



Tetrazole-Catalyzed Synthesis of Phosphoramidate Esters

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Abstract: 1H-Tetrazole selectively catalyzed sequential monoaddition of alcohol and amine to phosphonic dichlorides and provided phosphoramidate esters under mild conditions.

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Preparation of phosphonate and phosphoramidate esters is of current interest because of their utility as transition-state analogs for eliciting catalytic antibodies with amidase activity, and as inhibitors of natural enzymes.¹ In connection with our work on antibody-catalyzed hydrolysis of cocaine,² we sought to develop an efficient method for the high-yield conversion of phosphonic dichloride (1) to amidates (4) under non-forcing conditions so that a variety of alcohols and amines could be suitable substrates. Previously, we reported that mixed phosphonate diesters can be obtained in good selectivity, using the tetrazole-catalyzed coupling of (1) and two different alcohols.³ We now extend this catalytic protocol to the synthesis of phosphoramidates (4), including compounds that derive from hindered alcohols or amines. We have investigated the scope and limitations of the tetrazole method and determined the importance of addition sequence of the nucleophiles.

Table 1. Coupling of phosphonic dichloride (1) with alcohol and amine.

entry	R ¹ OH	R ² R ³ NH	R	product	Method A ^a	Method B ^a
1	MeOH	<i>n</i> -Bu ₂ NH	Ph	4 a	89 (38)	86 (5)
2	BnOH	<i>n</i> -Bu ₂ NH	Ph	4 b	69 (34)	26 (6)
3	MeOH	<i>n</i> -Bu ₂ NH	<i>n</i> -Pr	4 c	84 (19)	71 (4)
4	BnOH	<i>n</i> -Bu ₂ NH	<i>n</i> -Pr	4 d	68 (42)	38 (33)
5	MeOH	<i>n</i> -BuNH ₂	Ph	4 e	98 (43)	43 (26)
6	MeOH	<i>i</i> -Pr(Me)NH	Ph	4 f	82 (72)	82 (4)
7	BnOH	<i>s</i> -Bu ₂ NH	Ph	4 g	23 (7)	0 (0)
8	MeOH	5	Ph	4 h	40 (0)	15 (0)
9	Menthol	<i>n</i> -Bu ₂ NH	Ph	4 i	72 (40)	0 (0)
10	6	<i>n</i> -BuNH ₂	Ph	4 j	40 (20)	0 (0)

^a Isolated yield; the yields of reactions without any catalysis are in parenthesis.

The results of the sequential addition of nucleophiles to aryl and alkyl phosphonic dichlorides are shown in Table 1. The addition of alcohol followed by amine (Method A) was superior to those obtained with the alternative order (Method B). Butylamine and several secondary amines with increasingly bulky alkyl groups were chosen to determine the steric limitations to these multi-step coupling reactions. Ecognine methyl ester and menthol were investigated as representative hindered alcohols.

All reactions were carried out in pairs with and without tetrazole. Tetrazole was found to be an effective catalyst and the uncatalyzed yields were generally low (given in the parentheses) regardless the sequence of mixing nucleophiles. Under the condition of Method A,⁴ a catalytic amount of tetrazole routinely provides the highest overall yields of phosphoramidates (**4a-j**). Aryl and alkyl phosphonic dichlorides react equally well under catalytic conditions (compare entries 1-2 to 3-4, respectively). The addition of a primary alcohol followed by a non-bulky amine gave compounds (**4a-f**) ranging from 68% to 98% (entries 1-6). Substitution with increasingly hindered secondary amines reduced yields (entries 6-8). In the absence of tetrazole, *N*-norcocaine (**5**) was largely unconsumed even under forcing condition (refluxing benzene) and re-isolated in 70% yield; the use of tetrazole increased the desired product (**4f**) from 0% to 40% isolated yield (entry 8). Di-*s*-butyl amine and *t*-butyl amine defined the limit of steric hindrance for amine and gave no products with any alcohol (not shown). Hindered alcohols such menthol and ecgonine methyl ester (**6**) were efficiently reactive if they were added as the first nucleophile (entries 9-10). It can be generalized that the addition of alcohol and then amine (Method A) should be the choice for the synthesis of all amidates (**4**), and the chlorine atoms of dichloride (**1**) can be made to react in a stepwise fashion with an alcohol and an amine in reasonably high yields when tetrazole is used as catalyst.

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References and Notes:

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 4. Method A: To a solution of (**1**) (0.99 mmol), *i*-Pr₂NEt (5 mmol), and tetrazole (catalytic) in 15 ml of benzene was added MeOH (0.79 mmol) in 5 ml of benzene dropwise at 0 °C. The resultant solution was stirred for 1.5 h at rt, and *n*-BuNH₂ (2 mmol) was then added. After stirring for 12h, the reaction mixture was concentrated *in vacuo*. Chromatographic purification on silica gel afforded the desired product (eluent 25% EtOAc/CH₂Cl₂, 61 mg) in 98% yield.