Pergamon

Tetrahedron Letters, Vol. 37, No. 31, pp. 5585-5588, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01131-8

Selective Reduction of the Carbonyl Group in Organomercurials. A Facile Method for the Protection-Deprotection of the Mercurio Group and a New Route to Annulated Lactones

Pavel Kočovský,*,[a] Victoria Dunn,[a] Jason M. Grech,[a] Jiří Šrogl,[a,†] and William L. Mitchell[b]

[a]*Department of Chemistry, University of Leicester, LE1 7RH, U.K.*
[b]*GlaxoWellcome PLC, Stevenage, Herts. SG1 2NY, U.K.*

Abstract: Reduction of the carbonyl group in organomercurials can be carried out with retention of the mercury, provided it is protected by methylation. Thus, the bromomercurio aldehyde **6** is first methylated by MeCu to give **11**, whose reduction with $NaBH_4$, $LiAlH(t\text{-}BuO)_3$, L-Selectride®, or superhydride® affords the alcohol **12**. Mercury is then deprotected by treatment with $HgBr_2$ (**12** → **13**). The resulting alcohol **13** undergoes the palladium(II)-catalyzed carbonylation to produce the corresponding lactone **15**. Five- and six-membered lactones are readily accessible via this methodology. Copyright © 1996 Elsevier Science Ltd

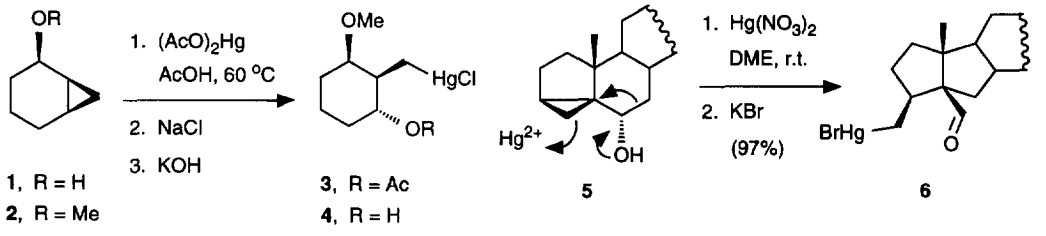
Organomercurials are frequently encountered intermediates in organic synthesis.[1] The usual role of mercury is to serve as a vehicle introducing a desired substituent. In most cases, after having served its purpose, mercury is removed by reduction.[1,2] This scenario is exemplified by the well known oxymercuration of olefinic double bonds[1] and by cyclopropane cleavage.[3-5] However, this is not the most economic strategy because, in general, stoichiometric processes, employing either expensive or toxic metals, should capitalize on the presence of the metal in the molecule by engaging it in more than one productive step.

As part of a program aimed at the more atom-economic utilization of organomercurials, we have recently shown that the C-HgX group can serve as a store of the carbon-metal bond. The mercurio group would be activated later in the synthetic scheme, eventually effecting, e.g., an intramolecular addition across a C=O or an activated C=C bond.[4-6]

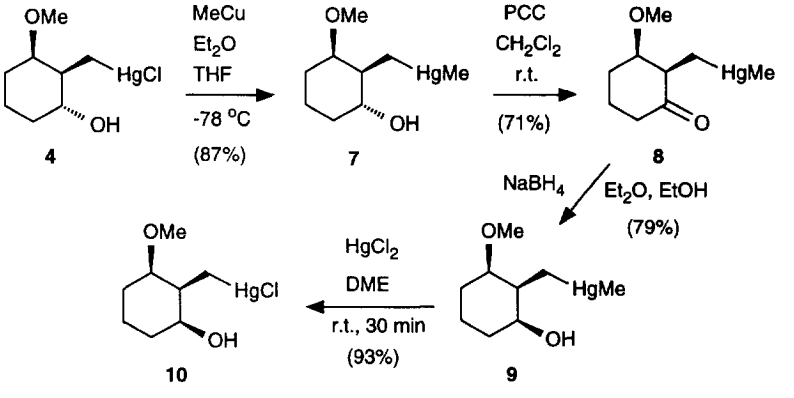
Organomercurials are relatively stable and easy-to-handle,[1] so that the R-HgX group (X = halogen) can be expected to survive a number of operations in a multiple-step sequence, before actually being activated and used. However, these compounds can easily be reduced even with relatively mild reducing agents,[1] which considerably limits the scope of this methodology. In order to avoid the latter flaw, we have developed a protocol that involves protection of the mercurio group from reduction and its subsequent deprotection.

We have shown earlier that, on reaction with MeCu, halomercurials (e.g., R-HgCl) undergo an instantaneous, high yielding methylation on mercury.[4,5] We now wish to report that the resulting methylmercurio derivatives R-HgMe are stable to a number of hydride reagents and that the halomercurio functionality can then be regenerated by treatment with HgX_2.

