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SELECTIVITY OF *N*- VERSUS *O*-ALKYLATION IN MITSUNOBU REACTIONS WITH VARIOUS QUINOLINOLS AND ISOQUINOLINOLS

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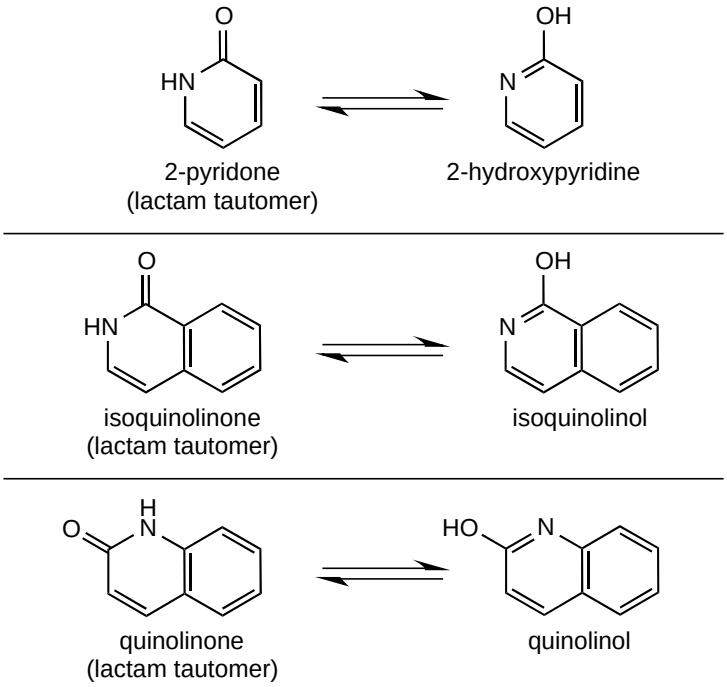
Abstract – Reacting quinolinols and isoquinolinols under Mitsunobu conditions can give rise to *N*-alkylated products in addition to the normally desired *O*-alkylated structures. An in-depth study of how the solvent, reagent equivalents, position of the quinoline/isoquinoline nitrogen and type of reacting aliphatic alcohol employed affect the ratio of *N*- versus *O*-alkylation is described.

The Mitsunobu reaction has been employed within the chemistry community for many years on many scaffolds and has been the subject of multiple reviews.[1,2] One such scaffold of interest is 2-pyridones (Scheme 1), which are similar to the quinoline and isoquinoline substructure.[3] However, an in-depth study of *N*- versus *O*-alkylation of quinolinols and isoquinolinols under Mitsunobu conditions has not been published. Since the Mitsunobu reaction is primarily utilized for *O*-alkylation, it would be beneficial to understand how altering the reaction conditions can affect the *N*- or *O*-alkylation outcome.

As with the tautomerism observed in 2-pyridones,[4] quinolinones and isoquinolinones (or quinolinols and isoquinolinols as they will be referred to throughout the paper for clarity) contain the same tautomeric traits as their simplified precursors as shown in Scheme 1.[5] The tautomeric equilibria of 2-hydroxypyridine was shown to depend on solvent polarity, with a pronounced shift to a greater population of the more polar lactam in more polar media.[6] It is this tautomeric equilibria that allows systems of this nature to react as ambident nucleophiles through the conjugate base resonance structures, often leading to mixtures of *O*- and *N*-alkylation. However, like with 2-pyridones, we observed that many factors can influence the alkylation ratio. These include, but are not limited to, solvation of the nucleophile (conjugate base of the heterocycle), the electrophilicity of the activated alcohol and the structure of the starting quinolinol or isoquinolinol.

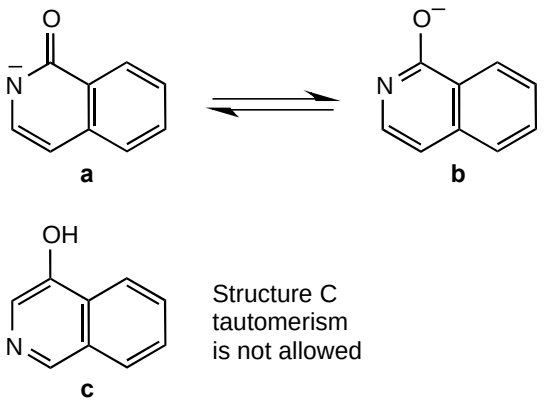


Scheme 1. (Iso)quinolinone tautomerism

In the reaction mixture, assuming tautomerization is allowed, the DEAD-PPh_3-adduct will deprotonate the phenol to the phenoxide and the conjugate base of the phenol will resonate. With oxygen having an electronegativity of 3.44 and nitrogen 3.04 on the Linus Pauling scale, one would expect the oxygen to bear more negative charge and the *O*-alkylation would dominate.

