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Tetrahedron Letters 45 (2004) 5559–5561
Tetrahedron Letters

Conversion of ketoximes to ketones with trimethylphosphine and 2,2′-dipyridyl diselenide

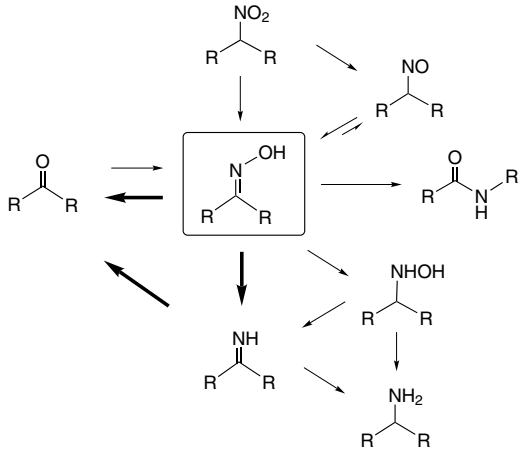
Manuel Martín, Gabriel Martínez, Fèlix Urpí* and Jaume Vilarrasa*

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain

Received 31 March 2004; accepted 1 June 2004

Abstract—Use of trimethylphosphine (Me_3P) and 2,2′-dipyridyl diselenide (PySeSePy) is an excellent method for the conversion of ketoximes to the corresponding ketones, since yields higher than 90% are obtained at rt within a few minutes (or hours for the more reluctant substrates, which do not react with Bu_3P/PhSSPh). In the simplest cases, the reaction can be completed with 30 mol% of PySeSePy, provided that an excess of phosphine is present in the reaction medium.

As it is well known, ketoximes occupy a central position in the chemical transformations that correlate ketones, nitroalkanes, amines, carboxamides, etc. (Scheme 1). These conversions include, or have a link with, industrially significant and/or venerable reactions, such as the Beckmann rearrangement,[1a,b] the Nef reaction,[1c,d] the Barton reaction,[1e,f] or the amination of active methylene groups via nitrosation and reduction.



Scheme 1.

Many of the efficient hydrolytic, oxidative or reductive methods that convert ketoximes into ketones (bold arrows in Scheme 1),[2] are not sufficiently mild to be applied to polyfunctional substrates. In this context, we focussed our attention on the work performed at Gif-sur-Yvette[3a,b,c] on the use of tributylphosphine (Bu_3P) and diphenyl disulfide (PhSSPh) for the above-mentioned conversion. The essence of this really smooth procedure[3] is that ketoximes are converted to $Bu_3P{=}O$ and *N*-(phenylsulfenyl)ketimines (i.e. *S*-phenyl thioketoximes),[4] which may be cleaved to ketimines and are readily hydrolysed to ketones during the workup. We have investigated modifications of this method aimed at finding even milder or simpler protocols.

We compared first the relative reactivity of Me_3P, Et_3P and Bu_3P[5] with PhSSPh and cyclopentadecanone oxime **1a** (Scheme 2) in anhydrous THF at rt at 0.1 M concentrations. While Me_3P (2.2 equiv) and PhSSPh (1.1 equiv) reacted quantitatively with **1a** within 5 min, to afford cyclopentadecanone **1b** after addition of water, Et_3P (2.2 equiv) and PhSSPh (1.1 equiv) required 30 min and Bu_3P (2.2 equiv) and PhSSPh (1.1 equiv) 1 h for the complete disappearance of **1a**, under identical conditions. Besides, we confirmed[3a] that PhSSPh could not be used in catalytic amounts, even with a large excess of Me_3P, otherwise the yields of ketone **1b** decreased. In our hands, the yields of **1b** turned out to be proportional

Keywords: Oximes; Ketones; Trimethylphosphine; 2,2′-Dipyridyl diselenide.

