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Preparation of Conformationally Restricted $\beta^{2,2}$- and $\beta^{2,2,3}$-Amino Esters and Derivatives Containing an All-Carbon Quaternary Center

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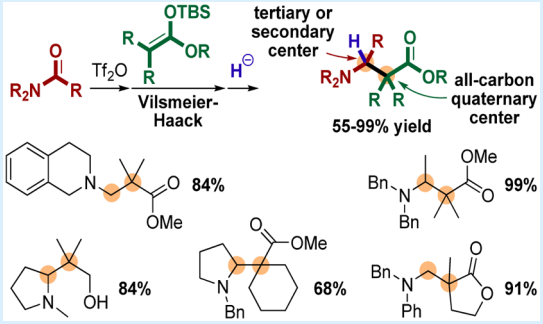
Supporting Information

ABSTRACT: β-Amino acids are routinely incorporated into peptidic drugs to increase their stability and to incur conformational biases. However, the synthesis of highly substituted β-amino acids still represents a great challenge. A new approach to their preparation is reported involving a Vilsmeier–Haack reaction with nonaromatic carbon nucleophiles. The highly challenging preparation of contiguous tertiary and all-carbon quaternary centers was successfully used to generate several $\beta^{2,2,3}$-amino esters, such as derivatives of homoproline, homoalanine, and homopipecolinic esters.



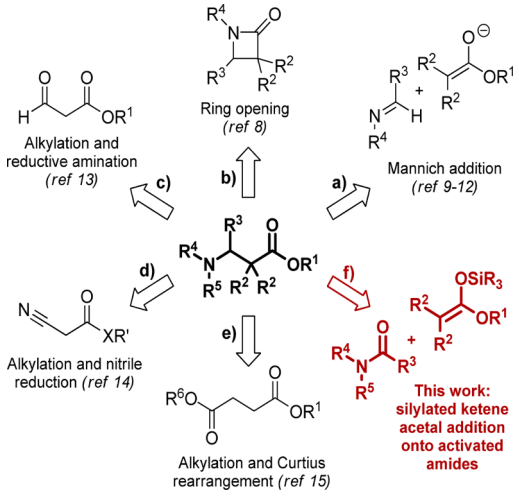
It is well established that the use of β-amino acids in peptides improves their metabolic lability and therefore enhances their stability against proteolytic degradation.[1] β-Peptides have thus been used to mimic natural peptide-based drugs in pharmacological studies. Not surprisingly, functionalized β-amino acids are found in several antifungal[2] and antibacterial[3] bioactive molecules, as well as in antitumor agents.[4] Moreover, the fact that substituted β-amino acids, and in particular $\beta^{2,2}$-amino acids (or α,α-dialkyl-β-amino acids) and $\beta^{2,2,3}$-amino acids (or α,α,β-trialkyl-β-amino acids), are known to incur restricted conformations to β-peptides has stimulated several research groups to use them for the rational design of new defined nanoscopic patterns such as helical secondary structures and foldamers.[5] However, their synthesis still remains a high challenge in organic chemistry[6] and, despite the fact that this field has gained considerable attention over the past decade, only a few synthetic approaches have been developed, with the majority of them being of limited scope.

Scheme 1 exemplifies the most common approaches to the construction of $\beta^{2,2}$-amino acids ($R^2 \neq H$).[7] The Mannich addition (a) and the formation of β-lactams by cycloaddition followed by ring opening (b) are among the most convergent approaches.

While the cycloaddition strategy is limited by the steric bulk of the substituents,[8] the Mannich addition[9] is restricted to the use of an unsubstituted nucleophile (R^2 = H), or specific substituents (R^2) on the nucleophile.[10] Moreover, almost all of these additions work only if these iminium ions are activated with an electron-withdrawing group on either the iminium carbon (R^3)[11] or nitrogen (R^4).[12]

The other approaches to $\beta^{2,2}$-amino acids mainly rely on alkylation strategies. The amino group could be derived from alkylated α-formylesters using a reductive amination (c)[13] or from nitrile reduction of alkylated cyanoesters or cyanoamides (d).[14] These two methods are inherently limited to no substitution at the β-position (R^3 = H). Finally, Curtius rearrangement of alkylated 1,4-diesters or derivatives (e) also

Scheme 1. Most Common Approaches to the Construction of $\beta^{2,2}$-Amino Acids



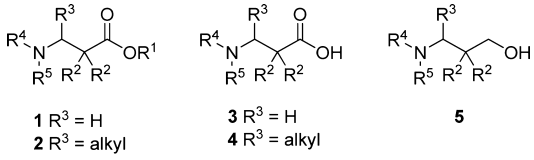


Figure 1. Accessible compounds via intermolecular Vilsmeier–Haack reaction.