With the above in mind, our initial interest in this area resulted from employing the quinolinol and isoquinolinol substructures in a medicinal chemistry program related to a rare disease target. Using starting materials containing these substructures, the Mitsunobu reaction generated mixtures of the desired *O*-alkylation products with the unexpected *N*-akylated adducts. We were thus prompted to explore the factors that influence the regioselectivity of this process in detail. This methodological query is important as there are many natural products that contain quinolinone and isoquinolinone motiefs.[7] Due to the lack of experimental data on these relatively simple aromatic systems, we wish to present our observations around the selectivity of *O*- versus *N*-alkylation under Mitsunobu conditions.

The first step in dissecting *N*- versus *O*-alkylation was to select a set of heterocycles where tautomerism of the conjugate base in the Mitsunobu reaction is allowed and not allowed. Based on the nitrogen's position within the ring, relative to the hydroxyl group, tautomeric conjugate base forms such as **a** and **b** can exist (Scheme 2). However, as in **c**, where the nitrogen and hydroxyl groups are not in a 1-2 or 1-4 orientation, tautomerism is not allowed and only *O*-alkylation can occur through the phenol's conjugate base.

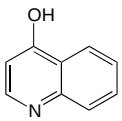
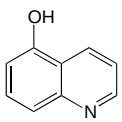
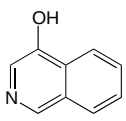


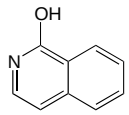
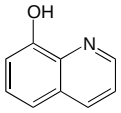
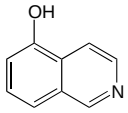
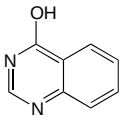
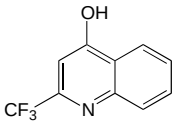
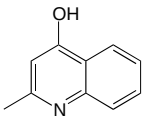
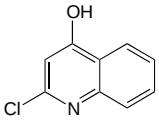
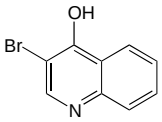
Scheme 2. Example of allowed and disallowed tautomers

In Table 1, a series of different quinolinols and isoquinolinols were subjected to Mitsunobu conditions (see Representative Procedure). Although the ^{1}H NMR of the *O*- and *N*-alkylated products are quite similar, the ^{13}C NMR spectra in DMSO-d_6 show dramatic shifts at the carbon attached to the resultant phenolic ether or carbonyl, depending on *O*- or *N*-alkylation allowing for easy identification of both products.

To begin, entries 3, 5, and 6 are heterocycles that are unable to tautomerize, which leads to only one conjugate base occurring at the phenol leading to only *O*-alkylated products. For the rest of the entries the positional requirements necessary for tautomerism are met and both the *N*- and *O*-alkylated products can be expected. Entries 1 and 2, where the nitrogen is located at ring position 4 and 5 respectively; about a 2:1 ratio of *O*- versus *N*-alkylation was observed. However, when the phenolic carbon is also next to the nitrogen atom, the trend changes (entry 4). 2-pyridones and 2-quinolinols are known to exist primarily in the imidic tautomeric form and thus the conjugate base of the nitrogen is the dominate nucleophile.[8] In this system, the nitrogen's lone pair is more available to react and a shift toward 85% *N*-alkylation is observed.

Table 1. *O*- versus *N*-Alkylation ratios with various quinoline and isoquinolinols, and quinazolinol

Entry	Structure	%*O*-Alkylation[a]	%*N*-Alkylation[a]	Yield[c]
1		70	30	91
2		63	27	87
3		100	0	90

4		15	85	85
5		100	0	90
6		100	0	93
7[b]		0	100	100
8		100	0	88
9		100	0	96
10		100	0	95
11		81	19	93

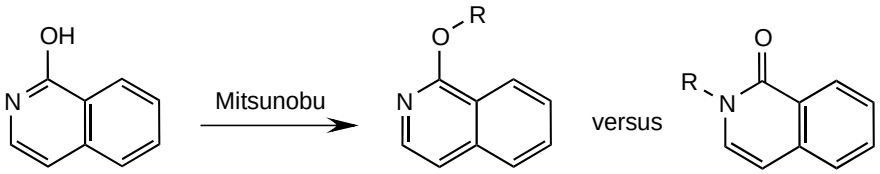
[a]Ratio was determined by ^{1}H NMR. [b]100% Alkylation occurred on N-2. [c]Combined isolated yield.

