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Synthesis of amides from unprotected amino acids by a simultaneous protection–activation strategy using dichlorodialkyl silanes

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Abstract—Reaction of L-phenylalanine (**1**) with dichlorodimethylsilane or other dichlorosilane derivatives **6b–d** and primary amines leads to the formation of amides probably via a cyclic silyl intermediate. It is also possible to use β-amino acids and *N*-alkylated amino acids (peptoid building blocks) as well as the amino dicarboxylic acid L-aspartic acid. The latter leads to almost exclusive formation of the α-amide.

The coupling of amino acids without the requirement of separate protection/deprotection and coupling steps is one of the great challenges in peptide synthesis. For instance, the number of steps involved in the synthesis of a dipeptide would then be greatly reduced and therefore the cost-price for industrial production would be drastically reduced.

In order to meet this challenge, a 'simultaneous *N*-protection and carboxyl-activation' strategy is called for. The very interesting approaches already reported in the literature represent significant steps towards realization of this strategy. In the amino acid *N*-carboxy anhydride (NCA) approach, phosgene is used to protect simultaneously the amino function and to activate the carboxylic acid moiety.[1] As well as problems concerning the use of phosgene on a large scale, the carboxylic acid moiety is activated to such an extent that it is difficult to limit the coupling to, e.g. the dipeptide stage, and consequently it is difficult to avoid polymerization to oligo- and polypeptides.[2] The elegant approach by Burger and Rudolph[3] has as a disadvantage the use of the toxic and expensive hexafluoroacetone, which precludes this approach e.g. for the preparation of the dipeptide-methyl ester aspartame on an industrial scale.

In this communication the first step is described towards using cost-effective silyl reagents for the preparation of peptide amides in a simultaneous protection–activation strategy.[4]

When L-phenylalanine (**1**) was treated in dichloromethane with commercially available dichlorodimethylsilane followed by addition of benzylamine under the conditions reported by Barlos et al. for the protection of histidine,[5] neither (silyl) intermediate nor product could be detected. However, it was speculated that the very poor solubility of L-phenylalanine as well as the liberation of HCl might impede the formation of and/or cause premature decomposition of the silyl intermediate **2** and consequently prevent the formation of L-phenylalanine-benzylamide **3a** (Scheme 1). Therefore, the solvent was changed to pyridine, in which L-phenylalanine almost completely dissolves and which can act as an acid scavenger. Now, the reaction with dichlorodimethylsilane and benzylamine proceeded almost quantitatively at room temperature to afford amide **3a**.[6] Carrying out the reaction at higher temperatures led to lower yields and no product could be detected at reflux temperature.[7] It turned out that pyridine was the best solvent/base for this reaction.[8] It was also found that this reaction is very sensitive to the bulkiness of the incoming amine nucleophile. As a result, primary amines with their amino group attached to a primary carbon atom gave excellent yields of amides **3a–d** (Scheme 1). However, the dipeptide **3e**, for which

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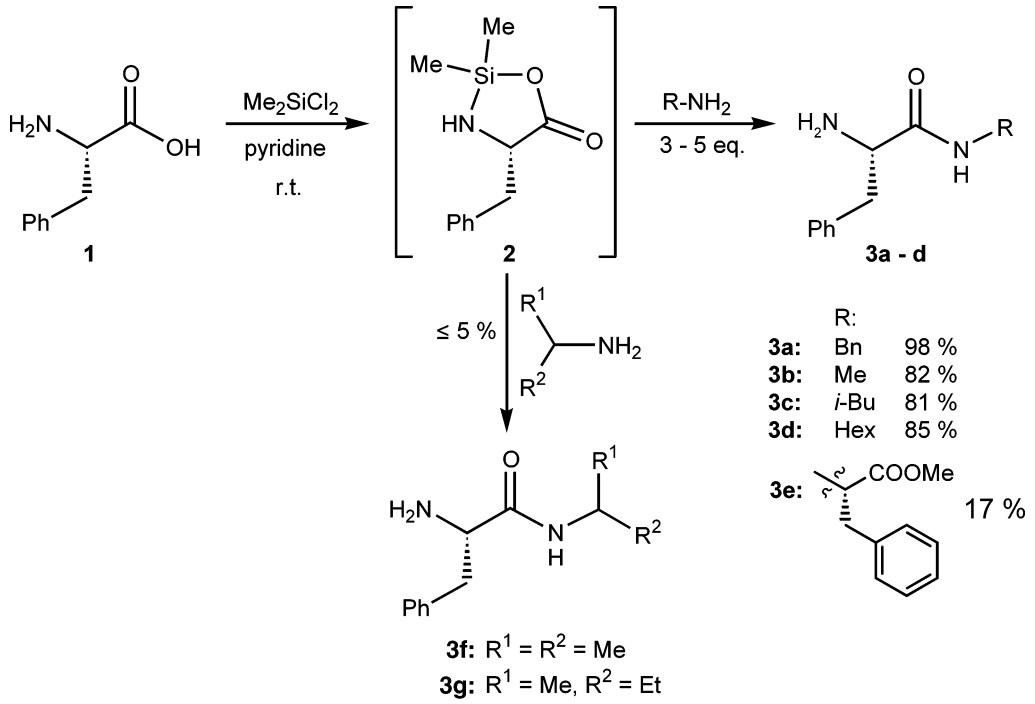


