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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3565–3567

Transesterification of trialkyl phosphates from alkyl bromides

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Received 8 December 2004; revised 10 March 2005; accepted 11 March 2005
Available online 5 April 2005

Abstract—The treatment of trialkyl phosphate with different alkyl bromides provides facile access to mixed phosphate esters. The presence of substoichiometric amounts of lithium bromide was found to be critical to this transesterification process, supporting a mechanism involving initial generation of phosphate anion, followed by its nucleophilic attack on alkyl bromide.

1. Introduction

The phosphate diester functional group forms the covalent link between nucleotides in the structure of nucleic acids, and many other biologically important molecules can be enzymatically phosphorylated to form phosphate monoesters in the course of the regulation of their physiological roles.[1] However, the bioactivity of biomimetic phosphate mono- and diesters can be limited by their cell permeability, owing to the negative charge carried by their ionized non-alkylated oxygens. In phosphate triesters this negative charge can be masked by enzymatically labile alkyl groups, representing one recent strategy that has been employed with success to increase cell permeability of such biomimetic compounds.[2]

Trialkyl phosphate esters can thus serve as useful final biomimetic targets or synthetic intermediates, and many methods exist for their synthesis.[3] Generally, alcohols can be phosphorylated by reaction with P(III) species,[4] followed by oxidation, or directly by reaction with activated P(V) species.[5,6] However, these methods require phosphorylating agents that are typically unstable, are rarely commercially available and usually require synthesis over several steps to prepare.[7,8] The use of phosphate diester anions as nucleophiles for the preparation of benzyl and allyl esters has also been reported,[9] but these methods have not been broadly applied to the general preparation of phosphate triesters through transesterification.

Over the course of our synthesis of phosphonates and phosphonamidates as potential enzyme inhibitors, we observed from time to time the formation of small amounts of dimethyl phosphate triesters in Arbusov reactions involving the condensation of trimethyl phosphite with various alkyl bromide amino acid derivatives.[10] Intrigued by this side reaction, we investigated further, presuming that the phosphorylating agent was in fact trimethyl phosphate, present as an oxidative impurity in the trimethyl phosphite. A rapid search of the literature provided little precedence for the putative transesterification reaction. The formation of mixed esters upon the condensation of phosphate triesters has been reported using harsh reaction conditions[11] or with highly activated alkylating agents,[12] and the transesterification of dimethyl phosphonate esters using alkyl chlorides is also known.[13] Using these analogous results and our serendipitous observations as a starting point, we have established mild reaction conditions that permit the rapid preparation of a variety of mixed phosphate triesters and have briefly studied the mechanism of this transformation.

Shown in Table 1 are the results from our exploration of the use of bromides as mildly activated alkyl donors for the transesterification of phosphate triesters, present in large excess as reaction solvents, analogous to conditions for the Arbusov reaction. In general, the unoptimized yields reported in Table 1 are good, and demonstrate the broad utility of the transformation. Some protected aminoalkyl bromide derivatives were also studied in the interest of ultimately applying this method to the synthesis of amino acid analogues.[14] To this end, a phosphate ester of homoserine was obtained in good yield from the corresponding bromide that was

Keywords: Phosphate triester; Transesterification; Bromide.
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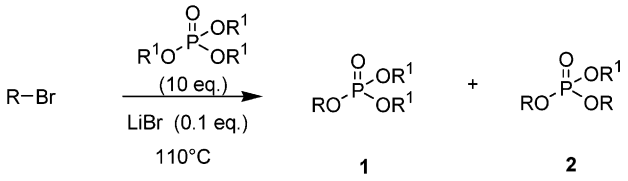
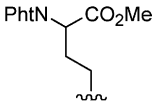
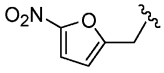
doi:10.1016/j.tetlet.2005.03.065

Table 1. Conversion of alkyl bromides to phosphates



Entry	Substrate (R–)	R^1	Time (h)	Yield **1**, %[a]	Yield **2**, %[a]
1	$PhtNCH_2$–	Me	12	76	21
2	$PhtNCH_2$–	Et	15	85	n/o[b]
3	$PhtNCH_2CH_2$–	Me	16	24[c]	n/o
4		Me	15	n/o	n/o
5	$PhC(O)CH_2$–	Me	11	60	40
6	$PhCO_2CH_2CH_2$–	Me	16	89	10
7		Me	14	76	n/o
8	$PhCH_2$–	Me	16	57	n/o
9		Me	14	~70% conversion 9:2 mixture of **1**:**2**	

