

# Catalytic Transfer Hydrogenation Reactions for Undergraduate Practical Programs

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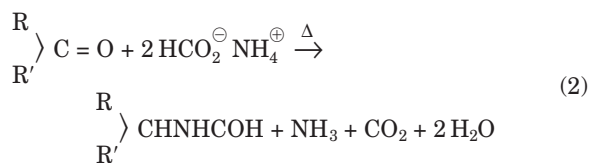
Catalytic transfer hydrogenation (CTH) reactions involve the transfer of hydrogen, in the presence of a suitable catalyst, between a donor compound,  $DH_x$ , and an acceptor compound, A (eq 1).



As a result of the transfer, unsaturated groups in A may be reduced and/or susceptible bonds may be cleaved by hydrogenolysis. Reviews of reactions of this type by Brieger and Nestrick (1) and by Johnstone, Wilby, and Entwistle (2) show that a wide variety of unsaturated groups can be reduced using an almost equally wide variety of donor compounds and catalysts. In the early work in this field the donor compound–catalyst combination used most frequently was cyclohexene in the presence of 5% or 10% palladium supported on carbon (Pd/C). However, as noted by Johnstone and his coauthors (2), the indifferent yields and long reaction times associated with many of the reactions investigated mediated against the acceptance of CTH as a generally useful synthetic technique.

The situation has changed significantly in recent years, particularly following the introduction of ammonium formate as a hydrogen donor. This cheap, nontoxic, crystalline salt is used by simply heating it, together with the acceptor compound, in a suitable refluxing solvent (often methanol or acetic acid) in the presence of 5% or 10% Pd/C. As indicated in Ram and Ehrenkaufers review of the use of ammonium formate in organic synthesis (3), the salt can be used to reduce or hydrogenolyze a variety of functional groups; yields are often excellent after comparatively short reaction times.

Ram and Spicer (4) have subsequently shown that, in addition to the groups listed by Ram and Ehrenkaufers (3), the carbonyl group in a number of aromatic aldehydes and ketones can be reduced to a methylene group, possibly via the intermediate arylcarbinol, using ammonium formate in the presence of 10% Pd/C at 100 °C. These last reductions are of particular interest when contrasted with the Leuckart reaction (5), in which carbonyl compounds undergo reductive ammonation when heated at high temperature (ca. 200 °C) for comparatively long periods, with ammonium formate in the *absence* of a catalyst (eq 2):



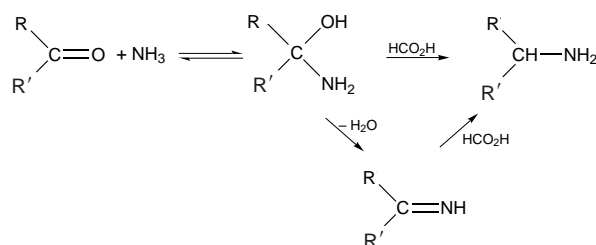
Under Leuckart conditions nitro groups are not reduced and aryl halides are not cleaved as they are under CTH conditions. Similarly, whereas aryl amines or their *N*-formyl derivatives are clearly stable under Leuckart conditions, aryl

amines appear to be hydrogenolyzed under CTH conditions, since aryl cyanides are reduced to aryl methanes (3).

Results cited in Moore's review (5) of the Leuckart reaction suggest that, at the high temperatures used, ammonium formate dissociates (eq 3).



The ammonia produced then reacts with the carbonyl compound to produce an  $\alpha$ -hydroxyamine, which may be reduced by formic acid directly, or indirectly via an imine:



In contrast, the simplest explanation of CTH using ammonium formate is that the catalyst facilitates both decarboxylation of the salt (eq 4) and subsequent reduction/hydrogenolysis of the acceptor compound. As indicated in the review by Johnstone and coauthors (2), however, the detailed mechanism of reduction may be complex.



Although CTH reactions using ammonium formate are not the panacea for all reductive ills, they do, in many cases, provide an attractive alternative to other available methods. This is particularly so in undergraduate practical programs where the low cost of the reactions and their simplicity, both in terms of apparatus and manipulations involved, are highly desirable features. In fact, examples of CTH reactions involving ammonium formate, suitable for use by undergraduates, are already available. Krishnamurthy and Sathyanarayan (6) have described the reduction of the double bond in cinnamic acid and in benzalacetophenone, and De, Gambhir, and Krishnamurthy have recently described the reduction of 4-vinylbenzoic acid in this *Journal* (7). Details of a reaction involving catalytic transfer hydrogenolysis are also available. Thus Lindeberg has published, also in this *Journal* (8), details of an enzyme-catalyzed synthesis of methyl *N*-benzyloxycarbonyl-L-aspartyl-L-phenylalaninate from which the *N*-protecting group is removed, by treatment with ammonium formate/10% Pd/C, to give Aspartame.

