Tetrahedron Vol. 46, No. 21, pp. 7531-7538, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

NEW AND EFFICIENT SYNTHESIS OF ω-NITROALCOHOLS AND SPIROKETALS BY CHEMIO- AND REGIOSELECTIVE REDUCTIVE CLEAVAGE OF 2-NITROCYCLOALKANONES.

Roberto BALLINI,*[a] Marino PETRINI,[a] and Goffredo ROSINI*[b]

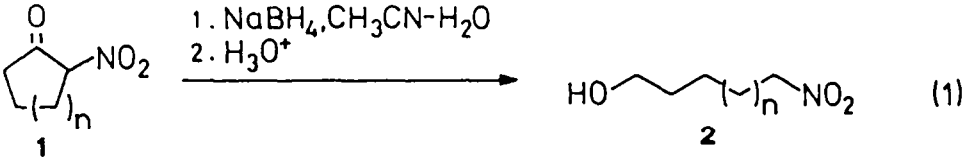
a.- Dipartimento di Scienze Chimiche dell'Università,
Via S. Agostino n. 1 - I 62032 Camerino - Italy.
b.- Dipartimemto di Chimica Organica "A. Mangini",
Viale Risorgimento n. 4 - I 40136 Bologna - Italy.

(*Received in USA* 30 *April* 1990)

Abstract: ω-Nitroalcohols have been prepared by a new and efficient chemio- and regioselective reductive cleavage performed on 2-nitrocycloketones with sodium borohydride in acetonitrile / water. This reaction opens a more practical and convenient route to the synthesis of spiroketals.

The preparation of 2-nitrocycloalkanones and their utility in organic synthesis has been comprehensively reviewed[1]. A peculiar reactivity of these compounds is the ring cleavage of the C(1)-C(2) bond by action of external nucleophiles under mild conditions. This reverse Claisen type condensation affords open-chain α,ω-disubstituted compounds, while intramolecular nucleophilic attack to the 2-nitro carbonyl residue has been extensively used by Hesse and his coworkers in their elegant " zip-reaction " to effect cycloenlargements.[2]

Although a new method for the synthesis of dicarboxylic acids or ketoacids by regioselective oxidative cleavage of 2-nitrocycloketones with hydrogen peroxide has been reported,[3] a well defined method for the reductive cleavage of 2-nitrocycloketones was still lacking. Here is reported a new and efficient procedure to carry on this reaction both mildly and regiospecifically. We discovered that the reduction of compounds 1 with a large excess of sodium borohydride (five equivalents) affords the open-chain ω-nitroalcohols 2 (eq. 1) when the reactions are performed at room temperature in acetonitrile / water



1 2 (1)

(3:2). Good to high yields were obtained with a number of differently sized rings (Table 1). A variety of solvents were tested (methanol, ethanol, THF / water, dioxane / water) but the presence of water was, apparently, essential for the ring-cleavage:in particular the mixture acetonitrile / water turned out to be the most effective.

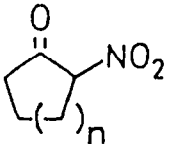
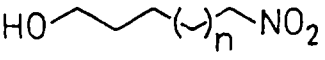
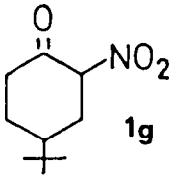
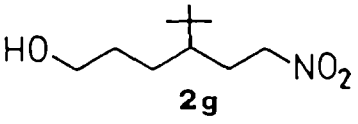
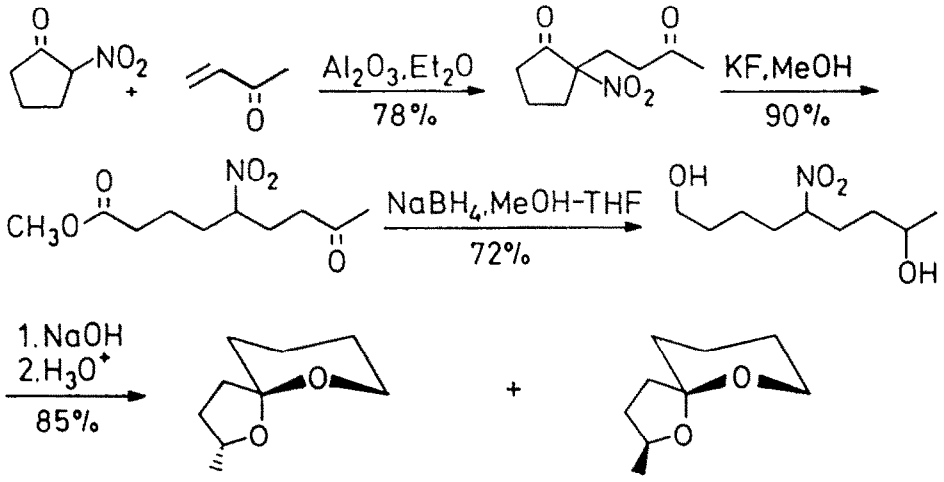
2-Nitrocycloalkanone 1	ω-Nitroalcohol 2	Yield %
		
