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DILITHIUM TETRABROMONICKELATE (II) AS A SOURCE OF SOFT NUCLEOPHILIC BROMIDE : REACTION WITH EPOXIDES

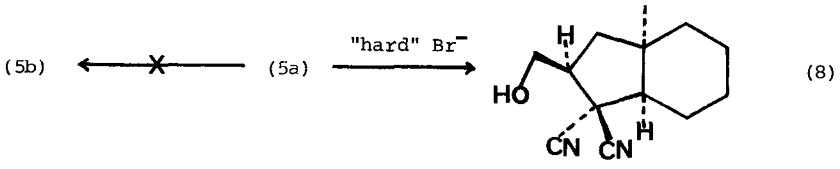
Robert D. Dawe, Tadeusz F. Molinski, and John V. Turner*

Research School of Chemistry, Australian National University,
P.O. Box 4, Canberra, A.C.T., 2600, Australia

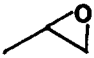
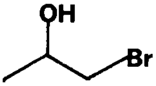
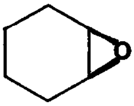
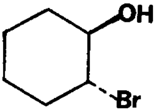
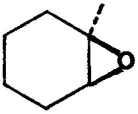
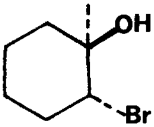
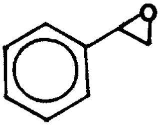
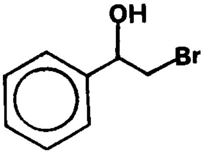
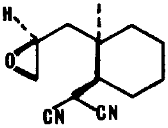
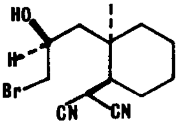
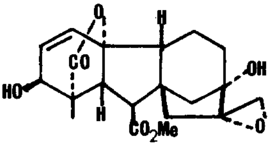
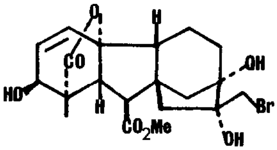
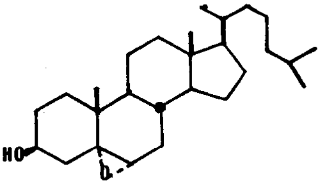
Summary: Dilithium tetrabromonickelate (II) in THF serves as a source of "soft" nucleophilic bromide and reacts regioselectively with epoxides to give bromohydrins in high yield.

As part of a program directed towards the synthesis of complex natural products, we recently required a non-aqueous source of "soft" nucleophilic bromide ion that would open epoxide rings with high regioselectivity without attacking other acid- and base-sensitive functional groups. A recently reported procedure[1] using bromine:triphenylphosphine unfortunately suffers from moderate regioselectivity in opening unsymmetrically substituted epoxides because of the borderline S_N2 mechanism, and from the propensity of this reagent to react with a range of nucleophilic functional groups;[2] the need to separate triphenylphosphine oxide from the halohydrin product is a further complication. For example we found using this procedure that the gibberellin epoxide (6a) only gave a 30% yield of bromohydrin (6b).

Methods based on hydrobromic acid[3] were clearly not appropriate and neither was the use of dry tetra-alkylammonium bromides,[4] or alkali metal bromides solublized with aprotic dipolar solvents (e.g. DMF or HMPA), since skeletal rearrangements can occur,[5,6] and also because the resultant "naked" bromide ion is relatively "hard" and can function as a base, as well as a nucleophile. It is notable that under these conditions the dinitrile epoxide (5a) underwent cyclization to (8) and gave none of bromohydrin (5b).



TABLE

ENTRY	SUBSTRATE [a]	TEMP.	TIME	YIELD %[11] BROMOHYDRIN (MAJOR:MINOR)	MAJOR ISOMER [b]	(ref)
1		0°	2h	90% (95:5)		(3)
2		25°	3h	∿100%		(1)
3		25°	18h	96%		(1)
4		0°	2h	97% (70:30)		(9)
5		25°	5h	∿100%		(11)
6		0°	0.3h	98%		(11)
7		65°	18h	∿0%	——	

We considered that a solution to the problem could lie in the generation and utilization of dilithium tetrabromonickelate (II) (Li_2NiBr_4) because this should be a source of "soft" bromide and also provide a "hard" but mild electrophile (i.e. Li^+) to facilitate epoxide ring-opening. In practice, anhydrous lithium bromide (2 eq) and nickel(II) bromide (1 eq), which is sparingly soluble in dry THF, readily dissolved together to give a dark blue-green solution (see *Procedure*) of the presumed tetrahedral complex, Li_2NiBr_4.[7]

