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Alternatives to 1-*H*-tetrazole in the preparation of phosphonate diesters and phosphonamidates from phosphonyl dichlorides

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Abstract—5-Ethylthio-1-*H*-tetrazole (SET) and 4,5-dicyanoimidazole (DCI) were examined as alternatives to 1-*H*-tetrazole to mediate the synthesis of phosphonate diesters and phosphonamidates from phosphonyl dichlorides through a two-step one-pot reaction in various organic solvents. SET and DCI were comparable to 1-*H*-tetrazole for catalyzing these reactions. SET afforded slightly greater yields than DCI while benzene was universally the best solvent for this reaction.

It is well known that 1-*H*-tetrazole is a valuable mediator for phosphitylation chemistry, especially in the preparation of oligonucleotides.[1] 1-*H*-tetrazole has also been established to mediate amine exchange in the synthesis of oligonucleotide phosphoramidates.[2] Employed as a catalyst, 1-*H*-tetrazole has been found to minimize symmetrical substitution of phosphonyl dichlorides in the preparation of mixed phosphonate esters.[3] Our group has been interested in the preparation of phosphonylated[4,5] or phosphorylated amino acids[6] as tetrahedral intermediate analogs inhibitors of metallopeptidases[7] and to this end, we have explored the aforementioned tetrazole-mediated chemistry.

Although dilute solutions in acetonitrile are available, solid 1-*H*-tetrazole is no longer readily accessible from commercial sources due to its explosive nature.[8] This impediment prompted us to explore alternatives to 1-*H*-tetrazole for *N*-phosphorylation of amino acids and amine exchange on phosphoramidites. Both 5-ethylthio-1-*H*-tetrazole (SET) and 4,5-dicyanoimidazole (DCI) have been identified to be comparable to 1-*H*-tetrazole (Tet) for the diastereoselective synthesis of phosphite triesters[9] and the activation of nucleoside phosphoramidites in oligonucleotide syntheses.[10] The reported efficiency of these reagents led us to examine them for the chemistry of interest to our group.

We found that SET and DCI were comparable to 1-*H*-tetrazole for the two-step one-pot preparation of mixed phosphonate diesters **1a** and **1b**, respectively, from methyl or phenylphosphonic dichloride in various solvents (Table 1). In general, SET afforded greater yields than DCI while benzene was universally the best solvent for this reaction. Based upon the successful results obtained for the preparation of the benzyl methylphosphonates **1a** and **1b**, the preparation of methylphosphonamidate **2** from methylphosphonic dichloride was compared for the three catalysts under similar conditions (Table 2). Because the first step in the synthesis of both the phosphonates and phosphonamidates from phosphonyl dichlorides is conserved, it was not surprising that the yields for the formation of **2** were similar to that for **1a**. As noticed for the preparation of phosphonates **1a**, SET provided a slightly greater yield for **2** than DCI.

In summary, 5-ethylthio-1-*H*-tetrazole and 4,5-dicyanoimidazole were found to be suitable alternatives to 1-*H*-tetrazole to catalyze the synthesis of mixed phosphonate diesters and phosphonamidates from phosphonic dichlorides.

Keywords: 5-Ethylthio-1-*H*-tetrazole; 4,5-Dicyanoimidazole; 1-*H*-Tetrazole; Phosphonate diester; Phosphonamidate.
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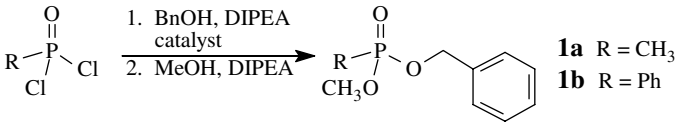
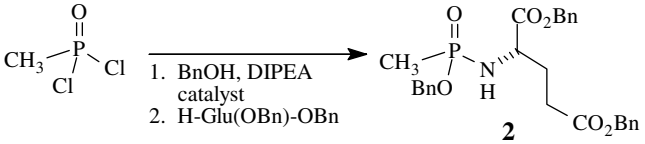
Table 1. Synthesis of benzyl methylphosphonates **2**[11,12]



