ORGANIC LETTERS

2000
Vol. 2, No. 20
3205−3208

Rhodium-Catalyzed Formylation of Organomercurials: Application to Efficient Polyol Synthesis

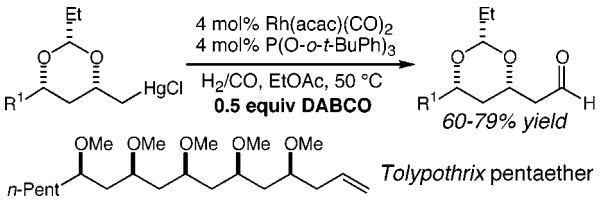
Stella T. Sarraf and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027

leighton@chem.columbia.edu

Received July 29, 2000

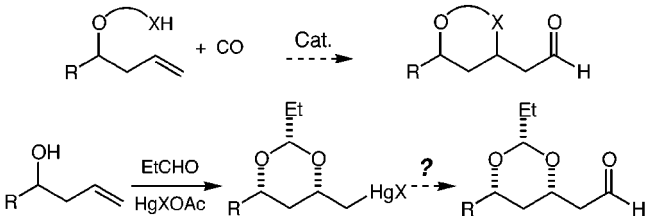
ABSTRACT



The rhodium-catalyzed formylation of organomercurials—a new transformation of organomercurials—is reported. The addition of 0.50 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) was found to promote the reaction, and it is postulated that the DABCO acts as a ligand for mercury. Several examples are presented to document the scope of the reaction. This reaction was developed in the context of a larger program focused on the development of efficient strategies for the synthesis of polyol-derived natural products, and an efficient (8 steps) synthesis of *Tolypothrix* pentaether that employs this methodology is reported.

The ubiquity of (1, 3, 5...) polyol segments in many biologically active natural products has led to the development of various strategies for their synthesis.[1] Our efforts in this regard have focused on various alkene carbonylation reactions.[2] One approach entails the addition of a tethered nucleophile and a formyl group across the alkene of a homoallylic alcohol (Scheme 1).[2c] Envisioning a two-step version of this transformation, we have recently disclosed the oxymercuration of homoallylic alcohol-derived hemiacetals depicted in Scheme 1.[3] In the second step, formylation of the resultant organomercurials would provide the desired aldehydes. An allylation reaction would then provide a new homoallylic alcohol for reiteration of the sequence. Herein we report the Rh(I)-catalyzed formylation of organomercurials and the first application of the strategy outlined above to the synthesis of a polyol-derived natural product.

Scheme 1



Direct carbonylations of organomercurial compounds are low yielding and require high temperatures and pressures; however, the use of transition metal catalysts has led to milder reaction conditions and improved yields. For example, rhodium and palladium have been used in the presence of

(1) (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635−645. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2012−2040. (c) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375−1378. (d) Smith, A. B.; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001−2004.

(2) (a) Leighton, J. L.; O'Neil, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 11118−11119. (b) Sarraf, S. T.; Leighton, J. L. *Tetrahedron Lett.* **1998**, *39*, 6423−6426. (c) Leighton, J. L.; Chapman, E. *J. Am. Chem. Soc.* **1997**, *119*, 12416−12417.

(3) (a) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403−405. (b) Dreher, S. D.; Hornberger, K. R.; Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3197−3200.

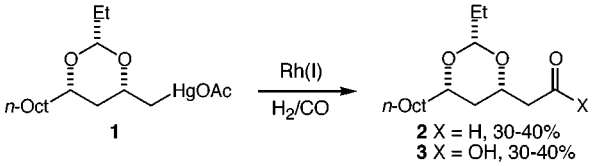
(4) (a) Larock, R. C. *Tetrahedron* **1982**, *38*, 1713−1754. (b) Baird, W. C., Jr.; Hartgerink, R. L.; Surridge, J. H. *J. Org. Chem.* **1985**, *50*, 4601−4605. (c) Walkup, R. D.; Park, G. *J. Am. Chem. Soc.* **1990**, *112*, 1597−1603. (d) Kocovsky, P.; Grech, J. M.; Mitchell, W. L. *Tetrahedron Lett.* **1996**, *37*, 1125−1128.