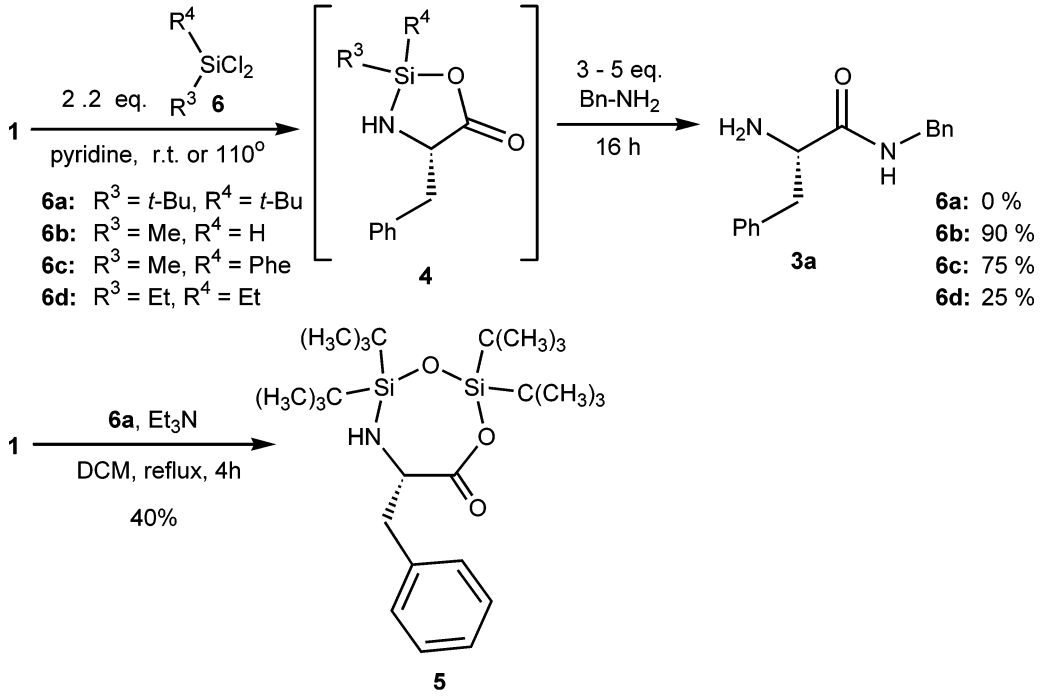
Scheme 1.

H–Phe–OMe-containing a primary amine attached to a *secondary* carbon atom was used as the amine nucleophile, was obtained in a much lower yield (17%). The use of isopropylamine or 2-aminobutane resulted in even lower yields of **3f** and **3g** ($\leq$5%, Scheme 1) and starting material **1** was recovered.

