

Transition Metal Catalyzed Oxidations. 14 [1]

Regeneration of Carbonyl Compounds by Oxidative Cleavage of Hydrazones with $\text{Zr}(\text{O}-t\text{-Bu})_4$ /*tert*-Butyl Hydroperoxide

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Dedicated to Prof. Günther Wulff on the Occasion of his 65th Birthday

Keywords: Cleavage reactions, Hydrazones, Oxidations, Transition metals, Zirconium, *tert*-Butyl hydroperoxide**Abstract.** A catalytic method with $\text{Zr}(\text{O}-t\text{-Bu})_4$ as the catalyst and *tert*-butyl hydroperoxide as the oxidant is describedto cleave phenylhydrazones **6–9**, **14–16** to the parent carbonyl compounds under mild and neutral oxidative conditions.

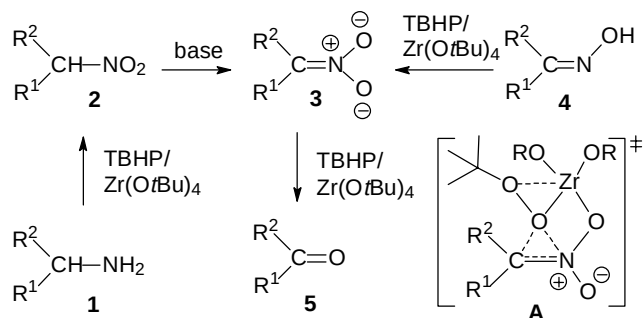
In a preceding paper we reported on the oxidation of primary aliphatic amines to aliphatic nitro compounds using *tert*-butyl hydroperoxide (TBHP) as the oxygen source and $\text{Zr}(\text{O}-t\text{-Bu})_4$ as the catalyst [2]. In some cases, particularly with benzylic amines and amines on primary carbon atoms, the oxidative cleavage to the corresponding carbonyl compounds was observed as a side reaction in ca. 5–10% yield (Scheme 1). In fact, a variety of reagents such as ozone [3], potassium permanganate [4], sodium percarbonate [5], sodium chlorite [6] or TBHP/ $\text{VO}(\text{acac})_2$ [7] have been used for the oxidative Nef reaction. Mechanistic considerations, *e.g.* the oxygenation of the *vinyl* C–N double bond in nitronates as opposed to the epoxidation of the *allylic* double bond in the Sharpless reaction, prompted us to investigate the catalytic TBHP/ $\text{Zr}(\text{O}-t\text{-Bu})_4$ system on the oxidative Nef reaction.

The oxygen transfer could happen as shown in the "di-spiro" transition state **A** in Scheme 1 followed by rearrangement to the carbonyl compound. In addition, oximes could be included in the oxidative cleaving reaction. They are oxidized to the corresponding nitronates and cleavage then proceeds as described above. Several oxidants for instance ozone [8], pyridinium chlorochromate [9], hydrogen peroxide [10] or dimethyldioxirane [11] have been proposed for their oxidative cleavage to carbonyl compounds.

Cyclohexylamine oxidized *in situ* to nitrocyclohexane and acetophenone oxime were used as model systems for the zirconium mediated oxidative cleavage with TBHP. Surprisingly, the reaction stopped in both cases at a conversion of maximally 60%. The corresponding ketones were formed in 36% over two steps starting from cyclohexylamine and in 55% yield from acetophenone hydroxylamine as determined by GC analysis (see Scheme 1). In both cases, a white precipitate of low solubility was formed on concentration of the reaction solutions. The exact nature of the precipitate is yet unknown but probably a complex of zirconium and four molecules of the nitronate was formed [12]. An indication in that direction came from the detection of acetophenone in the thermal or acidic decomposition of the complex formed with acetophenone oxime. However, the advantage of the mechanistically interesting *catalytic* process is lost by the low yields of the method particularly in view of the much better yields obtained in the oxidative cleavage of nitronates with dimethyldioxirane as recently reported by Adam *et al.* [13].

