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Catalytic, PMe_3-mediated conversion of secondary nitroalkanes to ketones: a very mild Nef-type process

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The senior author wishes to dedicate this work to Professor Joaquín Plumet (Universidad Complutense) on the occasion of his 60th birthday

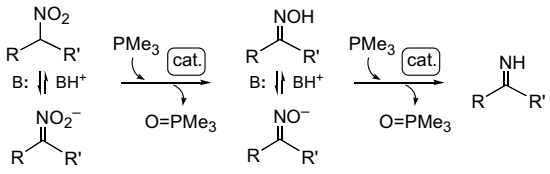
Abstract

Aliphatic secondary nitro compounds are converted to ketones at room temperature, usually in 90–100% yields, by a one-pot reaction with 220–250 mol % of trimethylphosphine (PMe_3) and 50–100 mol % of $^tBuC_6H_4SSC_6H_4{}^tBu$ or PhthN-SePh, or 20 mol % of both additives. Thus, very mild catalytic variants of the reductive Nef-like reactions are disclosed.

Keywords: Nitro compounds; Ketones; Catalysed Nef-like reaction; 4,4′-Bis-*t*-butyldiphenyl disulfide; *N*-(Phenylselenenyl)phthalimide; Trimethylphosphine

Nitronate anions are so easily generated that their reactions with conjugate double bonds (Michael additions), aldehydes (nitro-aldol, or Henry reaction) and other electrophiles (e.g., imines) have been widely used for the preparation of various starting materials.[1] Moreover, the strong electron-withdrawing character of the NO_2 group makes nitroalkenes very suitable substrates for Michael additions and cycloadditions.[2] The resulting nitro compounds can then be converted to amines,[1c] oximes,[3] hydrocarbons[1b,4] and, in the case of primary nitro groups, into nitrile oxides (for 3 + 2 cycloadditions)[5] and nitriles.[3b,6] Many methods, most of them oxidative, are also known for the conversion of nitro to carbonyl compounds (Nef-like reactions),[7] connecting the organic chemistry of the nitrogen compounds with the carbonyl chemistry. We report here a reductive method for the quick conversion of secondary nitroalkanes to ketones that can be performed at room temperature (rt).

The new method relies upon the use of the most reactive trialkylphosphine (namely PMe_3)[8] as the reducing agent and a suitable catalyst, and was inspired by a report of Zard et al.,[9] who treated γ-nitroketones and nitro-steroids with excesses of tributylphosphine (PBu_3) and diphenyl disulfide (PhSSPh) to obtain pyrroles and oxo-steroids, respectively. As in any reductive method,[7] nitro derivatives or their nitronate ions are expected to give the intermediate oximes (the main tautomers of the nitroso compounds) or their anions, which may be then converted to the imines in situ (Scheme 1); during the workup, the imines may be hydrolyzed to ketones (or reduced to amines or transformed to other functional groups).[7,9a,b] After an exhaustive search for reagents and catalysts that could work in an acceptable time and turnover at rt, we have found that PMe_3 and 4,4′-bis-*tert*-butyldiphenyl disulfide



Scheme 1. From nitroalkanes to oximes to imines.

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(^{t}BuC$_6$H$_4$SSC$_6$H$_4{}^t$Bu) or *N*-(phenylselenenyl)phthalimide (PhthN-SePh) are the reagents of choice.[10]

Since the cleavage of oximes to carbonyl compounds is feasible by several methods,[11] our main challenge was to perform the first step under conditions as mild as possible, in such a way that the improved procedure(s) could be applied to polyfunctional substrates (in advanced steps of total syntheses).

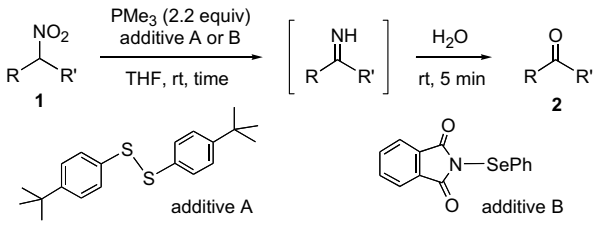
These optimized conditions are shown in Table 1. The reaction is carried out in a commercially available THF solution of PMe_3 (2.20 mL, 2.20 mmol) at rt under N_2 or Ar. The nitro compound (**1a**–**h**, 1 mmol) and 0.5 mmol (50 mol %) of catalyst A (^{t}BuC$_6$H$_4$SSC$_6$H$_4{}^t$Bu)[12,13] or B (PhthN-SePh) are added, without solvent. Although this is enough to achieve excellent yields of **2a**–**h** within a few hours, we have also examined the addition of 1 mmol (100 mol %) of A or B to shorten the reaction times even more; the times shown in Table 1 are for 100 mol % of additive. In practice, trimethylphosphine oxide ($Me_3P{=}O$, identified by ^{1}H and ^{31}P NMR) begins to precipitate within a few minutes from the THF solution. When the reaction via Method A is completed, partition between a nonpolar organic solvent and water leaves **2** and additive A in the organic layer and $Me_3P{=}O$ in the aqueous layer; a simple filtration of the organic layer over silica gel affords pure ketones **2**. In Method B, the products are separated by column chromatography. Yields are almost quantitative with both methods. Scaling up to 5 mmol the reaction of entry 2 (**1b**), quantitative yields of **2b** have been maintained. Various functional groups (see entries 3–8 of Table 1) are stable under these reaction conditions.