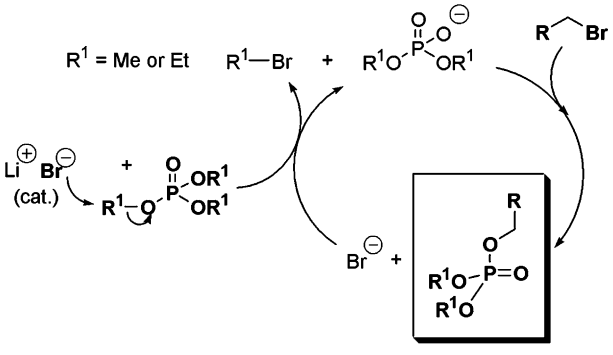
[a] Unoptimized yields of isolated, purified product.
[b] n/o: product not observed.
[c] 43% with 1 equiv LiBr.

prepared according to a previously published procedure.[15] Furthermore, it is clear that while more electrophilic activated alkyl bromides such as benzoylmethyl bromide (entry 5) leads to a slightly increased proportion of disubstituted phosphate triester (**2**), the monosubstituted product (**1**) is always the major product. This tendency is corroborated by the previously reported exhaustive substitution observed with highly activated pivaloylmethyl chloride,[7,13] and indicates that the degree of transesterification may be attenuated by controlling the electrophilicity of the alkylating agent.

The addition of LiBr, even at substoichiometric quantities, was found to be critical to conversion, demonstrating its importance in the operative mechanism of transesterification of trimethyl or triethyl phosphates. Adding 1.0 equiv of LiBr, as opposed to 0.1 equiv in the typical protocol, resulted in a marked increase in the rate of conversion of 2-phthalimidoethyl bromide (entry 3c), denoting its implication in the rate-limiting step of the overall transformation.

Halide ions, from fluoride to iodide, have been shown previously to be capable of generating phosphate anion from methyl and ethyl phosphate esters. For example, iodide is known to generate phosphate in the iodide-mediated transesterification of trimethyl phosphate.[13] Fluoride has also been shown to play this role in the transesterification of electrophilic trichloroethyl phosphate esters.[16,17] In consideration of this precedent, our current results are consistent with the initial attack of added bromide on the methyl or ethyl group of the phosphate triester, displacing the phosphate diester anion as a reactive intermediate. Nucleophilic attack by this intermediate on alkyl bromide would then lead to rapid formation of the monosubstituted transesterification product and regeneration of an equivalent of bromide (Scheme 1).

In summary, the reaction of a variety of different alkyl bromides with methyl and ethyl phosphate triesters has been shown to provide the corresponding monosubstituted transesterification products in good yields. The proposed mechanism is consistent with the mechanism determined for similar reactions known in the literature.[13,16,17] This simple reaction should provide easy access to a broad range of mixed phosphate esters from readily available and inexpensive starting materials.



Scheme 1. Proposed mechanism for transesterification with alkyl bromides studied herein.

2. Experimental

2.1. Typical procedure for phosphate transesterification from alkyl bromide

Trialkyl phosphate (10 equiv) was added to a mixture of alkyl bromide (1 equiv) and lithium bromide (0.1 equiv). The solution was stirred at 110 °C for 30 min up to overnight, depending on the substrate.[14] The mixture was then cooled to room temperature and EtOAc (5 mL) was added. The organic layer was washed four times with 15 mL H_2O, to remove traces of the residual trialkyl phosphate, and then with 10 mL brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain an oil that was purified by flash chromatography (100% EtOAc) to give the desired product.

Acknowledgements

This work was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada. The authors also acknowledge financial support in the form of scholarships from NSERC (R.C.) and the Université de Montréal (C.L.).

Supplementary data

Spectral characterization data (^1H, ^{13}C, ^{31}P NMR and HRMS) of all products. These supplementary data are available online with the paper in ScienceDirect and can be found, in the online version at doi:10.1016/j.tetlet.2005.03.065.

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14. Although most of the reactions represented in Table 1 were run overnight, when phthalimidomethyl bromide (entry 1) was allowed to react for 30 min, the conversion and yields were essentially identical as those obtained overnight. It is noteworthy that the optimal reaction time may be much shorter for some substrates, which would be advantageous if sensitive functional groups were present.
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