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The synthesis of amides and dipeptides from unprotected amino acids by a simultaneous protection–activation strategy using boron trifluoride diethyl etherate

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Abstract—The reaction of L-phenylalanine (**1**) with boron trifluoride diethyl etherate and primary amines leads to the formation of amides via a cyclic boron intermediate. It is also possible to use the amino dicarboxylic acid L-aspartic acid and *N*-alkylated amino acids (peptoid building blocks, e.g., NPhe-OH **9**). The latter can be used in the preparation of dipeptidomimetics.

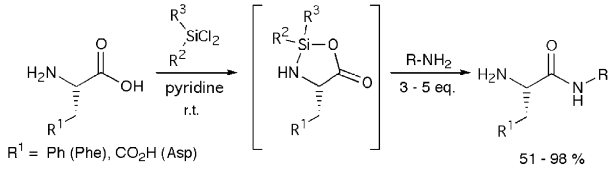
The coupling of amino acids without the requirement of separate amino protection/deprotection and coupling steps is one of the great challenges in peptide synthesis. For instance, the number of steps involved in the synthesis of a dipeptide would then be greatly reduced and, accordingly, its cost price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

In order to meet this challenge, a 'simultaneous *N*-protection and carboxyl-activation' strategy is desired. Some interesting approaches already reported in the literature represent significant steps toward the realization of this strategy, although each concept suffers from intrinsic disadvantages. In the amino acid *N*-carboxy anhydride (NCA) approach, phosgene is used to protect the amino function and simultaneously to activate the carboxylic acid moiety.[1] Unfortunately, in amino acid NCA's the carboxylic acid moiety is activated to such an extent that it is difficult to suppress polymerization to oligo- and polypeptides. The elegant approach by Burger et al.[2] involves the use of hexafluoroacetone which, however, because of its toxicity and high price precludes, for example, the preparation of the dipeptide methyl ester Aspartame on an industrial scale.

In the search for alternative strategies we recently reported the use of cost-effective silyl reagents for the preparation of amino acid amides in a simultaneous protection–activation strategy (Scheme 1).[3,4]

In this letter, we describe the use of boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) for this purpose and discuss its ability to increase the susceptibility of the carboxylic acid moiety toward a nucleophilic attack by an amine, including one present in an amino acid residue.

N-Substituted *B*,*B*-difluoroboroxazolidones (DFBONs) were prepared by Pedersen and co-workers[5] by refluxing *N*-benzyl substituted amino acids with $BF_3{\cdot}Et_2O$ and Et_3N in THF. NMR (^{19}F) data indicated that, indeed, a five-membered heterocycle was formed. Since then considerable structural information on boron complexes of amino acids has appeared in the literature.[6] Recently, DFBONs of *N*-unprotected Ser, Thr, Asp, and Glu were prepared for the simultaneous protection of both the



Scheme 1.

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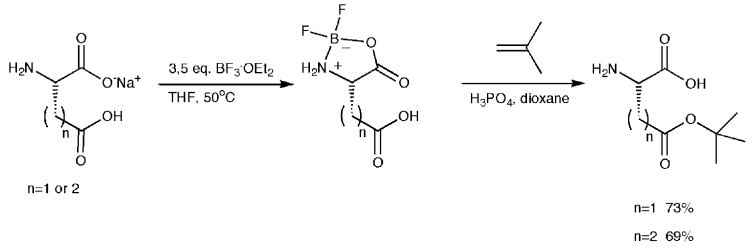
amine and carboxylic acid moieties, in order to be able subsequently to protect the side chain (Scheme 2).[7]

Although the above DFBONs are stable for several weeks in anhydrous solutions, they are sensitive to moisture and decompose easily, which facilitates their use in temporary protection (Scheme 2). This sensitivity might also be indicative of their reactivity toward nucleophiles on the α-carbonyl moiety and therefore for the application we envisioned, that is exposing DFBONs to amino nucleophiles.

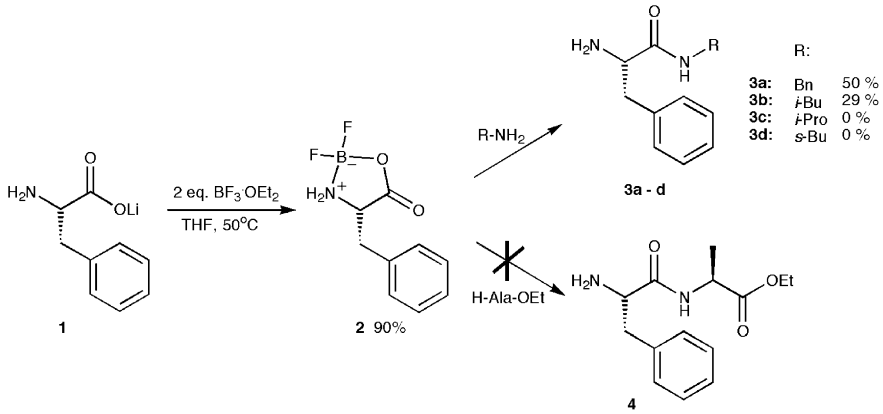
Starting from the lithium salt of L-phenylalanine (**1**), the corresponding 2,2-difluoro-1,3,2-oxazaborolidin-5-one **2** was prepared. The lithium salt is more soluble than L-phenylalanine itself and after 4 h at 50 °C with 2 equiv of $BF_3{\cdot}OEt_2$ in THF the conversion was complete according to TLC. It was possible to isolate the cyclic boron complex of L-Phe (**2**) by silica gel column chromatography in 90% yield (Scheme 3).

