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"BOP" AS A REAGENT FOR MILD AND EFFICIENT PREPARATION OF ESTERS

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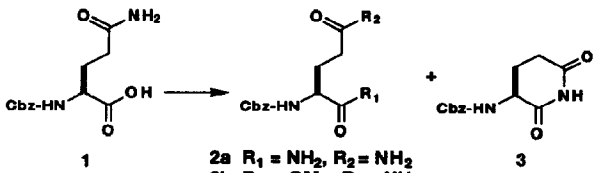
Abstract: *A simple procedure for preparation of esters under mild conditions employing the BOP reagent is reported. Acid and base labile protecting groups commonly used with amino acids e.g. t-butyl, Fmoc etc., are well tolerated under these conditions. The mechanism and scope of this reaction are briefly discussed.*

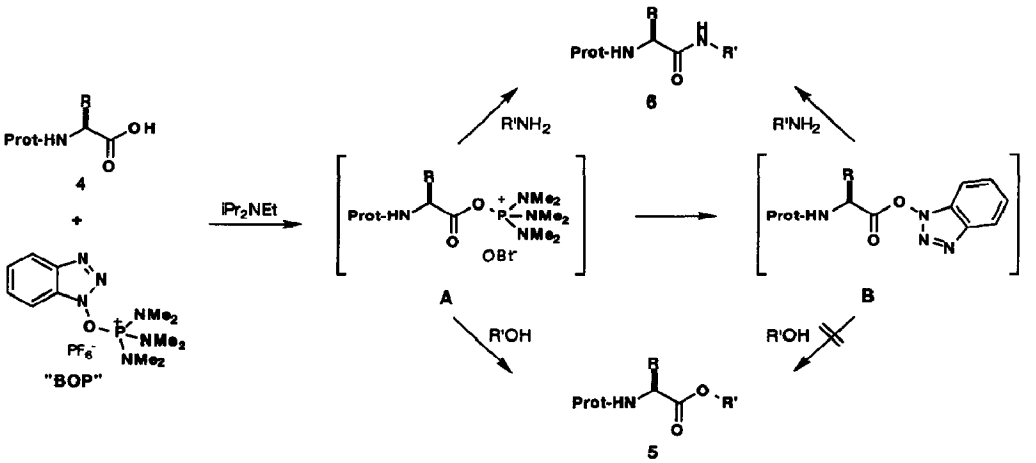
The formation of amide and ester bonds continues to attract significant attention, as evident by the wide range of reagents and reaction conditions that have been employed for their preparation.[1] In the field of peptide chemistry, reactions of amino acids bearing functionalized side chains often present a challenging task, the degree of difficulty depending on the nature of transformation desired.[2] In connection with one of our ongoing projects, we recently needed a simple transformation of N-α-Cbz-L-Gln-OH **1** to the corresponding amide **2a**. Upon treatment of a solution of **1** in anhydrous 2M NH_3/MeOH with BOP[3] at -20 °C, followed by work up after 3 h, none of the desired product was obtained. Instead, the methyl ester **2b** and the regioisomer **2c** were obtained in approximately equal amounts (35% and 30% respectively).



No.	Reaction Conditions	2a	2b	2c	3
1	a) BOP, iPr_2NEt, -20° C b) 2M NH_3/MeOH, -20° C c) -20° C to r.t. over 3 h	-	35%	30%	15%
2	same as above, except addnl 12h at r.t.	84%	-	-	-
3	a) IBuOCOCl, NMM, -20° C, CH_2Cl_2 b) 2M NH_3/MeOH, -20° C	88%	-	-	-

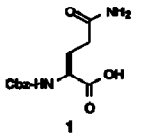
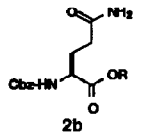
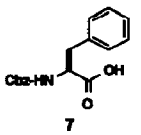
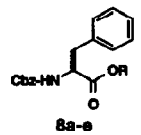
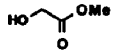
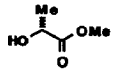
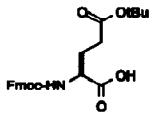
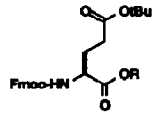
The cyclic imide **3**, which explains the formation of rearranged regioisomer **2c**, was also isolated in 15% yield. While the desired transformation was successfully accomplished by simply prolonging the course of reaction (overnight), wherein **2b** and **2c** would subsequently react with ammonia to give **2a** (84%), or more conveniently by the mixed ester activation procedure (88%),[4] the intermediacy of esters **2b** and **2c** prompted us to probe the mechanistic aspects of the BOP reagent, and if possible, exploit its utility for preparation of esters.

The proposed mechanism for this transformation is sketched below. An acid reacts with BOP to first generate the very reactive phosphonium intermediate **A**, which under normal conditions is transformed to the less reactive benzotriazolyl ester **B**. Amines can react with **A**, and are nucleophilic enough to react with **B** resulting in the formation of amides under epimerization free conditions. On the other hand, alcohols R'OH are poor nucleophiles and are unreactive toward **B**, and will react only with the highly electrophilic species **A**. Hence for ester formation, conversion of **A** to **B** needs to be slowed down i.e. the existence of intermediate **A** needs to be prolonged so that it get a chance to be intercepted by the alcohol. Additionally, the use of excess reagents (R'OH) may also help drive the reaction to completion.