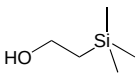
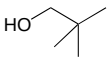
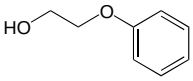
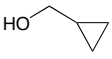
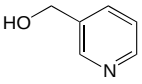
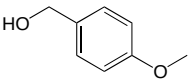
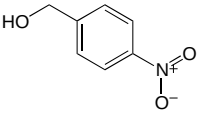
In entry 7, the carbonyl tautomer (lactam) is present almost exclusively due to the electronic effect of the nitrogen at position 4, rendering both the oxygen and position 4 nitrogen unreactive, giving exclusive *N*-alkylation at the 2 position. Entries 8 through 11 show the effect of substituents alpha to the potential reacting nitrogen or oxygen. In compounds **8-10**, regardless of tautomerism being allowed and solvation effects playing a role, the steric bulk of substituents dictate where alkylation will occur. This is readily apparent in compound **11**, where the R group is moved one position away from the nitrogen and results in a shift dramatic move toward more *N*-alkylation. Theoretical orbital energies/electron densities for many of the unsubstituted scaffolds have been previously calculated and well documented.[9] However, when moving to substituted analogs, such as entries 8-11, calculations at a higher level of theory are required to fully account for solvent and steric effects. The latter component is largely responsible for driving the *O*- versus

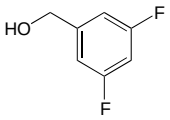
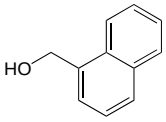
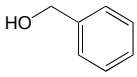
N-alkylation ratio in more decorated scaffolds and thus often makes these more complicated calculations less predictive of the true experimental outcome.

After the investigation of different spatial arrangements of the quinolinol/isoquinolinol nitrogen in relation to the phenol, we shifted toward how different reacting alcohols might alter *O*- versus *N*-alkylation, while keeping the remaining Mitsunobu reaction conditions constant. It is known that not just sterics surrounding the conjugate base can influence the Mitsunobu reaction, but the phosphonium salt intermediates can also influence the system's reactivity.

Table 2. *O*- versus *N*-Alkylation ratios with various alcohols



Entry	Alcohol	%*O*-Alkylation[a]	%*N*-Alkylation[a]	Yield[b]
12		4	96	96
13		33	67	72
14		33	67	84
15		20	80	80
16		---	>99	90
17		7	93	93
18		14	86	96

19		21	79	89
20		---	>99	97
21		15	85	85

[a]Ratio was determined by ^{1}H NMR. [b]Combined isolated yield.

In Table 2, a set of ten different alcohols was employed in the Mitsunobu reaction, using isoquinolone **4** as our substrate. The alcohols were chosen based on their polarities, steric hindrance to nucleophilic attack once activated and electronic properties. In all cases, *N*-alkylation was the prevalent outcome, which came as no surprise. Alcohols **13**, **14**, and **15** all led to the reaction producing a larger percentage of *O*-alkylated product relative to the others. If one assumes that the bulkiness of the activated alcohol does play a role in the transition state, then a greater percentage of *N*-alkylation with the cyclopropyl alcohol **15** can be expected. While the nitrogen is imbedded in the heterocyclic ring system, the phenol is more accessible. Thus sterically hindered alcohols such as *tert*-butyl **13** and phenyl ether **14** should react more at the exposed phenolic portion of the isoquinolone. However, the more electron dense nitrogen is still the better nucleophile.

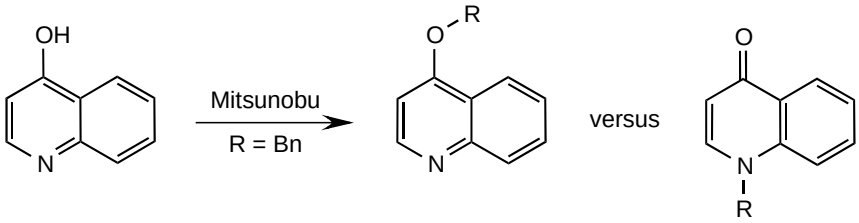
However, this reasoning does not hold true with *tri*-methylsilyl (TMS)-ethanol **12**. The combination of the elongated ethyl spacer along with the electron rich TMS moiety could however change this reacting alcohol's environment enough to warrant almost exclusive *N*-alkylation. One should note as important as the nucleophile is (the conjugate base) the nature of the electrophile also becomes important when sterics are involved. Another possibility is that due to the oxophilic nature of the silicon, a mechanism could be envisioned where the phenolic oxygen and the silicon from a weak bond interaction giving the nitrogen a tethered electrophile.

The last interesting observation to note is that the basic (pyridin-3-yl)-methanol **16** gave exclusive *N*-alkylation. The basicity and polarity of the pyridine clearly plays a role in the alkylation process, leading to the observed outcome.

