Tetrahedron Letters,Vol.26,No.28,pp 3369-3372,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

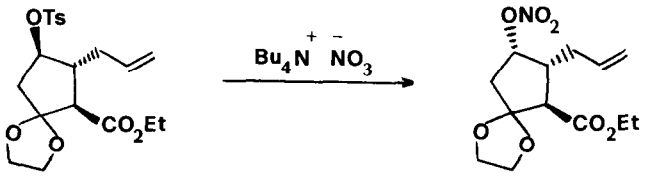
INVERSION OF CONFIGURATION OF ALCOHOLS THROUGH NUCLEOPHILIC DISPLACEMENT PROMOTED BY NITRATE IONS.

Gianfranco Cainelli, Francesco Manescalchi, Giorgio Martelli,
Mauro Panunzio and Laura Plessi.

Istituto Chimico "G.Ciamician" - Università di Bologna and C.S.F.M.-C.N.R.
Via Selmi, 2 40126 BOLOGNA- Italy.

Summary: Inversion of configuration of hydroxy functionalities in biologically significant structures has been performed under mild conditions through nucleophilic displacement by nitrate ion.

In connection with our studies in the prostaglandin area[1], we had recently the opportunity of searching a mild and efficient method to attain the inversion of a hydroxy functionality in a synthetic intermediate of our interest.
Altough a number of procedures[2] have been proposed in recent years for the purpose of inverting chiral alcohols, we found that better results could be obtained, in our case, by nucleophilic displacement of sulfonate of the alcohol by means of nitrate ions[1].

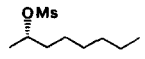
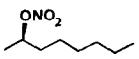
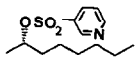
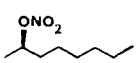
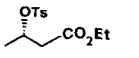
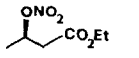
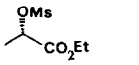
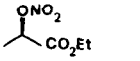
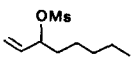
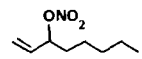
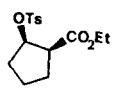
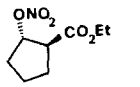
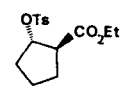
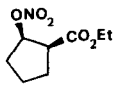
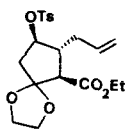
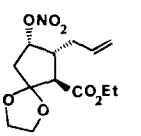
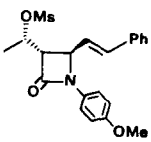
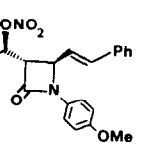


The nitroester prepared could be readily converted to hydroxy group by reductive processes and, due to the low basicity of nucleophile, the competing elimination reaction, a serious obstacle in several procedures, was almost completely suppressed. This positive result, prompted us to a broader investigation with the aim of exploring the scope and limitation of our method.
Concerning the nitroesters, a few ways have been described to accomplish their preparation: esterification of alcohols and methathetical reaction between alkyl

halides and silver nitrate[3], or mercury (II) nitrate[4].
In recent years we have been interested in the use, in organic synthesis, of phase transfer catalyst as tetralkylammonium salts and ion-exchangers.[5]
We have therefore taken into account the possibility of preparing nitroesters by reacting electrophiles like alkyl halides or sulfonates with tetrabutylammonium nitrate[6] or with an anion exchanger in the nitrate form (easily obtained by washing the chloride form of the resin Amberlyst A-26, as purchased from Rohm and Haas, with potassium nitrate aqueous solution).
Reactions have been performed by treating alkyl halides and sulfonates with nitrating agents in refluxing hydrocarbons. With low molecular weight materials the process has been performed in pentane, under pressure, in order to achieve the desired temperature and to easily remove the solvent. A 1.5 molar excess of tetra butyl-ammonium nitrate was usually sufficient to lead the reaction to completion.
Similar results have been obtained by means of the polymeric reagent, altough a much more substantial excess of the latter was usually needed.[7]
The method appeared to work well, giving high yields of nitroesters along with a few percentage of elimination products. The extent of this reaction has been found to be less than 10%, as evaluated from ^{1}H, ^{13}C NMR spectra of crude reaction products, even in the case of the tosylate of ethyl-2-hydroxy-butanoate (entry 3 of the Table), perhaps the substrate most likely to eliminate among the listed ones.
Results, summarized in the Table, show that our technique is useful in the steroid, prostaglandin, beta-lactamic fields, as well as for other biologically significant structures.[8]
The measurements of optical activity and the ^{13}C NMR spectra performed on the chiral alcohols obtained by reduction of the nitroesters gave evidence of high enantiomeric excess (e.e.), although a limited racemization almost always occurred.
The latter can be explained in terms of displacement of the nitroester group by nitrate anion in excess during the running of the reaction. As a matter of fact, a sample of (S)-2-octyl nitrate, refluxed for twenty hours with tetrabutylammonium nitrate, showed a partial racemization.
This handicap can be circumvented by the use of more efficient leaving groups in the original substrate allowing milder conditions and shorter reaction times. As can be seen from the Table (entry 2) the pyridyl sulfonates seem to meet this requirements giving the best result in terms of e.e. for the item so functionalized.
In the course of our research we have been aware of two papers[9,10] referring about alcohol epimerization performed by tetrabutylammonium nitrate over triflates of some sugar. We feel, nevertheless, to have herein demonstrate a noteworthy larger applicability of this technique for inverting the configuration of chiral alcohols.

