# Catalytic Aerobic Oxidative Cleavage of Oximes, Tosylhydrazones and *N,N*-Dimethylhydrazones to Carbonyl Compounds

Gonzalo Blay, Elisabeth Benach, Isabel Fernández, Sales Galletero, José R. Pedro,* Rafael Ruiz

Departament de Química Orgànica, Facultat de Química, Universitat de València, E-46100- Burjassot (València) Spain
Fax +34(963)864328; E-mail: Jose.R.Pedro@uv.es

*Received 3 August 1999; 19 November 1999*

**Abstract**: A new method for the aerobic oxidative cleavage of the C=N double bond of oximes and, tosyl- and *N,N*-dimethylhydrazones of ketones to yield their corresponding carbonyl compounds, with a Ni(II) complex catalyst, oxygen and pivalaldehyde has been developed.

**Key words**: protective groups, ketoxime, hydrazone, metal catalyst, Ni(II) complex

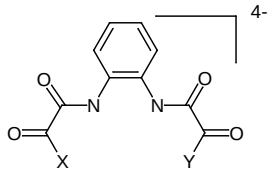
Nitrogen derivatives of carbonyl compounds such as hydrazones and oximes are important in organic chemistry. Highly crystalline hydrazone and oxime derivatives constitute a very efficient method for the isolation, purification and characterisation of aldehydes and ketones.[1] From the synthetic point of view, such derivatives not only serve as protective groups[2] of aldehydes and ketones but also have other uses. For example, metalated *N,N*-dimethylhydrazones have long been established as useful enolate equivalents in carbon-carbon bond forming reactions, and highly regio- and stereo-selective electrophilic substitutions in the α-position to the carbonyl group have been possible via this methodology.[3] On the other hand, oximes can be prepared from non carbonyl compounds (i.e., Barton reaction[4] or nitrosation of alkenes[5] and enols[6]) and, therefore, deoximation of such oximes provides an alternative method for the synthesis of carbonyl compounds.

Therefore, it becomes evident that the importance of developing hydrazone and oxime cleavage techniques that encompass the desirable features of good yield, general practicability, mildness, chemoselectivity and environmental friendship.

Deprotection of hydrazones and oximes can be achieved by either hydrolytic, reductive, or oxidative cleavage.[2] Acid hydrolysis can lead to condensation products or hydrolysis of sensitive groups, and in these cases oxidative or reductive cleavage may be a viable alternative. Further to the classical methods, some new ones have been reported in very recent years. For example, magnesium monoperoxyphthalate (MMPP),[7] dioxiranes,[8] and $Pd(OAc)_2$-$SnCl_2$[9] for hydrazones; 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane periodate (BAABCP),[10] silica supported sodium periodate[11] or chromium trioxide[12] under microwaves and Dess–Martin periodinane[13] for oximes; and titanium silicalite-1 (TS-1),[14] bis(1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane)peroxodisulfate (BAABCPS),[15] *o*-iodoxybenzoic acid (IBX)[16] and $BiCl_3$ under microwaves[17] for both oximes and hydrazones can be mentioned among them. Most of these methods require stoichiometric or excess amounts of reagent, and only the $Pd(OAc)_2$-$SnCl_2$, the $BiCl_3$ and the TS-1 procedures are catalytic, although they show some drawbacks. For instance, catalysis with $Pd^{2+}$-$Sn^{2+}$and TS-1 require reflux temperature while $BiCl_3$ under microwaves shows low turnovers and requires Teflon vessels and microwaves equipment that are not available in most organic synthetic laboratories.