* Corresponding authors. Tel.: +34-934021258; fax: +34-933397878; e-mail: jvilarrasa@ub.edu

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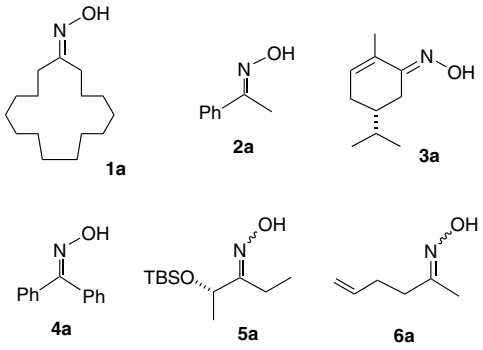
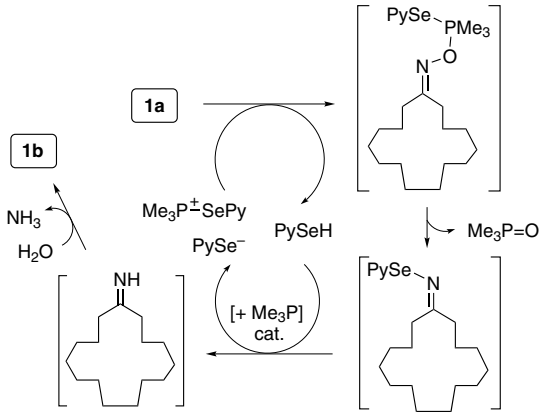
doi:10.1016/j.tetlet.2004.06.001



Scheme 2.



Scheme 3.

to the substoichiometric amounts of PhSSPh employed in each experiment.

When we added Me_3P/PhSSPh to other oximes (**2a**–**6a**), two drawbacks were noted. The first one was that some oximes were scarcely reactive. In fact, acetophenone oxime (**2a**) and carvone oxime (**3a**) reacted very slowly even by using an excess of reagents. For example, with a mixture of 4 equiv of Me_3P and 2 equiv of PhSSPh, 14 h were required to complete the consumption of **2a**, and oxime **3a** had not completely disappeared after 6 h. Moreover, benzophenone oxime (**4a**) hardly reacted even by heating the reaction mixture in a closed vial. The second shortcoming of the procedure was that oxime **3a** gave rise to a complex mixture of products, some of which arose from the conjugate addition of PhSH to the double bond. Combination of Me_3P with 2,2′-dipyridyl disulfide (PySSPy), diphenyl diselenide or 4,4′-bis(chlorophenyl) diselenide did not solve the above-mentioned problems.

2,2′-Dipyridyl diselenide, an orange solid readily prepared from selenium, $NaBH_4$, and 2-bromopyridine,[6] *turned out to be the co-reagent of choice*. As shown in Table 1, from the above-mentioned series of oximes (**1a**–**6a**),[7] the isolated yields of the corresponding ketones (**1b**–**6b**) are excellent, even in the most reluctant cases.

In the simplest cases, the conversions of ketoximes to ketones were instantaneous.[8] It seems that plausible intermediates have relatively short half-lives, especially the *N*-SePy intermediate (see Scheme 3), which would be readily cleaved under the reaction conditions (much more readily than the *N*-SPh intermediates mentioned above[3a–d]).

In fact, by monitoring the reaction by ^1H NMR, using a small molar excess of oxime **1a** as an internal reference, only $Me_3P{=}O$ (which appeared immediately) and signals that could be attributed to the imine were observed.[9] Another advantage of the method is that an excess of Me_3P is not required in simple cases (**1a** and **6a**, see entries 1 and 8 of Table 1). Moreover, no conjugate addition of 2-pyridylselenoate anion took place in the case of **3a**.

Conversion of ketoximes to ketones by using catalytic amounts of PySeSePy is also feasible, although the reactions are slower. For example, treatment of **1a** with 1.2 equiv of Me_3P and 0.2 equiv of PySeSePh, in THF at rt as usual, afforded after the workup 64% of **1b** within 6 h and 80% within 24 h; oxime **1a** remained. For the complete disappearance of oxime **1a**, with isolation of ketone **1b** in yields higher than 95%, we utilised 1.3 equiv of Me_3P and 0.3 equiv of PySeSePy (overnight), or 2.5 equiv of Me_3P and 0.3 equiv of PySeSePy (30 min).[10]

From the practical point of view, another advantage of our procedure is that the co-product 2-selenopyridone is so readily oxidised by air that PySeSePy (of orange colour) can be then recovered by column chromatography or by extraction. A further advantage is the well-known solubility of $Me_3P{=}O$ in water that makes the workup easy.[11]

Table 1. Reaction of oximes **1a**–**6a** with 2,2′-dipyridyl diselenide and Me_3P at rt

