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A comparison of N- versus O-alkylation of substituted 2-pyridones under Mitsunobu conditions

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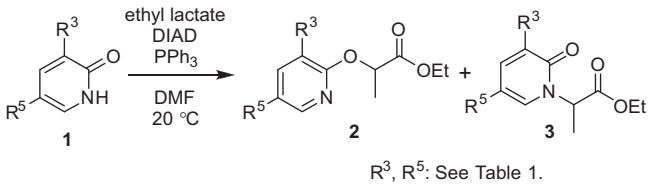
ABSTRACT

2-Pyridones are well-known ambident nucleophiles which are capable of reacting with electrophiles through either the nitrogen or oxygen atom to form *N*-alkyl-2-pyridones or 2-alkoxypyridines, respectively. It has been shown that the ratio of these products can be affected by a number of factors including the nature of the electrophile, the base used for deprotonation, and the solvent. We have now discovered a relationship between the ratio of N- and O-alkylation products and the nature of substituents on the pyridone ring when the Mitsunobu reaction is used to alkylate 2-pyridones.

Alkylated 2-pyridones are common structural motifs in a wide range of biologically active compounds. N-alkylated pyridones are commonly found in natural products such as camptothecin,[1] cytisine,[2,3] cerpegin,[4] and amphimedine.[5] O-alkylated pyridones are found less commonly in nature, but are important substructures of biologically active compounds such as taranabant (a discontinued anti-obesity drug),[6] pyriproxyfen (a pesticide),[7] tafenoquine (an antiplasmodial),[8] and lafutidine (a histamine H_2 receptor antagonist).[9] Synthesizing either N- or O-pyridones specifically, however, can be synthetically challenging because of the ambident nature of the pyridone system.

Although it is well known that alkylation of 2-pyridones can result in formation of both N- and O-substituted products,[10–13] relatively few systematic studies of this phenomenon have been published. Tieckelmann[14] demonstrated that the reaction outcome of pyridone alkylation was dependent in part on the counterion; Na^+ and K^+ salts generally gave predominantly N-alkylation or mixtures of products, while Ag^+ salts, following up on the work of Kornblum,[15] tend to favor O-alkylation. Tieckelmann also demonstrated that the O-alkylation of 2-pyridone Ag^+ salts was more selective in nonpolar solvents, and that O-alkylation of hindered electrophiles is favored regardless of solvent. In an excellent recent study, Mayr[16] has attempted to rationalize these findings based on computational methods. Comins has demonstrated the utility of the Mitsunobu reaction for producing alkylated 2-pyridones;[10] by eliminating the need for strong bases, a wider range of sensitive substrates can be used in the reaction. Although hindered alcohols were more selective for O-alkylation, primary alcohols tended to form both O- and N-alkylated products; as in the case of pyridone salts, the results varied greatly with the choice of solvent.

We became interested in using the Mitsunobu reaction to synthesize a series of pyridyl-substituted lactate esters that we required for the synthesis of a series of bacterial type three secretion system (T3SS) inhibitors.[17] Following the work of Lin et al.,[6] who synthesized benzyl 2-(pyridin-2-yloxy)propionate under Mitsunobu conditions en route to cannabinoid-1 receptor inverse agonists, we attempted to make the corresponding ethyl 2-(3,5-dichloropyridin-2-yloxy)propionate. Although Lin et al. noted the formation of 'some N-alkylated side products'; we observed that the reaction with 3,5-dichloro-2-pyridone gave substantial amounts of the undesired N-alkylated product in addition to the desired O-alkylated product (see Supplementary data). Furthermore, repeating the reaction with the unsubstituted 2-pyridone used by Lin produced nearly equal amounts of N- and O-alkylated materials.



Scheme 1. Mitsunobu reaction of substituted 2-pyridones and methyl lactate.

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Given the differences in product distribution of the substituted and unsubstituted pyridone substrates, we undertook a study of the effect that different substituents on the 2-pyridone ring have on the outcome of the reaction. Using racemic ethyl lactate as our alcohol component, we performed a series of Mitsunobu reactions with 2-pyridones substituted in either the 3- or 5-position (Scheme 1) and determined the relative ratios of N- and O-substituted products produced by these reactions. By choosing a series of 2-pyridones with substituents that would provide a range of electronic and steric properties, we hoped to elucidate the factors which influence the ultimate product distribution under Mitsunobu conditions.

Before we began our comprehensive study, we needed to assign the spectrum of both O- and N-alkylated products so that the ratios could be properly determined. Thus, we unambiguously synthesized the O-substituted compound ethyl 2-(3,5-dichloropyridin-2-yloxy)propionate via the nucleophilic displacement of 3,5-dichloro-2-fluoropyridine with the sodium alkoxide of ethyl lactate (see Supplementary data). Although little difference was found in the proton NMR spectra of N- and O-alkylated products in DMSO-d_6, the chemical shift of the lactate α proton quartet of the alkoxypyridine in $CDCl_3$ was sufficiently distinct from the α proton quartet of the corresponding *N*-alkylpyridone to assign the two isomers based on their respective NMR spectra.

