A New Method for the Preparation of α-Nitroacetophenones

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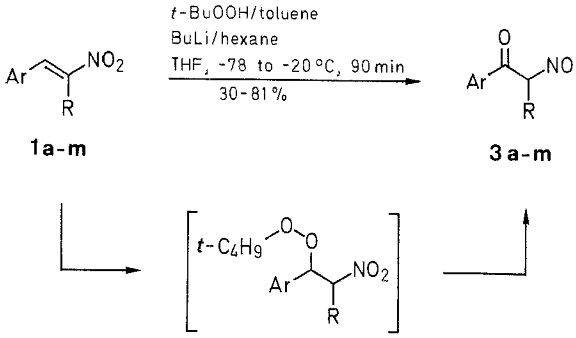
Treatment of readily available substituted β-nitrostyrenes with *tert*-butyl hydroperoxide and butyllithium gives synthetically useful α-nitroacetophenones in good yield.

Numerous methods for the preparation of α-nitroketones have been developed.[1-8] The most generally applicable and useful route is based on the acylation of nitroalkanes with *N*-acylimidazoles.[3] This procedure requires the use of the relatively expensive reagent, 1,1'-carbonyldiimidazole, and also involves the preparation of potentially explosive nitronate salts.

We now report a new method for the preparation of aryl nitromethyl (and 1-nitroalkyl) ketones by the oxidation of readily available β-nitrostyrenes[9] using lithium *tert*-butyl hydroperoxide, which has recently been introduced for the epoxidation of unsaturated esters and sulphones.[10] The oxidation proceeds satisfactorily for a wide variety of nitrostyrenes. Our initial experiments were conducted using 1.1 molecular equivalents of butyllithium and 1.5 molecular equivalents of *tert*-butyl hydroperoxide (Method A), and gave satisfactory yields with substrates **1a–h**. However, using these conditions, only poor yields of α-nitroketones were obtained from nitrostyrenes bearing electron-donating *ortho*-substituents (**1i** and **1l**), and strongly electron-donating substituents at other positions (**1j** and **1k**). This problem can be overcome for substrates **1i**, **1j**, and **1k** by increasing the amount of butyllithium to 2.5 molecular equivalents (Method B). So far, our efforts to effect efficient oxidation of *o*-methoxy-β-nitrostyrene (**1l**) have been unsuccessful. It should be pointed out that this method is effective for the synthesis of those nitroketones (**3e** and **3h**) which cannot be prepared by the *N*-acylimidazole method.[3]

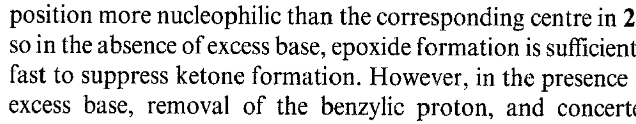
In most cases, monitoring of the reaction by TLC indicates the formation of a compound which is more mobile than the starting nitroalkene, before formation of the α-nitroketone can be detected. In the oxidation of β-nitrostyrene (**1a**), we have been able to isolate this intermediate by quenching the reaction mixture at −50 °C with saturated aqueous ammonium chloride, and identify it as the peroxide **2a**.[11] It is therefore reasonable to suggest that the oxidation reaction proceeds by addition of *tert*-butyl hydroperoxide anion to the nitroalkene, followed by base-induced fragmentation to yield the nitroketone. The role of the additional butyllithium which is needed in Method B is, presumably, to deprotonate at the benzylic position, thus promoting oxidation. In support of this hypothesis, we have not observed an intermediate peroxide in the oxidation of *p*-nitro-β-nitrostyrene (**1e**). In this case, lithium *tert*-butoxide produced by the reaction can abstract the acidic benzylic proton particularly readily.



1a-m **3a-m** **2a-m**

1, 2, 3	Ar	R	**1, 2, 3**	Ar	R
a	C_6H_5	H	**h**	$2\text{-}O_2NC_6H_4$	H
b	$4\text{-}CH_3OC_6H_4$	H	**i**	$2\text{-}CH_3C_6H_4$	H
c	$4\text{-}CH_3C_6H_4$	H	**j**	$4\text{-}(CH_3)_2NC_6H_4$	H
d	$4\text{-}ClC_6H_4$	H	**k**	$3,4\text{-}(CH_3O)_2C_6H_3$	H
e	$4\text{-}O_2NC_6H_4$	H	**l**	$2\text{-}CH_3OC_6H_4$	H
f	$3,4\text{-}(OCH_2O)C_6H_3$	H	**m**	C_6H_5	CH_3
g	$3\text{-}O_2NC_6H_4$	H			

