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One-pot synthesis of β-amino acid derivatives via addition of bis(*O*-silyl) ketene acetals on iminium salts

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The authors wish to dedicate this work to the memory of their friend Bernard Denise

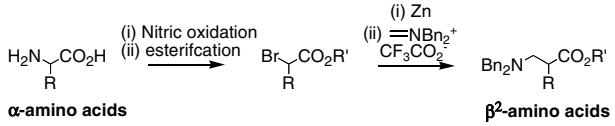
Abstract—We report here our findings on a new and highly efficient strategy for the synthesis of β-amino acids involving the addition of bis(*O*-silyl) ketene acetals on Mannich type iminium electrophiles.

1. Introduction

The Mannich reaction between a carbonyl compound and an in situ generated imine is a classical method for the preparation of β-amino ketones and represents one of the most important basic reaction types in organic chemistry.[1] It has also been extended to the preparation of β-amino acids[2] and β-lactams by the use of preformed enol synthetic equivalents.[3] However, this reaction is difficult to apply to the synthesis of compounds bearing no substituent in position 3. This is mainly due to the difficult access to a stable formyl imine equivalent. Many reagents were reported in the literature in order to overcome this limitation, for instance, the use of precursors such as *N*,*O*-acetals or aminals, which lead to formyl iminium ion by activation with a strong Lewis acid. However, these unstable reagents are difficult to prepare and to handle. Plus, their poor reactivity leads to low yields of aminomethylation.[4] Finally, the protecting groups of these aminomethylating agents have to be removed under harsh conditions.[5]

Knochel and co-workers reported the reaction of preformed dibenzylidene iminium trifluoroacetate salt, obtained from the corresponding *N*,*N*,*N*″,*N*″-tetrabenzyl aminal, with organozinc and magnesium derivatives.[6] We have recently shown that this reaction can be extended to zinc-enolates in a Reformatsky type reaction leading to β^2-amino acids bearing proteinogenic amino acids side chains[7] (Scheme 1).

In the reported strategy, zinc-enolates were generated after nitric oxidation and subsequent esterification of α-amino acids, and reacted with dibenzylidene iminium trifluoroacetate, leading after classical deprotection steps to β^2-amino acids. Enantiomerically pure Boc-β^2-homoleucine was obtained in a good overall yield starting from inexpensive (L)-leucine and using Oppolzer's sultam as the chiral auxiliary. However, if excellent selectivity was obtained in that case, further



Scheme 1. β^2-Amino acids synthesis by homologation of α-amino acids.

Keywords: β-Amino acids; Bis(*O*-silyl) ketene acetals; Mannich type iminium electrophiles.
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investigations demonstrated that unsatisfying diastereoselectivities were obtained for derivatives bearing side chains with poor steric hindrance. On a formal point of view, the homologation route we have developed could be considered as the aminomethylation of an ester enolate, as first reported by Evans et al.[8] and Oppolzer et al.[9] and then applied by Lelais and Seebach to the preparation of β^2-amino acids.[10] However, the aminomethylating reagents used in the previously described syntheses present severe limitations, which have hampered up-scaling. We hypothesized that the addition of dibenzylidene iminium trifluoroacetate onto ester enolates might circumvent all these restrictions. However, all the attempts with ester enolates generated by various bases have failed. Silyl enol ether derivatives have been reported as an alternative to ester enolates; they have been used for example in Mannich type reactions using preformed or in situ generated methylene iminium salts.[11] In order to get a general methodology, we reported recently that the in situ generated iminium ion can also be introduced on chiral silyl ketene *N*,*O*-acetals[12] (Scheme 2).