To supplement these CTH reactions involving ammonium formate, three further examples, which have been used successfully in undergraduate courses at the University of Plymouth, are described below. The first illustrates

the reduction of nitro compounds as reported by Ram and Ehrenkaufner (3, 9). Nitrobenzene is quantitatively reduced to aniline, as evidenced by TLC, by treatment with ammonium formate and 10% Pd/C for 30 min in refluxing methanol. Because it is difficult to purify small volumes of liquid by distillation, students characterize the aniline by converting it to the *N*-benzoyl derivative (benzanilide). The second and third reactions both illustrate reduction of a carbonyl to a methylene group and are based on the work of Ram and Spicer cited above (4). Specifically, students reduce benzophenone to diphenylmethane. Again, quantitative conversion occurs within 30 min and the reaction is easier to perform than the alternative Clemmensen or Wolff-Kischner reductions. Alternatively, students can reduce fluorenone to fluorene. This conversion, which was not investigated by Ram and Spicer, is particularly popular; students find the quantitative conversion of the bright yellow ketone to the snow-white hydrocarbon a welcome change from the conversion of one white compound to another!

## Experimental Procedure

### Reduction of Nitrobenzene

Methanol (10 mL), 10% Pd/C (250 mg), and ammonium formate (2.90 g) are added to nitrobenzene (1.23 g, 10 mmol) contained in a 100 mL conical flask having a B24 neck.<sup>1</sup> Any solids adhering to the joint are washed into the flask with more methanol (10 mL). A stirrer magnet is added, a water condenser is fitted, and the reaction mixture is stirred and heated, under gentle reflux, for 30 min. Some ammonium carbonate usually collects in the bottom of the condenser; it must be returned to the flask using a long glass rod because failure to do so could result in an explosion due to the condenser becoming blocked. The reaction mixture is cooled and filtered through a pad of filter-aid to remove the catalyst, and the pad is washed with methanol (2 × 10 mL). The filtrate and washings are evaporated to a volume of approximately 20 mL and a sample of the solution is chromatographed on a thin layer of silica gel HF 254, together with authentic specimens of nitrobenzene and aniline; 3% ethyl acetate in hexane is used as the mobile phase. The remaining methanol is then removed by evaporation and a solution of sodium hydroxide (20 mL, 2 mol L<sup>-1</sup>) is added to the residue of crude aniline, followed by benzoyl chloride (0.5 mL); **CAUTION:** do this in a fume chamber. The reaction mixture is shaken vigorously until the odor of the chloride is no longer apparent. Further portions of benzoyl chloride (2 × 0.5 mL) are then added and the reaction mixture is shaken vigorously after each addition, as before. The crude product is collected, washed thoroughly with ice-cold water, and dried. The yield of crude benzanilide is almost quantitative. Material recrystallized from ethanol has mp 160–161 °C; lit mp = 163 °C (10).

### Reduction of Benzophenone

Benzophenone (1.36 g, 7.5 mmol), 10% Pd/C (250 mg),

and ammonium formate (2.50 g) are heated in stirred, refluxing glacial acetic acid (10 mL) as described above for the reduction of nitrobenzene. Chloroform (20 mL) is added to the cold reaction mixture prior to removal of the catalyst, and the catalyst and pad of filter-aid are washed with more chloroform (20 mL). The filtrate and washings are transferred to a separatory funnel, washed first with water (2 × 20 mL) and then with saturated sodium carbonate solution (2 × 20 mL), and dried over anhydrous sodium sulfate. The solvent is then removed from the dry solution by evaporation. When the volume is approximately 15 mL, a sample of the solution is chromatographed together with authentic specimens of starting material and product, as described above for nitrobenzene/aniline. The remaining chloroform is evaporated, yielding chromatographically pure diphenylmethane as an oil, which tends to crystallize if stored in a refrigerator (mp = 26–27 °C [11]). The yield is virtually quantitative and the IR spectrum is identical to that of authentic material (12).

### Reduction of Fluorenone

Fluorenone (1.35 g, 7.5 mmol) is reduced as described above for benzophenone. Chromatographically pure fluorene with an IR spectrum identical to that of authentic material (13) is obtained in almost quantitative yield. The crude hydrocarbon can be recrystallized from hexane; pure fluorene has mp 116 °C (14).

## Note

1. In the event of subsequent evolution of gas from the reaction mixture becoming too vigorous, the use of a flask with a wide neck and a compatible condenser helps to prevent loss of material by "foaming" up and out of the condenser.

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