Subsequent treatment of **2** with benzylamine (2 equiv) led to the benzyl amide **3a**, which was obtained in 50% yield. Reaction of **2** with *iso*-butylamine afforded only 29% of the amide (Scheme 3). These yields were considerably lower that those recently obtained using dichlorodialkyl silanes (98% and 81%, respectively[4]). No product was isolated after reaction with *iso*-propylamine, *sec*-butylamine or L-alanine ethyl ester, indicating that the amine functionality has to be attached to a primary carbon atom and any steric encumbrance of the nucleophile is detrimental to the yield. Clearly, the reactivity of DFBONs like **2** is even more compromised by steric factors than that of earlier described cyclic silyl intermediates (see Scheme 1).

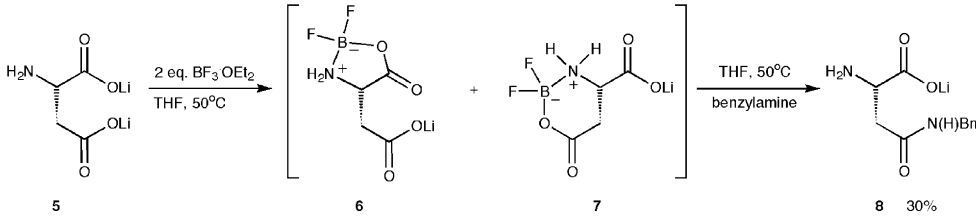
Despite the somewhat disappointing reactivity of the amino acid derived DFBONs with amino nucleophiles, we were interested whether the possibility of formation of cyclic boron congeners of different size would determine product selectivity. For this purpose we tested the di-lithium salt of L-Asp (**5**), which could give rise to formation of a five-membered **6** and/or six-membered **7** boron ring involving the amino function and the α- or β-carboxyl group, respectively (Scheme 4). The resulting boron complex of L-Asp was isolated in approximately 60% yield, but degraded on standing for several hours. Therefore, reaction with benzylamine was carried out



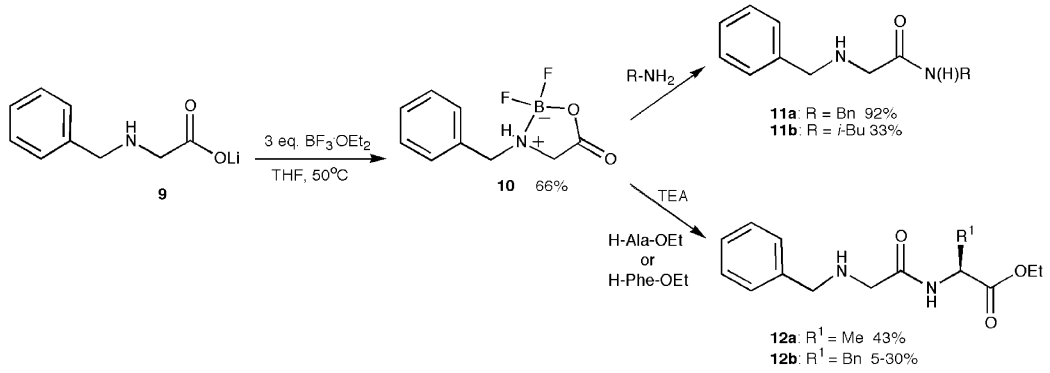
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

immediately after the isolation of the boron complex. Surprisingly, it was found that the reaction mixture contained 30% of β-L-Asp-NBn **8** only (Scheme 4). The formation of this product might, at first sight, be explained by assuming that the six-membered ring of the boron complex (**7**) is thermodynamically more favorable than the corresponding five-membered ring (**6**). However, these findings are in contrast with those of Wang et al.[7] A more plausible explanation would, therefore, be that under the basic coupling conditions an equilibrium exists between boron rings **6** and **7** and the formation of β-L-Asp-NBn (**8**) is preferred due to the much lower steric hindrance around the β-carbonyl moiety of **7** than around the α-carbonyl moiety of **6**.