This methodology allowed us to prepare a wide range of optically pure β^2-amino acids bearing alkyl or functionalized side chains, orthogonally protected for peptide synthesis. We have shown that the *N*,*N*,*N*′,*N*′-tetrabenzyl aminal can be very easily prepared on a 100 g scale, isolated and stored as a highly stable crystalline compound. Consequently, it represents a very convenient precursor for aminomethylating reagent. One possible improvement of the reported synthesis would be the reduction of the number of steps, for instance, by reducing the deprotection procedures. Among silyl enol derivatives, bis(*O*-silyl) ketene acetals constitute an original class of nucleophiles, as they can behave as 1,3-carbon, oxygen dinucleophiles resulting from the successive cleavage of both oxygen–silicon bonds. Kunz and co-workers have reported the reaction between bis(*O*-silyl) ketene acetals and *N*-galactosyl-aldimines in the presence of zinc chloride leading to disubstituted $\beta^{2,3}$-amino acid derivatives in high yields and diastereoselectivity.[13] However, the addition on non-substituted Schiff bases, (i.e., formylimine derivatives that would lead to β^2-amino esters) was not reported. Rudler and co-workers have recently shown that the addition of bis (*O*-trimethylsilyl) ketene acetals to pyridines and their derivatives, in situ activated with ethylchloroformate, could occur both at the α- and β-carbon atom with respect to the nitrogen atom, that is, on a formal point of view, at the carbon of an iminium.[14] Simultaneously, the same group and the group of Langer extended this strategy to other N-heterocyles.[15] The ease of preparation of bis(trimethylsilyl) ketene acetals and their clean reaction with activated imine electrophiles led us to explore their potential as nucleophiles in aminomethylation reactions with formyl iminium ion derivatives. If successful, such a reaction would lead to β^2-amino acid derivatives by a mononucleophilic addition reaction to iminium salts. Herein, we describe our preliminary results on the reactivity of bis(*O*-trimethylsilyl) ketene acetals toward various iminium electrophiles, results which led not only to β^2-amino acid derivatives, but also depending on the structure of the starting ketene acetals to α,β-unsaturated δ-amino acid derivatives.

2. Results and discussion

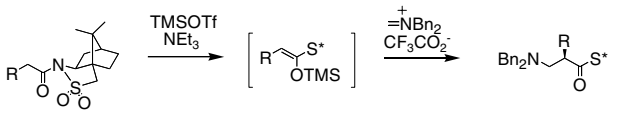
In a preliminary study, we have shown that in the presence of ethylchloroformate, imine **2** is able to add to bis(*O*-trimethylsilyl) ketene acetals, leading to a new product, obtained in 40% yield as a white solid, mp 130 °C. According to NMR data, its structure is consistent with the disubstituted β-amino acid **3a**[16] (Scheme 3).

The same behavior was obtained with the monosubstituted ketene acetal **1b**, which led to a 3:1 mixture of diastereomeric acids **3b**.

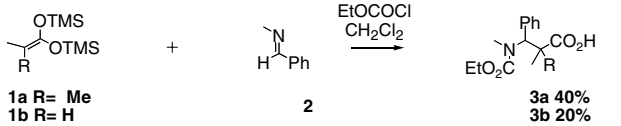
We assumed that the imine is first activated by the addition of the ethylcarbonyl group on the nitrogen atom leading to an iminium ion, which reacts then with the ketene acetal. Since the crucial intermediate in these transformations is an iminium salt, the scope of this methodology was analyzed by reacting various ketene acetals with different iminium salts. Thus, compounds **4a**–**c** were generated from the corresponding aminals in the presence of acetyl chloride or trifluoroacetic anhydride. They were reacted with different bis (*O*-trimethylsilyl) ketene acetals after isolation (**4a**) or in situ generated in a one-pot procedure (**4b** and **4c**) avoiding difficult handling of the iminiums and thus leading to better yields in these cases[17] (Scheme 4, Table 1).

Amino acid **5a** was obtained in 50% yield by condensing the isolated iminium salt **4a** on ketene acetal **1a**. In a one-pot procedure, compound **6a** was obtained as a white solid in 70% yield. Finally, ketene acetals **1a**–**e** were reacted with the iminium salt **4c** (i.e., dibenzylidene iminium trifluoroacetate) leading to compounds **7a**–**e**, obtained as solids or an oil (**7d**) in good yields. Interestingly, among the iminium salts, **4c** led to β^2-amino acid derivatives that could be debenzylated and suitably protected for peptide synthesis (Scheme 5).