Our last look into the Mitsunobu reaction was with the quinolinol **1** ring system and varying the solvent and equivalents as shown in Table 3. As previously mentioned, different solvents provide different degrees of solvation to the conjugate bases leading to changes in the relative nucleophilicity of the nitrogen versus

oxygen atoms.[10] Benzyl alcohol **21** with THF, which is also described in Representative Procedure, was the standard set of reaction conditions used in both Tables 1 and 3.

Table 3. *O*- versus *N*-Alkylation ratios with different solvents dielectrics and reactant equilibria



Entry	Conditions	%*O*-Alkylation[a]	%*N*-Alkylation[a]	(ε)[c]	Yield[d]
22	Et_2O, 2 eq (PPh_3, DEAD, alcohol)[b]	85	15	4.3	78
23	THF, 2 eq (PPh_3, DEAD, alcohol)[b]	70	30	7.6	84
24	DMF, 2 eq (PPh_3, DEAD, alcohol)[b]	40	60	37	96
25	CH_2Cl_2, 2 eq (PPh_3, DEAD, alcohol)[b]	70	30	8.9	95
26	THF, 4 eq (PPh_3, DEAD, alcohol)[b]	75	25	7.6	88
27	THF, 2 eq (PPh_3, DEAD) 8 eq alcohol	100	---	7.6	94

[a]Ratio was determined by ^{1}H NMR. [b]DEAD was 40% mixture in toluene (ε 2.4). [c]Dielectric constant (ε) Reflecting the solvent's ability stabilize charges. [d]Combined isolated yield.

Using the aforementioned Experimental, we performed the Mitsunobu reaction in solvents of different polarity, such as Et_2O, DMF and CH_2Cl_2. While CH_2Cl_2 gave the same ratio of products as THF, the effects of Et_2O favored *O*-alkylation even more than its precursors. Interestingly, DMF, which is the most polar of the four solvents (entry 24), reversed the alkylation ratio in favor of *N*-alkylation. This was expected, as the higher dielectric solvent will allow the development and stabilization of charges, leading to a thermodynamically controlled outcome. This table of solvents demonstrated the strong effect a solvent's solvation can play on the reacting nucleophile, as more polar solvents tend to lead to a greater ratio of the *N*-alkylated product when the electrophile is kept constant.

Lastly, while keeping THF as the solvent, we increased the amount of the alcohol, PPh_3 and DEAD to four equivalents instead of two (entry 26). Although not necessarily significant, the amount of *O*-alkylated product did increase, leading us to wonder what an even higher equivalent increase in reactants would do. In the last reaction (entry 27), we increased to eight equivalents of the alcohol, PPh_3 and DEAD. In this case, only the *O*-alkylated product was observed. By swamping the reaction with available electrophile, the more electronegative phenolic oxygen wins out. With an overabundance of electrophile, kinetics now determine the reaction outcome.

In conclusion, we have demonstrated that the location of the ring nitrogen relative to the phenolic oxygen can have a dramatic effect on *O*- versus *N*-alkylation. It tautomerism is not allowed or sterics block the nitrogen atom, then only *O*-alkylation is allowed. Also, the solvation of the conjugate base, as well as the reacting electrophile, can likewise have a large influence on the final ratio of *O*- versus *N*-alkylation in the quinolinol and isoquinolinol ring systems, which until now have been unexplored. By varying the solvent, reacting heterocycle and electrophilic alcohol, one should be able to shift the reaction toward whichever *O*- or *N*-alkylated product is desired. With the Mitsunobu reaction's mild conditions and tolerability of a large variety of functional groups, when compared to other similar reactions such as the Williamson alkylation,[12] which have harsher conditions and lower amount of allowable functional groups, the Mitsunobu reaction continues to be widely used in many modern synthetic schemes due to its ease and versatility.

EXPERIMENTAL

PPh_3 (89 mg, 0.34 mmole, 2 eq) and the quinolinol or isoquinolinol (25 mg, 0.17 mmole, 1 eq) were combined in a glass vial and purged with nitrogen. THF (700 µL) was then added followed by benzyl alcohol (44 µL, 0.34 mmole, 2 eq). A 40% by weight solution of DEAD in toluene (170 µL, 0.34 mmole, 1 eq) was then added dropwise to keep the reaction temperature below 30 ^{o}C. The reaction mixture was shaken at room temperature overnight and then purified on a Waters preparative LC/MS system with a gradient of 0 to 60% MeCN-H_2O to give the desired product with yields ranging from 50% to 98%. In instances where the isomers were not able to be separated, the percentage ratio was determined by ^{1}H NMR. Purified products were characterized by ^{1}H and ^{13}C NMR.

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