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N- vs. *O*-Alkylation in the Mitsunobu Reaction of 2-Pyridone

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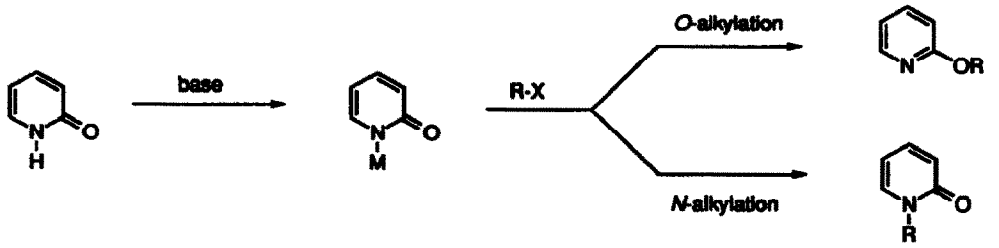
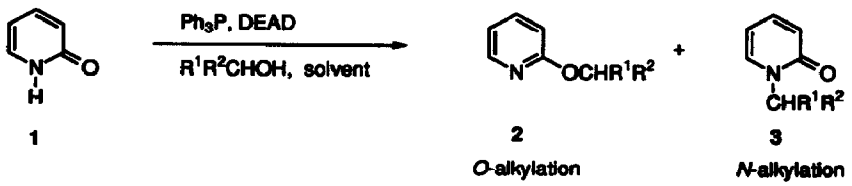
Abstract: *An N- vs. O-alkylation study of 2-pyridone with various alcohols and solvents under Mitsunobu conditions was carried out.*

The alkylation of ambident anions of 2-oxopyridines has been studied extensively,[1] for 2-alkoxypyridines[2] and *N*-alkyl-2-pyridones[3] are valuable synthetic intermediates. Alkylation is generally performed by treating a metal salt of the 2-pyridone with an alkyl halide. The regioselectivity depends on the nature of the metal, the structure of the alkyl halide, substituents on the pyridone ring, and the solvent.[1]



In general, *N*-alkylation is easier to achieve, although frequently mixtures result. With the sodium salt of 2-pyridone *N*-alkylation generally predominates, but an increase in the size of the alkyl halide favors *O*-alkylation. This phenomenon has been attributed to greater steric hindrance in the transition state leading to *N*-alkylation. To obtain predominantly *O*-alkylation, the silver salt in a non-polar solvent is frequently utilized.[1,4] Because of our interest in the synthesis of the pyridone-containing alkaloid camptothecin,[5] we investigated the alkylation of 2-pyridone under mild conditions using the Mitsunobu reaction.

Although the Mitsunobu reaction has been used to alkylate phenols and various heterocyclic compounds, to our knowledge the application of this mild alkylation to a pyridone ring system has not been reported.[6] The Mitsunobu reaction generally requires the nucleophile (HA) to have a pKa less than 13 for satisfactory alkylation to occur.[6,7] Since 2-pyridone has a pKa of 11.62[8], facile alkylation was anticipated.



Several reactions of 2-pyridone (1) were performed in various solvents using the alcohols: benzyl alcohol, 2-phenylethanol, 1-phenyl-2-propanol, 1-phenylethanol, 2-phenylpropanol, and 2-naphthalenemethanol. The results of our study are shown in the Table. In THF four of the alcohols gave clean *O*-alkylation (entries 2-5). Benzyl alcohol and 2-naphthalenemethanol were exceptions giving a mixture of *N*- and *O*-alkylation favoring the former. A solvent study was carried out using 2-phenylethanol (entries 7-12). In DME and, surprisingly, $CHCl_3$, clean *O*-alkylation occurred, whereas in CH_2Cl_2 *N*-alkylation predominated.

The *O*- and *N*-alkylated products (2 and 3) were easily separated by radial preparative-layer chromatography (silica gel, EtOAc/hexanes). In some cases only the major isomer was isolated as shown in the Table. The crude material was examined by ^1H NMR to determine the ratio of products. This was accomplished by comparing the integration of the *O*-methylene or *O*-methine proton of 2 (δ 4.4-4.6) and the C-5-H proton of 3 (δ 5.9-6.1).

This Mitsunobu reaction is mild, does not require the presence of a strong base, and allows the alkylation of 2-pyridones using a 1° or 2° alcohol as the "electrophilic" component. We have found this reaction to be useful for *N*-alkylation of 2-pyridones in certain cases, but it may prove to be more useful for *O*-alkylation. Our work compliments the existing methodology for *O*-alkylation of 2-pyridones which uses expensive silver salts.[1,4]

Experimental. To a solution of 2-pyridone (1 mmol), Ph_3P (1.5 equiv) and R^1R^2CHOH (1.25 equiv) in 20 mL of the indicated solvent was slowly added diethyl azodicarboxylate (1.5 equiv) at RT. The mixture was stirred at RT until complete by TLC analysis and then quenched with methanol (1 mL). Water was added and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated to give the crude product. Purification was performed using radial PLC (Chromatotron, Harrison Associates, Palo Alto, CA).

Table. Mitsunobu Reaction of 2-Pyridone with Alcohols (R^1R^2CHOH).

entry[a]	R^1	R^2	solvent[b]	2[c]	3[c]	2:3[d]
1	Ph	H	THF	20%	67%	1:4
2	$PhCH_2$	H	THF	88%	-	10:1
3	$PhCH_2$	CH_3	THF	63%	0	1:0
4	Ph	CH_3	THF	60%	0	1:0
5	$PhCHCH_3$	H	THF	89%	0	1:0
6	2-Naphth	H	THF	15%	54%	1:3.5
7	$PhCH_2$	H	DME	90%	-	34:1
8	$PhCH_2$	H	CH_2Cl_2	32%	37%	0.85:1
9	$PhCH_2$	H	CH_3CN	34%	28%	1.4:1
10	$PhCH_2$	H	DMSO	41%	19%	2.9:1
11	$PhCH_2$	H	Benzene	23%	19%	1.5:1
12	$PhCH_2$	H	$CHCl_3$	70%	-	20:1

[a]The reactions were performed on a 1 mmol scale. [b]In all examples 20 mL of solvent was used. [c]Yield of purified product obtained from radial preparative-layer chromatography (silica gel, EtOAc/hexanes). Satisfactory IR, ^1H and ^{13}C NMR, and microanalysis data were obtained for all new compounds. [d]The ratio was determined by ^1H NMR analysis of the crude product.

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