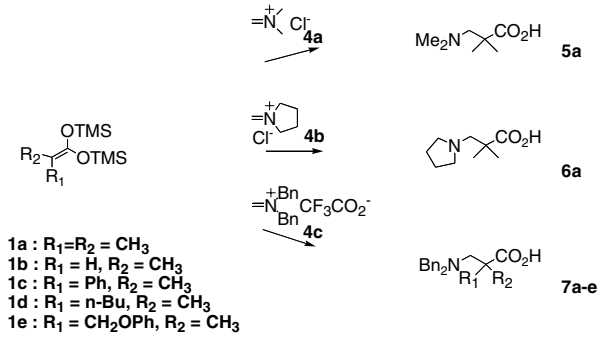
Noticeably, the use of bis(trimethylsilyl) ketene acetals led to carboxylic acid, avoiding additional deprotection



Scheme 2. Addition of chiral silyl ketene *N*,*O*-acetals on in situ generated iminium salt.



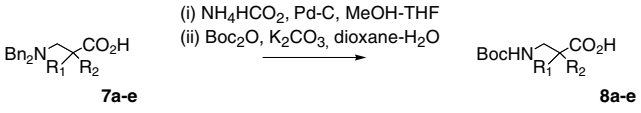
Scheme 3. Reaction of bis(*O*-trimethylsilyl) ketene acetals with imine in the presence of ethylchloroformate.



Scheme 4. Reaction of bis(*O*-trimethylsilyl) ketene acetals with different iminium salts.

Table 1. Yields of the reaction of bis(*O*-trimethylsilyl) ketene acetals with different iminium salts

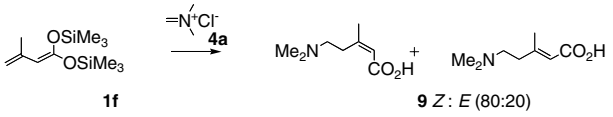
Ketene acetal	Iminium salt	Product [yield (%)]
1a	**4a**	**5a** (50)
1a	**4b**	**6a** (70)
1a	**4c**	**7a** (98)
1b	**4c**	**7b** (60)
1c	**4c**	**7c** (85)
1d	**4c**	**7d** (75)
1e	**4c**	**7e** (90)



Scheme 5. Debenzylation and *N*-Boc protection.

step. Debenzylations of compounds **7** were performed on Pd/C using ammonium formate as the source of hydrogen. In the case of compound **7e**, nitrogen deprotection required the addition of sodium hydrogenocarbonate to reach the completion of the reaction. It can be hypothesized that zwitterion formation decreased the rate of debenzylation because of steric hindrance generated by internal chelation. The resulting amines were then N-protected as *tert*-butyloxycarbonyl carbamates **8a**–**e** in good yields for deprotection–protection steps (65–80%).

The presence of an additional double bond in the ketene acetal modified the course of the reaction. Indeed, when the ketene acetal **1f** was reacted with the iminium salt **4a**, instead of the corresponding β^2-amino acid, the α,β-unsaturated-δ-aminoacid was obtained as a 80:20 mixture of *Z*:*E* isomers **9** in a vinylogous Mannich type reaction[18,19] (Scheme 6).



Scheme 6. α,β-Unsaturated-δ-aminoacids.

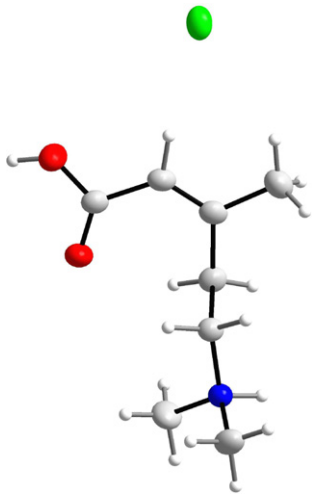


Figure 1. *Diamond* projection of the *Z* isomer of compound **9**.

The two isomers were partially separated by silicagel chromatography to give major *Z* isomer as white crystals suitable for an X-ray crystallographic structure determination. A *Diamond* projection of this compound confirmed the γ-addition of the trimethylsilylester enolate to iminium salt **4a**[20] (Fig. 1).

