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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Siya Ram & L. D. Spicer (1992) Temperature and Solvent Dependent Catalytic Transfer Hydrogenolysis in Aromatic Aldehydes and Ketones Via Ammonium Formate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:18, 2673-2681, DOI: 10.1080/00397919208021667

To link to this article: http://dx.doi.org/10.1080/00397919208021667

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SYNTHETIC COMMUNICATIONS, 22(18), 2673-2681 (1992)

TEMPERATURE AND SOLVENT DEPENDENT CATALYTIC TRANSFER HYDROGENOLYSIS IN AROMATIC ALDEHYDES AND KETONES VIA AMMONIUM FORMATE

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<u>Abstract</u>: Temperature control and solvent specification are used to reduce aromatic aldehydes and ketones to intermediate alcohols rather than methylene derivatives using HCO_2NH_4 as a catalytic hydrogen transfer agent. A mechanism for the catalytic reduction is proposed.

The development of fast and efficient methods for chemoselective reductions is a well recognized research objective.¹ In general, most attention has been concentrated on chemical reduction while chemoselective catalytic transfer hydrogenolysis²⁻¹¹ has been less well characterized. Selective transformations have also been reported using a variety of modified hydride reagents.^{12,13} Selectivity without modification of the parent reducing agent, however, has

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rarely been obtained. Here, and in the preceding communication,¹⁴ we report and characterize a catalytic method in which temperature and solvent play a significant role in the selective reduction of aromatic aldehydes and ketones using ammonium formate as the hydrogen donor.

Recently, the effectiveness of ammonium formate as a catalytic hydrogen transfer agent in organic synthesis has been reviewed.¹⁵ This agent has previously been employed in a variety of reduction reactions including the Leuckart reaction¹⁶ for conversion of aldehydes and ketones into primary and secondary amines and in the reduction of aralkyl ketones and aldehydes to alcohols⁴ and methylene derivatives.¹⁰ It has also been successfully used for reduction of α , β -unsaturated nitroalkenes⁵ and aliphatic and aromatic nitro compounds² and nitro esters¹⁷ without affecting functional groups such as nitriles, carbonyls, and esters.

The use of Raney Nickel HCO_2NH_4 to reduce analkyl ketones at room temperature produces high yields of corresponding alcohols with reaction times of 3-5 hr.⁴ In our work with Pd-C/HCO₂NH₄ to reduce aromatic aldehydes and ketones, however, the carbonyl was fully reduced to methylene with high efficiency at $115\pm5^{\circ}C$ in acidic media.¹⁰ We hypothesized nevertheless this reaction proceeds via an alcohol intermediate <u>2</u>, as illustrated in Scheme I where the palladium



Where R, = H, CH3, C2Hs, C8Hs

Scheme I

formate intermediates preceding 2 and 3 may eliminate Pd stepwise as shown or via a cyclic one-step concerted process. To investigate this mechanism we have studied this reaction at a lower temperature ($70\pm5^{\circ}C$), under neutral conditions, using benzaldehyde, acetophenone, propiophenone and benzophenone as model compounds. In each case, partial reduction of the carbonyl group to an alcohol was observed as shown in the Table. In the case of benzaldehyde, it should be noted benzylamine (13%) and dibenzylamine (71%) were also formed along

Substrate	Product ^a	Yield ^b %	Retention time of product ^C in <u>min, GC</u>
с ₆ н ₅ сно	с ₆ н ₅ сн ₂ он	16 ^d	4.85
с ₆ н ₅ сосн ₃	с ₆ н ₅ снонсн ₃	91	-
с ₆ н ₅ сосн ₂ сн ₃	с ₆ н ₅ снонсн ₂ сн ₃	80	5.86
с ₆ н ₅ сос ₆ н ₅	с ₆ н ₅ снонс ₆ н ₅	86	8.41

Table: Reduction of aromatic aldehydes and ketones to the corresponding alcohols.

^a All products were characterized by ¹H NMR, TLC, and M.P. ^b Isolated yields.

^C 5% Methyl silicone oil, OV-101, column size 50 cm x 1/8", temperature programmed 50°C (3 min hold) to 280°C (5 min hold) at a rate of 25°C/min, helium flow rate 30 ml/min.

^d Reduction of benzaldehyde under the reported conditions yielded dibenzylamine as the product (retention time 8.93 min under above GC conditions).

with benzyl alcohol as characterized by GC^{19} and ¹H NMR. At room temperature (ca. 25^oC), only starting materials are recovered in this reaction.

