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A novel reagent combination for the oxidation of highly electron deficient pyridines to *N*-oxides: trifluoromethanesulfonic anhydride/sodium percarbonate

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Abstract

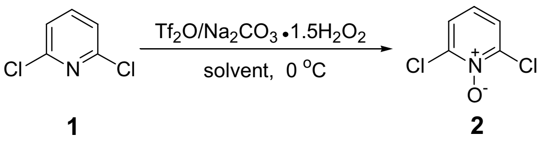
A novel reagent combination, $Tf_2O/Na_2CO_3 \cdot 1.5H_2O_2$, has been developed for the oxidation of highly electron deficient pyridines to their corresponding *N*-oxides. The N-oxidation reaction, utilizing the in situ generated peracid, proceeds under mild conditions that allow for a number of functional groups and substitution patterns on the pyridine ring.

Keywords: Pyridine; Pyridine *N*-oxide; Trifluoromethanesulfonic anhydride; Sodium percarbonate

The oxidation of pyridines to their *N*-oxides is often employed in drug discovery programs. Numerous methods have been developed to effect this transformation. In most cases the oxidation can be accomplished using a peracid[1] such as MCPBA or magnesium monoperphthalate.[2] It has been reported that electron deficient pyridines can be oxidized using catalytic MTO($MeReO_3$) and 30% H_2O_2 as the co-oxidant[3] or trifluoroacetic anhydride and hydrogen peroxide–urea complex.[4]

Recently, we encountered difficulties in transforming an electron deficient pyridine to its *N*-oxide using the aforementioned methods. We envisioned that replacement of the trifluoroacetate group of the peracid with a better leaving group may provide a more reactive peracid reagent, which will allow successful N-oxidation of electron deficient pyridines. Ideally the peracid reagent should be readily prepared in situ and the subsequent N-oxidation reaction should be performed under mild conditions that can tolerate common functional groups such as esters, nitriles and halogens. It has been reported that peroxytrifluoromethanesulfonic acid, generated by mixing trifluoromethanesulfonic anhydride (Tf_2O) with 80% hydrogen peroxide, can allow for the oxidation of sulfides to the corresponding sulfoxides.[5] Unfortunately, the formation of trifluoromethanesulfonic acid under these reaction conditions may not be suitable to compounds with acid sensitive functional groups. To overcome the formation of trifluoromethanesulfonic acid, we have identified a method of producing peroxytrifluoromethanesulfonic acid in situ under mild conditions by reacting trifluoromethanesulfonic anhydride with sodium percarbonate.

Our early studies on the use of the in situ generated formation of peroxytrifluoromethanesulfonic acid focused on the N-oxidation of 2,6-dichloropyridine as shown in Scheme 1. All reactions were monitored by LC/MS until starting pyridine was no longer consumed. Initial



Scheme 1. Oxidation of 2,6-dichloropyridine to *N*-oxide.

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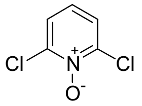
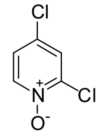
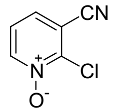
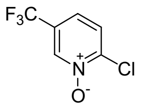
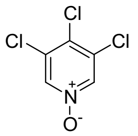
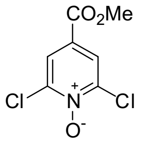
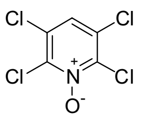
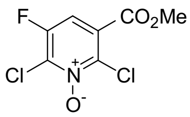
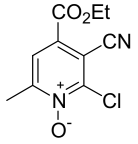
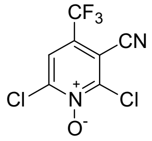
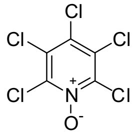
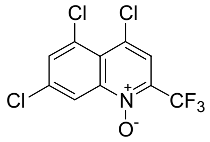
Table 1
Oxidation of 2,6-dichloropyridine **1** in CH_3CN at 0 °C

Entry	$Na_2CO_3 \cdot 1.5H_2O_2$ (equiv)	Tf_2O (equiv)	Time (h)	Yield[b] (%)
1	2.0	3.0	3.5	65
2	1.0	2.0	3.5	67
3	1.0	1.5	3.5	63
4	1.0	1.5	1.0	60
5	1.0	2.0	3.5[a]	70

[a] 1 h at 0 °C, then 2.5 h at rt.

[b] Isolated yields.

Table 2
Oxidation of pyridines with $Tf_2O/Na_2CO_3 \cdot 1.5H_2O_2$[6]

Entry	Product	Solvent	Time[a] (h)	Yield[b] (%)
1		CH_3CN	3.5	70
2		CH_3CN	3.5	65
3		CH_3CN	3.5	70
4		CH_3CN	3.5	41
5		CH_3CN	3.5	11
6		CH_3CN	Overnight	79
7		CH_3CN	Overnight	46
8		CH_3CN	Overnight	45
9		CH_3CN	Overnight	66
10		CH_3CN	Overnight	7
11		CH_3CN/ CH_2Cl_2	Overnight	25
12		CH_3CN	3.5	42

[a] 1 h at 0 °C, then warmed to rt.

[b] Isolated yields.

observations illustrated that the N-oxidation reaction proceeded well in acetonitrile but failed to produce any pyridine *N*-oxide in dichloromethane. Therefore, we surveyed different reaction conditions for N-oxidation by varying the reagent stoichiometry, reaction time and temperature using acetonitrile as the solvent and the results are summarized in Table 1. All reactions were performed once and the reaction yields reported are isolated yields. Comparable yields of pyridine *N*-oxide product were obtained under all the conditions summarized in Table 1. The highest yield obtained was realized using 1.0 equiv of sodium percarbonate (1.5 equiv of H_2O_2) and 2.0 equiv of trifluoromethanesulfonic anhydride (entry 5). Increasing the reaction time from 1 h (entry 4) to 3.5 h (entry 3) led to no real difference in N-oxidation product formation. There was no significant change in reaction yield when the reaction was initiated at 0 °C for 1 h and then allowed to warm to room temperature (entry 5 vs entry 2).