10.1021/ol006393o CCC: $19.00
Published on Web 09/13/2000

water and alcohols for the carbonylation of organomercurials to generate carboxylic acids and esters.[4] It seemed plausible that replacement of the ROH trap for the metal acyl with H_2 could lead to an aldehyde synthesis. In principle, a catalytic cycle similar to hydroformylation can be proposed,[5] and we therefore focused our attention on rhodium.

For our initial attempts at formylation we utilized Rh(acac)$(CO)_2$ (4 mol %) as catalyst and P-(O-*o*-*t*-BuPh)$_3$[6] (4 mol %) as the ligand. Subjection of unpurified organomercury acetate **1**, formed as previously described,[3a] to these conditions in a stainless steel pressure reactor (800 psi H_2/CO (1/1), CH_3CN, 50 °C) for 12 h led to the production of aldehyde **2** in 30−40% yield (two steps) along with substantial amounts of acid **3** (Scheme 2).[7,8] The acid

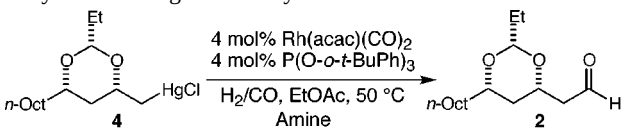
Scheme 2



byproduct is believed to result from hydrolysis of the mixed acetic anhydride formed upon acetate transfer at some point during the catalytic cycle.[4b]

To avoid this acetate transfer, it seemed reasonable to investigate the rhodium-catalyzed formylation of the organomercury chlorides. Although initial experiments were discouraging and produced very little of the desired aldehyde, it was soon discovered that the desired formylation could be promoted by the addition of amines. Subjection of organomercury chloride **4** to the action of Rh(acac)$(CO)_2$ (4 mol %) and P-(O-*o*-*t*-BuPh)$_3$ (4 mol %) in a stainless steel pressure reactor (800 psi H_2/CO (1/1), EtOAc, 50 °C) led to varying amounts of aldehyde **2** according to the amine used (Table 1). In these experiments the major identifiable byproduct was derived from simple reduction of the organomercurial to a methyl group. Interestingly, a breakthrough

Table 1.[a] Screening of Various Amines in the Rh-catalyzed Formylation of Organomercury Chloride **4**



amine	equiv	y (%)[b]	amine	equiv	y (%)[b]
N-Me-Morpholine	1.0	0	$Me_2NCH_2CH_2NMe_2$	1.0	22
				0.50	36
pyridine	1.0	0	 (DABCO)	1.0	46
quinuclidine	1.0	46		0.50	**70**

[a]All reactions were conducted in a stainless steel pressure reactor equipped with a pressure guage and a glass liner. [b]Isolated yield of purified product **2**.

was achieved with the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) that was highly dependent on the stoichiometry. Whereas the use of 1.0 equiv of DABCO led to the isolation of aldehyde **2** in 46% yield, the use of 0.50 equiv of DABCO produced **2** in 70% yield. The latter result stands in contrast to the poor results observed with 0.50 equiv of other diamines such as $Me_2NCH_2CH_2NMe_2$.

It is well-precedented that amines bind to mercury,[9] and we propose that certain amines promote the desired formylation reaction by binding to Hg, and that this interaction can be electronically and sterically tuned. ^{199}Hg NMR spectroscopy was employed to investigate the nature of the DABCO−organomercurial interaction.[10] Solutions of organomercury chloride **4**, **4** with 0.50 equiv of DABCO, and **4** with 1.0 equiv of DABCO in $CDCl_3$ displayed ^{199}Hg chemical shifts of −955, −935, and −923 ppm, respectively. These data suggested that different DABCO−RHgCl complexes are formed depending on the stoichiometry and are consistent with the 1:1 and 1:2 complexes depicted in Figure 1.[11,12]

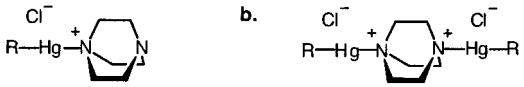


Figure 1. Proposed binding of DABCO to RHgCl (a) 1:1 and (b) 1:2.