On the other hand, to the best of our knowledge, only a few procedures for carbon-nitrogen double bond oxidative cleavage in aerobic conditions have been reported so far.[18]

In previous papers some of us have reported on the synthesis of monomeric square-planar complexes of different metals with bis-*N,N'*-disubstituted oxamides and related ligands (opba, Meopba and $Me_2$opba)[19] (Scheme 1). This kind of polychelating amido ligands, which have large donor capacities due to the presence of the deprotonated amido groups allows that unusually high oxidation state complexes of later first row transition metal ions can be attained. We have used the corresponding Co(III),[20] Fe(III),[21] and Ni(II)[22] complexes as catalysts in the aerobic epoxidation of olefins. We have also used the Co(III) complex in the oxidative decarboxylation[23] of α−hydroxy acids.

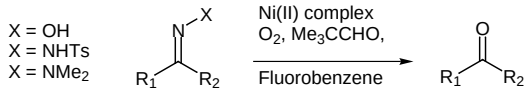



| X | Y | Ligand |
|---|---|---|
| O | O | opba |
| O | NMe | Meopba |
| NMe | NMe | $Me_2$opba |

**Scheme 1**

Herein, we wish to disclose the use of the Ni(II)$Me_2$opba complex as a catalyst for the aerobic oxidative cleavage of oximes, tosyl and *N,N*-dimethylhydrazones in the presence of an aldehyde as co-reductor and oxygen as oxidising agent (Scheme 2).[24]

The results for oxime cleavage are summarised in Table 1. Reactions were tested in fluorobenzene, dichloromethane and acetonitrile. Fluorobenzene was found the best solvent. Only in the case of *p*-nitroacetophenone oxime, did acetonitrile and dichloromethane gave better results,




**Scheme 2**

probably because of the low solubility of this compound in fluorobenzene. The yields for aromatic ketoximes in this solvent were good (80–96%) although the presence of electron withdrawing groups on the aromatic ring decreased the reaction rate and lowered the yields. With aliphatic ketoximes the yields were low (40%), and complex mixtures were obtained because of side reactions probably involving oxidation to nitro compounds.[25]

Oxidative cleavage of the C=N double bond also proceeded with tosyl- (Table 2) and *N*,*N*-dimethylhydrazones (Table 3). In these cases, blank probes showed a little extent of hydrazine exchange between the ketone and pivalaldehyde, probably catalysed by pivalic acid formed upon oxidation of pivalaldehyde. This undesired side reaction could be avoided by addition of a base such as imidazole or *N*-methylimidazole in the case of tosylhydrazones and of aromatic *N*,*N*-dimethylhydrazones, but not in the case of aliphatic *N*,*N*-dimethylhydrazones. However, the addition of base diminished the reaction rate, and additional amounts of pivalaldehyde and base were needed for complete reaction of the starting material.[26] The reaction works well with tosylhydrazones of aliphatic ketones and *N*,*N*-dimethylhydrazones of aromatic ketones[27] giving yields higher than 80% in most of the substrates tested but it does not seem to be of synthetic application for aromatic tosylhydrazones. Again, it was found that electron withdrawing groups on the aromatic ring decreased reaction rates and yields.

The method cannot be applied in the case of aldehyde derivatives because these compounds are over-oxidised to acids under our reaction conditions.

In summary, we have described a new catalytic method for the conversion of oximes, tosyl- and *N*,*N*-dimethylhydrazones to the corresponding ketones. Our method has good turnovers, uses oxygen as terminal oxidising agent, and avoids the use of stoichiometric amounts of toxic oxidants.

