**Nucleotide Analysis.** Mobile phase consisted of a 90:10 mixture of 1 mM *tert*-butylammonium dihydrogen phosphate (Aldrich) in 0.065 M $KH_2PO_4$ + methanol (OmniSolv, EM Science, Gibbstown, NJ). Glass-distilled water (OmniSolv, EM Science) was used for mobile-phase buffer preparation. Instrumentation consisted of a Waters M6000 pump, WISP 710B autosampler, M-490 variable-wavelength detector at 254 nm, and 840 data handling systems (Waters Chromatography Division, Milford, MA) connected to a DEC LA50 printer (Digital Equipment Corp., Marlboro, MA). A 5 μm Spherisorb S5ODS2 column, 150 × 4.6 mm (Regis Chemical, Morton Grove, IL), was used in series with a PP-18 Spheri-10 guard column, 30 × 4.6 mm (Brownlee Labs, Santa Clara, CA). Mobile-phase flow rate was 1 mL/min, and 20 μL of standards and samples were injected. Peak heights were used for quantitation and all results were normalized to [ATP] + [ADP] + [AMP] = 1 mM.

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# Selective Deuteriation of Arylalkanes with Mixed Metal Reagents

Kofi Ofosu-Asante and Leon M. Stock*

*Department of Chemistry, The University of Chicago, Chicago, Illinois 60637*

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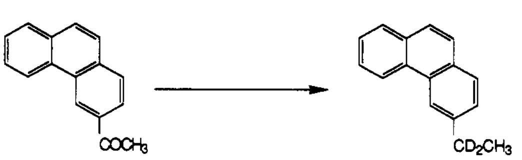
There are several procedures for introducing deuterium atoms into the benzylic positions of arylalkanes.[1-6] The most common procedures are base- and palladium-catalyzed deuterium–hydrogen exchange,[2,3] Clemmensen and palladium-catalyzed reduction of aromatic carbonyl compounds,[4,5] and lithium aluminum deuteride reduction of carbonyl groups to alcohols, tosylation of the alcohols, and the reduction of the tosylates to the hydrocarbons.[6] The preparative procedures have certain shortcomings. The base- and palladium-catalyzed exchange reactions, though selective, are rather slow and often require repetition of the reactions to attain a high degree of deuterium atom incorporation.[2,3] The Clemmensen reduction of carbonyl compounds is nonselective.[4,5] The reduction of a carbonyl compound to an alcohol, tosylation, and reduction produces both alkanes and alkenes.[6] In this paper, we report another facile, selective deuteriation approach that is based upon a mixed metal reagent. These reagents react rapidly and produce highly enriched isotopically pure products.

During the synthesis of some deuterium labeled tetrahydronaphthalene derivatives, it was observed that the use of aluminum chloride and lithium aluminum hydride at various stages of the synthesis had no effect on the deuterium atom content in the starting hydrocarbons. This observation and the fact that Brown and co-workers and Nystrom and Berger had used a mixture of aluminum chloride and lithium aluminum hydride to reduce diaryl ketones and aryl alkyl ketones[7-9] to the corresponding hydrocarbons, prompted us to adopt their method to introduce deuterium selectively in the benzylic positions in arylalkanes as illustrated in eqs 1 and 2.

tetralin-1,1-*d*$_2$ (1)



3-(ethyl-1,1-*d*$_2$)phenanthrene (2)

In their study, Nystrom and Berger observed that the ease and extent of reduction of the carbonyl group depended on the order of mixing of reactants and on the nature of the substituent present in the organic compound.[9] They established that optimal results were usually obtained when the mixture of the ketone and aluminum chloride in ether was added to a solution of equimolar quantities of aluminum chloride and lithium aluminum hydride in ether,[9] and the reaction mixture was stirred under dinitrogen at 35 °C.