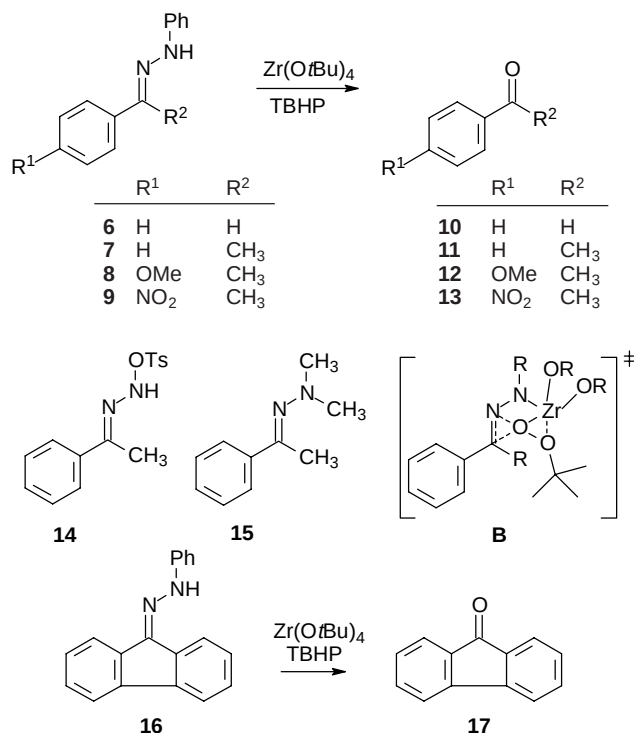
However, hydrazones represent another example of the C–N double bond containing group of compounds in which complex formation with the zirconium metal is not very likely. Their mild cleavage is of preparative importance since strong acid [14] or reduction using aqueous titanium(III) chloride [15, 16] very often cannot be tolerated by the substrate. For instance, in the asymmetric synthesis with (*S*)-2-methoxymethylpyrrolidine (SMP), the mild oxidative cleavage is effected using ozone [17]. More recently, dimethyldioxirane was employed as the reagent in hydrazone cleavage by Curci *et al.* [18a]. Yamashita *et al.* reported on the palladium-catalyzed deprotection of hydrazones [18b]. However, the method was restricted to *N,N*-dialkylhydrazones. It would be of advantage to use a *catalytic* procedure that is generally applicable also on larger scale for the cleavage of *N*-monoaryl or *N*-monoalkyl hydrazones under mild conditions.

Ligand exchange of the alcohols on the zirconium atom by the hydrazone substrate and the TBHP is postulated as the initial step in this type of transition metal oxidation (review [19]). The difference to transition state **A** with the nitronates in Scheme 1 is the *allylic* position of the C–N double bond as shown in transition state **B** (Scheme 2). In this respect, the



Scheme 1 Oxidation of amines and hydroxylamines to nitronates and their cleavage to carbonyl compounds *via* transition state **A**

situation is analogous to the Sharpless reaction, replacing a carbon and an oxygen atom of the allylic alcohols by two nitrogen atoms as depicted in **B**. The reaction was first tried with the phenylhydrazones of benzaldehyde **6** and three differently substituted acetophenones **7–9**. Very mild conditions at room temperature and dilute TBHP solutions in dichloromethane with 10 mol% of $\text{Zr}(\text{O}-t\text{-Bu})_4$ and small amounts of 3 Å molecular sieves to trap traces of water were employed. The keto hydrazones **7–9** were cleaved in good yields to the corresponding parent ketones **11–13** whereas the formation of small amounts of benzoic acid reduced the yield in the cleavage of the benzaldehyde hydrazone **6**. (Scheme 2 and Table 1).



