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A Convenient Two-Step One-Pot Synthesis of Phosphonamidates

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Abstract: Phosphonamidates are formed in high yield from a one-pot sequential reaction of a phosphonyl dichloride with an alcohol and then an amine in the presence of catalytic 1*H*-tetrazole. Undesired disubstitution of the phoshphonyl dichloride by the alcohol or the amine is minimal due to the presence of tetrazole. © 1997 Elsevier Science Ltd.

Phosphonamidates are continuing to be increasingly important as mechanistic probes for proteases,[1] potent inhibitors of peptidases as tetrahedral transition-state or high energy intermediate analogs,[2] or as phosphorylating agents of β-lactamases.[3] More recently there is increasing interest to pursue peptide-nucleotide adducts possessing a phosphonamidate moiety.[4] The preparations for simple phosphonamidates utilizing a readily available phosphonyl dichloride, require at least two synthetic steps as the phosphorus reagent is treated sequentially with an alcohol and amine. It is common to intercept the reactive monochloridate intermediate from the reaction of the phosphonyl dichloride with an alcohol without significant purification (i.e., filtration of salts) and react it immediately with an amine in a second step to generate the desired phosphonamidate.[5] Generally, this approach will provide the desired phosphonamidate, however, often there may be considerable formation of a symmetrically substituted phosphonate diester resulting from overreaction with the alcohol in the first step. Recently Zhao and Landry identified a strategy to minimize the formation of such symmetrically substituted phosphonate diesters during a two-step one-pot catlytic formation of asymmetric phosphonate diesters using 1*H*-tetrazole rather than other acylating-type catalysts.[6] Based on this success, we have focused on the utility of catalytic 1*H*-tetrazole in the formation of simple phosphonamidates in a two-step one-pot procedure in order to minimize the formation of symmetrically substituted phosphonate diester side products in the first step.

The molecules of interest in this study were phosphonamidates of glutamic acid as potential inhibitors of a glutamyl hydrolase. Therefore, the synthesis of a limited series of phosphonamidate esters with varying alkyl ligands to phosphorus was undertaken. It was also desired to vary the alcohol ligand to phosphorus allowing alternate deprotection strategies to ultimately generate phosphonamidoic acids.

Initial attempts at the preparation of phosphonamidate **1a** in ether utilizing a straightforward method[5] (i.e.; phenylphosphonyl dichloride is reacted with benzyl alcohol (BzlOH) in the presence of base, salts filtered, and the intermediate monochloridate is reacted with glutamic acid dibenzyl ester [Glu(OBzl)$_2$]) provided poor yields in addition to extensive formation of dibenzyl phenylphosphonate **2a** as observed by ^{31}P NMR in the crude

reaction mixture (**Table 1**). Realizing that the problem with this method was overreaction with benzyl alcohol in the first step, a modification of the method outlined by Zhao and Landry whereby the phenylphosphonyl dichloride is reacted sequentially with BzlOH and $Glu(OBzl)_2$ in the presence of *1H*-tetrazole in a solution of benzene was pursued. Another modification of Zhao and Landry's procedure was the reduction of the reaction time for the first step from 15 h to 2 hours as it had been previously noted that such a reduction in reaction time improved product yields.[7] In addition, during the course of these studies it was determined that the alcohol was consumed in approximately 2 hours as observed by TLC. The result under these modified conditions showed a significant increase in yield of phosphonamidate **1a** with a substantial decrease in the formation of **2a** (**Table 1**).

