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Reaction of N-Trityl Amino Acids with BOP: Efficient Synthesis of *t*-Butyl esters as well as N-Trityl Serine- and Threonine-β-lactones.

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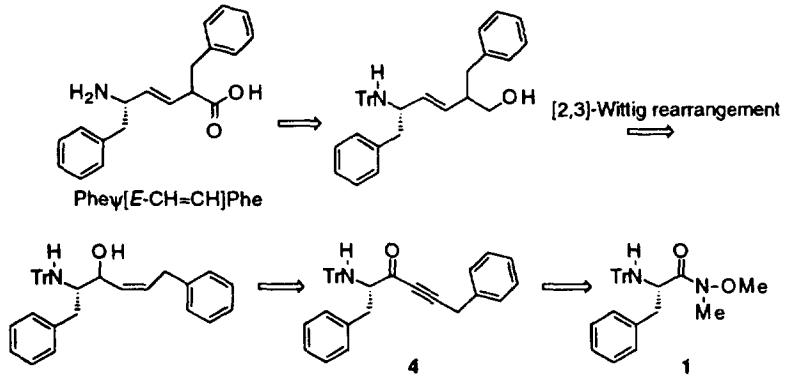
Abstract: Upon exposure to methoxymethylamine and BOP, the stable hydroxybenzotriazolyl amide of TrPheOH was isolated instead of the expected Weinreb amide. This amide behaves as an active amide similar to the Weinreb amide and could be used, among others, for the synthesis of *t*-Bu esters. Reaction of N-trityl serine and threonine led to the corresponding β-lactones in unprecedented high yields.

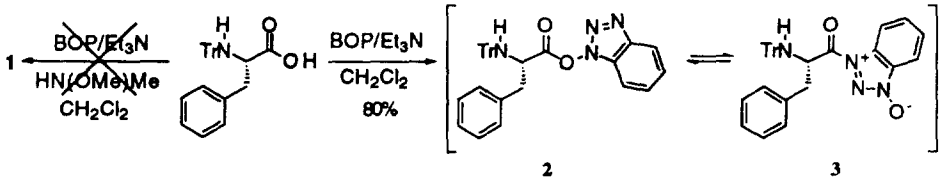
In our research on peptidomimetics containing alkene dipeptide isosteres, we were interested in the synthesis of the alkene dipeptide isostere of Phe-Phe. This dipeptide sequence is *e.g.* found in the neuropeptide Substance P[1]. Previously, we have employed the [2,3]-Wittig-Still rearrangement as the key reaction step in the preparation of alkene dipeptide isosteres of Phe-Gly and Gly-Ala[2]. In a retrosynthetic approach (Scheme 1) towards the synthesis of the alkene dipeptide isostere of Phe-Phe *viz.* Pheψ[E-CH=CH]Phe, we envisioned using the Weinreb amide **1**[3] of N-trityl phenylalanine as a starting material.



Scheme 1. Retrosynthesis of Pheψ[*E*-CH=CH]Phe *via* a [2,3]-Wittig rearrangement.

Since synthesis of the Weinreb amide of Boc-phenylalanine has been described in the literature[4], we did not anticipate any problems in the preparation of the corresponding amide derived from Tr-phenylalanine. We preferred to use the trityl group as an amino protecting group, since it has proved to be advantageous in our approach to the earlier reported alkene dipeptide isosteres[2]. Unfortunately, treatment of TrPheOH with

methoxymethylamine by the method of Fehrentz[4] using BOP/Et3N in dichloromethane did not result in the desired methoxymethylamide **1**. Instead, after workup, a mixture of two products was obtained, which were separated by column chromatography and identified as the hydroxybenzotriazole ester **2** and the hydroxybenzotriazolyl amide **3** of N-trityl phenylalanine[5]. Reaction of TrPheOH with BOP/Et3N in dichloromethane *in the absence of methoxymethylamine* furnished the same products in a combined yield of 80% (Scheme 2). After column chromatography one compound was obtained as a yellow oil (45%) whereas the other formed nice crystalline needles (55%, Scheme 2).



Scheme 2

Since it was not possible to assign unambiguously the structure of either the HOBt-ester **2** or amide **3** to the thus obtained compounds using NMR and IR spectroscopy and literature data are confusing in this respect[6], we decided to subject the crystalline compound to an X-ray crystallographic analysis. It was found that this compound was the HOBt-amide **3** (Figure 1) and - as expected - the thermodynamically more stable compound, since upon storage (1-3 weeks) the ester completely rearranged to the amide. Therefore, after a second purification step hydroxybenzotriazolyl amide **3** could be obtained in an overall yield of 76%.

