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Highly Efficient Diels-Alder Cycloadditions of 2-Pyridones With Bulky N-Sulfonyl Substituent

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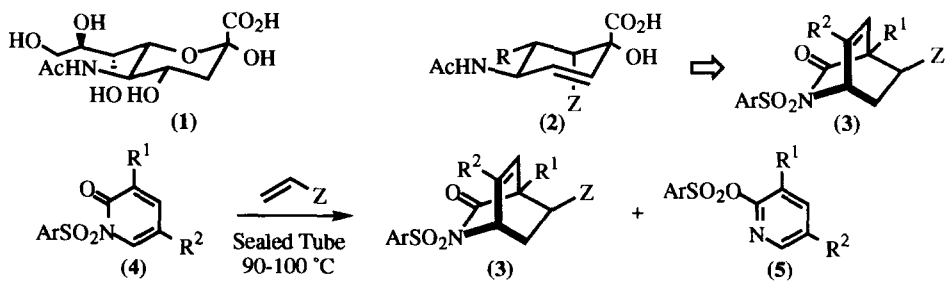
Dedicated to Prof. Gary H. Posner With Admiration and Gratitude

Abstract: The rearrangement of N-sulfonyl pyridones to the corresponding O-sulfonyl pyridinols during cycloaddition can be greatly retarded by introduction of steric congestion on either the pyridone ring or the sulfonyl group. Hence, significantly improved yields of cycloaddition are obtained for N-2,4,6-triisopropylbenzenesulfonyl 2-pyridones. Changes in the electronic nature of various substituents does not significantly alter the rate of migration.

There has been much interest in the carbocyclic analogues of N-acetyl neuraminic acid (NANA) **(1)** as inhibitors of sialidase in recent years.[1,2] Cleavage of NANA by sialidase is believed to be a key step in the viral infiltration of host cells and therefore, structural analogues which can inhibit the enzymes are valuable medicinal tools. We have recently embarked on a programme to prepare a number of such analogues, e.g. **(2)**, using a methodology based on synthesis and chemical manipulation of densely substituted bridged bicyclic lactams obtained from the cycloaddition of N-substituted 2-pyridones. It is known that cycloadditions of *N-alkyl* 2-pyridones are in general inefficient and only modestly regio and stereoselective.[3,4] The stereoselectivity of the cycloaddition can be improved when electron withdrawing groups such as vinyl[5] and toluenesulfonyl[6,7] are used as nitrogen substituents. The latter is particularly of synthetic significance to us since the sulfonyl substituent can be removed from the cycloadducts under mild, neutral conditions.[8] It has been argued that an electron withdrawing N-toluenesulfonyl substituent retards the amide-imidate resonance which contributes to the aromaticity of the pyridone and hence enhances the diene character of the pyridone.[3] However, no direct evidence of improved efficiency in cycloadditions of N-sulfonyl 2-pyridones **(4)** over the corresponding alkyl 2-pyridones has been reported to date. This is because cycloaddition to afford **(3)** is invariably accompanied by an irreversible rearrangement of the N-arylsulfonyl 2-pyridone to the thermodynamically more stable (aromatic)

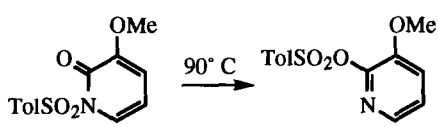


Scheme 1

PII: S0040-4039(97)10585-8

2-arylsulfonyloxypyridine (**5**) (Scheme 1) which proceeds at a comparable rate at the reaction temperature. Therefore, cycloadditions of N-toluenesulfonyl pyridones, although advantageous because of their stereoselectivity, are not necessarily more efficient than those of N-alkyl 2-pyridones. Furthermore, to date only those N-sulfonyl pyridones with strongly electron donating or withdrawing group (e.g. alkoxy or sulfonyl) at the 3-position are reported to undergo cycloaddition. The ability to obtain intermediates such as (**1**) with a diverse range of R^1 and R^2 is very important if a wide range of structural analogues of NANA are to be prepared. To achieve a more efficient cycloadditions of N-sulfonyl pyridones and also in order to diversify the range of pyridones that undergo cycloadditions, we investigated the factors that can significantly retard the migration of the arylsulfonyl group under cycloaddition conditions.