Scheme 1

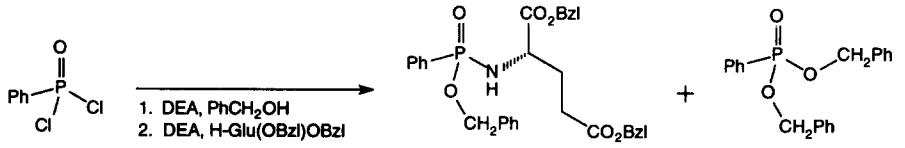

Table 1. Phenylphosphonamidate Optimization

catalyst	solvent	Yield (%)[a]	Product Ratio 1a : 2a[b]
none	Et_2O	9	3:1
none	CH_2Cl_2	44	6:1
1*H*-tetrazole	THF	61	52:1[8]
1*H*-tetrazole	Benzene	77	18:1
1*H*-tetrazole	CH_2Cl_2	80	32:1

(a) isolated yields after extractive workup and column chromatography
(b) product ratio determined by ^{31}P NMR[9];

In an attempt to maximize the yield for the formation of **1a**, other reaction solvents were investigated in the presence and absence of catalyst (**Table 1**). All reactions were monitored by TLC for the consumption of the BzlOH prior to addition of $Glu(OBzl)_2$. Although the formation of **2a** was minimal (2 to 5%) in all cases with 1*H*-tetrazole, the greatest yields were obtained in both benzene or CH_2Cl_2. It was noted that there was no significant difference in the outcome of the reaction whether the free amine or its tosylate salt was used in the second step of the reaction. Furthermore, it was observed that superior yeilds were obtained when the ratio of alcohol to phosphonyl dichloride was 1:1.1.

With the conditions optimize for the formation of **1a** the formation of **1b** was pursued by substituting methanol for BzlOH in the first of the two-step process (**Scheme 2**). Again, minimal formation of the symmetrically substituted phosphonate **2b** (R' = CH_3) was observed (< 1%) while maintaining good yields for the desired phosphonamidate **1b** in benzene (**Table 2**).

To establish that this methodology was applicable to a broader range of phosphonamidates, reactions with both methyl- and ethylphosphonyl dichloride were examined under the optimized conditions identified for reactions with phenylphosphonyl dichloride (**Scheme 2**, **Table 2**). Generally, the formation of the symmetrically substituted alkylphosphonate side-products **2b-f** for each of the reaction conditions below was minimal (< 7%). In addition, yields were generally favored for the reactions carried out in benzene rather than CH_2Cl_2. These results may be due to the enhanced reactivity of simple alkylphonsphonyl dichlorides leading to oversubstitution by either the alcohol or the amine in a more polar solvent.

Scheme 2

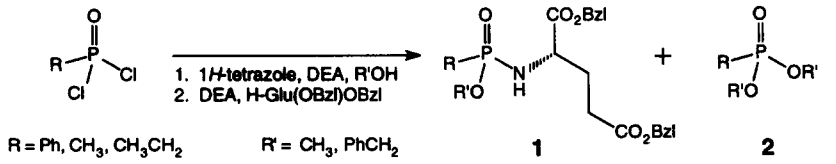

Table 2. 1*H*-Tetrazole Catalyzed Formation of Phosphonamidates

$RP(O)Cl_2$	R'OH	solvent	yield (%)[a]	Product Ratios[b]
R = Ph	R' = CH_3	benzene	52	**1b:2b** > 99 : 1
R = Ph	R' = CH_3	CH_2Cl_2	70	**1b:2b** 19 : 1
R = CH_3	R' = $PhCH_2$	benzene	79	**1c:2c** 15 : 1
R = CH_3	R' = $PhCH_2$	CH_2Cl_2	12	**1c:2c** 2 : 1
R = CH_3	R' = CH_3	benzene	74	**1d:2d** > 99 : 1
R = CH_3	R' = CH_3	CH_2Cl_2	45	**1d:2d** > 99 : 1
R = CH_3CH_2	R' = $PhCH_2$	benzene	82	**1e:2e** 32 : 1
R = CH_3CH_2	R' = $PhCH_2$	CH_2Cl_2	60	**1e:2e** 6 : 1
R = CH_3CH_2	R' = CH_3	benzene	73	**1f:2f** 14 : 1