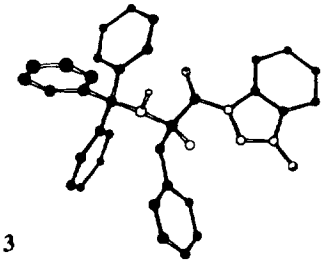
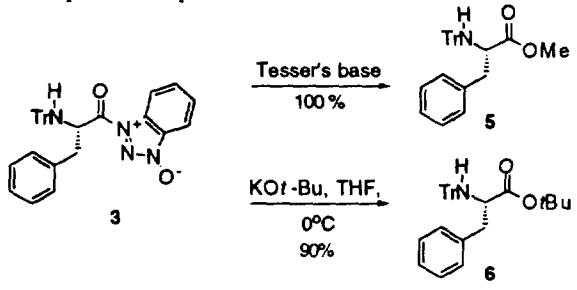


Figure 1. X-ray structure of the HOBt-amide **3**

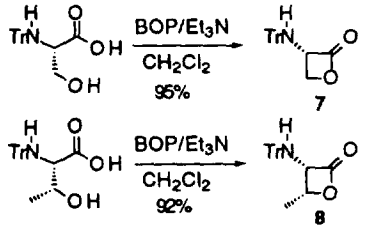
Indeed, when hydroxybenzotriazole is present, as part of the reagent or as an additive in the reaction mixture, amino acid HOBt-esters or HOBt-amides are likely intermediates during peptide coupling reactions. However, in the case of Cbz- or Boc-protected amino acids these reactive species were never isolated because of their instability during workup[7]. The relative stability of the HOBt-ester and amide derived from N-trityl amino acids, as compared to the corresponding derivatives from N-Boc or N-Cbz amino acids, is rather remarkable. It seems that the electron donating properties of the trityl group are sufficient for a decrease of the positive charge of the carbonyl-carbon to the extent that the HOBt-esters or amides of N-trityl amino acids are "armed" against attacks of nucleophiles like for example methoxymethylamine. By the same token, the Boc and Cbz group, by the virtue of their electron withdrawing properties, "disarm" Boc- or Cbz amino acids and the corresponding HOBt-ester or amides will be more sensitive for nucleophilic attack[8].

Since the HOBt-amides of N-trityl amino acids are both sufficiently stable and reactive, we consider them as interesting and possibly versatile alternatives of the Weinreb active amide. Therefore, a few preliminary experiments were carried out to corroborate this. For instance, the traditional use of Weinreb amides derived from amino acids for selective reduction to the corresponding α-amino aldehydes prompted us to reduce HOBt-amide **3** with DIBALH. Indeed, we obtained N-tritylphenylalaninal in 70% yield along with 30% of N-tritylphenylalaninol. Methanolysis of HOBt-amide **3** with Tesser's base resulted in quantitative formation of N-tritylphenylalanine methylester. More interestingly, treatment of HOBt-amide with two

equivalents of KO*t*Bu in THF gave the *t*-Bu ester in 90% yield. (Scheme 3). This represents a valuable addition to the existing methods for the preparation of *t*-Bu esters, many of which take place under acidic condtions[9]. Disappointingly, although TLC of the reaction of the lithium derivative of 3-phenyl-1-propyne with the hydroxybenzotriazolyl amide **3** indicated a clean conversion, the desired alkyne **4** (Scheme 1) turned out to be unstable upon work-up[10].



Scheme 3.



Scheme 4.

Although similar results were obtained for alanine, in attempts to prepare the HOBt-amide of N-trityl serine and threonine for further conversion to the corresponding *t*-Bu ester, we isolated quite unexpectedly the β-lactones of serine and threonine in very high yield, *viz.* 95 and 92% respectively[11] (Scheme 4). Unfortunately, treatment of the β-lactone of serine with KO*t*Bu in THF did not afford the corresponding t-Bu ester but led to formation of the dehydroalanine derivative. Deprotection of **7** with TFA/CH_2Cl_2 in the presence of one equivalent of p-TsOH according to the procedure described by Vederas[15] yielded the stable TsO^-salt of serine-β-lactone in a quantitative yield.

The need for a high yielding synthesis of the β-lactones **7** and **8** is demonstrated by a number of recent publications in which these compounds are used as key synthons. They are important starting materials in the synthesis of natural products[12] and of β-substituted alanines[13]. In addition, they are used as monomers in polymer chemistry[14].