a: n = 1		60
b: n = 2		82
c: n = 3		70
d: n = 4		50
e: n = 8		85
f: n = 11		76
 1g	 2g	75

Table 1 - Synthesis of ω-Nitroalcohols by Reductive Cleavage of 2-Nitrocycloalkanones.

ω-Nitroalcohols are an important class of functionalized aliphatic nitro compounds having two functional groups in two different oxidation states and they are susceptible to further transformations, owing to the versatility of the nitro and hydroxy groups. However, the potential and usefulness of our reaction can be better understood through its application to the synthesis of spiroketals.[5]

In the course of a program directed towards the total synthesis of spiroketalic pheromones[6] currently under way in our laboratories, we devised [7] a new procedure to synthesize the 1,6-dioxaspiro[4.5]decane components of Paravespula vulgaris.[8] Our strategy to prepare (E)- and (Z)-2-methyl-1,6-dioxaspiro[4.5]decanes reduced the building of spi-

roketal rings to (a) 1:4 addition of 2-nitrocycloketone to an α,β-unsaturated ketone or aldehyde; (b) nucleophilic regiospecific ring cleavage of the obtained 1,5-dicarbonyl derivative, (c) reduction of the corresponding diols and, finally, (d) nitro to carbonyl group interconversion by Nef reaction with simultaneous acid-catalyzed spiroketalization (Scheme 1). In spite of the simplicity of the single reactions involved in this sequence, the

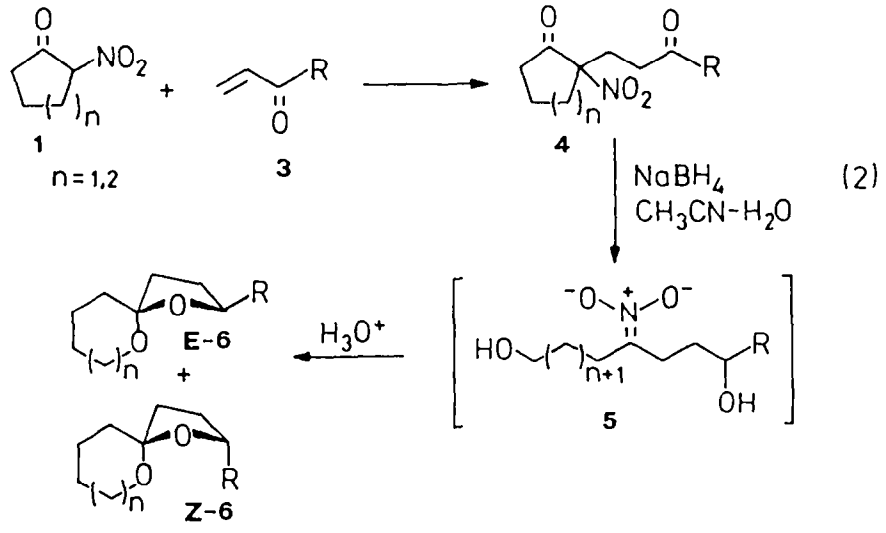


Scheme 1 - Synthesis of (E)- and (Z)-2-Methyl-1,6-dioxaspiro[4.5]decanes.

satisfactory yields of each step and the easy availability of the starting materials and reactants, there is still a drawback in our procedure, in that the reaction sequence is quite long, not being sufficiently tailored to the target of the synthesis.