The reactions of several ketones were carried out in accord with the recommendations of Nystrom and Berger.[9] The crude products were easily isolated by vacuum distillation or flash column chromatography. Although Nystrom and Berger did not report the formation of alkenes, we found that their method gave 6–17% alkene. Accordingly, we obtained the pure labeled alkanes by careful column chromatography. The experimental results for several representative ketones are reported in Table I.

The mixed metal reduction technique selectively introduced two atoms of deuterium in place of the oxygen atom in 35–45 min. The products were characterized by $^1H$ NMR, $^2H$ NMR, IR, and GC–MS, and the product distributions were calculated from gas chromatographic data. The deuterium content exceeded 96% of the expected value in every case with the monodeuterium derivative as the principal contaminant. The possibility of deuterium incorporation into the carbon adjacent to the original carbonyl group and into the aromatic position was investigated by IR and $^2H$ NMR spectroscopies. Both techniques showed that the arylalkanes were deuteriated selectively in the benzylic position. In each case, the IR spectrum revealed a new intense band at 2100–2200 cm$^{-1}$ due to $C_{Al-D}$ stretch. $^2H$ NMR spectroscopy revealed that the position adjacent to the former keto group was free of deuterium atoms, but that the aromatic positions contained about 2% deuterium atoms. The Clemmensen reduction, unlike the mixed metal and the palladium-catalyzed reductions, incorporates deuterium at the original carbonyl carbon, in the aromatic position, and in the adjacent carbon atom. These side reactions are minimized in the mixed metal procedure by the short reaction times.

A more striking disparity was observed between the reaction of 1-tetralone in the presence of palladium catalyst under dideuterium gas and in the presence of mixed metal deuteride. The former gave tetralin-*1,1,4,4-d*$_4$ and the latter gave tetralin-*1,1-d*$_2$, as shown in Figure 1A. The formation of the tetralin-*1,1,4,4-d*$_4$ in the palladium-cata-

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**Table I. Mixed Metal Reagent Deuteration of Ketones**[a]

| compound | method | yield, % | major product | composition, % | minor product | % |
|---|---|---|---|---|---|---|
| benzophenone | A, I | 84 | diphenylmethane-*1,1*-$d_2$ | 100 | – | – |
| benzophenone | B, I | 96 | diphenylmethane-*1,1*-$d_2$ | 100 | – | – |
| 3-bromoacetophenone | B, II | 79 | 3-(1-hydroxyethyl-*1*-$d_1$)-1-bromobenzene | 94 | 3-(vinyl-*1*-$d_1$)-1-bromobenzene | 6 |
| 1-tetralone | A, III | 87 | tetralin-*1,1*-$d_2$ | 85 | 1,2-dihydronaphthalene-*1*-$d_1$ | 15 |
| 1-acetonaphthone | A, III | 96 | 1-(ethyl-*1,1*-$d_2$)naphthalene | 93 | 1-(vinyl-*1*-$d_1$)naphthalene | 7 |
| 2-acetonaphthone[b,c] | A, III | 86 | 2-(ethyl-*1,1*-$d_2$)naphthalene | 84 | 2-(vinyl-*1*-$d_1$)naphthalene | 10 |
| 3-acetylphenanthrene[b,d] | A, II | 88 | 3-(ethyl-*1,1*-$d_5$)phenanthrene | 82 | 3-(vinyl-*1*-$d_1$)phenanthrene | 17 |

[a] The reactions were carried out for 30–45 min after the addition of the ketone. [b] The reaction was carried out for 2–3 h. [c] The crude product contained 6% of the alcohol. [d] Approximately 12% of the starting material and 1% of the alcohol were present in the crude product.