After assigning the ^{1}H NMR spectra to the proper isomer, we ran Mitsunobu reactions on all of the different 2-pyridones in our test set. By determining the effect that different substituents had on the ultimate O-/N-substitution ratio (found by integration of the lactate α protons), it was our hope that we could draw some important conclusions about the factors governing the outcome of the alkylation reaction. The results of the study are found in Table 1.

Table 1
Ratio of O-/N- substitution for Mitsunobu reaction of 2-pyridones[a]

Entry	R^3	R^5	O-/N-ratio[b]
1	–H	–H	0.95
2	–Cl	–H	1.09
3	–CN	–H	1.11
4	$-CF_3$	–H	1.03
5	–Me	–H	0.87
6	–OMe	–H	0.91
7	–H	–Cl	2.88
8	–H	–CN	1.27
9	–H	$-CF_3$	0.74
10	–H	–Me	1.45
11	–H	–OMe	5.75

[a] DIAD (3.0 mmol) was added to a solution of pyridone (2.5 mmol), ethyl lactate (3.0 mmol), and PPh_3 (3.0 mmol) in DMF (3.0 mL) at room temperature.
[b] Ratio determined by integration of lactate 2-position proton in ^{1}H NMR spectrum.

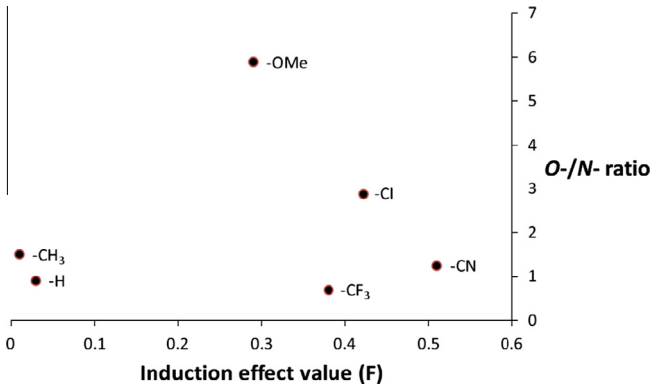


Figure 1. Plot of O-/N-ratio versus modified field constant *F*.

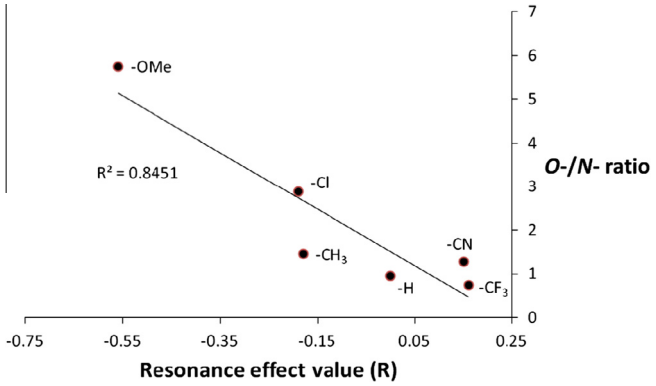
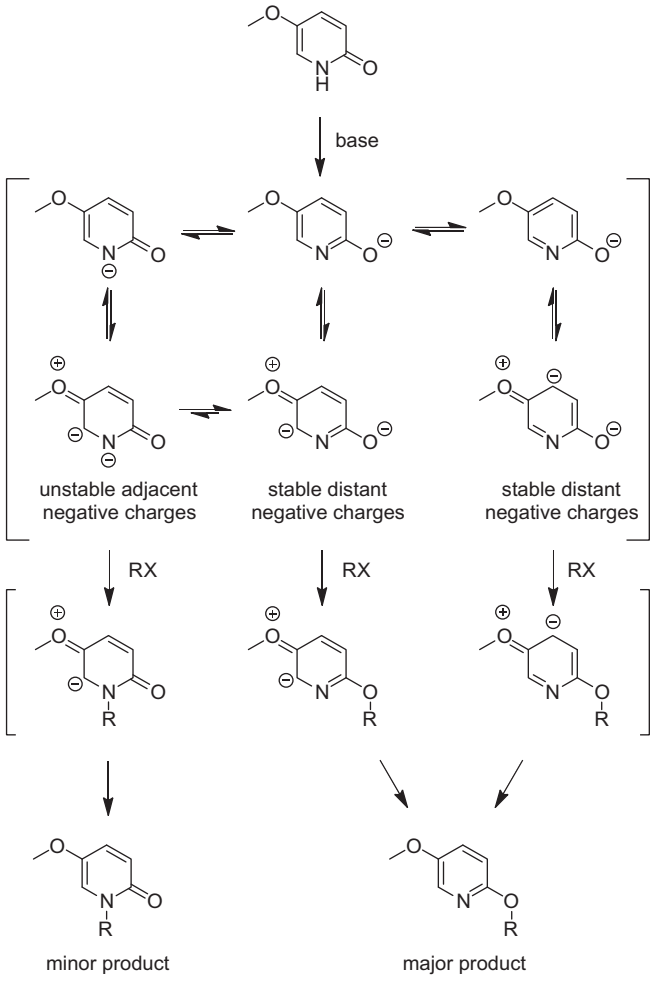
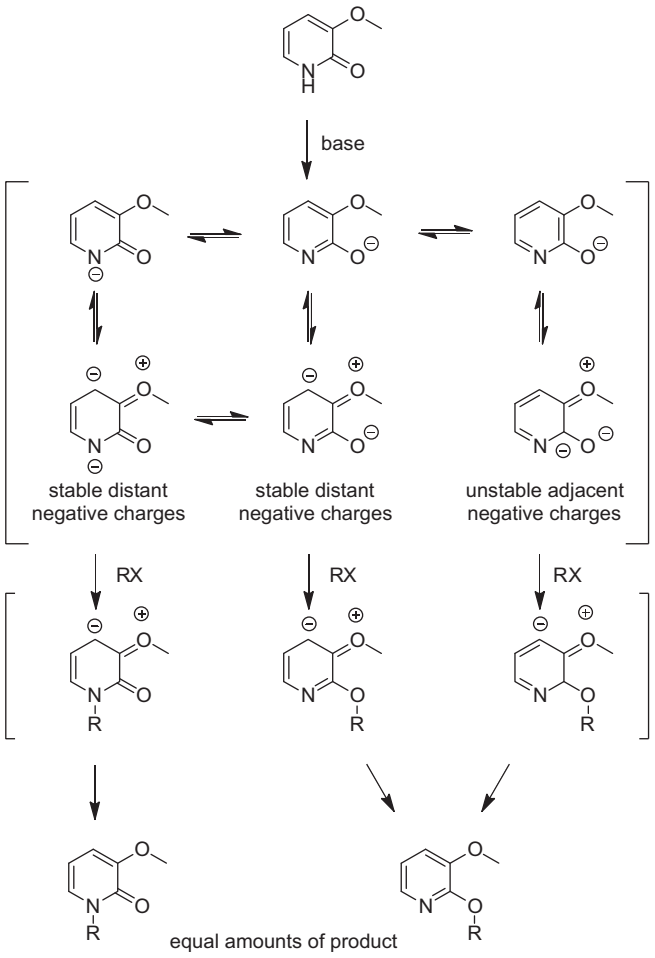