We found that cyclic nitrodicarbonyl derivatives 4 , obtained by 1:4 addition of 2-nitrocycloketones to α,β-unsaturated carbonyl compounds, were directly converted into spiroketals 6 by regiospecific reductive cleavage with sodium borohydride in acetonitrile/water (3:2) at room temperature (eq. 2). The tandem reductive ring cleavage and spiroketalization proceeded, very likely, via the dihydroxynitronate 5 that, by acidification, converts into a carbonyl derivative which spontaneously cyclizes to the spiroketal 6. By this method spiro[4.5] and spiro[4.6]ketal systems (pure isolated products) were obtained in good yields (Table 2) starting from 2-nitrocyclopentanone and 2-nitrocyclohexanone. The sequence leading to the execution of the present strategy to prepare spiroketals proceeds with an economy of steps and is more practical and efficient with respect to the original one.

We believe that the chemio- and regioselective reductive cleavage of 2-nitrocycloketones is another useful reaction that further increases a rich arsenal of methodologies for a convenient utilization of functionalized nitroalkanes in organic synthesis.



Compound **4**	Spiroketals **6**	Yield (%)
a	E/Z = 1.5	65
b	E/Z = 1.5	70
c	E/Z = 1.5	75
d		60

Table 2 - Synthesis of Spiroketals by Reductive Cleavage of Compounds **4a-d.**

EXPERIMENTAL.

All the reactions were monitored by gas chromatographic analyses, performed on a Carlo Erba Fractovap 4160 using a capillary column of duran glass (0.32mm x 25 mt), stationary phase OV1 (film thickness 0.4-0.45 nm). All ^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$, at 300 MHz on a Varian VXR 300. Chemical shifts are expressed in ppm downfield from tetramethylsilane. Mass spectra were determined on a Hewlett-Packard GC/MS 5988A. Melting points and boiling points are uncorrected. Elementary analyses were performed using a C, H, N Analyzer Model 185 from Hewlett-Packard. 2-Nitrocyclopentanone (1a), 2-nitrocycloheptanone (1c), 2-nitrocyclooctanone (1d), 2-nitrocyclopentadecanone (1f), 2-nitro-4-tert-butylcyclohexanone (1g), were obtained by nitration of the enol acetates of the corresponding cycloalkanones by standard methods.[11-13] 2-Nitrocyclohexanone (1b) and 2-nitrocyclododecanone (1e) were purchased from Aldrich Chimica. Compounds 4a-d were prepared as previously reported.[9,15,16]

Preparation of ω-Nitroalcohols (2) by Reductive Cleavage of 2-Nitrocycloalkanones (1) with Sodium Borohydride. General Procedure. Sodium borohydride (1.9 g, 0.05 mol) was added during 2 hr to a cooled (0°C) solution of acetonitrile/water (60 ml, 3:2) containing 2-nitrocycloalkanone 1 (0.01 mol). Stirring was continued for 2 hr and the solution was then acidified with 2N hydrochloric acid. The solution was extracted with diethylether (4 x 40 ml) and the organic layer was dried with sodium sulfate. After evaporation the crude product was purified by column chromatography using ethyl acetate-cyclohexane (1:1) as eluent.

5-Nitropentan-1-ol (2a). Yield 60%; $bp_{0.05mmHg}$ 195°C (K); IR (film) 3330(OH), 1545 $cm^{-1}(NO_2)$; ^{1}H NMR δ 1.4-2.1(m, 6H), 3.66 (t,2H, J=6 Hz), 4.38(t, 2H, J=7 Hz). Found: C, 71.23; H, 4.41; N, 5.48; $C_5H_{11}O_3N$ requires C, 71.14; H, 4.37; N, 5.53.

6-Nitrohexan-1-ol (2b). Yield 82%; $bp_{0.8mmHg}$ 200°C (K); IR (film) 3360 (OH), 1550 cm^{-1} (NO_2);^{1}H NMR δ 1.2-2.05 (m, 8H), 3.65(t, 2H, J=6.2Hz), 4.4(t,2H, J=7.3 Hz). Found: C, 49.13; H,8.93; N, 9.58; $C_6H_{13}O_3N$ requires C, 48.96; H, 8.90; N, 9.52.

7-Nitroheptan-1-ol (2c). Yield 70%, mp 35-36°C; IR(KBr) 3370(OH), 1550 $cm^{-1}(NO_2)$; ^{1}H NMR δ 1.3-1.42(m, 8H), 1.51-1.63(m, 2H), 1.93-2.08(m, 2H), 3.63(t, 2H, J=6.4Hz), 4.37(t, 2H, J=7.1Hz).Found: C, 52.02; H, 9.25; N, 8.75; $C_7H_{15}O_3N$ requires C, 52.15; H, 9.38; N, 8.75.

