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David H Bremner [a], Keith R Sturrock [a], Grant Wishart [a], Stewart R Mitchell [a], Stuart M Nicoll [a] & Gareth Jones [a]

[a] Division of Chemistry, School of Molecular and Life Sciences, University of Abertay Dundee, Bell Street, Dundee, Scotland, DD1 1HG

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A COMPARISON OF METHODS FOR N-OXIDATION OF SOME 3-SUBSTITUTED PYRIDINES

David H Bremner*, Keith R Sturrock, Grant Wishart, Stewart R Mitchell, Stuart M Nicoll and Gareth Jones

Division of Chemistry, School of Molecular and Life Sciences, University of Abertay Dundee, Bell Street, Dundee, Scotland DD1 1HG

Abstract: The results from the N-oxidation of four 3-substituted pyridines using five different reagents are reported. The best yields are obtained with m-chloroperoxybenzoic acid.

As part of a synthetic programme investigating the synthesis and reactions of novel thieno[2,3-b]pyridines[1] we required an efficient route to ethyl 3-pyridyl-acetate N-oxide (2a). There are a number of methods available for N-oxidation[2] and previously we used the most facile route utilising hydrogen peroxide (30%) in glacial acetic acid but in our hands we obtained only moderate yields after a lengthy reaction time and tedious work up. We therefore embarked upon an investigation of some other readily available oxidising agents in order to evaluate their potential in the N-oxidation of 3-substituted pyridines generally. The pyridines used are shown in scheme 1 and the oxidising agents studied were 30% hydrogen peroxide in glacial acetic acid[2] (method A), m-chloroperoxybenzoic

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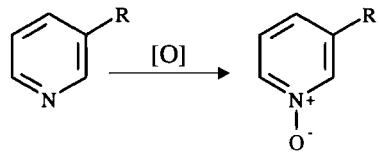
* To whom correspondence should be addressed

Scheme 1



1a-d 2a-d

a R=CH_2CO_2Et, b R=CH_3, c R=CH_2CH_3, d R=$CONH_2$

acid[3] (method B), sodium perborate monohydrate[4] (method C), potassium peroxymonosulfate[5,6] (methods D and E) and magnesium monoperoxyphthalate[7] (method F). Although, the oxidation of pyridines to their corresponding pyridine N-oxides is not new, this comparison will prove useful to others when cost and safety of reagents are important issues. Hydrogen peroxide in glacial acetic acid is one of the most commonly used reagents for the preparation of pyridine N-oxides and its use is well documented in the literature[2]. The oxidation of sulfides to sulfoxides and sulfones[8], the conversion of alkenes to oxiranes[9], and N-oxidations of heterocyclics[10] with m-chloroperoxybenzoic acid have also been reported. Sodium perborate monohydrate is a cheap, stable and widely used industrial oxidising agent which in laboratory reactions has been reported as an oxidant in the cleavage of 1,2-diketones[11], the oxidation of pyridines[12], anilines[13], sulfides[14], alkenes[15] and trialkylboranes[16]. Potassium peroxy-monosulfate, available under the commercial name of Oxone, has been utilised as a reagent for the oxidation of sulfides[17] and for the N-oxidation of heterocycles both in acid conditions[18,19] and neutral and basic conditions[20,6]. Magnesium monoperoxyphthalate is a newer reagent which is stable at ambient temperatures and has been shown to oxidise alkenes, ketones, sulfides, sulfoxides

and pyridines[7] in high yields, however many of these are not isolated yields but estimates determined by titration or glc.

The yields of products (2a-d) obtained by the oxidation of pyridines (1a-d) are shown in table 1. Method A gave acceptable yields of the N-oxides but took up to 72 hours for complete reaction and the work-up procedure was rather tedious requiring destruction of excess peroxide with carbon and removing solvents *in vacuo* prior to chromatography. Initially, in method B, m-chloroperoxybenzoic

Table 1 Reaction yields of pyridine N-oxides 2a-d

		METHOD					
Pyridine	N-Oxide	A	B	C	D	E	F
1a	2a	69	93	73	50	57	55
1b	2b	94	84	77	50	23	39
1c	2c	64	83	69	52	52	87
1d	2d	74	70	52	52	1	64

acid was used according to the literature procedure[9] but yields were low due, presumably, to loss of product during aqueous work-up. We therefore developed an improved novel work-up procedure which involves the exclusion of water. Thus after completion of the reaction (tlc), solid sodium metabisulfite was added to destroy any excess oxidising agent and then solid potassium carbonate was used to remove m-chlorobenzoic acid. After filtration of the solids the pure N-oxides were obtained in good yields by evaporation of the solvent followed by column chromatography. The yields from method C, based on that published by Greenhalgh[17], were disappointing and increasing the amount of oxidant used,

coupled with the use of higher boiling solvents or the application of ultrasound failed to produce any improvement. Since we were unable to complete the oxidation (according to tlc) the problem may lie in the solubility of the pyridine in water which is present as a requirement of the method. The use of sodium perborate (method D) gave reasonable yields of N-oxides except in the case of nicotinamide. However this method required heating at 60^{o} for 24 hr followed by a series of evaporations and filtrations before the product is isolated by column chromatography. It has been reported[6] that acetone in the presence of Oxone produces a dioxirane which acts as the oxidising agent in these reactions. However, in our hands (method E), the yields of ethyl 3-pyridylacetate N-oxide (2a) and 3-ethylpyridine N-oxide (2c) were comparable to that of Oxone in the presence of wet alumina (method C) and in the other two cases the yields were much lower. Magnesium monoperoxyphthalate gave an acceptable yield for 3-ethylpyridine N-oxide (2c) however the yields of the other N-oxides ranged from 39-64 % and the reaction times were in the region of 5 days. In many of these reactions the yields are well short of 100 % but all reactions were run until tlc had indicated that no starting material remained, except in the case of method D where unreacted starting material was recovered. Additionally the work up of these reactions afforded only the required product and none of the starting pyridines.