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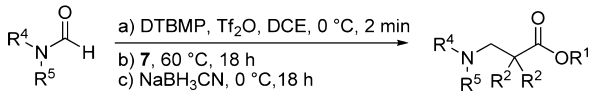
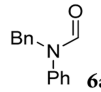
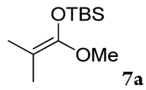
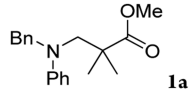
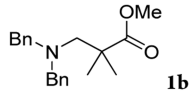
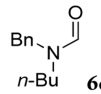
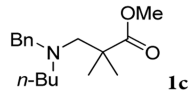
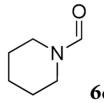
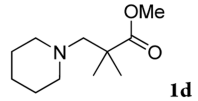
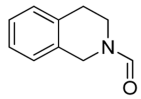
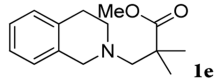
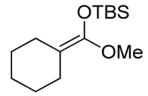
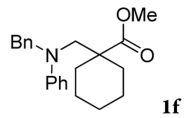
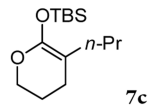
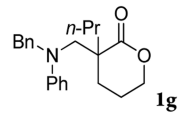
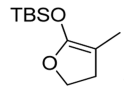
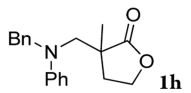
Table 1. Synthesis of $\beta^{2,2}$-Amino Esters[a]

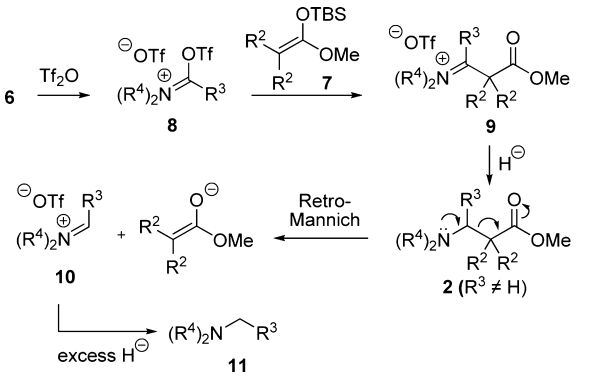


6 1

no.	amide	nucleophile	product	yield (%)
1	 6a	 7a	 1a	94
2	 6b	7a	 1b	99
3	 6c	7a	 1c	85
4	 6d	7a	 1d	65
5	 6e	7a	 1e	84
6	6a	 7b	 1f	89
7	6a	 7c	 1g	78[b]
8	6a	 7d	 1h	91[b]

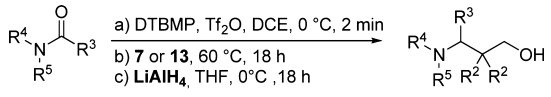
[a]DCE: 1,2-dichloroethane; DTBMP: 2,6-di-*tert*-butyl-4-methylpyridine; Tf_2O: trifluoromethanesulfonic anhydride. [b]The addition of AcOH (10 equiv) was required to significantly improve the yield.