Since all attempts to isolate the reactive intermediate-postulated to be the cyclic silane **2** failed, indirect mechanistic evidence was collected. Firstly, a dichlorodimethylsilane-mediated coupling reaction of acetic and benzoic acid with benzylamine did not furnish the amide product, indicating that the activated system in the case of L-phenylalanine has not simply a dicarboxydimethylsilyl (C(O)–O–Si(CH_3)$_2$–O–C(O)) or a C(O)–O–Si(CH_3)$_2$–Cl structure. Secondly, a dichlorodimethylsilane-mediated coupling reaction of *N*-benzyloxycarbonyl-L-phenylalanine, *N*,*N*-dibenzyl-L-phenylalanine and *N*-phthaloyl-L-phenylalanine with benzylamine did not give the amide product either, indicating that a free α-amine functionality is required indirectly proving that **2** is indeed the reactive intermediate. Thirdly, NMR experiments[9] were performed with L-phenylalanine in pyridine-d_5 to which varying amounts of dichlorodimethylsilane were added, giving independent support for the existence of a cyclic active intermediate. When 1.2 equiv. of dichlorodimethylsilane was added, one single activated compound was formed[9] according to the ^{1}H NMR spectrum bearing one dimethylsilyl functionality per amino acid residue and which was neither the L-phenylalanine–HCl salt nor its acid chloride congener. However, when dichlorodimethylsilane was titrated in the NMR tube it was observed that initially L-phenylalanine was first transformed to another intermediate (also bearing one dimethylsilyl functionality per amino acid residue) and after approximately 0.6 equiv. dichlorodimethylsilane, the final activated compound became visible. This observation corroborates that the carboxylic acid functionality of L-phenylalanine first reacts with dichlorodimethylsilane to give the linear C(O)–O–Si(CH_3)$_2$–Cl structure, which then cyclizes to give structure **2**.

Realizing that the silyl intermediate **2** was too unstable to be isolated, L-phenylalanine was now treated with di-*tert*-butyldichlorosilane to obtain a sterically crowded silyl intermediate (**4**: $R^3 = R^4 =$ *tert*-Bu, Scheme 2) which it was hoped would be less susceptible to nucleophilic attack at room temperature and therefore could be isolated. However, di-*tert*-butyldichlorosilane is apparently sterically crowded to such an extent that instead of **4**, the disilylated cyclic derivative **5** was isolated in 40% yield (Scheme 2).[10] This derivative however appeared to be resistant towards nucleophilic opening and treatment with benzylamine or methylamine at various temperatures did not lead to any detectable L-phenylalanine-amide product. Nevertheless, it appeared to be possible to use other commercially available dichlorosilane derivatives (**6b–d**, Scheme 2).[11] Derivatives **6c–d** were less bulky than di-*tert*-butyldichlorosilane but more so than dichlorodimethylsilane and consequently resulted in lower yields of the adduct. As expected only the somewhat less bulky chloromethylsilane **6b** gave a comparable yield of **3a**. For industrial use, however, dichlorodimethylsilane is the reagent of choice since being the raw material for silicones it is very cost-effective, available in large quantities and easy to handle.

Interestingly, it was also possible to apply this dichlorodialkylsilane-mediated amidation strategy to other

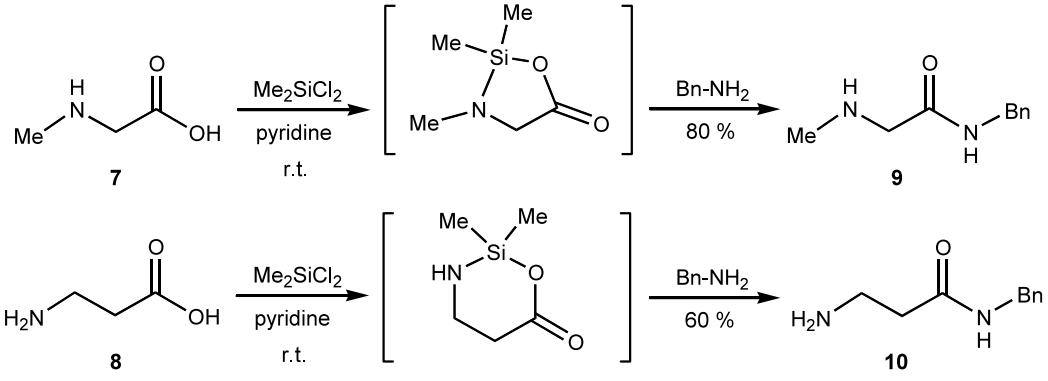


Scheme 2.

