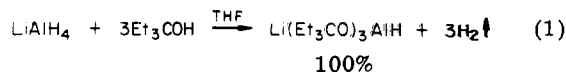


Lithium Tris[(3-ethyl-3-pentyl)oxy]aluminum Hydride. A New Remarkably Chemoselective Reagent for the Reduction of Aldehydes in the Presence of Ketones[†]

Summary: Lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride, a highly hindered lithium trialkoxyaluminum hydride synthesized from lithium aluminum hydride and 3-ethyl-3-pentanol, exhibits remarkable chemoselectivity (98–100%) for the reduction of aldehydes even in the presence of unhindered and reactive ketones such as cyclohexanone.

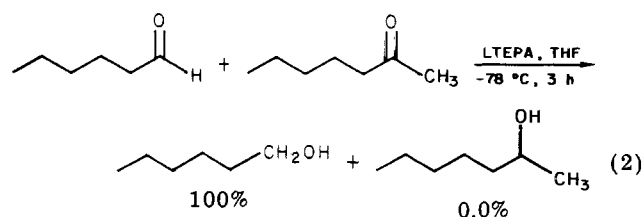
Sir: The carbonyl group of aldehydes and ketones plays a major role in organic synthesis. Efficient and highly chemoselective reduction of aldehydes in the presence of ketones continues to attract intense interest.¹ In recent years, a number of reagents have been developed for this selective transformation.² Several of these reagents can selectively reduce an aldehyde in the presence of a methyl ketone. However, the real challenge for a reagent lies in its ability to distinguish efficiently between an aldehyde and a more reactive ketone such as cyclohexanone. Unfortunately, most of these reagents are less successful in this respect. Accordingly, a number of hydride reducing agents were tested for this highly desirable goal. Of these, the chemoselectivity exhibited by lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride (LTEPA) was especially promising.

Lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride is conveniently prepared in quantitative yield by the addition of 3.05–3.2 molar equiv of 3-ethyl-3-pentanol to a tetrahydrofuran (THF) solution of lithium aluminum hydride (LiAlH₄) at 25 °C, followed by a gentle reflux of the resulting mixture for 1 h (eq 1).^{3,4}



The chemoselectivity of this new reagent was tested with four representative aldehyde–ketone pairs in competition experiments. Equimolar amounts of an aldehyde and a ketone were allowed to compete for a limited quantity of LTEPA (1 equiv). A standard solution⁵ of the reagent in THF was added to the aldehyde–ketone mixture maintained at the desired temperature (0 or –78 °C). After 2–4 h, the mixture was hydrolyzed with water and analyzed by GLC⁶ with an internal standard. The results are summarized in Table I.

At 0 °C, hexanal is selectively (99.6%) reduced in the presence of 2-heptanone (0.4% attack);⁷ lowering the temperature to –78 °C results in the *chemospecific* (100.0%) reduction of hexanal (eq 2). Likewise, benzaldehyde can be selectively (99.5%) reduced in the presence of acetophenone (0.5% attack).



Even more important is the remarkable chemoselective discrimination between hexanal (99.6%) and cyclohexanone (0.4% attack) at –78 °C (eq 3). The highest chemoselectivities reported for the reduction of an aliphatic aldehyde in the presence of cyclohexanone are with diisopropylcarbinol on alumina (86.6%)^{2f} and tributyltin hydride on silica gel (88.4%).^{2h}

Table I. Relative Reactivities of Aldehydes and Ketones toward Lithium Tri-*tert*-alkoxyaluminum Hydrides in Tetrahydrofuran^a

RCHO/R ₁ R ₂ CO	temp, ^b °C	ratio ^c of RCH ₂ OH/R ₁ R ₂ CHOH			
		LTBA ^d	LTAA ^e	LTMPA ^f	LTEPA ^g
hexanal/2-heptanone	0	99.0:1.0	99.5:0.5	99.0:1.0	99.6:0.4
	–78	99.5:0.5		99.8:0.2	100.0:0.0
benzaldehyde/acetophenone	0	99.0:1.0	99.0:1.0	99.0:1.0	99.5:0.5
	–78	87.0:13.0	92.0:8.0	92.2:7.8	93.6:6.4
hexanal/cyclohexanone	0	91.5:8.5	96.0:4.0	95.1:4.9	99.6:0.4
	–78	66.7:33.3	77.0:23.0	84.5:15.5	92.5:7.5
benzaldehyde/cyclohexanone	0	73.0:27.0		88.0:12.0	97.7:2.3
	–78				

^a Reaction mixtures were 0.25 M in both reagent and substrates. ^b Reactions at 0 °C were run for 2 h and those at –78 °C were run for 3–4 h. ^c Determined by GLC with an internal standard; the total yields of the alcohols were >90%.

^d LTBA = Li(*t*-BuO)₃AlH. ^e LTAA = Li(*t*-AmO)₃AlH. ^f LTMPA = Li(Et₂MeCO)₃AlH. ^g LTEPA = Li(Et₃CO)₃AlH.

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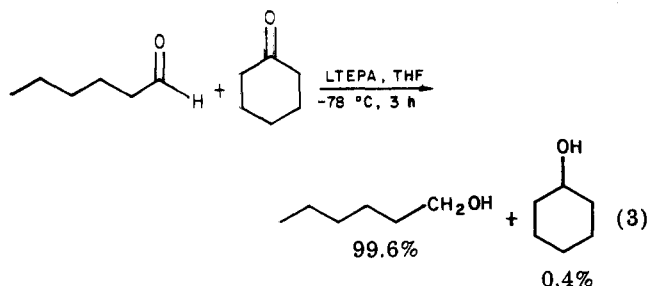
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(4) Hydrogen (2 equiv) is readily evolved at room temperature, and the evolution of the third equivalent of hydrogen is sluggish; it can be brought to completion under a gentle reflux. In refluxing THF, LTEPA did not react with an additional equivalent of 3-ethyl-3-pentanol (24 h, 0%). Although a slight excess of 3-ethyl-3-pentanol (3.05–3.2 equiv) was employed in the present study, even a stoichiometric amount is equally satisfactory.

