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A practical, efficient, and rapid method for the oxidation of electron deficient pyridines using trifluoroacetic anhydride and hydrogen peroxide–urea complex

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Abstract

A general method for the oxidation of electron-poor pyridines to their *N*-oxides using UHP and TFAA in either CH_2Cl_2 or CH_3CN was developed. The methodology proved to tolerate a number of functional groups and substitution patterns and proceeded on notoriously difficult to oxidize substrates.

Keywords: oxidation; pyridines; *N*-oxides; peroxides.

The oxidation of a pyridine to its *N*-oxide is usually perceived as a straightforward chemical transformation and is most often accomplished using a peracid[1] such as peracetic acid, MCPBA or magnesium monoperphthalate[2] and more recently $HOF{\cdot}CH_3CN$ complex.[3] In 1998, Sharpless described a method for the oxidation of electron deficient pyridines using catalytic MTO ($MeReO_3$) and 30% H_2O_2 as the co-oxidant.[4]

In the course of the development of a drug candidate, we encountered difficulties in the oxidation of an electron poor pyridine to its *N*-oxide. Using 3,4,5-trichloropyridine, we investigated a series of reagents for this transformation. We discovered that using trifluoroacetic anhydride (TFAA) in the presence of the hydrogen peroxide urea complex (UHP[5]) was the superior procedure (Table 1). The use of peroxytrifluoroacetic acid as an efficient oxidizing agent has been known for a long time. In 1954, Emmons reported the oxidation of electron poor anilines to nitrobenzenes using peroxytrifluoroacetic acid, which was generated from trifluoroacetic acid (TFA) and 90% H_2O_2.[6] This procedure was also utilized to oxidize pentachloropyridine.[7] However, we found that using TFAA was far more efficient than TFA in conjunction with UHP, which is more practical and safer to use than 90% H_2O_2. In the last few years, several reports appeared on the use of UHP in oxidations, namely for the conversion of amines to nitroalkane,[8] Baeyer–Villiger oxidations of ketones to lactones,[9] oxidations of sulfides to sulfones,[10]

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and more recently conversion of pyridines to pyridine *N*-oxides,[11] although this last protocol proceeded at 85°C in the solid state.

Table 1
Oxidation of 3,4,5-trichloropyridine in CH_2Cl_2

Entry	Reagent	Time (hours)	% Completion
1	UHP (2 eq), TFAA (2 eq)	5	96
2	ReMTO, 30% H_2O_2 (2 eq)	24	69
3	Oxone	24	No reaction
4	UHP (2 eq), TFA (2 eq)	24	56
5	UHP (2 eq), Ac_2O (2 eq)	24	No reaction
6	30% H_2O_2 (2 eq), TFAA (2 eq)	24	73
7	70% *t*BuOOH (1 eq)	24	No reaction

A rapid evaluation of different solvents using 2.1 equivalents of UHP and 2.0 equivalents of TFAA demonstrated that either THF, CH_2Cl_2 or CH_3CN provided an acceptable rate for the reaction to go to completion (Table 2). While methanol was ineffective, DMAC and toluene proved to slow down the reaction. We found that the yield of the reaction could depend on the solvent selected in the case of some of the substrates, but we could not identify a general trend which would guide us in solvent selection based on the starting material. CH_2Cl_2 and CH_3CN were usually preferred because of the increased solubility of some of the starting materials.

Table 2
Solvent effect of the oxidation of 3,4,5-trichloropyridine with TFAA and UHP

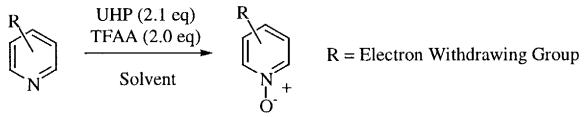
Entry	Solvent	Time	Yield (%)
1	THF	90 minutes	76
2	CH_3CN	<1 hour	74
3	CH_2Cl_2	5 hours	96
4	MeOH	7 days	---
5	DMAC	24 hours	27[a]
6	Toluene	24 hours	71[a]