Conclusions

From the results of the oxidations of the four 3-substituted pyridines to their corresponding pyridine N-oxides it is obvious that m-chloroperoxybenzoic acid (Method B) gives the highest yields. This would normally be the reagent of choice for anyone who was not concerned over the cost or safety of reagents in large scale synthesis. Moreover, we have developed an improved work up

procedure for water soluble products. Magnesium monoperoxyphthalate (Method F) has been proposed a safer and more cost effective alternative[7], however the present study shows that the use of this reagent does not give a significant improvement of reaction yields of 3-substituted pyridine N-oxides when compared to other existing oxidation methods.

Table 2 Data for pyridine N-oxides 2a-d

N-Oxide	Mpt (^{o}C) [Lit] / Bpt (^{o}C/mm Hg) [Lit]	υ_{N-O}/cm^{-1}
2a	96-98^{o} [97-98^{o}][21]	1163
2b	120^{o} / 4 mm [146-149^{o} / 15 mm][22]	1171
2c	100^{o} / 4 mm [125-126^{o} / 15 mm][23]	1162
2d	291-292^{o} [291-293^{o}][24]	1236

Experimental

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer. Column chromatography was performed using pressurised short path columns with Kieselgel 60, particle size < 0.063 mm (Merck No. 7729) and reactions were monitored with Merck DC-Alufoilien Kieselgel 60 F_{254} (Merck No. 5554). Oxone, sodium perborate, m-chloroperoxybenzoic acid, magnesium monoperoxyphthalate and the pyridines were purchased from Aldrich Chemical Company and were used without further purification.

Method A

Pyridine (1a-d, 1.0 g) was dissolved in glacial acetic acid (20 ml) and 30% hydrogen peroxide (3 ml) was added. The reaction was stirred at 70^{o}C until tlc

had indicated no more starting material remained (4-72 h). Activated charcoal (0.5 g) was added to destroy any excess peroxide and the solution was filtered through Celite before removing the solvent *in vacuo*. The resulting product was chromatographed on silica gel eluting with ethyl acetate to afford the corresponding pyridine N-oxide (2a-d).

Method B

Pyridine (1a-d, 1.0 g) was stirred in dichloromethane at room temperature and m-chloroperoxybenzoic acid (70%; 1.1 eq) was added portionwise. The mixture was stirred for 1 h and the excess oxidising agent was destroyed by the careful addition of sodium metabisulphite. The mixture was filtered and solid potassium carbonate was added to neutralise m-chlorobenzoic acid and the filtrate was subsequently dried over magnesium sulfate and all solids removed by filtration. The solvent was removed *in vacuo* to give the crude product which was chromatographed on silica gel eluting with ethyl acetate to give the appropriate pyridine N-oxide (2a-d,).

Method C

Pyridine (1a-d, 1.0 g) was added to a vigorously stirred suspension of wet alumina (prepared[17] by adding 10 ml of water to 50 g of Brockman grade 1 alumina (200 mesh) and shaking until a free flowing powder was obtained) and Oxone (1 eq.) in dichloromethane (20 ml). The reaction mixture was refluxed for 3 h, cooled and the solids filtered and washed with dichloromethane. The filtrate was evaporated to afford the crude product which was chromatographed on silica gel eluting with ethyl acetate to give the appropriate pyridine N-oxide (2a-d).

Method D

Pyridine (1a-d, 1.0 g) was dissolved in glacial acetic acid and sodium perborate.H_2O (1.5 eq.) was added. The mixture was heated at 60^0 for 24 h, filtered, and the solvent removed *in vacuo*. The resulting oil was flooded with acetone and filtered once more. The solution was dried over magnesium sulfate to give the crude product which was chromatographed on silica gel eluting with ethyl acetate to give the appropriate pyridine N-oxide (2a-d).

Method E[6]

Oxone (0.03 mol) in water (100 ml) was added dropwise to a mixture of pyridine (1a-d, 0.0126 mol), acetone (5 ml) and phosphate buffer (50 ml). Potassium hydroxide solution was added to maintain the pH at 7.5 - 8.0. The mixture was stirred for 2 h, extracted with dichloromethane, dried over magnesium sulfate and the solvent removed *in vacuo* to give the crude product. Chromatography on silica gel eluting with ethyl acetate to gave the appropriate pyridine N-oxide (2a-d).

Method F

Pyridine (1a-d, 1.0 g) in ethanol (30 ml) was stirred with magnesium monoperoxyphthalate (3.0 g, 90%) at room temperature until tlc indicated no starting material remained (approximately 5 days). The solid was removed by filtration, washed with chloroform, and the filtrate evaporated to yield the crude product which was chromatographed on silica gel eluting with ethyl acetate to give the appropriate pyridine N-oxide (2a-d).

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