(5) The solutions were standardized by hydrolyzing a known aliquot with a mixture of water, glycerine, and THF (1:1:1) and measuring the volume of hydrogen evolved; see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M., Eds. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975; p 241.

(6) GLC analyses were performed either on a Varian Model 1200 gas chromatograph (FID) with a 5% Carbowax 20M column, 8 ft × 0.125 in., or on a Hewlett-Packard Series 5880A gas chromatograph (FID) fitted with a data system with a 10-m SE-52 capillary column.

(7) To verify the reliability of such values, synthetic mixtures containing 0.2–1.0% of the authentic alcohols expected from the ketone reduction were examined by GLC.



Interestingly, even benzaldehyde, often less reactive in hydride reductions, is selectively (97.7%) reduced in the presence of cyclohexanone (2.3% attack).

The reactions are quite rapid even at $-78\text{ }^\circ\text{C}$ (2-4 h), and the conversions are over 90%. The results summarized in Table I clearly indicate that the new reagent is far superior to any of the reducing systems² currently available for the selective reduction of aldehydes in the presence of ketones.

Influence of the steric requirements of *tert*-alkoxy substituents on the chemoselectivity was also examined. Lithium tri-*tert*-butoxyaluminum hydride (LTBA)³ is less chemoselective than LTEPA. Yet the chemoselectivity observed with LTBA is equal to or better than that of the previously reported reagents² for the selective reduction of aldehydes in the presence of ketones. Lithium tri-*tert*-amyloxyaluminum hydride (LTAA)³ and lithium tris[(3-methyl-3-pentyl)oxy]aluminum hydride (LTMPA)⁸ are slightly better than LTBA. Thus, it is quite evident that increasing the steric requirements of the *tert*-alkoxy group enhances the chemoselectivity of the reagent to the aldehyde group, an interesting and useful observation.

In summary, lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride and other tri-*tert*-alkoxyaluminum hydrides are convenient reagents for reducing aldehydes, even in the presence of reactive ketones, with 98-100% chemoselectivity under mild conditions. The reagents are readily synthesized from LiAlH_4 and the corresponding alcohols. Further, the mildness and the remarkable functional group tolerance of these hindered lithium tri-*tert*-alkoxyaluminum hydrides⁹ should permit their use for chemoselective reductions in multifunctional molecules. Other unique reduction characteristics of these highly hindered trialkoxyaluminum hydrides are being actively investigated.

Acknowledgment. I thank Professor Herbert C. Brown of Purdue University for stimulating discussions.

Registry No. Hexanal, 66-25-1; 2-heptanone, 110-43-0; benzaldehyde, 100-52-7; acetophenone, 98-86-2; cyclohexanone, 108-94-1; LTEPA, 79172-99-9.

(8) Synthesized from 3-methyl-3-pentanol and LiAlH_4 in THF.

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Acetyl Hypofluorite as a Taming Carrier of Elemental Fluorine for Novel Electrophilic Fluorination of Activated Aromatic Rings

Summary: The new fluorinating reagent CH_3COOF , which is prepared in situ from F_2 , is used for electrophilic aromatic fluorinations of activated aromatic rings.

Sir: Several methods dealing with specific introduction of a fluorine atom into an aromatic ring are described in the literature. Yet this transformation is not a trivial task. The most widely used method is probably still the Balz-Schiemann procedure which requires a suitable aromatic amino group.

Recently, however, the use of electrophilic fluorinating agents is increasing. The expensive XeF_2 and CF_3OF , for example, were used several times with some success.¹ In quite a few cases, the latter reagent adds across double bonds or produces *gem*-difluorides and ketones.² Very recently a new and potentially explosive reagent CsSO_4F was used for fluorination of some substituted benzenes.³ Several groups also tried direct fluorination with elemental fluorine, but on a preparative scale these reactions are inefficient and produce mainly tars.⁴

We describe in this paper an indirect use of elemental fluorine for electrophilic fluorination of activated aromatic compounds in which relatively clean reactions were obtained unlike those employing direct action of F_2 , CF_3OF , and other reagents on aromatic rings.

We have already described the in situ synthesis and some of the chemistry of CF_3COOF and $\text{CF}_3\text{CF}_2\text{OF}$.⁵ The oxygen-bound fluorine in these compounds is similar or even more reactive than the one in CF_3OF . Thus, when several aromatic rings were treated with these fluoroxy reagents, usually low to very low yields of the desired fluorinated compounds were obtained along with various polymeric tars. However, we have found that bubbling elemental fluorine through a suspension of CH_3COONa or NaF in CFCl_3 (Freon) and acetic acid produces the novel acetyl hypofluorite, CH_3COOF (1).⁶ While this compound still possesses an electrophilic fluorine, it should be less polarizable and hence less reactive than the other known compounds possessing the OF moiety. In reactions with 1, neither a purification nor any isolation of this oxidizing reagent is necessary. Two methods were employed. In method A an aromatic compound is added to the reaction vessel in which 1 was formed at $-75\text{ }^\circ\text{C}$, and in method B the acetyl hypofluorite is transferred with the aid of a stream of nitrogen into a cold ($-75\text{ }^\circ\text{C}$) solution of the substrate in CFCl_3 or $\text{CFCl}_3/\text{CHCl}_3$. We found that usually method B is more suitable, especially when very activated rings are present. Some typical experiments are summarized in Table I.

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