**Table 1** Oxidative Cleavage of Oximes[a]

| Substrate | Solvent | Time (h) | Yield (%)[b,c] |
|---|---|---|---|
| Acetophenone oxime | $C_6H_5F$ | 5 | 90 |
| | $CH_2Cl_2$ | 8.5 | 49 |
| | $CH_3CN$ | 8.5 | 32 |
| *p*-Bromoacetophenone oxime | $C_6H_5F$ | 4.5 | 90 |
| | $CH_2Cl_2$ | 7 | 90 |
| | $CH_3CN$ | 7 | 82 |
| *p*-Methoxyacetophenone oxime | $C_6H_5F$ | 4.5 | 96 |
| | $CH_2Cl_2$ | 7 | 78 |
| | $CH_3CN$ | 6 | 75 |
| *p*-Methylacetophenone oxime | $C_6H_5F$ | 5 | 80 |
| *m*-Methylacetophenone oxime | $C_6H_5F$ | 4 | 60 |
| *p*-Trifluoromethylacetophenone oxime | $C_6H_5F$ | 6 | 45 (15) |
| *p*-Nitroacetophenone oxime | $C_6H_5F$ | 7.5 | 59 |
| | $CH_2Cl_2$ | 5.5 | 75 |
| | $CH_3CN$ | 6.5 | 77 |
| *m*-Nitroacetophenone oxime | $C_6H_5F$ | 6 | 52 (36) |
| Tetralone oxime | $C_6H_5F$ | 8.5 | 57 |
| 4-*tert*-Butylcyclohexanone oxime | $C_6H_5F$ | 20 | 32 |
| Cyclododecanone oxime | $C_6H_5F$ | 20 | 40 |
| 2-Undecanone oxime | $C_6H_5F$ | 6 | 32 |

[a] No reaction advance was observed under Ar.
[b] Yields refer to isolated and chromatographically pure compounds.
[c] Recovered unreacted starting material are in brackets.

The required oximes, tosylhydrazones and *N*,*N*-dimethylhydrazones were prepared by the standard procedures from commercially available ketones. $(NMe_4)_2[Ni(Me_2opba)]\cdot 4H_2O$ complex was prepared as described in the literature.[22] Fluorobenzene, pivalaldehyde and *N*-methylimidazole were commercially available and used without further purification. Reactions were monitored by TLC on Merck DC-Alufolien Kieselgel 60 $F_{254}$ plates which were visualised under UV radiation. Column chromatography was performed on SDS chromagel 60 silica gel.

**Table 2** Oxidative Cleavage of Tosylhydrazones[a]

| Substrate | Time (h) | Yield (%)[b,c] |
|---|---|---|
| Acetophenone tosylhydrazone | 7 | 61 |
| *p*-Bromoacetophenone tosylhydrazone | 6 | 46 |
| *p*-Methoxyacetophenone tosylhydrazone | 6 | 50 (10) |
| *p*-Nitroacetophenone tosylhydrazone | 7.5 | 48 (14) |
| Tetralone tosylhydrazone | 6 | 80 |
| 4-*tert*-Butylcyclohexanone tosylhydrazone | 24 | 74 |
| Cyclododecanone tosylhydrazone | 24 | 82 |
| 2-Undecanone tosylhydrazone | 24 | 80 |

[a] No reaction advance was observed under Ar.
[b] Yields refer to isolated and chromatographically pure compounds.
[c] Recovered unreacted starting material are in brackets.

**Oxime Cleavage; General Procedure**[28]

A solution of the oxime (0.18 mmol) in fluorobenzene (0.3 mL) was added to a solution of $(NMe_4)_2[Ni(Me_2opba)]\cdot 4H_2O$ complex (4 mg, $7.2 \times 10^{-3}$ mmol) and pivaladehyde (58 μL, 0.53 mmol) in fluorobenzene (0.3 mL). The reaction mixture was stirred under $O_2$ atm at r.t. Pivalaldehyde (58 μL, 0.53 mmol) was added after 1 h and stirring was continued until the oxime reacted completely as indicated by TLC. Then, the reaction was diluted with $Et_2O$ (40 mL), washed with sat. $NaHCO_3$ (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The product was further purified by column chromatography.