When the diphenylmethanol formed in the reduction of benzophenone with ammonium formate /10% Pd-C is allowed to react further by adding glacial acetic acid and raising the temperature to $115\pm5^{\circ}$ C, diphenylmethane is formed. These results clearly support the conclusion that in the reduction of aldehydes and ketones with this reaction an alcohol intermediate is generated which, subsequently, dehydrates to the carbocation under acidic conditions and finally reduces to the methylene derivative¹⁰. It is noted that in heterogeneous catalytic hydrogenations with palladium the hydrogen donor, formic acid, first combines with Pd_0 and generates a complex [H-Pd-CO₂H] which, subsequently, reacts with the substrate.¹⁸ We believe that a similar mechanism also operates with ammonium formate.

This reduction method proceeds smoothly with a variety of aromatic aldehydes and ketones¹⁰ and is generally completed within 10-30 min making it particularly useful for labeled molecules of biomedical interest such as those utilizing the C-11 radioisotope $(t_{1/2}$ -20.4 min) for positron emission tomography studies. Other approaches to the reduction of aldehydes and ketones via ammonium formate are in general kinetically slower.⁴ Reduction of aliphatic aldehydes and ketones with ammonium formate under the conditions reported here was unsuccessful.

We have now shown that $Pd-C/HCO_2NH_4$ can be used to reduce the >CO group to either >CHOH or CH_2 solely via manipulation of the reaction conditions rather than modification of the reducing agent, a very useful feature of this catalytic reagent. In general, $Pd-C/HCO_2NH_4$ appears to be a particularly advantageous hydrogenation catalyst where selectivity and rapidity are required.

Experimental:

All chemicals and solvents were obtained from Aldrich Chemical Company and were used without further purification. ¹H NMR spectra were obtained on General Electric GN-300 MHz and GN-500 MHz spectrometers. GC analysis was carried out using a 5% methyl silicone oil, OV-101 column. Most of the reactants and products in these reactions were identified by comparison of retention times with those from commercially available authentic samples. Otherwise, identification was based on ¹H NMR, IR, and mass spectral data.

Reduction of Benzaldehyde/Acetophenone/Benzophenone/

Propiophenone to the Corresponding Alcohols. General Procedure:

To a suspension of an appropriate aromatic ketone/aldehyde (1 mmol) and 10% palladium on carbon (0.2 g to 0.3 g) in CH₃OH (12-15 ml), ammonium formate (6-8 mmol) was added. The reaction mixture was then stirred under reflux conditions. Progress of the reaction was monitored both by GC analysis¹⁹ under conditions reported above and by thin layer chromatography at 5 min intervals. At completion, the reaction mixture was cooled to room temperature and diluted with ether (70-80 ml). The catalyst was then removed via filtration through a celite pad and the filtrate was washed with water and dried over anhydrous sodium sulfate. The organic layer on evaporation gave the corresponding alcohols illustrated in the Table. The products were characterized by comparison of ¹H NMR, IR and GC retention times with those from commercially available authentic samples. Reduction of Diphenylmethanol into Diphenylmethane:

To a solution of diphenylmethanol (0.45 g, 0.02 mol) in glacial acetic acid (10 ml), 10% palladium on carbon (0.25 mg)

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was added under an argon atmosphere, followed by addition of ammonium formate (1.24 g, 0.02 mol) in a single portion. The resulting reaction mixture was refluxed with stirring at 110° C and the reaction was monitored by GC^{19} at 10 min intervals. At 20 min, GC analysis showed complete disappearance of the starting material (retention time 7.46 min). The reaction mixture was cooled to room temperature and diluted with ether (80 ml). The catalyst was filtered off and the filtrate was washed with water (20 ml), saturated sodium bicarbonate (20 ml), then again with water (20 ml), and dried over Na_2SO_4 . The organic layer on evaporation gave 0.4 g (98%) of product, which was characterized by comparison with an authentic sample (Aldrich Chemical Co.) Acknowledgement:

NMR data were obtained at the Duke University NMR Spectroscopy Center which was established with support from the NIH, NSF and the North Carolina Biotechnology Center.

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19. Column 5% methyl silicone oil, OV-101, 50 cm x 1/8", temperature programmed $50^{\circ}C$ (3 min hold) to $280^{\circ}C$ (5 min hold) at a rate of $25^{\circ}C/min$; flow rate of helium gas 30 ml/min.

(Received in USA 10 May, 1992)