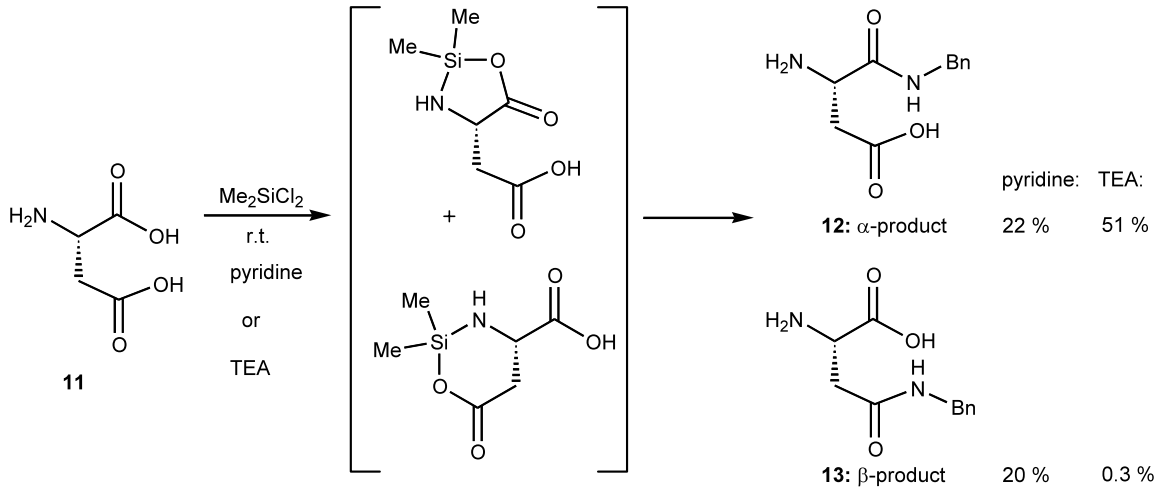
amino acid types.[11] As examples the reactions of *N*-methyl glycine (**7**: sarcosine) and β-L-alanine (**8**) are shown here (Scheme 3).[12] *N*-Methyl glycine is an *N*-alkylated amino acid derivative, which is used in the synthesis of a very important class of peptoid peptidomimetics.[13] β-Amino acids like β-L-alanine are the building blocks of the increasingly important β-peptides.[14] The lower yield of β-alaninebenzylamide **10** in the reaction of β-L-alanine as compared to the yield of peptoid amide **9** can be explained assuming the formation of a six-membered cyclic silyl intermediate, which may be less easily formed or less reactive than a five-membered cyclic silyl intermediate (Scheme 3).

The next challenge was to investigate the regiochemistry if *two* carboxylic acid moieties are present in the starting amino acids as is the case in L-aspartic acid and glutamic acid (see Scheme 4). We focused on L-aspartic acid **11** since this amino acid is a constituent of the commercially important high-intensity low caloric dipeptide sweetener aspartame (L-aspartyl-L-phenylalanine methyl ester: APM).[15,16] For the preparation of this dipeptide it is crucial that selective amidation occurs at the α-carboxylic acid moiety.

Indeed, it was found that it was possible to direct the regiochemistry of the reaction of L-aspartic acid using dichlorodimethylsilane. Use of pyridine as the base and solvent as described above led to an about equal (52:48) mixture of α- and β-products (**12** and **13**, respectively) in an overall yield of 44%. Pleasingly, when using triethylamine (TEA) as the base and solvent instead, a very good selectivity in favor of the α-product **12** was observed (α:β ratio of 99.4:0.6 with an overall amide yield of 51.3%). The highly selective formation of the α-product is consistent with the assumption that the stronger base TEA leads to the preferred formation of the kinetically favored five-membered cyclic intermediate (Scheme 4).[17] In the case of the weaker base pyridine, the formation of a significant amount of



Scheme 3.



Scheme 4.

β-product is consistent with the assumption that more of the thermodynamically favored six-membered ring intermediate is formed.

In conclusion, we have shown that it is possible to prepare amino acid amides via a simultaneous protection and activation strategy using commercially available silylating agents, in particular dichlorodimethylsilane. Moreover, it is possible to prepare the α-amide derived from L-aspartic acid with high regioselectivity. Obviously the scope of this method has to be further investigated and widened to the preparation of dipeptide derivatives.

