Deoxygenation of Amine Oxides by in situ-Generated Formic Pivalic Anhydride

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Abstract: A novel method for the highly efficient deoxygenation of tertiary and aromatic amine oxides is described. The initial step of the reaction is the *O*-formylation of the amine oxide by formic pivalic anhydride which is produced in situ. The approach has the advantage of superior convenience in preparation and work-up since all products of the reaction are solids or gases rendering the amine very readily separable.

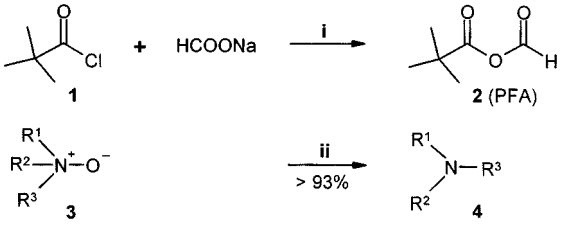
Key words: amine oxides, deoxygenation, formic pivalic anhydride, amines, decarboxylative fragmentation

Amine oxides are not only rewarding synthetic targets,[1] but multi-faceted compounds with numerous applications in synthetic organic chemistry, e.g., as intermediates in multi-step syntheses,[2] as protecting groups for tertiary and aromatic amines,[3] or as oxidants.[4] Furthermore, they are used in large-scale industrial processes, especially as solvents for cellulose[5] and as non-ionic surfactants.[6]

Several well-established methods for the reduction of amine oxides to the corresponding amines exist. The traditionally used approaches of catalytic hydrogenation[7] and reduction with phosphorous compounds[8] have been later complemented by more selective methods for deoxygenation, such as application of sodium hydrogen telluride,[9] trialkylamine-SO_2 complexes,[10] acetic formic anhydride,[11] tetrathiomolybdate[12] and hydride reagents.[13] In the present paper we would like to add yet another approach to the arsenal of known procedures, since the existing methods for the deoxygenation of amine oxides suffer from distinct drawbacks,[14] and none of these procedures seems to offer an equally high degree of convenience.

Deoxygenation of amine oxides is essentially the same process as the oxidation of organic compounds by amine oxides, the latter perhaps being the more frequently regarded procedure. All reductions of amine oxides to the corresponding amines have two steps in common, independent of the huge variety of agents and conditions used. A first reaction step – consisting of either a covalent chemical modification at the amine oxide, such as *O*-acylation and *O*-alkylation, or a complexation – is followed by transfer of two electrons to the amine with concomitant *N*-O bond cleavage. The formation of byproducts mainly arises from the occurrence of homolytic pathways, i.e., the transfer of two electrons in two separate steps, or originates in reactions competitive to the deoxygenation[15] in the second step. A well-known example for the latter case is the *Polonowski* reaction.[16] To achieve a reduction of amine oxides with optimum yields, a deoxygenation reagent would be desirable that is both a two-electron reductant, and the coreactant in the initial "complexation" reaction which should proceed as unambiguously as possible. This would limit the number of possible side-reactions during the second reaction step, the actual reduction.

We found formic pivalic anhydride (**2**, PFA) to react in the desired manner. Both tertiary and heteroaromatic amine oxides **3** are converted into the corresponding amines **4** in excellent yields (Scheme 1 and Table 1).[17] Very mild reaction conditions and the simplicity of the experimental approach are favorable features of the procedure, as discussed below.



Conditions: **i** = $CHCl_3$, rt, 30 min, - NaCl; **ii** = 1) PFA, 0°C to rt, 30 min, - CO_2; 2) K_2CO_3 (s), - Me_3CCOOK, - $KHCO_3$

Scheme 1

The fact that the procedure works for heteroaromatic amines as well (entries 9-11 in Table 1) was quite surprising as acetic formic anhydride, for instance, does not deoxygenate aromatic amine oxides at all.[11] Evidently, PFA is a much stronger deoxygenating reagent. Moreover, it shows a higher chemoselectivity than acetic formic anhydride since it does not induce *Polonowski*-type reactions.

The present method can be adapted to large-scale preparations without difficulties (Table 1, entry 2). No side-reactions were observed so far, regardless of the amine oxide employed. However, the effect of PFA on different functional groups remains to be tested in detail.