Based on the results shown in Schemes 3 and 4, it seems that steric encumbrance in either the nucleophile or the boron ring is disadvantageous for a ring-opening reaction, especially if this hindrance is in close proximity to the carbonyl-reaction center, that is, a substituent or side chain present on the α-carbon atom. Therefore, a side chain on the nitrogen rather than on a carbon atom might be more favorable for a nucleophilic attack on the α-carboxyl moiety. Indeed, this expectation was born out in experiment (Scheme 5). When the lithium salt **9** of *N*-benzylglycine (NPhe-OH)[8] was treated with $BF_3{\cdot}OEt_2$ the boron complex **10** was isolated in 66% yield. Subsequent reaction of **10** with 2 equiv of benzylamine or *iso*-butylamine led to higher yields of the amides **11a** and **11b** (92% and 33%, respectively) as compared to the DFBON of L-Phe (**2**). Moreover, reaction of **10** with L-alanine ethyl ester (2 equiv) led to dipeptidomimetic **12a** in an appreciable yield of 43% as compared to no product in the reaction of **2** with L-alanine ethyl ester. Even the L-phenylalanine ethyl ester, containing a large side chain, gave rise to the formation of the dipeptidomimetic product **12b**, although the conversion, estimated by TLC, seemed higher than the actual isolated yield (5%).

In conclusion, we have shown, for the first time, that it is possible to prepare commercially important product classes of amino acid amides and dipeptides from amino acids via a simultaneous protection and activation strategy using the inexpensive and readily available boron trifluoride diethyl etherate. The intermediate 2,2-difluoro-1,3,2-oxazaborolidin-5-ones (DFBONs) can be isolated. Their ring opening is more sensitive to the steric hindrance of the incoming nucleophile than the earlier described silyl intermediates, which is reflected in lower yields of the resulting amides. When the steric hindrance is removed from the reaction center, as in the case of the DFBON of a peptoid monomer, yields of the resulting amides increase and even dipeptidomimetic products can be isolated, albeit in moderate yields.[9]

References and notes

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9. General procedure for the preparation of 2,2-difluoro-1,3,2-oxazoborolidin-5-ones of amino acids: the lithium salt of the amino acid was obtained by stirring the appropriate amino acid in water with 1 equiv of LiOH until a clear solution was observed, followed by evaporation to dryness and extensive drying (P_2O_5) in vacuo.
2: To a suspension of 0.51 g L-Phe-OLi (**1**, 3.0 mmol) in 10 mL dry THF was added 750 μL (6.0 mmol) $BF_3{\cdot}Et_2O$. The mixture was stirred for 4 h at 50 °C during which a clear solution was formed. Progress of the reaction was monitored by TLC (R_f product: 0.9, *n*-BuOH/HOAc/EtOAc/H_2O, 1:1:1:1, v/v/v/v). Concentration of the reaction mixture and column chromatography on silica gel (eluent: EtOAc/*n*-hexane/MeOH, 1:1:0 to 1:0:0 to 98:0:2, v/v/v, R_f 0.37) afforded the L-Phe-BF_2 complex **2** as a white solid (0.58 g, 90%). Recrystallization from THF/*n*-hexane yielded white crystals. ^{1}H NMR (THF-d_8): δ 2.74 (dd, 1H, CH_A, J = 7.7 Hz, J = 15.0 Hz), 3.37 (dd, 1H, CH_B, J = 3.3 Hz, J = 15.0 Hz), 4.02 (m, 1H, αCH), 5.74 (br s, 1H, NH), 6.75 (br s, 1H, NH), 7.11–7.30 (m, 5H, CH, Ph). ^{13}C NMR (THF-d_8): δ 37.6 (CH_2, Ph), 59.1 (αCH), 128.5, 130.2, 130.3 (CH, Ph), 138.4 (C_q, Ph), 171.8 (C═O). ^{19}F NMR (THF-d_8): δ 73.89 (m), 74.76 (m, TFA as an external standard). IR: 1767 cm^{-1} (C═O). Mass $C_9H_{10}O_2$ NBF_2 mw 213; $[M+H]^+$ 214.1. The NMR sample was stable for at least 5 days.
10: Prepared and purified as described for **2**, giving a white solid in 66% yield. R_f 0.44 (silica gel, eluent EtOAc/hexanes, 1/1, v/v). ^{1}H NMR (THF-d_8): δ 3.52–3.66 (m, 2H, NCH_2CO, J = 7.0 Hz), 3.89 (dd, 1H, CH_BPh, J = 9.2 Hz, J = 13.6 Hz), 4.30 (dd, 1H, CH_APh, J = 2.9 Hz, J = 13.2 Hz), 7.09 (br s, 1H, NH), 7.38–7.48 (m, 5H, CH, Ph). ^{13}C NMR (THF-d_8): δ 51.5 (NCH_2CO), 52.9 (NCH_2Ph), 130.1, 130.9 (CH, Ph), 134.5 (C_q, Ph), 168.2 (C═O). ^{19}F NMR (THF-d_8): δ 76.77 (m), 78.26 (m, TFA as an external standard). IR: 1793–1754 cm^{-1} (d, C═O). Anal. Calcd for $C_9H_{10}O_2NBF_2$: C 50.75, H 4.73, N 6.58%; found: C 50.64, H 4.31, N 6.89%.