Oxidation of β-methyl-β-nitrostyrene (**1m**) using Method A led not to the expected nitroketone **3m** but to 1-methyl-1-nitro-2-phenyloxirane (**4m**) in 95% yield. This epoxide has been prepared previously, although less efficiently.[12,13] However, use of Method B allowed the preparation of 2-nitro-1-phenyl-1-propanone (α-nitropropiophenone, **3m**) in 66% yield. In order to rationalise these results, we need to consider the respective fates of the two peroxides **2a** and **2m**. The greater substitution at the centre α to the nitro group in **2m** renders an anion at that position more nucleophilic than the corresponding centre in **2a**, so in the absence of excess base, epoxide formation is sufficiently fast to suppress ketone formation. However, in the presence of excess base, removal of the benzylic proton, and concerted formation of the carbonyl group, can compete effectively with ring closure.



1m **4m**

Table. Oxidation of Substituted Nitrostyrenes **1** to α-Nitroacetophenones **3**

Product	Method	Yield[a] (%)	mp (°C)[b] or bp	Lit. mp (°C) or Molecular Formula[f]	MS (70 eV)[e] *m/z*	IR (KBr)[c] $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR[d] (DMSO-d_6), δ α-C$\underline{H}_n$NO$_2$
3a	A	78	103–104	104–106[3]	165; 105	1700	6.55
3b	A	77	159–160	156–161[5]	195; 135	1679	6.47
3c	A	72	151–152	146.5–149[5]	179; 119	1694	6.50
3d	A	71	170–171	164.5–166[3]	199; 139 (^{35}Cl)	1696	6.53
3e	A	81	150–151	$C_8H_6N_2O_5$[l] (210.1)	210; 150	1706	6.62
3f	A	71	167–169	169–170[5]	209; 149	1680	6.44
3g	A	62	94–95	93–94[3]	210; 150	1713	6.66
3h	A	64	137–138	$C_8H_6N_2O_5$[l] (210.1)	210; 150	1721	6.33
3i	B	64	93–94	$C_9H_9NO_3$ (179.2)	179; 119	1700	6.45
3j	B	70	170–171	$C_{10}H_{12}N_2O_3$[g] (208.2)	208; 148	1671	5.79[h]
3k	B	58	145–146	$C_{10}H_{11}NO_5$[l] (225.2)	225; 165	1685	6.48
3l	B	30	119–120	$C_9H_9NO_4$[l] (195.2)	195; 135	1678	6.12
3m	B	66	120/0.8 mbar[i]	124/2 mbar[j,2]	179; 105	1696[k]	6.22

[a] Yield of homogeneous, purified product.
[b] Uncorrected, measured with a Kofler hot-stage apparatus.
[c] Recorded on a Nicolet FT 20SXB Infrared spectrophotometer.
[d] Measured on a Bruker WM-300 spectrometer.
[e] Obtained on an AEI MS902.
[f] Satisfactory microanalyses obtained: C ±0.21, H ±0.22, N ±0.25.
[g] Microanalysis low on C, H, and N, suggesting presence of tightly bound water.
[h] $CDCl_3$ was used.
[i] Kugelrohr distillation oven temperature, pressure.
[j] Boiling point, pressure.
[k] Capillary film.
[l] Secondary amine salts of these compounds have been reported without data for the nitroketones themselves.[1]

α-Nitroacetophenones (3a–l) and 2-Nitro-1-phenyl-1-propanone (3m); General Procedures:

Method A (for α-Nitroketones **3a–h**): A solution of *tert*-butyl hydroperoxide (3.4 molar in toluene; 1.32 mL; 4.5 mmol) in THF (distilled from potassium benzophenone ketyl; 20 mL) is cooled to −78 °C and stirred in a nitrogen atmosphere. Butyllithium (1.0 M in hexanes; 3.30 mL; 3.3 mmol) is added dropwise over 10 min. A solution of the β-nitrostyrene (**1a–h**; 3 mmol) in THF (10 mL) is then added dropwise. The mixture is allowed to warm to −20 °C and stirring is continued for 90 min at this temperature. The reaction is quenched by the addition of 1 normal HCl (10 mL). EtOAc (30 mL) is then added and the organic phase is separated, washed with saturated NaCl solution and dried ($MgSO_4$). The solvent is removed on the rotary evaporator and the crude product recrystallized from EtOH (10 mL).

Method B (for α-Nitroketones **3i–m**): Method A is altered by increasing the amount of butyllithium used initially (1.0 M in hexanes; 7.50 mL, 7.5 mmol), and increasing the amount of 1 normal HCl (25 mL) in the quench.

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