Although no clear trend is readily apparent from the data in Table 1, we would only point out that DABCO is unique in that the two amines are conformationally locked in proximity to each other and therefore interact strongly. This effect is manifested, for example, in the unusually low (∼3) pK_a of $(DABCOH_2)^{2+}$, as compared with a pK_a of ∼7 for $(H_3NCH_2CH_2NH_3)^{2+}$.[13] Drawing an analogy to Lewis basicity, the 1:2 complex is unique among the amines screened in that the donor is an sp^3-hybridized amine with unusually low basicity. Finally, we note an interesting mechanistic postulate in the

(5) Insertion/transmetalation of rhodium into the C−Hg bond would lead to essentially the same rhodium alkyl intermediate that is produced during our previously reported hydroformylation of enol acetals. See refs 2a,b.

(6) Jongsma, T.; Challa, G.; Van Leeuwen, P. W. N. M. *J. Organomet. Chem.* **1991**, *421*, 121−128.

(7) Two equivalents of acetic acid are formed in the combined oxymercuration and carbonylation. Control experiments showed that the aldehyde product was not affected by the presence of acetic acid.

(8) The carboxylic acid could be generated directly in 60% yield by performing the same experiment in the absence of H_2.

(9) (a) Brodersen, K. and Hummel, H.-U. in *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1987; Vol. 5, pp 1047−1097.

(10) (a) Canty, A. J.; Barron, P.; Healy, P. C. *J. Organomet. Chem.* **1979**, *179*, 447−458. (b) Michel, E.; Perie, J.; Lattes, A. *J. Organomet. Chem.* **1981**, *204*, 1−12. (c) Al-Showiman, S. S. *Inorg. Chim. Acta* **1988**, *141*, 263−274. (c) Black, D. S. C.; Deacon, G. B.; Edwards, G. L.; Gatehouse, B. M. *Aust. J. Chem.* **1993**, *46*, 1323−1336.

(11) For the 1:1 complex, an oligomeric (-RHgCl−DABCO−RHgCl−DABCO-)$_n$ structure is also possible.

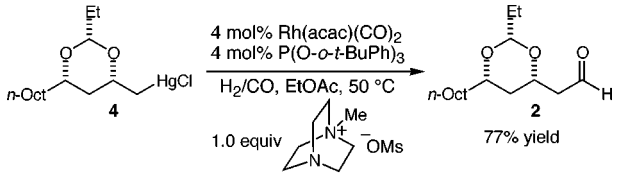
(12) Related DABCO-metal complexes have been reported: (a) Quagliano, J. V.; Banerjee, A. K.; Goedken, V. L.; Vallarino, L. M. *J. Am. Chem. Soc.* **1970**, *92*, 482−488. (b) Yokobayashi, H.; Nagase, K.; Sone, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2569−2573.

(13) Paoletti, P.; Stern, J. H.; Vacca, A. *J. Phys. Chem.* **1965**, *69*, 3759−3762.

experiments employing 0.50 equiv of DABCO. As the organomercury chloride is consumed, HCl is produced, and therefore a proton can replace the consumed RHgCl on the DABCO. In this fashion both amines remain complexed throughout the reaction, and the effectiveness of the DABCO ligand is not reduced.