As the examples listed in the Table indicate, epoxides undergo highly regioselective attack by Li_2NiBr_4 to yield, after work-up, bromohydrins with bromine predominantly at the less-hindered terminus. Reagent sensitivity to the steric environment about the epoxide can be gauged from the observation that epoxymethylcyclohexane (3a) gives the trans-bromohydrin (3b) in high yield whereas epoxycholestane (7a)[8] failed to react even under forcing condition presumably because of increased hindrance along the β-vector to a transition state for trans-diaxial epoxide opening. Even styrene oxide (4a), which is electronically prone to nucleophilic attack at the benzylic position[9] reacts to give mainly the primary bromide (4b); here the regioselectivity is similar to that observed during attack by sodium methoxide.[10]

The mildness of the procedure is evident from the formation of bromohydrins from both the bis-nitrile epoxide (5a)[11] (c/f 8) and the gibberellin epoxide (6a)[11] which is prone to degradation in both acid and base. Moreover, we have noted that 1 mole of (6a) consumes 0.5 mole Li_2NiBr_4 but that excess reagent is not deleterious to the sensitive gibberellin product (6b).

Although the precise nature of the bromo-alkoxy intermediate before work-up (phosphate buffer, pH7) has yet to be determined, potential clearly exists for making alkoxy derivatives in situ by the addition of appropriate electrophiles; moreover, Li_2NiBr_4 itself should find wider use in substitution reactions requiring a stereochemically sensitive source of "soft" nucleophilic bromide ion. Studies in these areas are underway.

Procedure

(a) *Preparation of Li_2NiBr_4 reagent*

Anhydrous LiBr (6.96 g, 0.08 mol) and $NiBr_2$ (8.72 g, 0.04 mol) were stirred in dry THF (95 ml) at ~25°. After ~48 h, the stirring was stopped and any undissolved material allowed to settle, to reveal a clear dark blue-green solution of Li_2NiBr_4 (~0.4 M).

(b) *Opening of epoxides*

To a solution of epoxide (1 mmol) in THF (~3 ml) was added an excess of Li_2NiBr_4 reagent (4 ml, 1.6 mmol). After being stirred for the specified time, the reaction mixture was then treated with phosphate buffer (~5 ml, 10%, pH7) and extracted with methylene chloride. This was then dried (Na_2SO_4) and concentrated to reveal the bromohydrins.

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References and Notes

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7. The complex has been prepared previously in molten dimethylsulphone at 128° for spectroscopic studies: G.P. Smith, C.H. Liu, and T.R. Griffiths, J. Am. Chem. Soc., 86, 4796 (1964). In control experiments using LiBr and $NiBr_2$ separately with (3a), we found reactions were slow and gave mixtures of products.
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9. R.E. Parker and N.S. Isaacs, Chem. Rev. (ACS), 59, 737 (1959).
10. W. Reeve and I. Christoffel, J. Am. Chem. soc., 72, 1480 (1950).
11. Yields are based on isolated products and isomer ratios were determined by integration of 200 MHz ^{1}H-nmr signals or G.C. analysis. New compounds had satisfactory elemental analyses (HRMS or combustion) and consistent spectroscopic characteristics; selected data are:

    (5b) IR (film) 3570 cm^{-1} (OH), ^{1}H-NMR ($CDCl_3$) δ 1.19 (s, 3H), 2.41 (br s, 1H, OH), 3.38 and 3.47 (AB of ABX J_{AB}=9.8, J_{AX}=7.9, J_{BX}=3.6, 2H, H_2CBr), 3.94 (m, 1H, HCOH), 4.27 (d, J=2.5, 1H, HC$(CN)_2$) ^{13}C-NMR ($CDCl_3$) δ 41.1 (H_2CBr), 68.0 (HCOH); MS m/z (M$^+$, 1%), 205 (M$^+$-H_2CBr, 100%).

    (6b) Mp 136° (dec); $[\alpha]_D^{25}$ = +56° (c =0.52 $CHCl_3$); IR ($CHCl_3$) 3500 (OH), 1775 (lactone), 1730 (ester) cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.21 (s, 3H, CCH_3), 2.75 (d, J=10.7, H-5) 3.18 (d, J=10.7, H-6), 3.40 (s, 3H, exch, OH), 3.58 (ABq, J=8·47, H-17, H-17'), 3.76 (s, 3H, OCH_3), 4.07 (d, $J_{2,3}$=3.17, H-3), 5.91 (dd, J=3.17 and 9.42, H-2) 6.29 (d, $J_{1,2}$=9.42, H-1).

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