Entry	Oxime	PySeSePy (equiv)	Me_3P (equiv)	Solvent	Reaction time	Ketone (yield)
1	**1a**	1.1	1.2	THF	5 min	**1b**, 99%
2	**1a**	1.1	2.5	THF	<2 min	**1b**, 99%
3	**1a**	1.1	2.5	Et_2O[a]	<2 min	**1b**, 99%
4	**2a**	2.0	5.0	Et_2O	5 min	**2b**, 90%
5	**3a**	2.5	2.5	THF	5 h[b]	**3b**, 94%
6	**4a**	2.5	2.5	THF	3 h	**4b**, 99%
7	**5a**	1.1	2.2	THF	30 min	**5b**, 92%
8	**6a**	1.1	1.2	THF	<2 min	**6b**, 97%

[a] CH_3CN was also efficient.

[b] Substrate and reagents were mixed at 0 °C; stirring was then maintained at rt.

In summary, the conversion of sterically congested and/or conjugate ketoxime groups to ketones can be achieved in excellent yields with Me_3P/PySeSePy. This reagent combination, reported here for the first time, has advantages with regard to Bu_3P/PhSSPh.

Acknowledgements

Thanks are due to the Ministerio de Ciencia y Tecnología for support. The senior author (J.V.) dedicates this work to the late Prof. Barton, whom he met in Gif-sur-Yvette in the fall of 1979.