Scheme 2 Oxidation of various hydrazones to carbonyl compounds via transition state **B**

Table 1 Oxidative cleavage of phenylhydrazones **6–9** and **14–16** to their corresponding carbonyl compounds

Hydrazone compound	Carbonyl	Reaction time (h)	Yield (%)
6	10	6	61 ^{a)}
7	11	6	75
8	12	6	80
9	13	9	80
14	11	24	40 (GC)
15	11	24	27 (GC)
16	17	7	76

^{a)} various amounts of benzoic acid were also formed

As expected, the reaction time in the oxidative cleavage of the acceptor-substituted hydrazone **9** of 4-nitroacetophenone was somewhat longer but the isolated yield of acetophenone was identical. By contrast, the very electrondeficient C–N double bond of the tosylhydrazone **14** reacted only very slowly

and after one day the conversion was only 40% as determined by GC. Much stronger oxidation reagents such as sodium percarbonate [5], conc. TBHP at elevated temperatures [20], or dimethyldioxirane [21] are required to cleave tosylhydrazones. An even slower reaction was observed with the acetophenone 1,1-dimethylhydrazone **15**. In this case, the required proton on nitrogen for rapid ligand exchange was missing and the oxygenation was very slow in agreement with our mechanistic model (see above). Finally, the steric requirements were changed with the phenylhydrazone **16** as the substrate. The reaction time did not change significantly and the isolated yield of fluorenone (**17**) was in the same order of magnitude (76%) as with the acetophenones.

In summary, a catalytic method is presented that cleaves phenylhydrazones of various carbonyl compounds in good yields under very mild neutral oxidative conditions employing $\text{Zr}(\text{O}-t\text{-Bu})_4$ as the catalyst and TBHP as the oxidant.

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Experimental

Oxidative Cleavage of Nitronates and Oximes

A solution of nitrocyclohexane was prepared by *in situ* oxidation of cyclohexylamine (99 mg, 1 mmol) with TBHP (6 mmol), $\text{Zr}(\text{O}-t\text{-Bu})_4$ (0.04 ml, 0.1 mmol) and 3 Å molecular sieves (0.6 g) in CH_2Cl_2 (10 ml) (4 h, GC monitoring) according to the published procedure [2]. Potassium *tert*-butoxide (135 mg, 1.2 mmol) was then added, and the reaction was quenched after further 5 h of stirring. Chromatographic workup [2] afforded cyclohexanone (35 mg, 36%). Similarly, acetophenone oxime (1.35 g, 10.0 mmol) was treated with $\text{Zr}(\text{O}-t\text{-Bu})_4$ (0.4 ml, 1 mmol), 3 Å molecular sieves (1.5 g), and TBHP (10 ml of 3.66 molar solution in dry CH_2Cl_2 , 59 mol). On concentrating of the solution at reduced pressure, a white precipitate was formed that was collected by filtration. The solvent was removed under reduced pressure and the residue purified by bulb to bulb distillation to yield acetophenone (0.66 g, 55%).

Oxidative Cleavage of Hydrazones (General Procedure)

A solution of the hydrazone (1 mmol) in dry CH_2Cl_2 (10 ml) was treated with 200 mg of freshly activated molecular sieves (3 Å). After stirring for 30 min, $\text{Zr}(\text{O}-t\text{-Bu})_4$ (0.1 mmol) was added. The mixture was again stirred for 30 min and a solution of TBHP (2 ml, 3.5 mol/l in CH_2Cl_2) was added within 5 min. The reaction was stirred for the times indicated in Table 1 (TLC monitoring). After conversion of the starting material, silica gel (1 g) was added to remove the zirconium catalyst, and the suspension was filtered. The filtrate was mixed with an aqueous solution of Na_2SO_3 (10 ml, 0.5 mol/l) to reduce the excess of TBHP. The mixture was stirred for 30 min, the phases were separated, the organic phase was dried (MgSO_4), filtered, and the product purified by flash chromatography on silica gel (dichloromethane). For yields see Table 1.

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