Scheme 2. Undesired Retro-Mannich Reaction



lead to the desired unnatural amino acid.[15] In all cases, restrictions concerning the synthesis of starting materials lead to a lack of versatility in the nature of the substituents (R) and

Table 2. Synthesis of $\beta^{2,2}$- and $\beta^{2,2,3}$-Amino Alcohols



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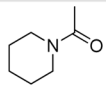
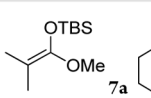
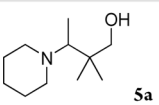
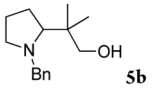
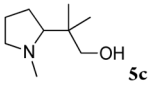
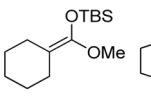
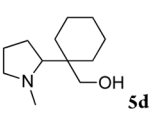
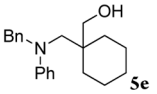
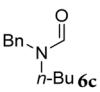
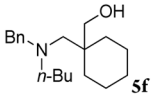
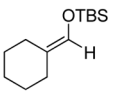
no.	amide	nucleophile	product	yield (%)
1	 12a	 7a	 5a	40
2	 12b	7a	 5b	42
3	 12c	7a	 5c	84
4	12c	 7b	 5d	63
5	 6a	7b	 5e	55
6	 6c	7b	 5f	63
7	6a	 13a	5e	63
8	6c	13a	5f	58

serious difficulties are often encountered in the preparation of the all-carbon quaternary center (with two R^2 substituents).

Herein, we report a novel intermolecular Vilsmeier–Haack-type addition of nonaromatic carbon nucleophiles onto activated amides followed by in situ reduction[16] to efficiently generate all-carbon quaternary centers in a racemic version (Scheme 1f). This strategy rapidly gives access to $\beta^{2,2}$- and $\beta^{2,2,3}$-amino esters (**1** and **2**, respectively) and acids (**3** and **4**, respectively), as well as to 1,3-amino alcohols **5** (Figure 1).[17]

$\beta^{2,2}$-Amino esters were synthesized from silylated ketene acetals **7** and formamides **6** (Table 1). The reaction was very high yielding when performed with a variety of *N*-benzylformamides (entries 1–3). Cyclic formamides could also be used successfully (entries 4–8). Hindered nucleophiles derived from methyl cyclohexanecarboxylate (entry 6) or lactones (entries 7 and 8) also furnished the desired $\beta^{2,2}$-amino esters in good to excellent yields.

The construction of $\beta^{2,2,3}$-amino esters, bearing a tertiary center adjacent to the quaternary carbon, turned out to be a lot more challenging. Delightfully, the nucleophilic addition took place smoothly. However, problems arose during the attempted reduction of the resulting iminium ion **9** (Scheme 2). After hydride addition, β-amino ester **2** spontaneously underwent a retro-Mannich reaction in situ, presumably driven by steric

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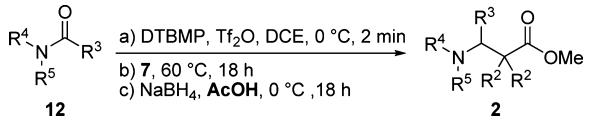
Table 3. Synthesis of $\beta^{2,2,3}$-Amino Esters



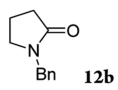
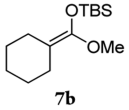
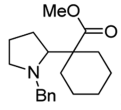
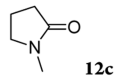
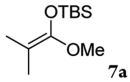
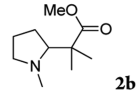
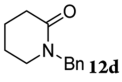
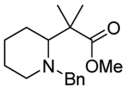
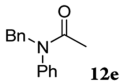
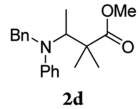
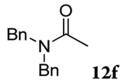
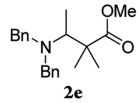
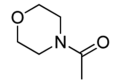
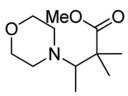
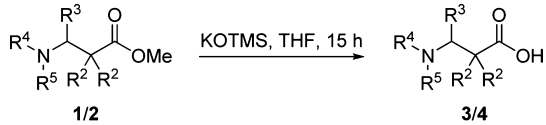
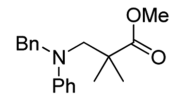
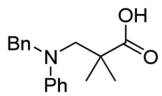
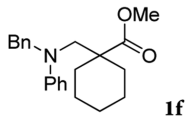
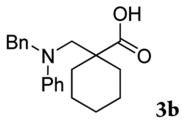
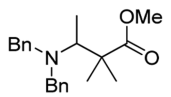
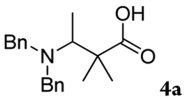
no.	amide	nucleophile	product	yield (%)
1	 12b	 7b	 2a	68
2	 12c	 7a	 2b	68
3	 12d	7a	 2c	67
4	 12e	7a	 2d	68
5	 12f	7a	 2e	99
6	 12g	7a	 2f	55

Table 4. Saponification to $\beta^{2,2}$ and $\beta^{2,2,3}$-Amino Acids



no.	amino ester	temperature	product	yield (%)
1	 1a	rt	 3a	quant
2	 1f	reflux	 3b	quant
3	 2e	reflux	 4a	95

decompression.[18] An ensuing reduction of the resulting iminum ion **10** led to the isolated corresponding amine **11**.

