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Synthesis of Functionalized Nitroalkanes by Oxidation of Oximes with Urea-Hydrogen Peroxide Complex and Trifluoroacetic Anhydride

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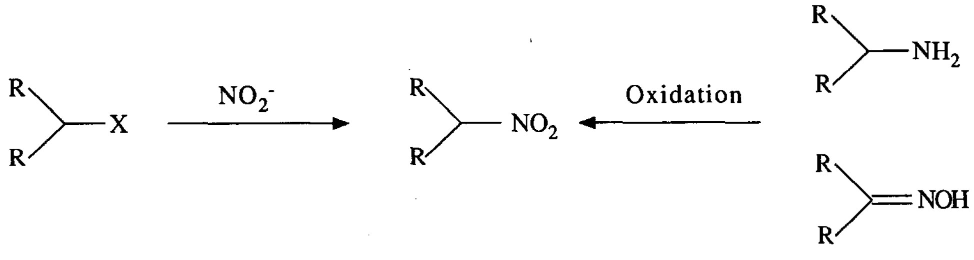
Abstract: Reaction of urea-hydrogen peroxide complex with trifluoroacetic anhydride in acetonitrile at 0°C affords in a safe and easy fashion anhydrous solutions of peroxytrifluoroacetic acid. These can be used to oxidize aldoximes to nitroalkanes in good yields. Ketoximes fail to react in these conditions and are cleaved to the parent carbonyl compounds.

The remarkable synthetic properties of the nitro group have ensured long standing studies of their utilization in organic synthesis[1] . The interest has been heightened by the discovery of new methods to turn the nitro group into a wide range of other useful functionalities, including its direct replacement by hydrogen atoms[2] .

However poor attention has been paid to the inverse operation, i.e. the search for new protocols to convert other groups into the nitro one. The existing systems consist mostly in : (i) the displacement of good nucleofuges by nitrite anion[1b], and (ii) oxidation of nitrogeneous derivatives (amines, oximes etc.)[3] .



The former method is undoubtely the most popular, but the bidentate character of the nitrite anion often restrict its usefulness, indeed modest to large amounts of alkyl nitrites are always produced in this process. These become practically the sole products if large substituents are present in the proximity of the leaving group[4] .

Nitrite scavengers may work out possible separation problems but do not affect product distribution[5] . Silver nitrite in ether has been revealed of some benefit on several occasions[6] .

The oxidation of nitrogen derivatives although less explored seems to offer a well grounded alternative to the above cited methods. Amines can usually be converted to nitro compounds by strong oxidizing agents as peracids[7] or ozone[8] . The use of dimethyldioxirane represent a milder option to achieve this transformation[9] . Oximes are oxidized using either sodium perborate in glacial acetic acid[10] or peroxitrifluoroacetic acid in acetonitrile[11] and the latter procedure has been successfully employed by Mosher[12] for the synthesis of the chiral nitrocompound **2**. Since oximes are readily obtained from the corresponding aldehydes, these can be regarded as ideal substrates for the direct preparation of optically active nitroalkanes.

Unfortunately the synthesis of peroxitrifluoroacetic acid involves the use of the very hazardous 90% hyrogen peroxide, by now no longer commercially avalaible. Some hydrogen bonded adducts of hydrogen peroxide with DABCO[13] and urea have already been used as an alternative to anhydrous H_2O_2. The urea-hydrogen peroxide complex (UHP) alone or in combination with carboxylic anhydrides is capable to oxidize a good many organic substrates[14] .

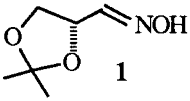
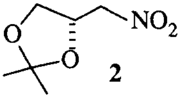
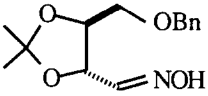
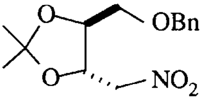
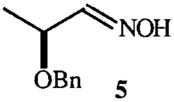
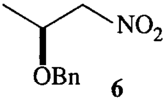
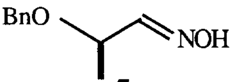
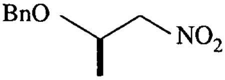
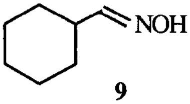
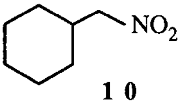
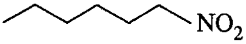
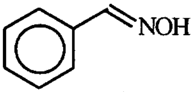
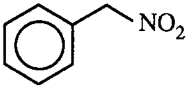
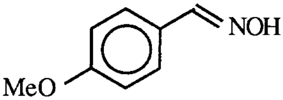
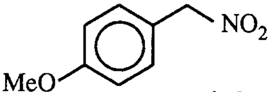
We found that solutions of peroxitrifluoroacetic acid can be suitably obtained treating UHP with trifluoroacetic anhydride (TFAA) in acetonitrile at 0°C. These can be used to convert aldoximes into the corresponding nitroalkanes in good yields. Oximes bearing α stereogenic centers afford the parent nitrocompound with complete retention of the original configuration[15] (see table, entries 1-4) .