8-Nitrooctan-1-ol (2d). Yield 50%; $bp_{0.03mmHg}$ 190°C (K); IR (film) 3370(OH), 1550 $cm^{-1}(NO_2)$;^{1}H NMR δ 1.3-1.42(m, 8H), 1.51-1.63(m,2H),1.93-2.08(m, 2H), 3.63(t, 2H, J=6.4Hz), 4.37(t, 2H, J=7.1Hz). Found: C, 54.87; H, 9.82; N, 7.85; $C_8H_{17}O_3N$ requires C,54.83; H, 9.78; N, 7.99.

12-Nitrododecan-1-ol (2e). Yield 85%; mp 43-45°C; IR(KBr) 3360(OH), 1560 $cm^{-1}(NO_2)$; ^1H NMR δ 1.2-2.05(m,20H), 3.63(t, 2H, J=6.3Hz), 4.38(t, 2H,J=7.11Hz). Found: C, 62.75; H, 10.87; N, 6.15; $C_{12}H_{25}O_3N$ requires C, 62.60; H, 10.94; N, 6.08.

15-Nitropentadecan-1-ol (2f). Yield 76%; mp 61-63°C; IR(KBr) 3350(OH), 1560 $cm^{-1}(NO_2)$; ^1H NMR δ 1.22-1.42(m, 22H), 1.5-1.63(m,2H), 1.95-2.08(m, 2H), 3.63(t, 2H, J=6.7Hz), 4.38(t, 2H,J=6.9Hz). Found: C, 65.75; H, 11.37; N, 5.06; $C_{15}H_{31}O_3N$ requires C, 65.89; H, 11.43; N, 5.12.

6-Nitro-4-tert-butylcyclohexan-1-ol (2g). Yield 75%; mp 98-100°C; IR (KBr) 3225(OH), 1545 $cm^{-1}(NO_2)$; ^1H NMR δ 0.89(s, 9H), 0.9-2.4(m, 7H), 4.05-4.12(m,1H), 4.29-4.38(m, 1H).Found: C, 58.93; H,10.35; N, 6.79; $C_{10}H_{21}O_3N$ requires C, 59.08; H, 10.41; N, 6.89.

Synthesis of Spiroketals (6) from Compounds 4. General Procedure.

A 100 ml flask equipped with a reflux condenser and a magnetic stirrer was charged with **4** (5mmol) dissolved in 300 ml of acetonitrile/water (3:2). The solution was ice-bath cooled by ice-bath and sodium borohydride (0.94g, 25 mmol) added in one portion. Stirring was continued at 0°C for 10 min and then the cooling bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was subsequently cooled again to 0° , quickly acidified with 2N hydrochloric acid and extracted with diethylether (4x30 ml). The organic phase was dried with magnesium sulfate, and the solvent removed by distillation, affording the crude product which was finally purified by distillation.

2-Methyl-1,6-dioxaspiro[4.5]decane (6a). Yield 65 % (E/Z=3:2); bp_{75mmHg}88°C (lit[7] bp_{75mmHg}120°C in a K apparatus); analytical data are in agreement with those previously reported[7].

2-Ethyl-1,6-dioxaspiro[4.5]decane (6b). Yield 70 % (E/Z=3:2); bp_{70mmHg}140°C (K); ^1H NMR δ 0.89(t, 3H, J=7.3Hz, E isomer), 0.92(t, 3H, J=7.3Hz, Z isomer), 1.34-2.12(m, 12H), 3.44-3.61(m, 1H), 3.77-4.03(m, 2H); ^{13}C NMR δ 10.08, 10.49, 20.28, 20.35, 25.29, 25.38, 28.44, 28.98, 29.50, 30.53, 34.01, 37.44, 38.59, 61.43, 61.50, 79.25, 82.18, 105.25, 105.48; MS(m/e): 170(M+), 141, 123, 115, 112, 97, 69, 55, 41. Found: C, 70.45; H, 10.58; $C_{10}H_{18}O_2$ requires C, 70.54; H, 10.66.