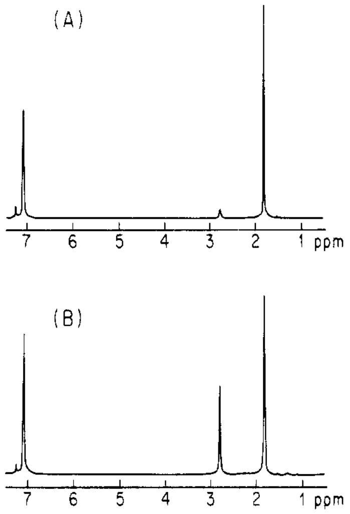

**Figure 1.** $^1$H NMR (500 MHz) spectra of the reduction products of 1-tetralone using (A) palladium-catalyzed reduction with dideuterium, and (B) with a mixed metal reagent reduction through aluminum chloride and lithium aluminum deuteride.

lyzed reaction is not surprising. Indeed, it was observed previously that the palladized carbon in the presence of dideuterium gas not only reduces the carbonyl group but also effects deuterium–hydrogen exchange in the 4-position.[3] The mixed metal reagent cannot accomplish this exchange reaction.

Mechanistically, the mixed metal hydride reduction appears to follow the same path as the catalytic reduction.[10-13] Both reactions proceed via an intermediate alcohol followed by hydrogenolysis to produce the hydrocarbon.

## Experimental Section

All the starting materials including lithium aluminum deuteride (98% *d*) and heavy water (99.8%) were commercially available and were purified as necessary.

$^1$H NMR spectra were recorded at 500 MHz. The $^2$H NMR spectra were recorded at 400 MHz on solutions in dichloromethane. The deuterium content and isotopic purity were determined from mass spectroscopic data that were obtained with an HP GC–MS system.

**Mixed Metal Deuteride Reduction Procedure. Method A.** The reduction was effected via the approach of Nystrom and Berger.[9] In a typical reaction, lithium aluminum deuteride (0.42 g, 10 mmol) in dry ether (10 mL) was stirred for 15 min under dinitrogen as aluminum chloride (1.4 g, 11 mmol) in dry ether (10 mL) was slowly added. Five minutes after the addition, a mixture of benzophenone (1.7 g, 10 mmol) and aluminum chloride (1.4 g, 11 mmol) in dry ether (20 mL) was added to the solution of mixed metal hydride. The reaction mixture was vigorously stirred for 45 min under dinitrogen, and the reaction was quenched with heavy water (10–15 mL) followed by 6 N sulfuric acid (11 mL). The reaction mixture was further diluted with water (25 mL), and the aqueous layer was extracted with four portions of ether (4 × 30 mL). The combined organic layers were washed with water, 10% sodium bicarbonate solution, and again with water and dried. The solvent was removed under vacuum to recover the product (1.4 g, 84%).

**Method B.** The same procedure as described in method A was used except that the ketone was dissolved in ether (without the addition of aluminum chloride) and then added to the equimolar quantities of lithium aluminum deuteride and aluminum chloride.

The original products proved to be mixtures of the desired labeled compound contaminated with the starting material, the intermediate alcohol, and the alkene. Flash chromatography and vacuum distillation were used to isolate these materials in some experiments. Subsequent work revealed that column chromatography was more suitable, and the crude products were purified by this method to obtain the arylalkanes as noted in the table. In method I, the crude product was chromatographed on silica gel (60–200 mesh, 140A) with hexane as eluent; in method II, the alkene was separated by elution with hexane as described in I and the alcohol was eluded with ether; in method III, the crude product was chromatographed on silica gel (230–400 mesh, 60A) with hexane as eluent.

The alkanes were characterized by GC–MS and NMR spectroscopy. The deuterium content exceeded 96% of the expected value in every case with the $d_1$ compound as the principal contaminant.

**Acknowledgment.** We thank the Gas Research Institute for financial support.

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# Ortho-Directed Lithiation in $\pi$-Deficient Diazinyl Heterocycles

Ronald J. Mattson* and Charles P. Sloan

*CNS Chemistry, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 26492-7660*

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Over the past decade, the ortho-directed aromatic lithiation reaction has become a valuable and efficient synthetic method. While this reaction has been thoroughly studied with some heterocycles such as pyridine, very few ortho-lithiations of pyrazines, pyrimidines, or pyridazines have been reported, and none in high yield. 5-Bromo- and 5-methylpyrimidines are reported to lithiate at C-4[1,2] and

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