Table 1. Deoxygenation of Amine Oxides with PFA

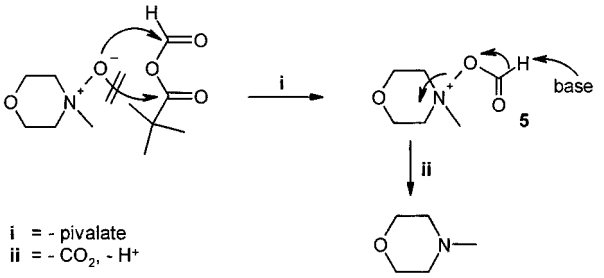
	Amine Oxide [a]	Amine [b]	Yield (%)
1	*N*-Methylmorpholine-*N*-oxide	*N*-Methylmorpholine [d]	~100
2	*N*-Methylmorpholine-*N*-oxide[c]	*N*-Methylmorpholine [d]	99
3	Trimethylamine-*N*-oxide	Trimethylamine [d]	~100
4	Tribenzylamine-*N*-oxide	Tribenzylamine	97
5	Triethanolamine-*N*-oxide	Triethanolamine	98
6	Dimethyloctylamine-*N*-oxide	Dimethyloctylamine	95
7	Dimethylaniline-*N*-oxide	Dimethylaniline	~100
8	Dimethyldodecylamine-*N*-oxide	Dimethyldodecylamine	93
9	Pyridine-*N*-oxide	Pyridine	98
10	Nicotinic acid-*N*-oxide	Nicotinic acid [e]	92
11	2-Picoline-*N*-oxide	2-Picoline	98

[a] 5 mmol of starting material was used, product purity determined by GC. [b] See (15) for experimental procedure. [c] 0.1 mol of starting material. [d] Purity and yield determined additionally by capillary electrophoresis (CE). [e] Isolated by extraction into water, n. d. by GC.

Pivaloyl formic anhydride (**2**) is a rather labile reagent that is difficult to dose exactly as it always contains at least traces of pivalic acid, formic acid, and the symmetric anhydrides. However, it is prepared in situ from pivaloyl chloride (**1**) and dry, pulverized sodium formate in chloroform. In that way, a controlled dosage became possible. To ensure that complete formation of PFA has occurred before the addition of the amine oxide, it is recommended to employ reaction times of 30 min or longer.

The deoxygenation of the amine oxides **3** by PFA is an exothermic reaction that proceeds smoothly at 0 °C. No reaction between PFA (**2**) and the product amine **4** was observed at this temperature. However, higher temperatures (rt) or the lack of cooling during the reaction, apparently favor the formation of amines generated in *Polonowski*- type side-reactions with subsequent formylation over the desired *O*-acylation of the amine oxide, *N*-formylmorpholine being the major by-product.

The first step of the deoxygenation reaction is the nucleophilic attack of the negatively-charged oxygen in **3** at the carbonyl group of the mixed anhydride producing an *N*-oxyformylammonium cation **5**. Strong steric hindrance prevents a reaction at the pivaloyl carbonyl group accounting for the highly regioselective attack at the formyl group. This is the advantage over the other mixed formic anhydrides, which deoxygenate amine oxides if the "proper" carbonyl reacts, but can also provoke *Polonowski*-type reactions if the "wrong" carbonyl group is involved. The *O*-formylated amine oxide **5** immediately undergoes an intramolecular redox reaction, in which the formic ester is oxidized to carbon dioxide while the amine oxide is reduced to corresponding amine. The *N*-O bond is cleaved during this decarboxylative fragmentation. In Scheme 2, the course of the reaction is shown for *N*-methylmorpholine-*N*-oxide as an example.



Scheme 2

The fact that no deoxygenation of amine oxides occurs with the non-acylating mixtures of formic acid and pivalic acid, or sodium formate and pivalic acid, is a strong indication of the *O*-formylated amine oxide **5** being the actual reagent for the subsequent reduction step. The assumption of a concerted two-electron reaction mechanism is supported by the observations that no by-products indicative of homolytic pathways are found, and that the release of CO_2 is occurring synchronously with the addition of the amine oxide to the PFA solution.

Perhaps the biggest advantage of the procedure in terms of general applicability is the fact that pure amines are obtained without the need to laboriously separate by-products or purify the product. The addition of anhydrous potassium carbonate converts pivalic and formic acid into their solid potassium salts, and NaCl, the by-product of the in situ-generation of PFA, is a solid as well. Thus, all other products of the deoxygenation reaction are easily separable by filtration, and the remaining amine solution can be used for manipulations without further purification steps. Simple evaporation of the solvent yields a pure product.

In summary, we have introduced an improved approach towards the deoxygenation of tertiary and heteroaromatic amine oxides. Being admittedly only one of many other similar methods, the procedure presented is attractive for the ease of preparation and work-up, and the exclusive use of simple chemicals.

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