

# Dialkyl phosphite as highly selective *N*-alkylating agent using *p*-toluene sulphonic acid as catalyst

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The presence of carbon–nitrogen bond is widely found in different useful synthetic intermediates, organic solvents, dyes, fine chemicals, biologically relevant molecules (e.g. amino acids, DNA and RNA bases etc), pharmaceuticals, agrochemicals, and catalysts.<sup>1</sup>

Amines and their derivatives are prevalent functionalities in various natural products and unnatural synthetic targets. Due to its unique biological properties, the amine moiety has played a central role in chemotherapeutics of numerous diseases.<sup>2</sup> Polyamines and peptidomimetics have constituted some of the most popular targets in recent combinatorial approaches in drug development.<sup>3</sup> Because of such versatile importance of amines, development of versatile and efficient methods for the synthesis of amines has attracted much attention and is still occupying an active area of research.

“N-Alkylation” is the very important reaction in synthetic organic chemistry to prepare secondary and tertiary amines. Common synthetic methods for the preparation of dialkylamines have included direct N-alkylation,<sup>4</sup> amide reduction,<sup>5</sup> or the more popular reductive amination protocol,<sup>6</sup> alcohols/metal catalysts,<sup>7</sup> alcohols/Ph<sub>3</sub>P/ DDQ.<sup>8</sup> Although these methods appear deceptively simple and quite reliable but practical success are relatively limited. All of these methodologies have at least one disadvantage such as over alkylation, low chemical selectivity, lengthy synthetic steps, use of toxic and dangerous reagents (e.g. alkyl halides and alkyl sulfate) and also sometimes appear problematic from environmental standpoints. In particular mono-methylation of primary amines is very difficult to acquire by the conventional direct methylation due to competing over methylation leading to mixture of secondary, tertiary and the quaternary ammonium salt.<sup>9</sup>

Thus development of simple, mild, and selective methods for mono-*N*-alkylation is still a major challenge in organic synthesis with the need to overcome these problems.

R. Gancarz<sup>10</sup>, in 1994, used dialkylphosphite for alkylation of primary amines but the product was a mixture of secondary, tertiary and the quaternary ammonium salt and the yield is very poor (the starting material recovered 4-80%).

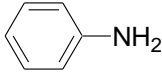

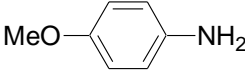
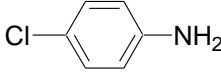
To eliminate all such problems mentioned above or at least some of them we have explored to develop a new methodology in my previous project and therefore my previous project is based on selective alkylation of primary amines using dialkylphosphite as highly selective alkylating agent using PTSA as catalyst.

We started our investigation with 1:1 mixture of 4-Methyl aniline and diethyl phosphite, as model for optimization, in different temperature under neat condition using 10 mol% P-toluene sulphonic acid as catalyst. Under this reaction conditions we got a mixture of secondary, tertiary and the starting amine in different ratios. To eliminate the overalkylated product we performed a series of experiments and finally reached the optimum reaction conditions. We observed the effects of the catalyst, PTSA under different concentration (0-10 %) and temperature (30°C – 120°C)

The scope of the reaction was studied with a variety of amines under the optimized reaction condition (Table 1).

**Table 1.** Alkylation of amine

$$\begin{array}{ccc}
 \text{R}_1\text{-NH}_2 + \text{HPO(OR)}_2 & \xrightarrow[\text{Solvent free, } 120^\circ\text{C}]{\text{PTSA (10 mol \%)}} & \text{R}_1\text{-NH}^{\text{R}} \\
 \text{1} & \text{2} & \text{3}
 \end{array}$$

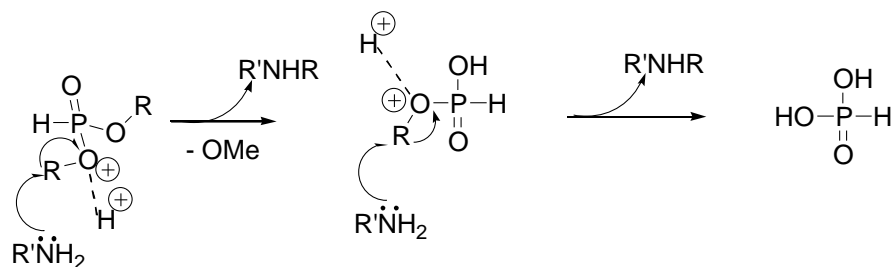
Amine	R	Products	Time (min)	Yield (%) <sup>a</sup>
	Et	3b	240	43
	Et	3d	300	51
	Et	3f	245	46
	Et	3h	280	50

<sup>a</sup>Isolated yield of mono-*N*-alkylated product; <sup>b</sup>over alkylated product was not indicated here

As evident from the Table 1, this new PTSA catalysed selective *N*-alkylation is a general and practically useful methodology.

According to the observed experimental condition and stoichiometric ratio of the reagents, the probable mechanism may be according to the following path. PTSA reacts with the

dialkyl phosphite, which activates the Carbon-Oxygen bond and accelerates the N- alkylation (Scheme 2).



Scheme 2

In summary, we demonstrated here the use of dialkyl phosphite as an efficient, mild and eco-friendly reagent for the alkylation of amines in high yield without using base or solvents. The chemo-selectivity and generality of the reactions is under investigation.

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