We prepared a number of N-sulfonylated 2-pyridones[7] and measured the rate of their rearrangement to the corresponding 2-sulfonyloxypyridine in temperature range similar to that used in cycloadditions. The corresponding 2-sulfonyloxypyridines were also independently prepared for reference.[7] Thus, a solution of N-sulfonyl pyridone (circa 0.10 M) was heated in a constant temperature oil bath and small aliquots were withdrawn at intervals. The proportion of N-sulfonyl pyridone and O-sulfonyl pyridinol was determined by NMR. The rates of migration and half-lives were determined from a graph of concentration of N-sulfonyl pyridone versus time. In repeat experiments, these values were reproducible within ±5%. Our first observation was that the rearrangement followed a typical first order reaction kinetics. Secondly, we found that the rate of rearrangement is slower in less-polar media. The activation energies for the rearrangement of N-toluenesulfonyl 3-methoxy-2-pyridone (**3**, R^1 = OMe, R^2 = H) in different solvents were determined from a plot of rate constant versus 1/RT (R is the gas constant). The values were found to be 50 $KJmol^{-1}$ in toluene, 30 $KJmol^{-1}$ in dichloroethane and 18 $KJmol^{-1}$ in ethyl acetate. This can also be demonstrated by comparison of the rate of migration of the same pyridone at 90°C in polar/non-polar solvent mixtures (Table 1). All reactions were performed side by side in sealed tubes at 90°C. The rate of migration, as demonstrated by $t_{10\%}$ (time required for 10% migration of pyridone to pyridinol) considerably decreases as polarity of the solvent decreases. The difference between the rates of cycloaddition were minimal as expected (data not shown).[9] Although this data suggests that neat petroleum ether is perhaps the best medium, most pyridones were found to be insoluble in this solvent. Toluene, on the other hand is a better solvent for pyridones although still quite non-polar and was therefore the solvent of choice in further experiments.



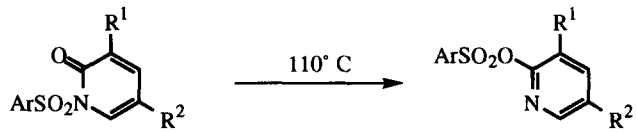
% Polar Solvent	$t_{10\%}$ (hours) Dichlorethane/Petroleum ether	$t_{10\%}$ (hours) Ethyl Acetate/Toluene
0	Not Performed	150
25	170	125
50	140	96
75	116	87
100	98	50

Table 1

The results of the influences of the steric and electronic factors are summerised below (Table 2). As can be seen, the electronic nature of substituent on either ring has only a small effect on the rate of rearrangement. For instance, the half lives for migration of N-tosyl pyridones with hydrogen substituent, a methoxy substituent and a nitro substituent at 3-position of the pyridone ring, (entries 3, 4 and 6), are relatively similar. At the same time, changing the 4-substituent of the benzenesulfonyl group from methyl to methoxy or nitro groups (entries 6, 11 and 12) also has a very small effect on the rate of migration.

It should be noted that the rate of N → O migration in 2-pyridone of other stronger electron withdrawing groups such as acetyl and trifluoroacetyl is much faster than that of the toluenesulfonyl.[10,11] Although this may be attributed to their small size (see later), it could also mean that changing the 4-substituent of the arylsulfonyl group is a relatively small electronic change and does not significantly influence the rate of migration.

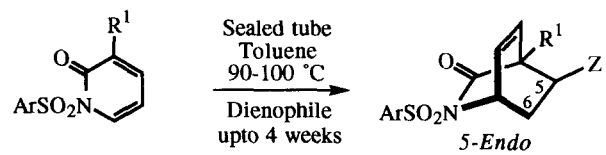
On the other hand, the steric influence of the substituents appear to play a very important role in slowing down the migration. This steric effect can be observed with substituents both at the nitrogen and at the 3-position of the pyridone ring. For example, N-methanesulfonyl pyridones undergo faster migration than the N-arylsulfonyl pyridones. On the other hand, N-tosyl 3-(^{t}butyldimethylsilyloxy)-2-pyridone undergoes a much slower migration than the N-tosyl 3-methoxy-2-pyridone (entries 4 and 5).