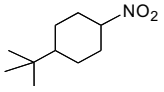
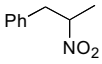
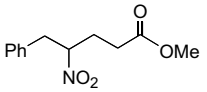
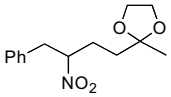
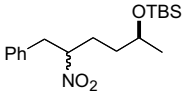
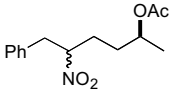
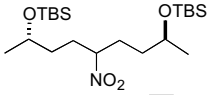
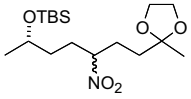
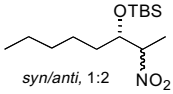
The reactions are slower for the nitro-aldol derivatives **1i** and **1j** (i.e., with nitro groups sterically more crowded and/or electronically surrounded by σ-EWGs, see entries 9 and 10).[14] In these cases, Method A yields a mixture of ketone and *N*-(phenylsulphenyl)ketimine; to obtain the desired ketone, a workup with an aqueous solution of NaH_2PO_4 rather than just water alone is required, besides stirring the final mixture for 1 h. In the light of the results, Method B is more convenient than A for **1i** and **1j**.

Furthermore, these last substrates show a drawback, which may be common to other nitro-aldol reaction products. An inversion of the stereocenter α to the carbonyl group takes place, as determined by chiral HPLC (Chiralpak AD-H). It does not depend on the pH of the buffered solution added to hydrolyse the imines, as it happens either at pH 4, 7, or 10. On the other hand, enantiopure ketones **2i** and **2j**, prepared independently, are configurationally stable under the reaction conditions. Since α-OBn and α-OTBS *N*-(phenylsulfenyl)ketimines (also obtained independently)[14b] do not undergo configuration inversions under the reaction conditions, the racemization must occur at the imine stage. In short, quick imine–enamine equilibria (see Scheme 2) are likely responsible for the epimerization of the α-stereocenters.

As usual for other well-known reactions involving P(III) and P(V) derivatives, the active species from PMe_3 and ArSSAr (Method A) must be the phosphonium salt, ArS–PMe_3^+ ArS^-, and/or $(ArS)_2PMe_3$, depending on the medium polarity and reaction conditions. When PhthN-SePh is employed (Method B), the active species are expected to be PhSe–PMe_3^+ $PhthN^-$ and/or its P-pentavalent species. In practice, we have never detected oximes

Table 1
Conversion of nitro compounds to ketones



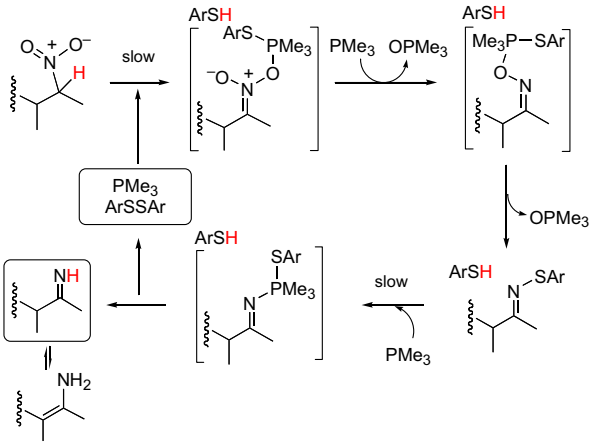
Entry	Substrate		Method A:[a] time, yield (%)	Method B:[b] time (h), yield (%)
1		**1a**	15 min, 97	2, 96
2		**1b**	15 min, 98	2, 98
3		**1c**	30 min, 95	3, 95
4		**1d**	30 min, 94	3, 96
5		**1e**	30 min, 98	3, 98
6		**1f**	30 min, 95	3, 91
7		**1g**	30 min, 96	3, 94
8		**1h**	30 min, 94	3, 96
9	 *syn/anti*, 1:2	**1i**	12 h, 84[c]	12, 90
10		**1j**	12 h, 70[c,d]	12, 76[d]

[a] Method A: 1.0 mmol of **1** and 1.0 mmol of additive A are added to a 1.0 M PMe_3 solution in THF (2.2 mL) at 0 °C under N_2 or Ar; the bath is removed and stirring is maintained at rt for the time indicated.

[b] Method B: 1.0 mmol of additive B is used instead of A.

[c] In these cases, a special workup is required (see the main text).