2-Ethyl-1,6-dioxaspiro[4.6]undecane (6c). Yield 75 % (E/Z=3:2); bp $_{75mmHg}$135°C (K); ^1H NMR δ 0.86(t, 3H, J=7.5Hz, E isomer), 0.88(t, 3H, J=7.5Hz, Z isomer), 1.32-2.10(m, 14H), 3.42-3.58(m, 1H), 3.67-3.80(m, 1H), 3.89-4.00(m, 1H); ^{13}C NMR δ 9.85, 10.25, 23.30, 23.40, 28.22, 29.57, 29.74, 30.27, 30.45, 30.66, 30.87, 38.19, 38.82, 39.00, 39.04, 61,96, 62.54, 78.97, 81.29, 109.97, 110.42; MS(m/e) 184(M+), 155, 125, 115, 97, 85, 55, 41. Found: C, 71.63; H, 10.87; $C_{11}H_{20}O_2$ requires C, 71.69; H, 10.94.

1,6-Dioxaspiro[4.6]undecane (6d). Yield 60%; bp_{75mmHg}120°C (K)[12]; ^1H NMR δ 1.25-1.48(m, 2H), 1.56-2.06(m, 10H), 3.49-3.60(m, 1H), 3.65-3.76(m, 1H), 3.81-3.88(m, 2H); ^{13}C NMR δ 23.43, 24.60, 29.53, 30.84, 38.15, 38.51, 62.56, 66.67, 110.59; MS(m/e) 156(M+), 126, 115, 97, 87, 69, 55, 41. Found: C, 69.03; H, 10.11; $C_9H_{16}O_2$ requires C, 69.19; H, 10.32.

ACKNOWLEDGMENTS.

We thank the Consiglio Nazionale delle Ricerche (C.N.R.)-Italia and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST)-Italia for financial support.

REFERENCES AND NOTES.

1.- Fisher,R.H.; Weitz,H.M. Synthesis 1980, 261.

2.- Stach, H.; Hesse, M. Tetrahedron 1988, 44, 1573.

3.- Ballini, R.; Marcantoni, E.; Petrini, M.; Rosini, G. Synthesis 1988 , 915.

4.- A related utilization of sodium borohydride is found in the synthesis of conjugated nitrocyclohexenes: Dampawan, P.; Zajac, W.W. Jr. Tetrahedron Lett., 1982, 915.they reported that the reduction of 2-nitrocyclohexanones with a stoichiometric amount of sodium borohydride in ethanol gave the corresponding β-nitroalcohols whereas the use of borohydride in excess precluted the isolation of the β-nitroalcohol or the nitroalkene. The procedure of Dampawan and Zajac can be considered part of the overall process designed by Hassner et al. for the transposition of a carbonyl group to an adjacent position: Hassner, A.; Larkin, J.M.; Dowd, J.E. J. Org. Chem. 1968, 33, 1733.

5.- We have been struck from the important role of spiroketals as structural elements of naturally occurring substances from many sources, including insects, microbes, plants, fungi, and marine organisms. For a recent, comprehensive and very useful review on the chemistry of spiroketals, see: Perron, F.; Albizati, K.F. Chem.Rev. 1989, 89, 1617. We agree with their decision to use the term "spiroketal" and not "spiroacetal", although this latter is more correct according to the IUPAC standards.

6.- Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E.; Angew. Chem. Int. Ed. Engl. 1986, 25, 941.

7.- Rosini, G.; Ballini, R.; Marotta, E.; Tetrahedron, 1989 , 45, 5935.

8.- Francke, W.; Hindorf, G.; Reith, W. Angew. Chem. Int. Ed. Engl., 1978, 17, 862.

9.- Elfehail, F.; Dampawan, P.; Zajac, W.W. Jr. Synth. Commun., 1980, 10, 929.

10.- Ballini, R.; Sorrenti, P. Org. Prep. Proc. Int. 1984, 16, 289.

11.- Dampawan, P.; Zajac, W.W. Jr. Synthesis, 1983, 545.

12.- 1,6-Dioxaspiro[4.6]undecane 14 has been synthesized by Utimoto, K. (Pure & Appl. Chem. ,1983, 55, 1845) in a 60 % yield, but no analytical data were reported.

13.- Stach, H.; Hesse, M. Helv. Chim. Acta, 1987, 70, 315.

14.- Nakashita, Y; Hesse, M. Helv. Chim. Acta, 1983, 66, 845.