% at 250, 270 and 290 °C, respectively, while with a 1 mL min^{-1} flow rate, the conversion increased to 97, 99 and >99% at 250, 270 and 290 °C,

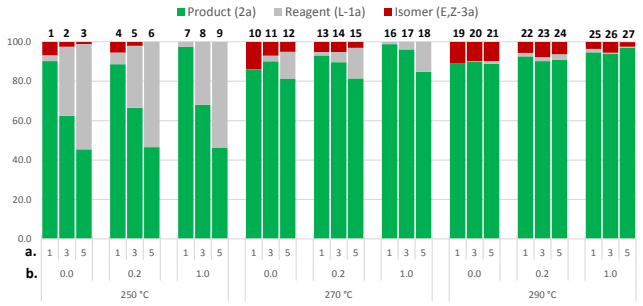


Figure 1 Composition of the crude reactor effluents (HPLC values, %) and optimization of the continuous-flow thermolysis on MetO derivative L-**1a**. (**a.** flow rates, mL min^{-1}; **b.** equiv. DMAD)

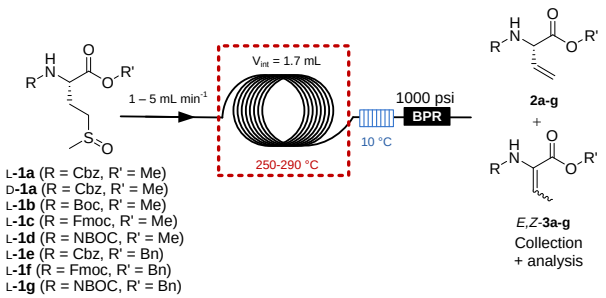
respectively (entries 1-3, 10-12 and 19-21). The product ratio (**2a**/*E*,*Z*-**3a**) was also significantly affected by the temperature and the residence time. At 250 and 270 °C, a larger amount of *E*,*Z*-**3a** was observed at longer residence times, and this amount increased with the temperature as well (entries 1-3 and 10-12). Such observations are consistent with previous literature reports.[3a,3b,3d,6]

At 290 °C, the effect of the temperature on the appearance of *E*,*Z*-**3a** dominated the effect of the residence time (Figure 1, entries 19-21). Since the *E*,*Z*-dehydrobutyrine isomers are difficult to separate from vinylglycine, their formation is still problematic.[6] Based on this preliminary study, an acceptable compromise between good conversion and low *E*,*Z*-**3a** contamination required 270 °C, 5 mL min^{-1} flow rate and 34 s residence time (Figure 1, entry 12), in which case the daily productivity of VG derivative reached 46 g day^{-1}.

Preliminary tests for accessing larger scales of VG derivatives ruled out a scaling-out approach.[13] The thermolysis of L-**1a** in a larger internal-diameter continuous-flow reactor led to a significant decrease of the conversion, most likely as a consequence of the appearance of temperature gradients across the section of the reactor.

A liquid-liquid extraction and separation module (Figure 2) was implemented after the reactor to eliminate the residual sulfoxide L-**1a** in the aqueous waste, while redirecting the organic stream for further purification. Attempts to remove the *E*,*Z*-**3a** isomers using an in-line cartridge filled with supported scavengers such as silica-adsorbed cysteamine failed, leading to increased amounts of *E*,*Z*-**3a** by base-catalyzed isomerization of vinylglycine **2a**.[18]

In order to improve the efficiency of the thermolysis and to



Scheme 1 Continuous-flow thermolysis of methionine derivatives **1a-g**

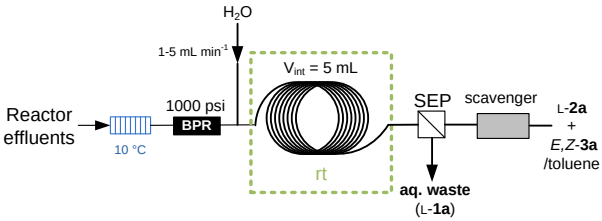


Figure 2 In-line purification with an extraction/separation module

get a complete picture of the competitive reaction pathways, a computational study was undertaken. Computations were performed at the B3LYP/6-31+G* level of theory to rationalize the formation of dehydrobutyrine isomers *E,Z*-**3**, and the corresponding results are presented in Figure 3. The initial thermolysis from a model MetO derivative **1** to vinylglycine derivative **2** proceeds with an activation barrier of 25.2 kcal mol^{-1}, and is an endothermic reaction ($\Delta H°$ = 6.6 kcal mol^{-1}). The direct isomerization of compound **2** towards dehydrobutyrine derivatives *E,Z*-**3** through a thermal [1,3]-shift has a high activation barrier (69.4 kcal mol^{-1}), and is an exothermic reaction ($\Delta H°$ = -6.5 kcal mol^{-1}). The high activation barrier can be correlated with the increased amount of dehydrobutyrine isomers at higher temperatures.[3a,3b,3d,6] However, the natural by-product of the reaction, *i.e.* methylsulfenic acid (MeSOH), and its confined presence with vinylglycine triggers a much more favorable pathway towards dehydrobutyrine isomers. This competitive route proceeds through the formation of Markovnikov adduct **4** (ΔG^{TS} = 22.0 kcal mol^{-1}), which then undergoes thermolysis towards dehydrobutyrine derivatives *E,Z*-**3** (ΔG^{TS} = 17.8 kcal mol^{-1}). These results emphasize that in a confined system or without proper quench to suppress methylsulfenic acid, a more favorable competitive reaction path takes place and eventually leads to significant contamination with dehydrobutyrine isomers. Last, the epimerization from L- to D-vinylglycine proceeds under these conditions through a [1,3]-shift with a very high activation barrier (see Supporting Information). This is to be correlated with the low epimerization observed under these conditions.