Thus, upon addition of BOP to a premixed solution of N-α-Cbz-L-Phe-OH 7 and excess MeOH in CH_2Cl_2 at -20 °C, and quenching after 15 min with gradual warming to RT, the methyl ester **8a** was obtained in 95% yield after work up and chromatographic purification. By conducting the reaction at low temperatures, the existence of intermediate **A** is ensured. By using excess alcohol and having it present even before the coupling reagent is added, the chances of trapping intermediate **A** with R'OH as soon as it is formed are maximized. In an alternate experiment, 7 was prestirred in CH_2Cl_2 with BOP at RT for 15 min to allow for conversion of **A** to **B**, and this was followed by treatment with excess MeOH. Not surprisingly, only unreacted starting material was detected under these conditions. This lends support to our proposition that alcohols will react only with phosphonium ester intermediate **A** and not with benzotriazolyl ester **B**.

Having established the reaction conditions in our model study, we next set out to briefly investigate the scope and limitations of this reaction, and the results are summarized in the following table.[5]

Entry #	Amino acid	Alcohol	(equiv)	Product	-OR	Yield
1	 1	MeOH	(74.0) (1.1)	 2b		95% >68%
2	 7	MeOH	(74.0) (1.1)	 8a-e	8a 	95% 97%
3			(10.0) (1.05)		8b 	95% 85%
4			(10.0)		8c 	76%
5			(10.0) (3.0) (1.5) (1.05)		8d 	75% 84% 79% 86%
6			(10.0)		8e 	-
7	 9	MeOH	(1.1)	 10a-c	10a 	93%
8			(1.1)		10b 	89%
9			(1.1)		10c 	88%

N-α-Cbz-L-Gln-OH **1** was smoothly converted to the methyl ester **2b** in 95% yield. While initially a large excess of the alcohol component was employed, we have subsequently determined that it is not a strict criteria for this transformation. Thus, methyl esterification of **7** can be accomplished with 1.1 equivalents of methanol (entry 2, **8a**, 97%). The reaction also proceeds well with sterically more hindered secondary alcohols like 2-propanol and functionalized alcohols such as methyl glycolate (entry 4, **8c**, 76%) and R-(+)-methyl lactate (entry 5, **8d**, 75-86%). Once again, the excess alcohol is not necessary for high yield conversions, as demonstrated in the latter instance. Not surprisingly, esterification with the sterically hindered t-BuOH could not be accomplished. To evaluate the tolerance of acid and base labile functionalities under these conditions, we next

investigated the esterification of N-α-Fmoc-Glu(OtBu)-OH **9** bearing the acid labile t-butyl ester side chain and the base sensitive fluorenylmethyl carbamate moiety. Using the established protocol and employing 1.1 equivalents of methanol, the methyl ester **10a** was obtained in 93% yield (entry 7). This is a definite advantage over the classical Fischer esterification which is not compatible with molecules possessing acid sensitive functionalities,[6] and the DCC/DMAP procedure which may be inappropriate for compounds with very base labile functionalities.[7] Treatment of **9** with benzyl alcohol gave the orthogonally protected **10b** bearing acid, base, and hydrogenolysis labile functionalities (89%). The application of this procedure can also be extended for preparation of thioesters, as evident by conversion of **9** to **10c** upon treatment with benzyl mercaptan (entry 9, 88%).

In summary, this communication provides additional insight into the mechanism of BOP mediated coupling reactions. We have extended the use of this reagent normally employed for forming amides, to the preparation of esters under mild and efficient conditions. The reaction tolerates both acid and base sensitive functionalities, a feature not conveniently attainable with classical ester forming reagents. The well precedented use of BOP in the field of peptides and peptide based combinatorial libraries[8] coupled with our findings should augment its utility in similar endeavors requiring ester bond formations.

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We wish to thank Drs. David A. Campbell and Eric M. Gordon for helpful discussions during the progress of this work.

Notes and References :

1 a) Bodanszky, M.; Klausner, Y. S.; Ondetti, M. A. "Peptide Synthesis"; 2nd Ed.; Wiley: New York, 1976. b) Haslam, E. *Tetrahedron* **1980**, *36*, 2409.
2 Bodanszky, M.; Martinez, J. *Synthesis* **1981**, 333.
3 BOP : Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. For the introduction of this reagent to peptide coupling reactions, see Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *14*, 1219.
4 Vaughan, J. R., Jr. *J. Am. Chem. Soc.* **1951**, *73*, 3547.
5 A general experimental procedure is as follows: Alcohol R'OH (1.1 mmol) is added to a solution of N-α-protected amino acid (1.0 mmol) and iPr_2NEt (0.26 mL, 1.5 mmol) in CH_2Cl_2 (2 mL) at -20 °C (CCl_4/dry ice bath) under argon. After stirring for 15 min at -20 °C, BOP (0.44 g, 1 mmol) is added, and the reaction mixture is left for overnight stirring with gradual warming to RT. The next day (total reaction time = 10 to 14 h), the reaction mixture is suspended in CH_2Cl_2 and washed sequentially with pH = 4 buffer (Aldrich), satd. aq. NaCl, satd. aq. $NaHCO_3$, and satd. aq. NaCl. Drying (Na_2SO_4) and concentration *under vacuo* affords the crude product, which is purified by silica gel flash chromatography. All the products are characterized by MS, ^1H, and ^{13}C NMR.
6 a) Curtius, T. *Ber. dtsch. Chem. Ges.* **1883**, *16*, 753. b) Fischer, E. *Ber. dtsch. Chem. Ges.* **1901**, *34*, 433; **1908**, *41*, 850.
7 Partial removal of the Fmoc group during synthetic transformations of Fmoc-protected amino acids with reagents involving the use of DMAP has been frequently observed in our labs; D. A. Campbell, unpublished data.
8 a) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science*, **1991**, *251*, 767. b) Needels, M. A.; Jones, D. G.; Tate, E. H.; Heinkel, G. L.; Kochersperger, L. M.; Dower, W. J.; Barrett, R. W.; Gallop, M. A. *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 10700.

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