References and notes

1. For leading references, see: (a) Gawley, R. E. *Org. React.* **1988**, *35*, 1; (b) Maruoka, K.; Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 763; (c) Pinnick, H. W. *Org. React.* **1990**, *38*, 655; (d) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1999; p 1227; (e) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 4076; (f) Barton, D. H. R. *Pure Appl. Chem.* **1968**, *16*, 1.
2. For a review, see: (a) Corsaro, A.; Chiacchio, U.; Pistarà, V. *Synthesis* **2001**, 1903; For some very recent papers, see: (b) Li, D.; Shi, F.; Guo, S.; Deng, Y. *Tetrahedron Lett.* **2004**, *45*, 265 (ionic liquids on silica gel); (c) De, S. K. *Tetrahedron Lett.* **2003**, *44*, 9055 ($SiBr_4$/wet silica gel); (d) Narsaiah, A. V.; Nagaiah, K. *Synthesis* **2003**, 1881 ($SbCl_5$); (e) Imanzadeh, G. H.; Hajipour, A. R.; Mallakpour, S. E. *Synth. Commun.* **2003**, *33*, 735 ($KMnO_4$/alumina); (f) Lijser, H. J. P.; Fardoun, F. H.; Sawyer, J. R.; Quant, M. *Org. Lett.* **2002**, *4*, 2325 (chloranil, hν); (g) Hosseinzadeh, R.; Tajbakhsh, M.; Niaki, M. Y. *Tetrahedron Lett.* **2002**, *43*, 9413 (2,6-dicarboxypyridinium chlorochromate), and references cited therein; (h) Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* **2002**, *43*, 4023 (HIO_3 in CH_2Cl_2); (i) Khazaei, A.; Vaghei, R. G. *Tetrahedron Lett.* **2002**, *43*, 3073 (polymeric N,N-dichloro sulfonamide), and references cited therein; (j) Shirini, F.; Zolfigol, M. A.; Mallakpour, B.; Mallakpour, S. E.; Hajipour, A. R.; Baltork, I. M. *Tetrahedron Lett.* **2002**, *43*, 1555 ($Mg(HSO_4)_2/SiO_2$); (k) Salehi, P.; Khodaei, M. M.; Goodarzi, M. *Synth. Commun.* **2002**, *32*, 1259 (γ-picolinium chlorochromate); (l) Zhou, J.-F.; Tu, S.-J.; Feg, J.-C. *Synth. Commun.* **2002**, *32*, 959 ($HCOOH/SiO_2$/MW).
3. (a) Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2243; (b) Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1984**, 337; (c) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Tetrahedron Lett.* **1984**, *25*, 3707; For related works, see: (d) Lukin, K. A.; Narayanan, B. A. *Tetrahedron* **2002**, *58*, 215; (e) Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1986**, *27*, 4623.
4. For a classical review on this class of compounds, called in general N-sulfenylimines, or sulfenimines, see: Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689.
5. Review on trialkylphosphines: Valentine, D. H.; Hillhouse, J. H. *Synthesis* **2003**, 317.
6. Toshimitsu, A.; Owada, H.; Terao, K.; Uemura, S.; Okano, M. *J. Org. Chem.* **1984**, *49*, 3796, and Ref. 6 cited therein.
7. All the oximes were known compounds, save (*S*)-2-*tert*-butyldimethylsilyloxi-3-pentanone oxime (**5a**), an *E*–*Z* mixture (70:30 ratio in $CDCl_3$): colourless oil; R_f 0.37 (90:10, hexanes/EtOAc); IR (film) 3300–3200, 3150, 1660, 1122 cm^{-1}; HRMS (+FAB): calcd for $[M+H]^+$ $C_{11}H_{26}NO_2Si$ 232.1733, found 232.1734. Isomer *E*: ^1H NMR ($CDCl_3$, 400 MHz): δ 8.34 (br s, 1H), 4.38 (q, $J = 6.4$ Hz, 1H), 2.4–2.73 (m, 2H), 1.28 (d, $J = 6.4$ Hz, 3H), 1.16 (t, $J = 7.4$ Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 164.9, 70.1 25.8, 22.1, 18.1, 17.3, 11.0, −4.8, −4.9. Isomer *Z*: ^1H NMR ($CDCl_3$, 400 MHz): δ 8.74 (br s, 1H), 5.18 (q, $J = 6.4$ Hz, 1H), 2.4–2.3 (m, 2H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.10 (t, $J = 7.4$ Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 166.1, 63.7, 25.8, 22.3, 21.2, 18.1, 10.6, −4.9, −5.2. For the preparation of the starting ketone, see: (a) Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414; (b) Ferreró, M.; Galobardes, M.; Martín, R.; Montes, T.; Romea, P.; Rovira, R.; Urpí, F.; Vilarrasa, J. *Synthesis* **2000**, 1608.
8. Typical procedure for the reduction of ketoximes to ketones with 2,2′-dipyridyl diselenide and trimethylphosphine. To a stirred solution of the oxime (1.0 mmol) and 2,2′-dipyridyl diselenide (1.1 mmol) in THF (5 mL), at rt under nitrogen, was added trimethylphosphine (1.0 M toluene solution, 2 mL, 2.2 mmol). The reaction was monitored by TLC until no oxime remained, and then water (1.0 mL) was added. The resulting solution was stirred at rt for 30 min before removing the solvents under vacuum. *Isolation by Method A*. The resulting crude was purified on silica gel by flash column chromatography (CH_2Cl_2) to provide pure ketone. Further elution with CH_2Cl_2/MeOH, 98:2, afforded 2,2′-dipyridyl diselenide. *Isolation by Method B.* The residue was partitioned between a saturated $NaHCO_3$ aqueous solution and diethyl ether. The aqueous phase was extracted three times with ether. The ethereal phases were combined, dried ($MgSO_4$) and evaporated under vacuum to give the ketone in a pure condition. By bubbling air through the remaining aqueous phase and extracting with an organic solvent, PySeSePy was recovered.
9. On TLC, ketone **1b** was immediately and exclusively noted, that is the imine was quickly hydrolysed on silica gel, as could be expected.
10. Representative procedure for the deoximation of **1a** with substoichiometric amounts of 2,2′-dipyridyl diselenide. To a stirred solution of oxime **1a** (50 mg, 0.21 mmol) and 2,2′-dipyridyl diselenide (20 mg, 0.064 mmol) in THF (1.5 mL), at rt under nitrogen, was added trimethylphosphine (1.0 M toluene solution, 520 μL, 0.52 mmol). The reaction mixture stirred at rt for 30 min. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography (CH_2Cl_2) to give **1b** (47 mg, 100%).
11. On the other hand, the method has the disadvantage that it cannot be applied to highly branched ketoximes, such as camphor oxime, as they gave rise to fragmentation products (nitriles). This is a feature of ketoximes with a quaternary α-carbon atom, since strong activation or dehydration conditions cause fragmentations with formation of tertiary carbenic ions: (a) Suginome, H.; Furukawa, K.; Orito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 917, and references therein; (b) Kirihara, M.; Niimi, K.; Momose, T. *J. Chem. Soc., Chem. Commun.* **1997**, 599. In our case (camphor oxime), fragmentation took place even by adding the reagents at −78 °C. Moreover, other groups that also react with R_3P/RSSR should be previously protected; for instance, in competition experiments we noted that primary alcohols react more rapidly than oximes.