**Tosylhydrazone Cleavage; General Procedure**

Tosylhydrazone (0.22 mmol) was added to a solution of $(NMe_4)_2[Ni(Me_2opba)]\cdot 4H_2O$ complex (4 mg, $7.2 \times 10^{-3}$ mmol), pivalaldehyde (70 μL, 0.64 mmol), and *N*-methylimidazole (18 μL, 0.37 mmol) in fluorobenzene (0.8 mL). The reaction mixture was stirred under $O_2$ atm at r.t. The following reagents were then added: After 2 h of reaction, pivalaldehyde (70 μL, 0.64 mmol) and *N*-methylimidazole (18 μL, 0.37 mmol); after 4 h of reaction, pivalaldehyde (70 μL, 0.64 mmol), and *N*-methylimidazole (18 μL, 0.37 mmol) and Ni(II) complex (2 mg, $3.6 \times 10^{-3}$ mmol). Stirring was continued until complete reaction of the starting material. The reaction mixture was concentrated and chromatographed to give the expected product. In some cases, an additional filtration through a short pad (2 cm) of basic alumina was required to eliminate traces of pivalic acid.

**Table 3** Oxidative Cleavage of *N*,*N*-Dimethylhydrazones[a]

| Substrate | Time (h) | Yield (%)[b,c] |
|---|---|---|
| Acetophenone *N*,*N*-dimethylhydrazone | 7 | 90 |
| *p*-Bromoacetophenone *N*,*N*-dimethylhydrazone | 20 | 70 |
| *p*-Methoxyacetophenone *N*,*N*-dimethylhydrazone | 20 | 81 |
| *p*-Methylacetophenone *N*,*N*-dimethylhydrazone | 20 | 86 |
| *m*-Methylacetophenone *N*,*N*-dimethylhydrazone | 20 | 82 |
| *p*-Trifluoromethylacetophenone *N*,*N*-dimethylhydrazone | 20 | 60 (30) |
| *p*-Nitroacetophenone *N*,*N*-dimethylhydrazone | 20 | 46 (43) |
| *m*-Nitroacetophenone *N*,*N*-dimethylhydrazone | 20 | 60 (30) |
| Tetralone *N*,*N*-dimethylhydrazone | 20 | 88 |
| Benzophenone *N*.*N*-dimethylhydrazone | 48 | 95 |

[a] No reaction advance was observed under Ar.
[b] Yields refer to isolated and chromatographically pure compounds.
[c] Recovered unreacted starting material are in brackets.

***N*,*N*-Dimethylhydrazone Cleavage; General Procedure**

A solution of the *N*,*N*-dimethylhydrazone (0.18 mmol) in fluorobenzene (0.3 mL) was added to a solution of $(NMe_4)_2[Ni(Me_2opba)]\cdot 4H_2O$ complex (4 mg, $7.2 \times 10^{-3}$ mmol), pivaladehyde (59 μL, 0.54 mmol), and *N*-methylimidazole (7.4 mL, 0.15 mmol) in fluorobenzene (0.3 mL). The reaction mixture was stirred under $O_2$ atm at r.t. The following reagents were then added: After 2 h of reaction, pivalaldehyde (59 μL, 0.54 mmol) and *N*-methylimidazole (7.4 mL, 0.15 mmol); after 3 h of reaction, Ni (II) complex (4 mg, $7.2 \times 10^{-3}$ mmol); after 4 h of reaction, pivalaldehyde (59 μL, 0.54 mmol). Stirring was continued until complete reaction of the starting material. Isolation of the product was achieved as described above for tosylhydrazone cleavage.

## Acknowledgement

Financial support is gratefully acknowledged from the Dirección General de Enseñanza Superior e Investigación Científica (grant PB97-1411).