A typical experimental procedure is as follows: (CAUTION : special care must be taken when using peroxide derivatives.) To a stirred suspension of UHP (60m.mol, 5.8g) in CH_3CN (30ml), TFAA (50m.mol,10.5g) dissolved in CH_3CN (10ml) was added dropwise at 0°C and stirring was continued at this temperature for 30min. This solution was then added dropwise to a mechanically stirred mixture of oxime (5m.mol) and Na_2HPO_4 (0.138mol, 20g.) in CH_3CN (50ml) at 0°C. After stirring at this temperature for the appropriate time (see table), most of the solvent was removed under reduced pressure and the residue was dissolved in $NaHCO_3$ sol satd. and extracted with ether. The ethereal solution was washed with 5% Na_2SO_3 (starch-iodide test negative) and dried over $MgSO_4$. The crude material, after evaporation of the solvent, was purified by flash chromatography.

Ketoximes are not converted into nitro derivatives in our conditions, indeed they are uncleanly cleaved to their parent carbonyl compounds[16]. It is worth noting that the success of this reaction strongly depends from the electronic density on the nitrogen atom. Benzaldoximes bearing electon withdrawing groups in 4 position (e.g. 4-cyano benzaldoxime) are completely inert toward oxidation. The oxime derived from benzaldehyde requires a larger excess of reagent (20 eq.) to be completely converted and finally 4-methoxy benzaldehyde oxime reacts according to the standard procedure.

In conclusion we feel that from now on a consistent number of other functionalized nitroalkanes will be readily and safely available by simple oxidation of the corresponding oximes with UHP-TFAA system.

Acknowledgements: Financial assistance form MURST-Italy is gratefully acknowledged.

ENTRY	OXIME	NITROCOMPOUND	REACTION TIME h	YIELD [a] %
1	 **1**	 **2**	4	75
2	 **3**	 **4**	4	80
3	 **5**	 **6**	2	78
4	 **7**	 **8**	2	68
5	 **9**	 **10**	3	70
6	 **11**	 **12**	2	73
7	 **13**	 **14**	7	60[b]
8	 **15**	 **16**	5	65

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a) Yields of pure,isolated products.

b) 20 equivalents of oxidant are required.

References and Notes

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14. Cooper, M.S.; Heaney, H.; Newbold, A.J.; Sanderson, W.R. *Synlett* **1990**, 533.
15. Some characterization data for new compounds follows:
    2: oil, $[\alpha]_D^{20}$: -16.5° (c1.5, $CHCl_3$). Lit.[11] $[\alpha]_D^{20}$: -17° (c1.13, $CHCl_3$) IR (cm^{-1},neat): 1550 (NO_2). ^{1}H-NMR (300MHz,$CDCl_3$) δ(ppm) : 1.37 (s,3H); 1.43 (s,3H); 3.86 (dd,1H,J=4.5, 9.0Hz); 4.18 (dd,1H,J=6.3, 9.0Hz); 4.42 dd,1H,J=5.7, 2.8Hz); 4.51 (dd,1H ,J= 7.0,12.8Hz); 4.65-4.80 (m,1H). MS m/e 146, 116, 86, 43.
    4: oil. $[\alpha]_D^{20}$: +4.51° (c6.2 $CHCl_3$) IR (cm^{-1}, neat) 1550 (NO_2); ^{1}H-NMR (300MHz, $CDCl_3$) δ(ppm) 1.41 (s,6H); 3.56 (dd, 1H, J= 7.0, 9.5Hz); 3.75 (dd, 1H, J=4.7,9.5Hz); 3.94-4.02 (m,1H); 4.46 - 4.65 (m,3H); 4.55 (s,2H); 7.25- 7.40 (m,5H). MS m/e: 266, 179, 107, 91.
    6: Bartoli,G.; Marcantoni, E.; Petrini, M. *J.Chem.Soc.Chem.Comm.* **1991**, 793.
    8: oil; $[\alpha]_D^{20}$: +12.9° (c3.35 $CHCl_3$); IR (cm^{-1}, neat): 1550 (NO_2); ^{1}H-NMR(300MHz $CDCl_3$) δ(ppm) 1.05 (d,3H, J=6.7Hz); 2.58- 2.72 (m,1H); 3.35 (dd,1H, J=7.0, 9.5Hz); 3.49 (dd, 1H, J= 4.6, 9.5 Hz); 4.27 (dd, 1H, J= 7.7, 11.9Hz); 4.49-4.52 (m, 2H); 4.57 (dd, 1H, J=5.9,11.9Hz); 7.25-7.40 (m,5H). MS m/e: 161,107, 91, 79.
16. *N,N*-Dialkylhydrazones are cleaved in a similar fashion using magnesium monoperoxyphtalate in methanol: Enders,D.; Plant,A. *Synlett* **1990**, 725.

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