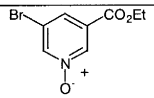
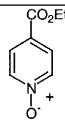
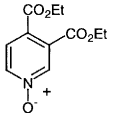
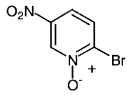
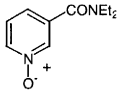
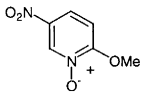
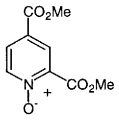
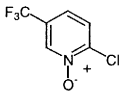
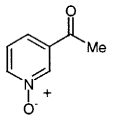
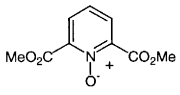
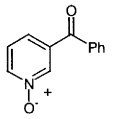
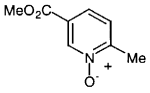
a) % Conversion after 24 hours

We found that the oxidation of pyridines to their *N*-oxides using our protocol proceeded efficiently on a number of electron deficient substrates (Table 3). For instance, carbonyls (esters, amides, ketones) are tolerated and no Baeyer–Villiger oxidation was observed. The reaction also proceeds in the presence of halides, trifluoromethyl groups, nitriles, and even nitropyridines. The oxidation also permits a number of different substitution patterns and only proved to be much slower in the case of a 2,6-disubstituted pyridine.

As a general procedure, the pyridine was dissolved in the preferred solvent (10 volumes) and UHP (2.1 equivalents) was added to the solution, which was cooled to 0°C. TFAA (2.0 equivalents) was then slowly added to the reaction mixture (the reaction is exothermic). The reaction was followed by TLC and HPLC analysis until completion. In the cases where the reaction required more than 30 minutes,

Table 3
Oxidation of pyridines using UHP (2.1 equiv.) and TFAA (2.0 equiv.)



Entry	Product	Solvent	Time (min)	Yield (%)	Entry	Product	Solvent	Time (min)	Yield (%)
1		CH_2Cl_2	15	91	8		CH_3CN	10	83
2		CH_2Cl_2	10	70	9		CH_3CN	30	98
3		CH_2Cl_2	120	82	10		CH_3CN	10	63
4		CH_2Cl_2	120	56[a]	11		CH_3CN	10	98
5		CH_2Cl_2	15	82	12		CH_3CN	45	48
6		CH_2Cl_2	1 day	55[b]	13		CH_3CN	30	98
7		CH_3CN	90	81					

a) No HCl wash in the work-up

b) 38% of starting material was recovered

it was allowed to warm to room temperature. The reaction was quenched with an aqueous solution of $Na_2S_2O_3$ and stirred for 15 minutes to destroy any residual peroxides before being poured into a 0.5 M HCl solution and extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude product was purified by either trituration with methyl *t*-butyl ether or by a filtration on a plug of silica gel to afford the pure pyridine *N*-oxides.

In conclusion, we have developed an efficient, rapid, and practical method for the oxidation of electron-poor pyridines to their *N*-oxide. The methodology requires relatively safe and commercially available reagents and proved to tolerate a number of functional groups and substitution patterns.

References

1. Swern, D. *Organic Peroxides*; Wiley: New York, 1971; Vol. 2, pp. 355–533.
2. Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015–1017.
3. Daya, S.; Kol, M.; Rozen, S. *Synthesis* **1999**, 1427–1430.
4. Copéret, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740–1741.
5. Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533–535.
6. Emmons, W. D. *J. Am. Chem. Soc.* **1954**, *76*, 3470–3472.
7. Roberts, S. M.; Suschitzky, H. *J. Chem. Soc. (C)* **1968**, 1537–1541.
8. Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron Lett.* **1992**, *33*, 4835–4838.
9. Astudillo, L.; Galindo, A.; Gonzalez, A. G.; Mansilla, H. *Heterocycles* **1993**, *36*, 1075–1080.
10. Balicki, R. *Synth. Commun.* **1999**, *29*, 2235–2239.
11. Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *1*, 189–191.