The unsaturated δ-aminoacid obtained as its ammonium chloride salt has a trans geometry between the acid function and the methyl group. This class of amino acids is a useful tool for structure–activity relationship studies of biologically active peptides.[21]

3. Conclusion

In summary, bis(*O*-trimethylsilyl) ketene acetals represent a good alternative to enolates for the synthesis of β^2-amino acids using iminium ions as aminomethylating agents. Indeed, ketene acetals can be (i) easily prepared and (ii) reacted at room temperature in a one-pot procedure with in situ prepared iminium ions. We are currently working on an asymmetric synthesis and the extension of this strategy for the preparation of various substituted δ-aminoacids.

Acknowledgments

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16. *General procedure for the introduction of an imine in the presence of ethyl chloroformate:* A dichloromethane (2.5 mL/mmol) solution of ethylchloroformate (1.9 equiv) was slowly added at room temperature to a solution of bis(trimethylsilyl) ketene acetal (1.05 equiv) and benzylidene-methylamine in dichloromethane (20 mL/mmol). Stirring for 12 h followed by evaporation of the solvent and flash column chromatography (AcOEt/EP, 60/40) gave the product. *3-(Ethoxycarbonyl-methyl-amino)-2,2-dimethyl-3-phenyl-propionic acid* **3a**: 40% yield (0.25 g); solid mp 130 °C; ^{1}H NMR (200 MHz, D_2O): δ: 11.3 (s, 1H); 7.31 (s, 5H); 5.86 (s, 1H); 4.22 (q, 2H, $J = 7.0$ Hz); 2.70 (s, 3H); 1.43 (d, 6H, $J = 5$ Hz); 1.32 (t, 3H, $J = 7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ: 183.1; 158.3; 129.0; 127.7; 64.2; 62.3; 47.2; 33.4; 33.2; 26.9; 22.7; 15.1; MS: calcd for $C_{15}H_{22}NO_4$ [M+H] 280, found 280. *3-(Ethoxycarbonyl-methylamino)-2-methyl-3-phenyl propionic acid* **3b**: 20% yield (global) (0.11 g); oil; ^{1}H NMR (200 MHz, D_2O): major product: δ: 8.30 (s, 1H); 7.20–7.31 (s, 5H); 5.24 and 5.35 (d, 1H, $J = 10$ Hz); 4.02 (m, 2H); 3.29 (m, 1H); 2.68 (s, 3H); 1.18 (m, 3H); 1.02 (d, 3H, $J = 6$ Hz); minor product: δ: 8.30 (s, 1H); 7.20–7.31 (s, 5H); 5.41 and 5.54 (d, 1H, $J = 10$ Hz); 4.10 (m, 2H); 3.17 (m, 1H); 2.50 and 2.67 (s, 3H); 1.20 (m, 3H); 1.23 (d, 3H, $J = 6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ: major product: 177.8; 156.6; 155.8; 137.2; 127.0; 60.8; 60.6; 39.0; 28.3; 20.4; 13.5; minor product: 177.8; 156.3; 155.4; 137.2; 127.0; 60.7; 58.8; 39.5; 27.6; 26.4; 24.1; 14.6.
17. *General procedure for the introduction of iminium salt:* A dichloromethane (4 mL/mmol) solution of acetyl chloride or trifluoroacetic anhydride (1.1 equiv) was slowly added at room temperature to a solution of bis(trimethylsilyl) ketene acetal (1.05 equiv) and aminal in dichloromethane (20 mL/mmol). Stirring for 12 h followed by evaporation of the solvent and flash column chromatography (AcOEt/EP, 60/40) gave the product. *3-Dimethylamino-2,2-dimethyl propionic acid* **5a**: 50% yield (0.20 g); white solid mp 150 °C; ^{1}H NMR (200 MHz, D_2O): δ: 3.24 (s, 2H); 2.76 (s, 6H); 1.16 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ: 179.5; 65.3; 45.5; 41.4; 23.3; MS: calcd for $C_7H_{16}NO_2$ [M+H] 146, found 146. *2,2-Dimethyl-3-pyrrolidin-1-yl-propionic acid* **6a**: 70% yield (0.44 g); white solid mp 185 °C; ^{1}H NMR (200 MHz, D_2O): δ: 3.57 (m, 2H); 3.34 (s, 2H); 3.05 (m, 2H); 1.93 (m, 4H); 1.20 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ: 179.7; 63.1; 56.8; 41.7; 23.4; 22.9. *2-Methyl-2-dibenzylaminomethyl propionic acid* **7a**: 98% yield (3.5 g); white solid mp 198–200 °C; ^{1}H NMR (250 MHz, D_2O): δ: 7.4 (s, 10H); 4.3 (s, 4H); 3.4 (s, 2H); 1.1 (s, 6H); ^{13}C NMR (62.5 MHz, D_2O): δ: 179.4; 131.4; 130.1; 129.1; 128.5; 59.4; 40.8; 23.3; HRMS: calcd for $C_{19}H_{23}NO_2$ [M+H] 298.180, found 298.179. *2-Dibenzylaminomethyl-propionic acid* **7b**: 60% yield (2.5 g); white solid mp 196–198 °C; ^{1}H NMR (250 MHz, CD_3OD): δ: 7.49 (m, 10H); 4.43 (d, 2H, $J = 20$ Hz); 4.27 (d, 2H, $J = 20$ Hz); 3.39–3.25 (m, 1H); 3.08 (m, 1H); 2.78 (m, 1H); 1.07 (d, 3H, $J = 10.8$ Hz); ^{13}C NMR (62.5 MHz, D_2O): δ: 177.6; 130.9; 130.08; 129.2; 53.8; 34.8; 14.5. HRMS: calcd for $C_{18}H_{21}NO_2$ [M+H] 284.163, found 284.164. *2-Phenyl-2-dibenzyl aminomethyl-propionic acid* **7c**: 85% yield (3 g); colorless glue; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.31–7.13 (m, 15H); 3.59 (m, 2H); 3.25–3.18 (br, 2H); 3.18–3.08 (m, 2H); 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 177.6; 142.8; 133.7; 129.9; 128.9; 128.5; 128.3; 127.6; 127.4; 127.2; 126.3; 126.1; 61.1; 57.6; 49.4; 25.9. HRMS: calcd for $C_{24}H_{25}NO_2$ [M+H] 360.195, found 360.195. *2-Dibenzyl aminomethyl-hexanoic acid* **7d**: 75% yield (2.5 g); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.40–7.28 (m, 10H); 3.99 (d, 2H, $J = 12$ Hz); 3.54 (d, 2H, $J = 12$ Hz); 2.86 (tr, 1H); 2.67 (m, 1H); 2.64 (m, 1H); 2.52 (m, 1H); 1.85 (m, 1H); 1.27 (m, 5H); 0.88 (t, 3H, $J = 6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 175.7; 134.6; 129.7; 129.4; 128.8; 128.3; 127.2; 58.1; 55.6; 54.2; 39.6; 29.2; 28.4; 22.7; 13.8. HRMS: calcd for $C_{21}H_{27}NO_2$ [M+H] 326.211, found 326.211. *2-Phenyl etherhydroxy-2-dibenzylamino methyl-propionic acid* **7e**: 90% yield (1.5 g); white solid mp 192–194 °C; ^{1}H NMR (250 MHz, CD_3OD): δ: 7.60–7.51 (m, 10H); 7.33–7.27 (m, 2H); 7.14–7.11 (m, 1H); 6.96–6.94 (d, 1H, $J = 8$ Hz); 6.94–6.93 (d, 1H, $J = 4$ Hz); 4.70 (m, 4H); 3.30 (AB, 2H, $J = 4$ Hz); HRMS: calcd for $C_{24}H_{25}NO_3$ [M+H] 376.190, found 376.190.
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19. *5-Dimethylamino-3-methyl-pent-2-enoic acid* **9**: 30% yield (global) (0.12 g); white solid mp 135 °C; ^{1}H NMR (250 MHz, CD_3OD): cis compound: δ: 5.78 (s, 1H); 3.17 (m, 2H); 2.90 (m, 2H); 2.80 (s, 6H); 1.84 (s, 3H); trans compound: δ: 5.72 (s, 1H); 3.16 (m, 2H); 2.87 (m, 2H); 2.80 (s, 6H); 2.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ: 170.2; 155.4; 118.2; 55.5; 43.1; 35.1; 18.4.
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