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6. General experimental procedure for the preparation of L-phenylalanine-amides **3a**–**g** as shown in Scheme 1: L-phenylalanine (330 mg, 2.0 mmole) was suspended in pyridine (10 mL, distilled from CaH_2) under a nitrogen atmosphere at ambient temperature (approx. 23°C) and dichlorodimethylsilane (267 μL, 2.2 mmole) was added in one portion. During 2 min the mixture turned clear and the temperature rose from 23 to 28°C. Subsequently, 6 mmole of the selected amine was added (in most cases giving a suspension) and the reaction mixture was stirred for another 16 h and monitored with TLC (using chloroform/methanol/ammonia 60/45/20 v/v/v, *sec*-butanol/formic acid/water 75/15/10 v/v/v and *n*-butanol/acetic acid/ethyl acetate/water 1/1/1/1 v/v/v/v). The reaction mixture was concentrated in vacuo and the resulting residue chromatographed on silica gel (eluent: dichloromethane/methanol 100/0 to 95/5 v/v) to furnish the pure L-phenylalanine-amide.
7. The silyl intermediate probably easily decomposes at higher temperatures.
8. Besides pyridine the following solvents were tried in the coupling reaction of L-phenylalanine with benzylamine using dichlorodimethylsilane: THF, dichloromethane, *N*,*N*-dimethyl-acetamide (DMA), *N*,*N*-dimethylformamide, *N*-methylpyrrolidone (NMP), 1,4-dioxane, 1,2-dichloroethane, acetone, DMSO, chloroform, acetonitrile and sulpholane; the maximum L-phenylalanine-benzylamide yield obtained was 25% (using DMA and NMP). When triethylamine (2 equiv. based on L-phenylalanine) was added before the addition of dichlorodimethylsilane, the yields in these solvents significantly increased (for instance to 80% in DMA and NMP, to 50% in acetonitrile and 48% when triethylamine was used as the solvent itself) but they were still lower than in pyridine (98%).
9. A solution of L-phenylalanine in pyridine-d_5 was transferred into a dry NMR tube under a nitrogen atmosphere and dichlorodimethylsilane was added via a microsyringe. When 1.2 equiv. of dichlorodimethylsilane was added in one portion, the single activated compound displayed the following chemical shifts (in pyridine-d_5, with the most downfield pyridine-H at 8.50 ppm): 7.2–6.9 ppm (5 H, m), 4.42 ppm (1 H, dd), 3.18 ppm (1 H, dd), 2.84 ppm (1 H, dd) and 0.40 (6 H, bs). To prove that this compound was not simply the L-phenylalanine acid chloride·HCl salt, the latter was separately synthesized from

L-phenylalanine and PCl_5 in dichloromethane; in pyridine this compound rapidly polymerized.

10. Compound **5**: ^1H NMR (pyridine-d_5): δ 1.20 (bs, 18H, CH_3, *t*Bu), 1.25 (bs, 18H, CH_3, *t*Bu), 2.93 (dd, 1H, CH_A, $J=8.8$ Hz, $J=13.2$ Hz), 3.36 (dd, 1H, CH_B, $J=4.8$ Hz, $J=13.6$ Hz), 3.96 (dd, 1H, αCH, $J=4.8$ Hz, $J=8.8$ Hz), 7.24–7.56 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 19.8 (C_q, *t*Bu), 21.2 (C_q, *t*Bu), 27.3, 27.6, 27.7 (CH_3, *t*Bu), 40.9 (CH_2), 57.0 (αCH_2), 126.4–129.3 (CH, Ph), 137.4 (C_q, Ph), 173.2 (C=O). Mass $C_{25}H_{45}O_3NSi_2$ mw 463; [M+H$^+$] 464.4; Mass $C_{17}H_{27}O_2NSi$ mw 305; [M+H$^+$] 306.
11. General experimental procedure for the preparation of L-phenylalanine-benzylamide using the dichlorodialkylsilane reagents as shown in Scheme 2. L-Phenylalanine (330 mg, 2.0 mmole) was suspended in pyridine (10 mL, distilled from CaH_2) under a nitrogen atmosphere at ambient temperature (approx. 23°C) and 2.2 mmole of the dichlorodialkylsilane was added in one portion. After 1 min 3–5 equiv. of benzylamine was added and the reaction mixture was stirred for another 16 h, monitored with TLC and worked up (as above).
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17. For the coupling experiments with L-aspartic acid, a similar experimental procedure as given in Ref. 6 was used. The α-product (α-L-aspartic acid-benzylamide) and the β-product (β-L-aspartic acid-benzylamide) were determined on HPLC by comparison of the peak areas with those of reference solutions of known concentration.