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A Straightforward Synthesis of α-Amino Phosphonate Monoesters Using BroP or TPyClU

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Abstract: Monoesters of N-protected α-amino phosphonic acid were prepared from phosphonic acid using BroP or TPyClU as activating agent. This reaction proceeds with good yield, even with hindered alcohols. Copyright © 1996 Published by Elsevier Science Ltd

Synthesis of monophosphonates usually involves hydrolytic (LiOH, NaOH)[1] or nonhydrolytic (NaI, TMSBr, PhSH)[2] selective ester cleavage of symmetrical[1] or unsymmetrical phosphonate diesters.[1,3] This synthesis requires, however, preparation of the corresponding phosphonate diester and necessitates selective cleavage of the ester. Phosphonic acid monoesters can also be prepared via monotransesterification of bis-*p*-nitrophenyl phosphonates with an alcohol in the presence of DBU, followed by hydrolysis of the corresponding alkyl PNP phosphonates.[4] Another strategy is based upon direct monoesterification of phosphonic acid with alcohols in the presence of condensing reagents such as DCC[5a], DCC/base,[5b] CCl_3CN[6] or $SOCl_2$.[7] However, these methods require severe conditions (large excess of alcohol, reflux) and are inefficient with hindered alcohols. Karanewsky[8] described an alternative procedure in which phosphonic acid monoesters are prepared in a two-step procedure proceeding by DCC-DMAP-mediated esterification of phosphonous acids and oxidation of the resulting phosphonous ester. This method is efficient with sterically hindered alcohols but is incompatible with amino acids bearing an oxidizable lateral chain.

We report here a convenient route for the synthesis of phosphonic acid monoesters via reaction of the corresponding phosphonic acid with different alcohols using commercially available BroP[9] or TPyClU[10] reagents. Using BroP, reaction of the amino phosphonic acid **1** with isopropanol gave exclusively the phosphonate monoester in a quantitative yield (Table 1: **2a**).[11] Even with more sterically hindered alcohols (Table 1: **2d,e**), yields were still good. Unfortunately, the monoesters were contaminated with HMPA which could not be removed by either washing or chromatography because it seemed to complex with the monophosphonate. To by-pass this drawback, we used TPyClU. With this reagent, all the monophosphonates were also obtained in good yield (Table 1) and, in addition, could be purified by chromatography, crystallization or precipitation of their dicyclohexylamonium salt.

Monoesterification using DCC was also reevaluated. We obtained compound **2a** in good yield using DCC, but the reaction did not progress in the presence of base (Table1: **2a**). Moreover, the monophosphonate could not be completely separated from DCU. The same reaction using BOP or PyBOP gave a mixture of

phosphonate monoester and diester since the second esterification was very fast due to HOBt-mediated activation, as we have shown in a previous paper.[12]

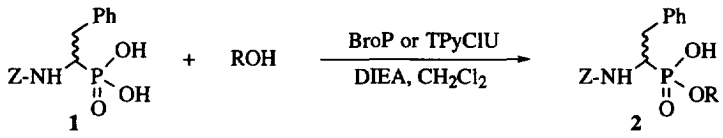

Table 1: Esterification of **1**

Compound	ROH	BroP Estimated yield %	TPyClU Yield[a] %	DCC %	DCC/DIEA %
2a	*i*-PrOH	98[b]	83	80[a]	5[a]
2b	$PhCH_2OH$	100[c]	86		
2c	(*S*)-HOCH(CH_3)COOEt	100[c]	80		
2d	(*S*)-HOCH(i-Pr)COOBzl	72[c]	70		
2e	*t*-BuOH	80[b]	65		

a- Product isolated by chromatography or precipitation as DCHA salt and analysed by MASS(FAB$^+$), ^{1}H and ^{31}P NMR. b- Yield determined using an internal standard. c- Yield determined by ^{1}H NMR because the products still contained HMPA after purification (**2b** and **2c** by washing, **2d** by chromatography).

To verify the enantiomeric purity of the monophosphonate, (*R*)-**1**[13] was monoesterified with benzyl-L-hydroxy-2-isovalerate using BroP to give the monophosphonate **2d** in optically pure form.[14]

In conclusion, activation of amino phosphonic acids with BroP or TPyClU is an efficient, racemization-free route to obtain the corresponding monoesters.

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11- The general procedure is as follows: To a solution of phosphonic acid **1** (1 eq.), alcohol (1.1 eq., except with *t*BuOH:3eq.) and BroP or TPyClU (1.1 eq.) in CH_2Cl_2 (2 ml/mmol) was added DIEA (2.1 eq.). After reaction (5 h-12 h) at room temperature (BroP) or at reflux (TPyClU), CH_2Cl_2 was evaporated and the residue was dissolved in AcOEt. The organic phase was washed with $KHSO_4$ (5%) and brine, dried over Na_2SO_4, filtered and evaporated under vacuo.
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14- Epimerisation was shown to be less than 0.5% by HPLC comparison with the diastereomers prepared from (*R,S*)-**1**.

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