

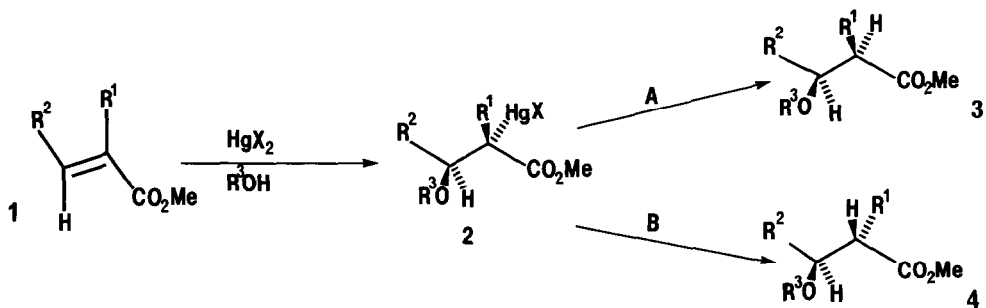
STEREOSELECTIVE DEMERCURATION OF α -MERCURIOCARBOXYLATES

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Summary: Organomercurials, obtained by oxymercuration of α, β -dialkyl- α, β -unsaturated esters, undergo demercuration with a stoichiometric amount of sodium borohydride to give products arising predominantly (70-86%) from a net inversion of stereochemistry; conversely, demercuration with 1,3-propanedithiol occurs predominantly (80-95%) with net retention of stereochemistry.

The oxymercuration of α, β -unsaturated carbonyl compounds generally proceeds more slowly than that of isolated alkenes; nevertheless it is possible to obtain α -mercurio- β -alkoxy addition products in good yields with the regiochemistry of the addition being controlled by the carbonyl group¹. With appropriate α - and β -alkyl substituents in the alkene **1**, centres of relative asymmetry are generated as a consequence of the stereospecificity of the oxymercuration reaction. While the organomercurials **2** are at present of somewhat limited synthetic interest, the demercuration products **3** and **4** are of some general interest and the ability to select for either **3** or **4** would be of some potential synthetic value. This Letter deals with preliminary studies on the stereoselective demercuration of organomercurials to give predominantly either **3** or **4** depending on the method of demercuration.



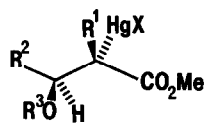
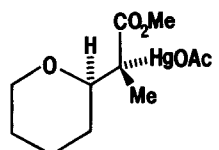
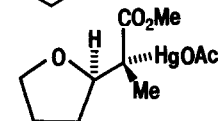
Perhaps the most generally used demercuration procedure employs an excess of alkaline sodium borohydride. In 1973, Maskens and Polgar² reported that, for acyclic cases such as 2a, this reagent provided a nearly equal ratio of diastereomers; this result was further substantiated by Bartlett and Adams³. A radical chain reaction pathway is the generally accepted mechanism for this reaction⁴. As a prelude to our investigation described below using 1,3-propanedithiol, the results of Maskens and Polgar were corroborated using an excess of sodium borohydride; however, to our surprise, when just slightly more than a stoichiometric amount of reducing agent was used (1.1 molar equivalents of hydride, Method B;) the demercuration proceeded to give a preponderance (2.3-6:1) of diastereomer 4, as shown in Table 1. More detailed studies are underway to clarify the mechanistic aspects of this reaction.

A second class of demercuration reagents, which includes alkaline hydrogen sulfide², alkaline sodium trithiocarbonate³ and sodium amalgam, have also been reported and are presumed to operate by an ionic reaction pathway. The stereoselectivities of these reagents have been shown to be widely divergent³ with sodium trithiocarbonate having perhaps the greatest demonstrated propensity to effect demercuration by a net retention of configuration. In view of the known⁵ ability of 1,3-propanedithiol to form an insoluble oligomeric mercury thiolate precipitate, we have investigated its applicability as a demetalating reagent⁶. The results (Method A) presented in Table 1 show that in general demercuration proceeded with a high degree of selectivity (10-19:1) for overall retention of stereochemistry at the α -position, and is suggestive of a mechanism involving intramolecular proton delivery from the thiol group to the α -carbon during demercuration³. The single exception was 2g in which an internal proton source (a β -hydroxy group) was present.