On the basis of this proposal that the DABCO binds to the mercury, and that there is something unique about this interaction when the other amine is also complexed, it was straightforward to predict that the monoquaternized salt $(DABCO\text{-}Me)^{+}(OSO_2CH_3)^{-}$ should be an effective amine additive. Indeed, subjection of organomercury chloride **4** to the conditions outlined in Table 1 with 1.0 equiv of this amine led to the production of aldehyde **2** in 77% yield (Scheme 3). While this experiment does not provide direct

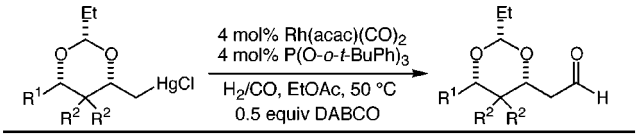
Scheme 3



evidence of an interaction between the amine and mercury, it is nevertheless consistent with the proposal and provides strong circumstantial evidence for it.

With these initial results established, we endeavored to explore the scope of the reaction. Table 2 outlines our results

Table 2.[a] Rh-Catalyzed Formylation of Organomercury Chlorides



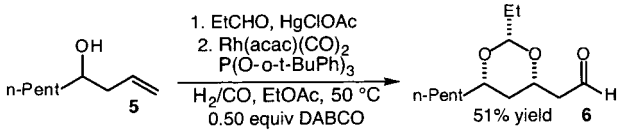
entry	R^1	R^2	y (%)[b]
1	*n*-Pent	H	77
2	$BnOCH_2$	H	70
3	$TBSOCH_2CH_2$	H	79
4	(*E*)-*i*-PrCH=CH	H	61
5	*n*-Pent	Me	60

[a]All reactions were conducted in a stainless steel pressure reactor equipped with a pressure guage and a glass liner. [b]Isolated yield of purified product.

for the carbonylation of several representative organomercury chlorides.[3a] Several solvents were screened, with EtOAc consistently providing the best results. Several ligands for rhodium were screened as well, with bulky triaryl phosphites proving to be the most effective.[14] There was a range of functional group tolerance at the 6-position of the 1,3-dioxane ring; alkyl, benzyloxy, and silyloxy groups are all well tolerated (entries 1−3). An alkene substituent (entry 4) was also tolerated albeit with diminished yield. Apparently, transmetalation and formylation are significantly faster than simple hydroformylation of the disubstituted alkene. Finally, alkyl substitution within the 1,3-dioxane ring (entry 5) seems to have a slightly deleterious effect, leading to a moderate yield of the desired aldehyde.

From a process point of view it would be desirable to render the oxymercuration and carbonylation reactions a one-pot procedure. Besides being more efficient, this would eliminate completely the handling of organomercurial intermediates. We have established preliminarily the feasibility of this approach as described in Scheme 4. Thus, homoallylic

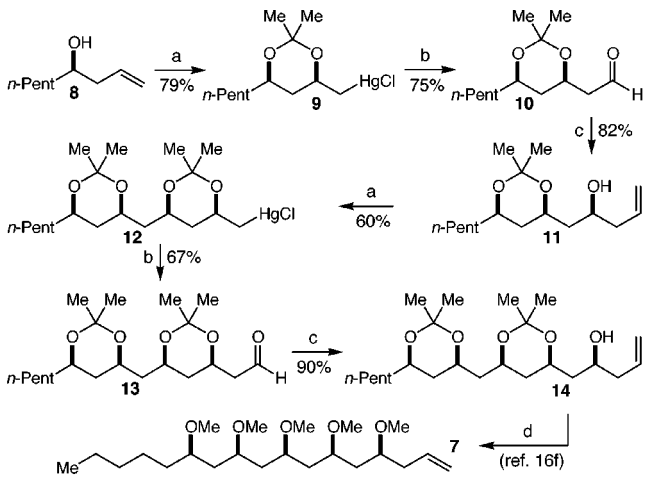
Scheme 4



alcohol **5** was subjected to the previously reported oxymercuration conditions with HgClOAc and EtCHO. The reaction mixture was simply concentrated in vacuo and then directly subjected to the formylation conditions reported here. This one-pot procedure delivered aldehyde **6** in 51% yield.