From these results, we expected that proper *in situ* quenching of methylsulfenic acid would suppress the formation of Markovnikov adduct **4**, and hence its thermolysis towards *E,Z*-**3**. A variety of sulfenic acid scavengers have been previously reported,[3b,6,19] but few are compatible with a development in a continuous-flow mesofluidic thermolysis reactor. Dimethyl acetylenedicarboxylate (DMAD) attracted our attention since it is a strong electrophile with a good tolerance to high temperatures, and it was successfully used in the past for quenching sulfenic acids.[19] The results of the thermolysis of L-**1a** in the presence of substoichiometric (0.2 equiv.) or stoichiometric amounts of DMAD are presented in Figure 1 (entries 4-9, 13-18, 22-27). The experiments at 250 and 270 °C showed that 1 equivalent of DMAD suppressed the formation of the dehydrobutyrine isomers at the shortest residence times (Figure 1, entries 9 and 18). At 290 °C, up to 5.5% dehydrobutyrine isomers were still present in the crude mixture, despite the presence of DMAD. These results suggest that at higher temperatures, the competitive thermal [1,3]-isomerization is most likely the predominant pathway leading to the formation of the dehydrobutyrine isomers, while at lower temperatures (270 °C), the predominant isomerization pathway involves methylsulfenic acid.

With the in-line quench of methylsulfenic acid, the best conditions for the thermolysis of L-**1a** required 270 °C, 1 mL min^{-1} flow rate and 1.7 min residence time (Figure 1, entry 16) with 99% conversion.[20] The remaining traces of L-**1a** could be efficiently removed using the in-line extraction/separation module described in Figure 2, or by chromatography on silica gel. The Michael adduct from the mono-addition of methylsulfenic acid on DMAD could be easily removed from the crude vinylglycine samples by chromatography on silica gel. The enantiomeric excess was determined by HPLC and was consistently >97%. Similar results were observed in the D-series.

Next, we transposed the optimized conditions for the thermolysis of substrates **1b-g** (Table 1). The thermolysis of substrate L-**1b** failed and led to complete decomposition, as expected from the literature results.[12o] As summarized in Table 1, the thermolysis of derivatives **1c-1g** proceeded with excellent selectivity. The residual sulfoxide (1-3%) was removed by liquid-liquid extraction with water (see Figure 2).

Conclusions

In summary, we have developed a convenient, scale-independent and highly-selective procedure for the continuous-flow preparation of VG derivatives using super-heated toluene. The successful development of this continuous-flow process relied on a computational rationalization of the various competitive reaction pathways. The competitive formation of dehydrobutyrine derivatives was suppressed with the *in situ* quenching of the thermolysis by-product methylsulfenic acid. The implementation of an in-line liquid-liquid membrane separator enabled the integration of downstream purification.

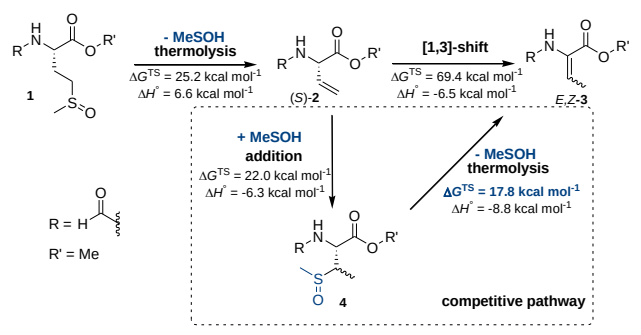


Figure 3 Competitive reaction pathways computed at the B3LYP/6-31+G* level of theory

Table 1 Thermolysis of MetO derivatives L-**1b-g** [a]

	Residual **1b-g** (%)	**2b-g** (%)	*E,Z*-**3a-g** (%)
1b [b]		decomposition	
1c [b]	2	98	-
1d [c]	2	98	-
1e [b]	1	99	-
1f [b]	2	98	-
1g [b]	3	97	-

[a] HPLC conversion
[b] 10 g L^{-1} feed solution
[c] 5 g L^{-1} feed solution

Acknowledgements

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20 Typical procedure: a feed solution of L-**1a** (10 g L^{-1}) and DMAD (1.0 equiv.) was prepared in toluene, and conveyed to the thermolysis reactor (T = 270 °C, back pressure P = 1000 psi) via a HPLC pump set at 1 mL min^{-1}, with a 1.7 min residence time in the thermolysis reactor. The reactor

effluents were directed to a waste tank until the reactor reached steady state. After 5 min, the reactor effluents were collected and sampled every 10 min for analysis (HPLC).
Continuous liquid-liquid extraction: the reactor effluent was cooled down to 10 °C and mixed with a stream of water (1 mL min^{-1}) and directed to an extraction/separation module consisting of a tubular PFA reactor (5 mL internal volume, 1/8" o.d.) and a continuous-flow liquid-liquid membrane separator (Zaiput Flow Technologies®). The aqueous stream was connected to a waste tank, and the organic (toluene) stream was collected and analyzed.