[d] Disappearance of **1j** is complete, but a fragmentation by-product is always formed in ca. 20% yields.[14a]

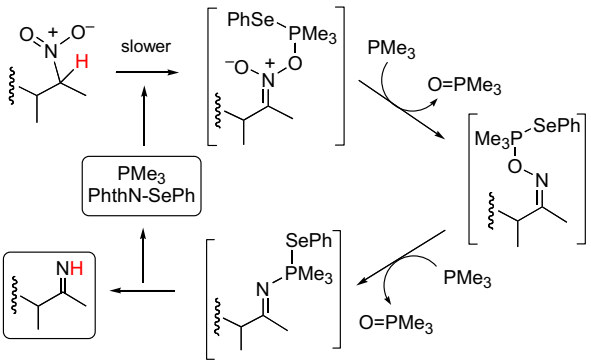


Scheme 2. Proposed mechanism for the reaction of nitro compounds with PMe_3/ArSSAr, where Ar = 4-^{t}BuC$_6$H$_4$ (Method A).

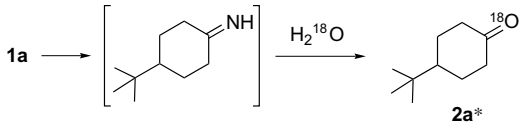
as intermediates by NMR (even working with substoichiometric amounts of PMe_3). It may mean that oximes disappear as soon as they are formed—from independent experiments we know that oximes react more rapidly than nitro compounds—and/or that oxime derivatives, more reactive than oximes themselves, are directly involved in the next step. A phosphonium oximate is drawn in the mechanism suggested in Scheme 2 (Method A) as well as in Scheme 3 (Method B), for the sake of simplification.

With the additive B, we have never detected or trapped selenenylimines (RR′C=N–SePh) as intermediates under the reaction conditions of Scheme 3 or any others, by contrast to what happens with analogous S derivatives.[9,14b] Thus, in Scheme 3 we have depicted that the cleavage of the oximate takes place by attack of an external molecule of PMe_3 to SePh, loss of O=PMe_3 and trapping of PhSe–PMe_3^+ by the N atom. The role of phthalimide anion as a base (to give phthalimide molecule in the first step) and that of the resulting phthalimide molecule and/or the starting nitro compound as proton sources have not been indicated in Scheme 4, to simplify the figure.

It is worth noting that, if catalyst A and B are used together, the process takes place at a higher rate, so that



Scheme 3. Proposed mechanism for the reaction of nitro compounds with PMe_3/PhthN-SePh (Method B). Proton exchanges involving PhthN$^-$/PhthNH are not drawn (see the main text).



Scheme 4. Hydrolysis of the ketimine with O-labeled water.

the amounts of A and B can be reduced. For example, we have examined the combination of 0.2 equiv of A, 0.2 equiv of B, and 2.5 equiv of PMe_3 on **1a**–**d**; it is much more efficient than 0.4 equiv of either A or B with the same amount of PMe_3.[15] An explanation for this intriguing fact is that catalyst A is preferable for the first step (as the nitro-to-oximate reduction is 'slower' with additive B, Scheme 3, than the first 'slow' step with additive A, Scheme 2), whereas PhthN-SePh show no tendency or a much lower tendency to give selenenylimines, as mentioned above; thus, both types of additives co-operate, increasing the rates of the slowest steps or bypassing them.

As shown in Scheme 4, when a sample of the intermediate imine from **1a** was quenched with 120 mol % of ^{18}O-labeled water (95% of $H_2{}^{18}O$) in a NMR tube, the corresponding ketone (^{18}O-labeled 4-*tert*-butylcyclohexanone, **2a***) was obtained. The highfield isotopic shift of the carbonyl carbon atom (^{13}C NMR) was exactly 50 ppb, as expected.[16] A MS of the ketone indicated the practically complete incorporation of the label. Similarly, compound **1b** gave **2b*** ($\Delta\delta = 0.050$ ppm).

In conclusion, we have developed a very smooth catalytic procedure for the nitro-to-ketone conversion. Its scope and limitations have been investigated. The procedure is very useful for the preparation of ^{18}O-labeled ketones. Owing to the mildness of the protocol, we hope to show or see soon its application to advanced steps of total syntheses of complex molecules.

Acknowledgments

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Supplementary data

Experimental procedures and characterization data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.110.

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13. We recommend the use of ^{t}BuC_6H_4SH/^{t}Bu$C_6H_4SSC_6$ $H_4{}^t$Bu to avoid the stench of benzenethiol (thiophenol, PhSH) and other relatively volatile ArSH. The relative odors of thiols have been evaluated: (a) Nishide, K.; Ohsugi, S.; Miyamoto, T.; Kumar, K.; Node, M. *Monatsh. Chem.* **2004**, *135*, 189; for bis-TMS derivatives, see: (b) Patra, P. K.; Shanmugasundaram, K.; Matoba, M.; Nishide, K.; Kajimoto, T.; Node, M. *Synthesis* **2005**, 447.
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