We rationalized that the undesired retro-Mannich reaction could be suppressed using two different strategies. The first one was to perform the reduction of iminium **9** using a much stronger reducing agent, such as $LiAlH_4$. The latter reduced the ester group on intermediate **9** or **2** prior to any retro-Mannich side reaction, as successfully demonstrated in Table 2, leading to the corresponding 1,3-amino alcohols derivatives **5**.

In sharp contrast with Mannich reactions reported to work with iminium ions bearing no more than one substituent on carbon,[9] we showed that amides other than formamides were impeccably compatible with our method, leading to highly congested $\beta^{2,2,3}$-amino alcohols (entries 1−4). Another remarkable advantage of our method is the great reactivity of the iminium ion resulting from the amide activation. In fact, we could perform the addition of silyl enol ethers of esters (**7b**, entries 5 and 6) and even of aldehydes (**13a**, entries 7 and 8) and obtain the same products (**5e** and **5f**) in comparable yields. Mannich additions using the latter nucleophiles are usually not working and require the more reactive enol ethers of esters.

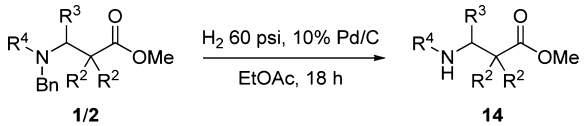
The undesired retro-Mannich reaction (Scheme 2, **2** to **10**) could be suppressed using another strategy. We envisaged that reduction of iminium ion **9** in a slightly acidic medium would secure the protonation of the resulting amine **2** as it is generated, thus preventing the cleavage to **10**. After optimization, it was revealed that acetic acid worked charmingly well, as exemplified in Table 3. Homoproline esters (entries 1 and 2) and homopipecolinic esters (entry 3) bearing a quaternary center were successfully prepared, as well as a series of acyclic $\beta^{2,2,3}$-amino esters (entries 4−6).

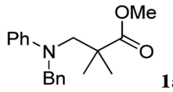
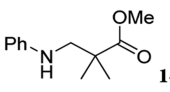
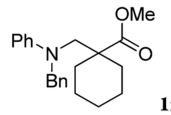
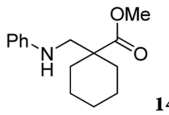
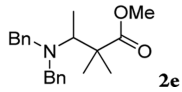
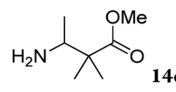
The free acid derivatives were obtained essentially in quantitative yields from treatment of methyl esters with potassium trimethylsilanolate (KOTMS, Table 4).

Furthermore, the free amine derivatives were obtained upon hydrogenolysis of the corresponding benzylamino compounds (Table 5). The reaction proceeded under H_2 pressure in high to quantitative yields.

In conclusion, the present study has established a new method for the synthesis of unnatural β-amino esters bearing an all-carbon quaternary center ($\beta^{2,2}$-amino esters) and even the very challenging contiguous all-carbon quaternary and tertiary centers ($\beta^{2,2,3}$-amino esters) which are essentially not accessible from usual methods. The corresponding β-amino acids and 1,3-amino alcohols were also prepared efficiently. The development

Table 5. Debenzylation of $\beta^{2,2}$ and $\beta^{2,2,3}$-Amino Esters



no.	amino ester	product	yield (%)
1	 1a	 14a	quant
2	 1f	 14b	quant
3	 2e	 14c	84[a]

[a]The hydrogenation was run over 2 days in order to remove both benzyls.

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of a chiral version of our method is underway and will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) Addition of carbon nucleophiles such alkyl or allyl zinc or magnesium to iminium ion **9** resulted in no reaction.

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