With the initial reaction conditions identified, we set out to determine the scope of the reagent combination $Tf_2O/Na_2CO_3 \cdot 1.5H_2O_2$ versus a variety of electron deficient pyridines. As shown in Table 2, the reaction proceeded well with a number of electron deficient pyridines to provide the corresponding pyridine *N*-oxide products in modest to good yield. The mild reaction conditions employed allow for a variety of functional groups such as esters, nitriles and halogens. It was observed that in general the reagent combination $Tf_2O/Na_2CO_3 \cdot 1.5H_2O_2$ appears to be more efficient in oxidizing electron deficient 2,6-disubstituted pyridines. Entry 11 illustrates that N-oxidation of the extremely electron deficient pentachloropyridine using 1:1

Table 3
Oxidation of 2,6-dichloro-5-fluoro-nicotinic acid methyl ester

Entry	Reagents	Solvents	Time[a] (h)	Yields[b] (%)
1	Tf_2O (2.0 equiv), $Na_2CO_3 \cdot 1.5H_2O_2$ (1.0 equiv)	CH_3CN	15	45
2	UHP (2.1 equiv), TFAA (2.0 equiv)	CH_3CN	24	0
		CH_2Cl_2	24	2
3	ReMTO, 30% H_2O_2 (2.1 equiv)	CH_2Cl_2	24	0
4	UHP (2.1 equiv), TFA (2.0 equiv)	CH_3CN	24	0
		CH_2Cl_2	24	0
5	30%H_2O_2 (2.1 equiv), TFAA (2.0 equiv)	CH_3CN	24	0
		CH_2Cl_2	24	1
6	MCPBA (2.1 equiv)	CH_3CN	24	0
		CH_2Cl_2	24	0
7	70% *t*BuOOH (2.1 equiv)	CH_3CN	24	0
		CH_2Cl_2	24	0
8	Oxone (2.1 equiv)	CH_3CN	24	0
		CH_2Cl_2	24	0

[a] All reactions were performed at 0 °C for 1 h, then warmed to room temperature.

[b] Isolated yields.

acetonitrile/dichloromethane proceeds with modest yield (25%) that is comparable to the reported N-oxidation conditions employing TFA and H_2O_2 at elevated temperature (20% yield).[7] Additionally, we chose to directly compare our new N-oxidation conditions to a variety of known N-oxidation conditions using 2,6-dichloro-5-fluoro-nicotinic acid methyl ester as the substrate. As illustrated in Table 3, $Tf_2O/Na_2CO_3 \cdot 1.5H_2O_2$ was the only reagent that afforded the desired pyridine *N*-oxide product with moderate yield, all other reagents investigated failed to provide the pyridine *N*-oxide product in any appreciable (>5%) yield.

In summary, we have developed a practical method for the oxidation of highly electron deficient pyridines to their corresponding *N*-oxides. The reagent combination appears to be relatively safe and all reagents are commercially available. Moreover, the reaction takes place under mild conditions that allows for the presence of acid sensitive functional groups and different substitution patterns on the pyridine ring. In addition this new reagent combination has the potential to be utilized in a variety of other oxidation transformations and future studies will focus on the scope of this reagent combination and will be reported in due course.

References and notes

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6. *General procedure*: To an oven-dried 4-dram vial were added 2,6-dichloro-5-fluoro-nicotinic acid methyl ester (224 mg, 1.0 mmol), sodium percarbonate (157 mg, 1.0 equiv) and anhydrous acetonitrile (5.0 mL). To the suspension, cooled in a water-ice bath, was added dropwise trifluoromethanesulfonic anhydride (339 μL, 2.0 equiv). Bubbles formed during the addition of trifluoromethanesulfonic anhydride. The mixture was stirred at 0 °C for 1 h, then at room temperature for 14 h. Most of the solid sodium percarbonate disappeared after 3 h. The reaction mixture was poured into a mixture of crushed ice (10 g) and saturated sodium bicarbonate (4 mL). After stirring for 30 min, the mixture was extracted with dichloromethane (3 × 20 mL). The combined dichloromethane solution was washed with brine (20 mL) and dried over sodium sulfate. The aqueous solution was treated with 10% aqueous $Na_2S_2O_5$ solution to quench the residual peroxide. After concentration, the dichloromethane solution was loaded onto a 20 g ISOLUTE silica cartridge and eluted with hexanes/EtOAC (5:1) to provide the desired pyridine *N*-oxide (109 mg) in 45% yield as a white solid. ^1H NMR (400 Hz, $CDCl_3$) δ 4.01 (s, 3H), 7.60 (d, $J = 7.04$ Hz, 1H). ^{13}C NMR (400 Hz, $CDCl_3$) δ 53.79, 113.74 (d, $J = 23.18$ Hz), 126.12 (d, $J = 7.73$ Hz), 137.16 (d, $J = 28.97$ Hz), 140.61, 154.46 (d, $J = 256.26$ Hz), 162.13 (d, $J = 2.58$ Hz). Elemental Anal. Calcd for $C_7H_4Cl_2FNO_3$: C, 35.03; H, 1.68; N, 5.89; Cl, 29.54. Found: C, 35.26; H, 1.55; N, 5.62; Cl, 29.62.
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