Acknowldgement
The authors would like to express their gratitude to Dr. Patrizia Andreoli for her valuable contribution.

TABLE

	Substrate	Method	Time (hours)	Solvent	Nitrate (Yield %)	Reduction (Yield %)	Inversion (Yield %)
1.		B	3	Toluene		(90) C (85)	94.5[a]
2.		A	0.5	Benzene		(70) C (85)	100[a]
3.		A B	6 6	Benzene Benzene		(90) C (87) (90) C (87)	94[a] 94[a]
4.		B	5	Pentane[b]		(90) D (85)	78[a]
5		A	2	Toluene		(76) D (83)	-
6.		A	4	Pentane[b]		(86) C (80)	90[c]
7.		A	4	Pentane[b]		(80) C (80)	88.5[c]
8.		A	6	Benzene[b]		(95) D (74)	90[c]
9.		A	3	Benzene[b]		(70) D (60)	90[c]
10.	α cholestan-3-yl p-toluene sulfonate	B	2	Toluene	β cholestan-3-yl nitrate	(80) C (60)	100[c] [11]
11.	Methyl-3αp-toluene sulfonyloxy-5β-cholate	A	7	Toluene	Methyl 3β nitroxy -5β-cholate (60)	C (83)	100[c] [12]

Method A: $(n\text{-}Bu_4)N^+NO_3^-$; Method B: Amberlyst A-26 NO_3^- form.;
Method C: $H_2/Pd/C/10\%/CH_3OH$; Method D: Zn/CH_3COOH;
a: enantiomeric excess; b: 120 °C in sealed tube; c: evaluated by ^1H and ^{13}C NMR analyses.

References and notes.

1. Cainelli, G., Giacomini, D., Martelli, G., Panunzio, M., Spunta, G., Tetrahedron, in press.
2. Mitsunobu, T., Sano, T., Wada, M., Bull.Chem.Soc.Jpn. 46, 2833, (1973).
   Bose, A.K., Lal, B., Hoffman, W.A., Manhas, M.S., Tetrahedron Lett., 1619 (1973).
   Corey, E.J., Nicolau, K.C., Shibasaki, M., Machida, Y., Shiner, C.S., Tetrahedron Lett., 3183, (1975).
   Lattrell, R., Lohaus, G., Justus Liebig Ann.Chem., 901, (1974).
   Kruizinga, W.H., Strijtven, B., Kellog, R.M., J.Org.Chem., 46, 4322, (1981).
   Torisawa, Y., Okabe, H., Ikegami, S., Chem.Lett., 1555, (1984).
3. Boschan, R., Merrowand, R.T., Van Dolah, R.W., Chem.Rev., 55, 485, (1955).
4. McKillop, A., Ford, M.E., Tetrahedron, 30, 2467, (1974).
5. Cainelli, G., Manescalchi, F., Contento, M., "Organic Synthesis Today and Tomorrow" (IUPAC), Trost, B.M. and Hutchinson, C.R. Eds. Pergamon Press, Oxford and New York, pp.19-28.
6. Buckles, R.E., and Harris, L., J.Am.Chem.Soc., 79, 886, (1957).
7. The resin can be regenerated by washing with a 1 Molar solution of $NaNO_3$.
8. The yields are reported for isolated chromatographically pure products and have not been optimized. ^1H, ^{13}C NMR, MS, IR spectra were enterely consistent with the assigned structures and satisfactory combustion analyses were obtained.
9. Afza, N., Malik, A., Voelter, W., Z.Naturforsch, 39b, 840, (1984).
10. Binkley, R.W., Koholic, D.J., J.Carbohydr.Chem., 3, 85, (1984).
11. Linstead, R.P., J.Am.Chem.Soc., 62, 1766, (1940).
12. Hodosan, J., Rev.Roum.Cim., 14, 1057, (1969).

(Received in UK 15 May 1985)