(a) isolated yield following extractive workup and column chromatography
(b) product ratios determined by ^{31}P NMR[9]

The 1*H*-tetrazole catalyzed formation of benzyl phosphoramidates and benzyl phosphoramidothioates of glutamic acid dibenzyl ester was also explored briefly using $PhOP(O)Cl_2$ and $PhP(S)Cl_2$, respectively, under the optimized conditions identified for phosphonamidate formation. However, it was observed that the first step reaction of the alcohol with either the phosphoryl or thiophosphonyl dichloride was incomplete after 24 h. These results merely confirm the more reactive nature of the phosphonyl dichlorides toward nucleophiles. However, further investigations may identify conditions favorable for such reactions.

The mechanism for the 1*H*-tetrazole catalysis in phosphonate ester formation has not yet been clearly established although it has been postulated that it functions by nucleophilic catalysis.[6] More thorough investigations into the specific mechanism are currently underway in our laboratory. It can be concluded, however, that the use of catalytic 1*H*-tetrazole allows for the efficient and convenient formation of

phosphonamidates involving a simple two-step one-pot reaction. As a result biologically relevant phosphonamidates are now more easily accessible in good yield.

EXPERIMENTAL DETAILS

All solvents, alcohols, and phosphonyl dichlorides were freshly distilled prior to use. In the cases where glutamic acid dibenzyl ester was used as the free amine, its tosylate salt was neutralized immediately prior to use by extraction from 10% aqueous Na_2CO_3 with CH_2Cl_2, drying over $MgSO_4$, and concentration *in vacuo*. *Typical experimental procedure*: A flask was charged with 1*H*-tetrazole (.010 g, 0.13 mmol) and benzene (9 mL) under an $Ar_{(g)}$ atmosphere followed by the addition of phenylphosphonic dichloride (0.199 mL, 1.40 mmol) and the temperature was reduced to 4 ^{0}C. Benzyl alcohol (0.131 mL, 1.27 mmol) was added dropwise via syringe followed by the dropwise addition of diisopropyl ethylamine (DEA; 0.244 mL, 1.40 mmol). The reaction mixture was stirred and allowed to warm to room temperature until benzyl alcohol was consumed (approximately 2 h) as monitored by TLC. Glutamic acid dibenzyl ester (0.761 g, 1.52 mmol) and DEA (0.544 mL, 3.18 mmol) were dissolved in benzene (4 mL) and added dropwise to reaction mixture and allowed to stir for an additional 3 h. The reaction mixture was concentrated *in vacuo* and the resulting oil was partitioned between 10% aqueous HCl and methyl *t*-butyl ether (MTBE) and the organic layer collected. The aqueous layer was extracted once more with MTBE, the organic layers combined, washed with water, brine, dried over $MgSO_4$, concentrated *in vacuo* to a pale yellow oil. The crude product was purified by flash chromatography (Silica gel, hexane:ethyl acetate 1:1, *v:v;* $R_f = 0.20$) to give a colorless oil).

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8. Although the ratio of **1** to **2** was high, a considerable amount of disubstitution by H-Glu(OBzl)OBzl was observed as the phosphonodiamidate by ^{31}P NMR, thus resulting in a low yield.
9. Two signals in an appoximate ratio of 60:40 were observed by ^{31}P NMR for each of the purified phosphonamidate products (**1a** - **1f**), presumably diastereomers resulting from the stereogenic phosphorus center. ^{31}P NMR chemical shifts (relative to phosphoric acid) for each of the phosphonamidate products and phosphonate diester side-products were as follows: **1a** δ 22.1, 22.8; **1b** δ 21.7, 22.4; **1c** δ 32.9, 33.6; **1d** δ 33.6, 34.2; **1e** δ 36.4, 37.0; **1f** δ 37.1, 37.6; **2a**: δ 19.3; **2b** δ 20.9; **2c** δ 32.2; **2e** δ 35.3; **2f** δ 32.0.

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