The assignment of stereochemistry for products 3 and 4 was based on the literature^{2,7} data for methyl (2R*,3S*)-3-methoxy-2-methylbutanoate (3a) and methyl (2S*,3S*)-3-methoxy-2-methylbutanoate (4a). The *threo* isomer (3a) exhibits upfield chemical shifts (1.09 and 1.11 δ) in the proton n.m.r. spectrum for the α - and β -methyl doublets compared to the *erythro* isomer (4a) (1.15 and 1.18 δ). Recently a number of related examples have been reported⁸ which indicate a general and consistent trend in which a *threo* isomer shows an upfield doublet (ca. 1.1 δ) for an α -methyl group compared to the corresponding *erythro* isomer (ca. 1.2 δ). By analogy then, the demercuration isomer showing an upfield α -group (α -methyl for 2b,c,e,f, h,i; α -methylene for 2d) was assigned the *threo* configuration (3); the isomer with a low-field α -group was assigned the *erythro* configuration (4). The diastereomeric pair 3g/4g were also distinguishable on the basis of existing literature data⁹.

While the use of 1,3-propanedithiol gave high levels of diastereoselectivity, sodium borohydride has performed in a decidedly modest manner in several cases. We are currently examining the use of other hydride reagents in an effort to improve the selectivity for isomer 4. In addition the effects of pre-existing chiral centres in the alkene 1 on the stereochemistry of the initial oxymercuration¹ and the subsequent demercuration are also being examined.

Table 1

Organomercurials ¹	demercuration method	isolated yield ² (%)	diastereomer ratio ³ (3:4)	α -Me, major diastereomer (δ , CDCl ₃)	
					
2a, R ¹ =R ² =R ³ =Me X=OAc	A B	99 85	95:5 20:80	1.17 1.10	
2b, R ¹ =R ³ =Me R ² =Et, X=OAc	A B	72 83	95:5 23:77	1.13 1.06	
2c, R ¹ =R ³ =Me R ² =n-Pr, X=OAc	A B	93 92	91:19 30:70	1.13 1.06	
2d, R ² =R ³ =Me R ¹ =Et, X=OAc	A B	73 86	95:5 25:75	1.65(α -CH ₂) 1.52(α -CH ₂)	
2e, R ¹ =R ² =R ³ =Me X=CO ₂ CF ₃	A B	74 69	95:5 28:72	1.17 1.10	
2f, R ¹ =R ³ =Me R ² =i-Pr, X=CO ₂ CF ₃	A B	90 90	90:10 20:80	1.16 1.10	
2g, R ¹ =R ² =Me R ³ =H, X=OAc	A B	85 95	57:43 ⁴ 20:80	1.18 ⁵ 1.18 ⁵	
2h		A B	92 90	95:5 14:86	1.20 1.11
2i		A B	85 86	90:10 23:77	1.25 1.15

- all organomercurials were prepared by oxymercuration of the requisite (E)- α,β -unsaturated ester, and were stereochemically homogeneous as evidenced by proton n.m.r.; the corresponding chloromercury derivatives proved to be unsatisfactory due to poor solubility in the demercuration solvent.
- yields reported are for chromatographically (SiO₂) purified products; all new compounds gave satisfactory i.r., n.m.r. and mass spec data
- measured by ¹H n.m.r. integration
- ratio increased to 80:20 when H₂O used as solvent
- diastereomer ratio measured by ¹³C n.m.r. (ref. 8).

Experimental: Method A; The organomercurial 2 (2.5 mmol) in absolute ethanol (10 mL) was added dropwise to a stirred suspension of sodium bicarbonate (5 mmol) in ethanol (25 mL) containing 1,3-propanedithiol (2.75 mmol) and cooled to 0°C. On completion of the addition the reaction mixture was stirred for 0.5 h at 0°C then 1h at room temperature. Residual thiol was precipitated by addition of mercuric acetate then the reaction mixture was filtered, concentrated to a small volume under reduced pressure and partitioned between methylene chloride and water. The organic layer was separated, dried, filtered then concentrated under reduced pressure.

Method B: Sodium borohydride (0.55 mmol) in absolute ethanol (5 mL) was added dropwise to a stirred solution of the organomercurial 2 (2.0 mmol) in ethanol (20 mL) at 0°C under nitrogen. After 0.5 h at 0°C and 0.5 h at room temperature, the reaction mixture was decanted, the residue washed with additional alcohol then the combined organic solution were reduced to a small volume under reduced pressure before partitioning between methylene chloride and water. The organic layer was then separated, dried, filtered and concentrated under reduced pressure.

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