	Ar	R^1	R^2	half life (hrs.)		Ar	R^1	R^2	half life (hrs.)
1	Me	OMe	H	24	9	4-(MeO)-C_6H_4	H	H	98
2	Me	OSiMe$_2$-t-Bu	H	60	10	4-(MeO)-C_6H_4	NO_2	H	120
3	4-(Me)-C_6H_4	H	H	105	11	4-(MeO)-C_6H_4	OMe	H	76
4	4-(Me)-C_6H_4	NO_2	H	100	12	4-(NO_2)-C_6H_4	OMe	H	125
5	4-(Me)-C_6H_4	OSiMe$_2$-t-Bu	H	>360	13	2,4,6-(Me)$_3$-C_6H_2	OMe	H	140
6	4-(Me)-C_6H_4	OMe	H	75	14	2,4,6-(Me)$_3$-C_6H_2	H	H	155
7	4-(Me)-C_6H_4	H	OCH_2Ph	95	15	2,4,6-(i-Pr)$_3$-C_6H_2	OMe	H	200
8	4-(Me)-C_6H_4	H	NO_2	100	16	2,4,6-(i-Pr)$_3$-C_6H_2	H	H	255

Table 2

Indeed, we also found that the migration of N-arylsulfonyl 2-pyridones where the aryl group contains bulky ortho substituents to sulfonyl, are much slowed down. For example, the rearrangement of N-2,4,6-trimethylbenzenesulfonyl 2-pyridones is much slower than that of corresponding N-tosyl 2-pyridones, *whatever the electronic nature of substituent at the 3-position.* The rearrangement of N-2,4,6-triisopropylbenzenesulfonyl (N-2,4,6-TiPBS) 2-pyridones is even slower, the rate being less than half of that of the corresponding toluenesulfonyl pyridones. This slowing down means that on the time scale of cycloaddition (typically 96-120 hours), migration becomes relatively insignificant.



R^1	Dienophile	Yield (5-endo unless stated) Ar = 2,4,6-(i-Pr)$_3$-C_6H_2	Yield (5-endo unless stated) Ar = 4-(Me)-C_6H_4
OMe	Methyl acrylate	92% (66% at reflux)	55%
OMe	Acrylonitrile	50%	35%
OMe	Maleic anhydride	78%	40%
OMe	N-Me maleimide	95%	59%
H	N-Me maleimide	83%	61%
H	Methyl acrylate	24% (5-endo : 6-endo = 0.6)	10% (5-endo : 6-endo = 0.6)
Me	N-Me maleimide	80%	71%
Me	Methyl acrylate	81% (5-endo : 6-endo = 4.0)	51% (5-endo : 6-endo = 4.0)
Br	Methyl acrylate	44% (5-endo : 6-endo = 2.8)	trace

Table 3

Hence, a combination of less-polar medium and bulkier nitrogen substituents is expected to slow down the migration of sulfonyl group and improve the yields of cycloadditions. A number of comparative reactions were carried out under similar conditions, results of which are summerised above (Table 3). In all cases, improved yields of cycloaddition were obtained, with only trace amounts of rearranged pyridinol observable in crude reaction mixtures of pyridones with bulky N-substituents. Pyridones with no or only weakly activating substituents (e.g. Br and Me) also undergo cycloadditions under these conditions albeit with longer reaction times (2-4 weeks) and no regioselectivity. It is significant that 3-bromo N-2,4,6-TiPBS-2-pyridone affords a better regioisomeric ratio in cycloaddition to methyl acrylate than does N-2,4,6-TiPBS-2-pyridone. This demonstrates a slight but observable steric and electronic influence of the 3-bromo substituent which is paralleled in cycloaddition chemistry of 2-pyrones and their bromo derivatives.[12] Interestingly, 3,5-dibromo N-2,4,6-TiPBS-2-pyridone affords a single 5-endo regioisomer in 60% yield in cycloaddition to methyl acrylate under these conditions.

Perhaps the most striking observation is that N-2,4,6-TiPBS-2-pyridone undergoes a faster reaction and affords a better yield of cycloaddition to methyl acrylate than N-benzyl pyridone does. In a competition reaction, N-2,4,6-TiPBS-2-pyridone reacted at least five times faster than N-benzyl-2-pyridone towards methyl acrylate. Indeed, under similar reaction conditions the reaction of N-2,4,6-TiPBS-2-pyridone and methyl acrylate affords 24% yield of cycloadduct whereas only trace amounts of cycloadduct is observed with N-benzyl-2-pyridone. *Thus we can finally prove for the first time that a pyridone with an electron withdrawing sulfonyl substituent reacts faster with a dienophile than does a pyridone with an alkyl substituent.*

In summary, this investigation has shown that the yield of cycloadditions of 2-pyridones can be improved by placing bulky arylsulfonyl substituents at nitrogen and using less-polar media. In addition, we have also extended the range of N-sulfonyl pyridones which undergo cycloadditions to those with electronically weak or even no substituents on the ring. The chemical manipulation of these bicyclic lactams as previously shown,[7] allows the development of efficient methodologies for the total synthesis of natural products or biologically interesting molecules such as N-acetyl neuraminic acid.

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