## References

(1) Shriner, R. L.; Fuson, R. C.; Curtin, D. H.; Morrill, T. C. *The Systematic Identification of Organic Compounds*, 6th ed., Wiley: New York, 1980.
(2) Kocienski, P. J. In *Protecting Groups*; Enders, D.; Noyori, R.; Trost, B. M., Eds.; Thieme: Stuttgart, 1994.
Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, 2nd ed., Wiley Interscience: New York, 1991.
(3) Corey, E. J.; Enders, D. *Chem. Ber*. **1978**, *111*, 1337; and references cited therein.
(4) Kabalka, G. W.; Pace, R. D.; Wadgaonkar, P. P. *Synth. Commun.* **1990**, *20*, 2453.
Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. *J. Am. Chem. Soc.* **1961**, *83*, 4076.
Barton, D. H. R.; Beaton, J. M. *J. Am. Chem. Soc.* **1961**, *83*, 4083.
(5) Kadzayanskas, N. S.; Zefirov, N. S. *Russ. Chem. Rev. (Engl. Transl.)* **1968**, *37*, 543.
(6) Williams, D. L. H. *Nitrosation*; Cambridge University Press: Cambridge, 1988, pp 1–43.
(7) Enders, D.; Plant, A. *Synlett* **1990**, 725.
(8) Altamura, A.; Curci, R.; Edwards, J. O. *J. Org. Chem.* **1993**, *58*, 7289.
(9) Mino, T.; Hirota, T.; Yamashita, M. *Synlett* **1996**, 999.
(10) Hajipour, A. R.; Mahboubghah, N. *J. Chem. Research., Synop.* **1998**, 122.
(11) Varma, R. S.; Dahiya, R.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 8819.
(12) Bendale, P. M.; Khadilkar, B. M. *Tetrahedron Lett.* **1998**, *39*, 5867.
(13) Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **1999**, 760.
(14) Joseph, R.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1994**, *35*, 5493.
(15) Kumar, P.; Hegde, V. R.; Pandey, B.; Ravindranathan, T. *J. Chem. Soc., Chem. Commun*. **1993**, 1553.
Hajipour, A. R.; Mohammadpoor-Baltork, I.; Kianfar, G. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2655.
(16) Bose, D. S.; Srinivas, P. *Synlett* **1998**, 977.
(17) Boruha, A.; Baruah, B.; Prajapati, D.; Sandhu, J. S. *Synlett* **1997**, 1251.
Boruha, A.; Baruah, B.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1997**, *38*, 4267.
(18) Friedrich, E.; Lutz, W.; Eichenauer, H.; Enders, D. *Synthesis* **1977**, 893.

Maroulis, A. J.; Kalambokis, E. A. *J. Chem. Res., Synop.* **1993**, 278.
(19) Ruiz, R.; Surville-Barland, C.; Aukauloo, A.; Anxolabehere-Mallart, E.; Journaux, Y.; Cano, J.; Muñoz, M. C. *J. Chem. Soc., Dalton Trans*. **1997**, 745
(20) Estrada, J.; Fernández, I.; Pedro, J. R.; Ottenwaelder, X.; Ruiz, R.; Journaux, Y. *Tetrahedron Lett.* **1997**, *38*, 2377.
(21) Ruiz, R.; Triannidis, M.; Aukauloo, A.; Journaux, Y.; Fernández, I.; Pedro, J. R.; Cervera, B.; Castro, I.; Muñoz, M. C. *J. Chem. Soc., Chem. Commun*. **1997**, 2283.
(22) Fernández, I.; Pedro, J. R.; Roselló, A. L.; Ruiz, R.; Ottenwaelder, X.; Journaux, Y. *Tetrahedron Lett.* **1998**, *39*, 2869.
(23) Blay, G.; Fernández, I.; Formentín, P.; Pedro, J. R.; Roselló, A. L.; Ruiz, R.; Journaux, Y. *Tetrahedron Lett.* **1998**, *39*, 3327.
(24) Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59; and references cited therein.
(25) Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron Lett.* **1992**, *33*, 4835.
(26) A similar effect on yields and rates was found when base was added to oxime cleavage reactions. However, in those reactions, hydroxylamine exchange in the absence of base was not observed and therefore the use of base was not required.
(27) In the case of aliphatic *N*,*N*-dimethylhydrazones, the ketone is obtained by hydrazine exchange with pivalaldehyde and not by an oxidative process.
(28) We have carried out the reaction on a 2 mmol scale and similar results were obtained if good stirring and good contact surface with oxygen is maintained.

Article Identifier:
1437-210X,E;2000,0,03,0403,0406,ftx,en;P04599SS.pdf