R	Solvent	Catalyst	**1a** Yield (%)[a]	R	Solvent	Catalyst	**1b** Yield (%)[a]
CH_3	Benzene	Tet	81	Ph	Benzene	Tet	70
CH_3	THF	Tet	76	Ph	THF	Tet	69
CH_3	CH_2Cl_2	Tet	66	Ph	CH_2Cl_2	Tet	46
CH_3	CH_3CN	Tet	73	Ph	CH_3CN	Tet	61
CH_3	Benzene	SET	82	Ph	Benzene	SET	67
CH_3	THF	SET	70	Ph	THF	SET	53
CH_3	CH_2Cl_2	SET	61	Ph	CH_2Cl_2	SET	59
CH_3	CH_3CN	SET	61	Ph	CH_3CN	SET	61
CH_3	Benzene	DCI	75	Ph	Benzene	DCI	62
CH_3	THF	DCI	74	Ph	THF	DCI	53
CH_3	CH_2Cl_2	DCI	73	Ph	CH_2Cl_2	DCI	56
CH_3	CH_3CN	DCI	68	Ph	CH_3CN	DCI	61

[a] Spectroscopic yield based on ^{31}P NMR.

Table 2. Synthesis of phosphonamidates[12,13]



Solvent	Catalyst	Yield (%)[a]
Benzene	Tet	80
Benzene	SET	83
Benzene	DCI	75

[a] Spectroscopic yield based on ^{31}P NMR.

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11. *Synthesis of phosphonate diesters* **1**. To a flask charged with the catalyst (0.14 mmol) was added alkyl phosphonic dichloride (1.40 mmol) dissolved in solvent (9 mL) under an Argon (g) atmosphere via syringe. The temperature was reduced to 0 °C, followed by dropwise addition of benzyl alcohol (0.131 mL, 1.27 mmol) and diisopropyl ethylamine (DIPEA, 0.244 mL, 1.40 mmol). The reaction mixture was stirred for 0.5 h at 0 °C, then another 2.5 h at rt. Methanol (0.051 mL, 1.27 mmol) and diisopropyl ethylamine (0.244 mL, 1.40 mmol) were added dropwise, and the reaction mixture was stirred for 3 h. Concentration in vacuo afforded crude products as oil from which the ^{31}P NMR analyses were performed in $CDCl_3$.
12. Anhydrous solvents obtained from commercial sources were used in all reactions. When used in reactions, *N*,*N*-diisopropyl ethylamine (DIPEA) was anhydrous as purchased from commercial sources. For the preparation of **2**, the acid salt of glutamic acid dibenzyl ester was neutralized immediately prior to use by extraction with CH_2Cl_2 from saturated $NaHCO_3$. ^1H and ^{31}P NMR spectra were recorded on a Bruker DRX 300 MHz NMR Spectrometer.
13. *Synthesis of phosphonamidate* **2**. To a flask charged with the catalyst (0.14 mmol) was added alkyl phosphonic dichloride (1.40 mmol) dissolved in solvent (9 mL) under an Argon (g) atmosphere via syringe. The temperature was reduced to 0 °C, followed by dropwise addition of benzyl

alcohol (0.131 mL, 1.27 mmol) and diisopropyl ethylamine (0.244 mL, 1.40 mmol). The reaction mixture was stirred for 0.5 h at 0 °C, then another 2.5 h at rt. Glutamic acid dibenzyl ester (0.416 g, 1.27 mmol) and diisopropyl ethylamine (0.244 mL, 1.40 mmol) were added dropwise, and the reaction mixture was stirred for 3 h. Concentration in vacuo afforded crude products as oil from which the ^{31}P NMR analyses were performed in $CDCl_3$.