Vederas and coworkers have described the synthesis of N-Boc and N-Cbz protected serine-β-lactone in 60-80% yield using the Mitsunobu reaction. It was only possible to prepare N-sulfene protected β-lactones of threonine and *allo*-threonine, in a moderate yield of 45 - 55%, by activating the carboxylgroup with 4-bromobenzenesulfonyl chloride in pyridine followed by ring closure[15]. The N-*trityl* protected serine-β-lactone has been described by Sheehan[16], who established cyclisation using DIC in 15% yield. To our knowledge, higher yields were never reported, which was one of the reasons to disclose these rather unexpected results.

In summary, in attempts to synthesize the Weinreb active amide of N-trityl protected amino acids, we have isolated an equilibrium mixture of a HOBt-ester and HOBt-amide. The equilibrium can be shifted towards the amide, which can be considered as a versatile alternative of the Weinreb active amide. In addition to the usual reactions of the Weinreb active amide, the HOBt-amide can be used for the preparation of *t*-butyl esters. Reaction of N-trityl serine or N-trityl threonine with BOP led to the highest yields of the corresponding β-lactones reported thus far.

ACKNOWLEDGMENTS: We thank Dr. J.J. Kettenes-van den Bosch for recording several NMR spectra and Dr. W. Heerma and C. Versluis for recording and interpretation of the mass spectrum of **3**.

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5. **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (d, 1H, NH, J = 9.9 Hz), 2.99 and 3.18 (8 lines, 2H, CH_2Ph, J_{AB} = 13.6 Hz, J_{AX} = 7.3 Hz, J_{BX} = 5.9 Hz), 4.20 (dt, 1H, $CHCH_2Ph$, J_{NH} = 9.9 Hz, J_{AX} =7.0 Hz, J_{BX} = 6.2 Hz), 6.81-8.32 (m, 24 H, Tr, Ph, OBt). ^{13}C NMR (300 MHz, $CDCl_3$) δ 41.5 (CH_2Ph), 56.7 ($CHCH_2Ph$), 71.5, 108.6, 120.2, 124.5-130.0, 135.6, 145.4 (aromatic C's), 170.4 (C=O, ester). IR (KBr) 1816 cm^{-1} (C=O).
3: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (m, 3H, CH_2Ph and NH), 4.69 (m, 1H, $CHCH_2Ph$), 6.88-7.92 (m, 26H, Tr, Ph, OBt). ^{13}C NMR (300 MHz, $CDCl_3$) δ 42.0 (CH_2Ph), 52.5 ($CHCH_2Ph$), 71.0, 115.1, 116.0, 126.4-132.5, 136.3, 145.4 (aromatic C's), 171.9 (C=O, amide). IR (KBr) 1726 cm^{-1} (C=O). FABMS m/z 525.1 $(M+H)^+$.
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10. In contrast, the corresponding Boc-protected ynone could be prepared in 90% yield: Overhand, M.; Hecht, S.M. *J. Org. Chem.* **1994**, *59*, 4721-4722.
11. **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (d, 1H, NH, J = 11.0 Hz), 3.12 and 3.52 (7 lines, 2H, CH_2, J_{AB} = 5.6 Hz, J_{AX} = 4.7 Hz, J_{BX} = 5.7 Hz), 4.61 (8 lines, 1H, CH, J = 11.0 Hz, J_{AX} =4.6 Hz, J_{BX} = 6.0 Hz), 7.22-7.54 (m, 15H, Tr). ^{13}C NMR (300 MHz, $CDCl_3$) δ 64.5 (CH), 70.6 (CH_2), 70.7, 127.0-128.4, 145.1 (aromatic C's), 172.0 (C=O). IR (KBr) 1826 cm^{-1} (C=O). m.p. 188-190 °C.
8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, 3H, CH_3, J = 6.0 Hz), 2.80 (d, 1H, NH, J = 9.5 Hz), 4.21 (5 lines, 1H, $CHCH_3$, J_1 = 6.1 Hz, J_2 = 6.2 Hz), 4.74 (dd, 1H, CHC=O, J_{NH} = 9.5 Hz, J = 5.9 Hz), 7.22-7.54 (m, 15H, Tr). ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.0 (CH_3), 64.5 (CHC=O), 76.1 ($CH(O)CH_3$), 70.9, 127.0-128.7, 145.3 (aromatic C's), 172.6 (C=O). IR (KBr) 1817 cm^{-1} (C=O). m.p. 139-142 °C.
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