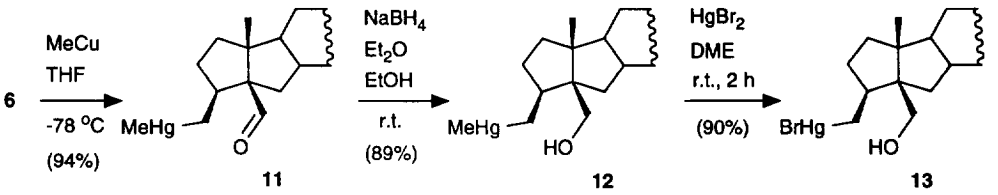
To develop this method, we have utilized two model compounds: the chloromercurio alcohol **4** and the steroidal aldehyde **6**. The former compound was prepared from the cyclopropyl alcohol **1**,[8] via a sequence involving protection of the OH group by MeI/NaH methylation (**1** → **2**; 69%), cyclopropane ring opening[3,5] with $(AcO)_2Hg$ (**2** → **3**; 74%), and saponification (**3** → **4**; 98%).[9] The aldehyde **6** has been readily obtained from the cyclopropyl derivative **5** (which, in turn, was prepared in four steps from cholesterol[10]) via the mercury(II)-mediated rearrangement.[4]



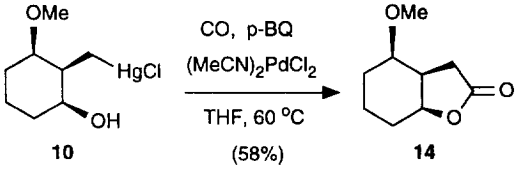
The chloromercurio alcohol **4** was first methylated with MeCu (generated in situ from equimolar amounts of MeLi and CuI) to afford the methylmercurio derivative **7**.[11] The latter compound was then oxidized with pyridinium chlorochromate (PCC) and the resulting ketone **8** stereoselectively reduced with $NaBH_4$ to give the inverted alcohol **9** as the major product (16:1). Finally, the chloromercurio grouping was regenerated by treatment with $HgCl_2$ (**9** → **10**).

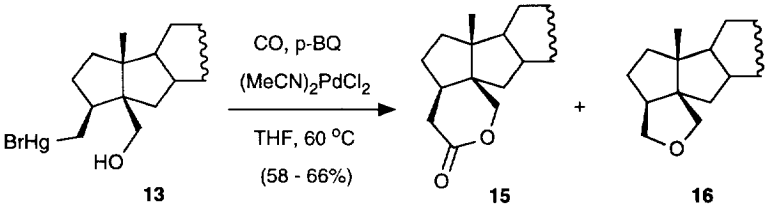


Similarly, methylation of the steroidal aldehyde with MeCu (**6** → **11**),[4] followed by the $NaBH_4$ reduction, gave the alcohol **12**. Treatment of the latter product with $HgBr_2$ furnished the bromomercurio alcohol **13**. A brief screening showed that the reduction (**11** → **12**) can also be carried with $LiAlH(t\text{-}BuO)_3$, L-Selectride®, or superhydride® in high yields.[12] By contrast, treatment with $LiAlH_4$ led to the reduction of both functional groups.



On heating at 60 °C with $(MeCN)_2PdCl_2$ (10 mol%) and 2 equivs of *p*-benzoquinone (*p*-BQ) in THF under an atmosphere of CO for 4 days,[13] the chloromercurio alcohol **10** has been almost quantitatively consumed, giving almost exclusively the five-membered lactone **14**, which was isolated as a pure compound in 58% yield.[14] On the other hand, the organomercurial **13** exhibited high conversion to the corresponding lactone only when the reaction was carried out with a stoichiometric amount of Pd^{2+} (still in the presence of *p*-BQ which, apparently, serves as a ligand[15]). The six-membered lactone **15** (55%)[16] thus formed, was accompanied by the tetrahydrofuran derivative **16** (11%).[17] The catalytic version (8 mol% of Pd^{2+}, 60 °C, 7 days) gave rise to a mixture of **15** (14%) and **16** (44%), with the latter product dominating. These results indicate that the lactonization will be less successful if a competing pathway, such as a 5(O)^n-*exo*-tet cyclization,[18] is available. By contrast, synthesis of 5-membered lactones does not seem to suffer from that kind of competition, for the only available 4-(O)^n-*exo*-tet cyclization is much less likely.