Figure 2. Plot of O-/N-ratio versus modified resonance constant *R*.

It is immediately evident that the substituent at the 3-positon has very little effect on the product distribution of the reaction; very little change is noted over the entire range of 3-substituted compounds. It is somewhat surprising that even the presence of a bulky $-CF_3$ substituent at the 3-position did not bias the alkylation toward the N-substituted products through steric effects. Conversely, the substituent at the 5-position had a substantial impact on the ultimate outcome of the reaction, with the distribution ratio ranging from 0.70 ($-CF_3$) to 5.90 (–OMe).



Scheme 2. Proposed rationale for observed product distribution in 5-substituted 2-pyridones.



Scheme 3. Proposed rationale for observed product distribution in 3-substituted 2-pyridones.

Given the electronic properties of these two substituents, it is tempting to correlate the product distribution with the electron donating/withdrawing capacities. Surprisingly, when the ratio of products is plotted versus the modified field constant *F*,[18] the correlation is poor (Fig. 1). When the distribution ratio is plotted versus the modified resonance constant *R*,[18] however, the correlation becomes clear (Fig. 2); substituents with a high resonance contribution at the 5-position favor O-alkylation, while substituents with little resonance contribution favor nearly even mixtures of N- and O-substitution.

This behavior can be rationalized in terms of the resonance structures available to the 5-substituted pyridones. After deprotonation of the 2-pyridone, three tautomeric forms can be drawn (see Scheme 2 as illustrated for 5-methoxypyridone). After the resonance contribution is taken into account, three corresponding triply charged intermediates are possible. However, the resonance form that is ultimately converted into the N-alkylated product possesses relatively unstable adjacent negative charges, and would thus be less populated. In contrast, the two resonance forms ultimately leading to O-alkylated products have relatively more stable, separated, negative charges; these two forms would be more populated, and therefore produce predominantly the O-alkylated product to a degree that is dependent on the resonance contribution of the 5-substituent. This same behavior is not observed for the 3-substituted pyridones (see Scheme 3 as illustrated for 3-methoxypyridone) because the corresponding high energy resonance form with adjacent charges causes only one of two possible oxygen-charged species to be underpopulated with respect to the nitrogen-charged intermediate. With no substantial barrier to N-alkylation, roughly equal mixtures of N- and O-alkylated products would be produced, regardless of the substituent at the 3-position.

We have demonstrated that the Mitsunobu reaction of 2-pyridones and ethyl lactate produces a range of possible outcomes based on the nature of the substituents on the 2-pyridone ring. By comparing the electronic properties of the substituents with the ratio of O- and N-alkylation products, we have determined that the Hammett resonance contribution (*R*) of the substituent at the 5-position has a profound impact on the ultimate product distribution, while neither the resonance contribution of the 3-substituent nor the Hammett field constant (*F*) for either substituent causes a significant effect.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.054.

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