As a demonstration of the effectiveness of the approach to polyol synthesis outlined here, we have developed a synthesis of *Tolypothrix* pentaether (**7**, Scheme 5), a natural product isolated from the blue-green algae *Tolypothrix conglutinata* and *Scytonema mirabile*.[15,16] Our synthesis began with an oxymercuration of homoallylic alcohol **8** with HgClOAc, acetone, and 5 mol % $Yb(OTf)_3$ to give organo-

Scheme 5



[a](a) HgClOAc, 5 mol% $Yb(OTf)_3$, acetone. (b) $Rh(acac)(CO)_2$, P(O-*o*-*t*-BuPh)$_3$, 0.50 equiv DABCO, 800 psi H_2/CO, EtOAc, 50 °C. (c) (-)-*ipc*$_2$B$CH_2CH{=}CH_2$, Et_2O, -78 to 23 °C. (d) i. *p*-TsOH, MeOH; ii. KH, Me_2SO_4, THF.

mercury chloride **9** in 79% yield.[3b] Subjection of this material to the formylation protocol outlined above gave aldehyde **10** in 75% yield. The first iteration of the three-step sequence was then completed with a diastereoselective (>10:1) Brown allylation[17] to produce homoallylic alcohol **11** in 82% yield. With this material in hand, the sequence was simply repeated to produce organomercury chloride **12**, aldehyde **13**, and homoallylic alcohol **14** in 60, 67, and 90% yields, respectively. Alcohol **14** is an intermediate in a Brückner synthesis of the natural product, and their final steps involved acetonide deprotection using *p*-TsOH in methanol, and permethylation with KH and dimethyl sulfate to provide a 50% yield (two steps) of *Tolypothrix* pentaether.[16f] By making use of these final steps we have thus achieved an eight-step synthesis of *Tolypothrix* pentaether from alcohol **8**, which compares favorably to a previous shortest linear sequence of 16 steps.[16f]

In combination with the previously reported oxymercuration reaction,[3] the rhodium-catalyzed carbonylation of organomercurial chlorides reported here is an effective method to generate aldehydes relevant to polyol synthesis. The efficient production of protected 3,5-dihydroxyalkanals from homoallylic alcohols employs only readily available reagents (acetone, HgClOAc, H_2, CO, DABCO) and is thus an attractive synthetic method. Although our future efforts will focus on rendering the process catalytic in mercury, and/or discovering other metals capable of similar chemistry, the present work highlights both a new reaction of organomercurials and a unique approach to tuning the reactivity of organomercurials for organic synthesis.

Acknowledgment. The National Institutes of Health (National Institute of General Medical Sciences − R01 GM58133) is acknowledged for financial support of this work. We thank Pharmacia and Upjohn for a graduate fellowship to S.T.S., and Merck Research Laboratories and DuPont Pharmaceuticals for generous financial support. J.L.L. is a recipient of a Sloan Research Fellowship, a Camille Dreyfus Teacher-Scholar Award, a Bristol-Myers Squibb Unrestricted Grant in Synthetic Organic Chemistry, a Cottrell Scholar Award from the Research Corporation, an Eli Lilly Grantee Award, an AstraZeneca Excellence in Chemistry Award, and a GlaxoWellcome Chemistry Scholar Award.

Supporting Information Available: Experimental procedures and characterization data for all products in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006393O

(14) We have discovered that the commercially available tris(2,4-di-*tert*-butylphenyl) phosphite is equally effective as P(O-*o*-*t*-BuPh)$_3$.

(15) (a) Mynderse, J. S.; Moore, R. E. *Phytochemistry* **1979**, *18*, 1181. (b) Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, *56*, 631−637.

(16) For syntheses of *Tolypothrix* pentaether, see ref 14b and (a) Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525−6528. (b) Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6529−6532. (c) Priepke, H.; Weigand, S.; Brückner, R. *Liebigs Ann.* **1997**, 1635−1644. (d) Priepke, H.; Brückner, R. *Liebigs Ann.* **1997**, 1645−1655. (e) Weigand, S.; Brückner, R. *Liebigs Ann.* **1997**, 1657−1666. (f) Allerheiligen, S.; Brückner, R. *Liebigs Ann.* **1997**, 1667−1676.

(17) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−439.