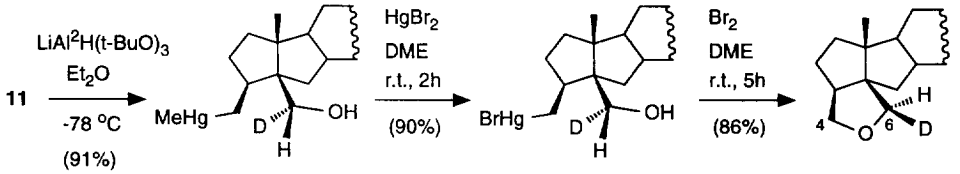
In conclusion: We have developed a protocol for the protection/deprotection of the organomercurials, namely via the methylation-demethylation. The protected organomercurials are stable to a number or hydride reagents, enabling a selective reduction of an aldehyde or ketone group, present in the molecule. The resulting halomercurio alcohols readily afford either 5- or 6-membered lactones on the Pd(II)-catalyzed carbonylation. This protocol represents a novel approach to the synthesis of lactones and supplements those in existence.[19]

Acknowledgment. We thank the EPSRC for an earmarked studentship to V. D. and grant No GR/H65535 and GlaxoWellcome PLC and EPSRC for a CASE award to J. M. G. We also thank Dr. Adolf Gogoll for NOE experiments.

References and Notes

* Correspondence author; e-mail: PK10@Le.ac.uk
† Current address: Department of Chemistry, Emory University, Atlanta, Georgia 30322, USA.

1. (a) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (b) Larock, R. C. *Solvomercuration - Demercuration Reactions in Organic Synthesis*; Springer: Berlin 1986. (c) Kočovský, P. *Organometallics* **1993**, *12*, 1969.
2. Trapping of the radical, generated by the hydride reduction, via addition to a double bond, seems to be the only notable exception: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986.
3. (a) Collum, D. B.; Mohamadi, F.; Hallock, J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6882. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094.
4. Kočovský, P.; Šrogl, J.; Pour, M.; Gogoll, A. *J. Am. Chem. Soc.* **1994**, *116*, 186.
5. Kočovský, P.; Grech, J. M.; Mitchell, W. L. *J. Org. Chem.* **1995**, *60*, 1482.
6. Organomercurials can be transmetalated with Cu[4,5] and Pd.[7]
7. Kočovský, P.; Šrogl, J.; Gogoll, A.; Hanuš, V.; Polášek, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1086.
8. (a) Dauben, W. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 468. (b) Kawabata, N.; Ikeda, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 563.
9. All new compounds gave satisfactory spectral and analytical data. All yields refer to isolated (preparative) yields.
10. (a) Aburatani, M.; Takeuchi, T.; Mori, K. *Synthesis* **1987**, 181. (b) Wagner, A. F.; Wallis, E. S. *J. Am. Chem. Soc.* **1950**, *72*, 1047.
11. The diagnostic feature for the MeHg group is a singlet (83%) and a doublet (17%) of the methyl group in the ^{1}H NMR spectrum, which appear at 0.22 ppm; the doublet (J = 102 Hz) corresponds to the coupling with the less abundant ^{199}Hg isotope.
12. The reduction turned out to be stereoselective, as revealed by using $LiAl^2H(t\text{-}BuO)_3$, which gave mainly the alcohol **i**. The configuration at the new center of chirality (i.e. C-6) has been established via converting the latter alcohol into the rigid tetrahydrofuran derivative **iii**; the NOE technique has been used to unequivocally assign the signals to the respective protons of the CH_2-O-CH_2 group in the unlabeled analogue **16** [δ 3.41 (d, J = 9.1 Hz, 6α-H), 3.47 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 8.8 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.8 Hz, 4β-H), 3.95 (t, J = 9.0 Hz, 4α-H), 4.00 (d, J = 9.1 Hz, 6β-H) ppm]. An almost identical stereoselectivity has been observed for super deuteride® (87:13). Reduction of the deuterated aldehyde with $LiAlH(t\text{-}BuO)_3$ gave a complementary result.



i (85 : 15) ii iii

13. Kočovský, P.; Grech, J. M.; Mitchell, W. L. *Tetrahedron Lett.* **1996**, *37*, 1125.
14. **14:** IR ν(C=O) 1770 cm^{-1}; ^{13}C NMR δ 177.3 ppm.
15. Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790.
16. **15:** IR ν(C=O) 1740 cm^{-1}; ^{13}C NMR δ 174.3 ppm.
17. **16** arises from an intramolecular substitution reaction that dominates in the absence of CO.[7]
18. For notation, see: Kočovský, P.; Stieborová, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1969.
19. For an overview of the methods available for construction of lactones, see, e.g.: (a) Bartlett, P. A. in "Olefin Cyclization Processes that form Carbon-Heteroatom Bonds" *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p. 411. (b) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC: Boca Raton, FL, 1986; Vol. I and II. For a recent, Pd-catalyzed procedure, analogous to halolactonization, see: (c) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298.

(*Received in UK* 8 *May* 1996; *revised* 3 *June* 1996; *accepted* 7 *June* 1996)