

REDUCTION OF ALDEHYDES AND KETONES TO METHYLENE DERIVATIVES USING AMMONIUM FORMATE AS A
CATALYTIC HYDROGEN TRANSFER AGENT^{1,2}

Siya Ram* and Leonard D Spicer

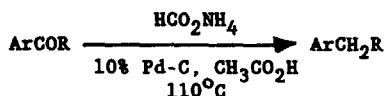
P.E.T. Facility/Nuclear Medicine
Departments of Radiology and Biochemistry
Duke University Medical Center
Durham, North Carolina 27710

Summary. Various aromatic aldehydes and ketones were reduced to the corresponding hydrocarbons using ammonium formate as the hydrogen source.

The transformation of the carbonyl group of aldehydes and ketones to methylene derivatives can be achieved by chemical methods such as Clemmensen reduction³, Wolff-Kishner reduction⁴, $\text{LiAlH}_4\text{-AlCl}_3$ ⁵, $\text{NaBH}_4\text{-CF}_3\text{CO}_2\text{H}$ ⁶, $\text{Et}_3\text{SiH-BF}_3$ or $\text{CF}_3\text{CO}_2\text{H}$ ⁷⁻⁹, HI-Phosphorus¹⁰⁻¹¹ or by catalytic hydrogenation¹². Catalytic transfer hydrogenation of the carbonyl group, however, has been reported only by Brieger and coworkers¹³⁻¹⁴ using various hydrogen donors, palladium-carbon as the catalyst and ferric chloride as the Lewis acid promoter. In general, this reaction requires 3-12 hrs for completion. Recently, the effectiveness of ammonium formate as a catalytic hydrogen transfer agent in organic synthesis has been reviewed¹⁵. This agent has previously been employed in the Leucart Reaction¹⁶ for conversion of aldehydes and ketones into primary and secondary amines.

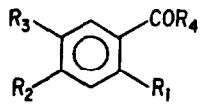
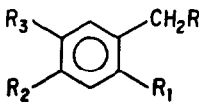
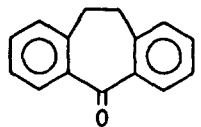
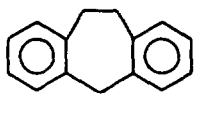
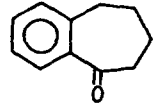
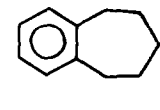
In our ongoing program to develop efficient and fast synthetic methods for ^{11}C - α -amino acids (^{11}C -half life = 20.4 min) such as [^{11}C -carboxyl]phenylalanine, (^{11}C -carboxyl) tyrosine, etc., via reductive carboxylation of acylnitromethane derivatives, we have developed a mild and rapid reduction of aromatic aldehydes and ketones to the corresponding methylene derivatives using ammonium formate as shown in Scheme 1.

SCHEME 1



R - H, alkyl, aryl, heteroaryl

Table 1 Reduction of aldehydes and ketones to the corresponding methylene derivatives using HCO_2NH_4 with 10% Pd-C at 110°C

Substrate	Product ^b	Reaction Time in Min	Yield ^a %	Retention Time of Product ^d GC	Relative R _f Value of Product ^c TLC	
						
1.	$\text{R}_1 = \text{OH}, \text{R}_2 = \text{OCH}_3$ $\text{R}_3 = \text{R}_4 = \text{H}$	18	63	4.67	0.54	
2.	$\text{R}_1 = \text{R}_2 = \text{OCH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$	10	57	4.54	5.89	
3.	$\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = \text{OCH}_3, \text{R}_4 = \text{H}$	25	70	3.01	3.95	
4.	$\text{R}_1 = \text{R}_4 = \text{H}$, $\text{R}_2 = \text{R}_3 = \text{OCH}_3$	20	68	4.35	3.49	
5.	$\text{R}_1 = \text{R}_2 = \text{OCH}_3$, $\text{R}_4 = \text{CH}_3, \text{R}_3 = \text{H}$	20	64	4.87	8.75	
6.	$\text{C}_6\text{H}_5\text{CHO}$	$\text{C}_6\text{H}_5\text{CH}_3$	20	1.5(10) ^e	0.97	--
7.	$\text{C}_6\text{H}_5\text{COCH}_3$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3$	30	21(55) ^e	2.14	3.07
8.	$\text{C}_6\text{H}_5\text{COC}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_5$	15	92	5.46	2.05
9.	$3\text{-C}_6\text{H}_5\text{COC}_5\text{H}_4\text{N}$	$3\text{-C}_6\text{H}_5\text{CH}_2\text{C}_5\text{H}_4\text{N}$	20	68	2.94	0.90
10.			10	41	4.00	2.27
11.			30	54	1.63	3.90
12.	$[\text{C}_6\text{H}_5\text{CH}=\text{CH}]_2\text{CO}$	$[\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2]_2\text{CO}$	10	88	1.90	1.57

(a) Unoptimized, isolated yields are based on a single experiment (b) Characterized via comparison with authentic samples (IR, ^1H NMR, TLC and m p) (c) Relative R_f value = distance travelled by product/distance travelled by starting material on TLC, using E Merck silica gel plates, mobile phase ethyl acetate Hexane (7/93) (d) 5% Methyl silicone oil, OV-101, column size 50 cm x 1/8", temperature programmed 50°C (1 min hold) to 280°C (3 min hold) with rate of $25^\circ\text{C}/\text{min}$, helium flow rate 30 ml/min. (e) Yields in parentheses represent longer reaction times and are based on GC analysis as described in text

A typical procedure for reduction of aldehydes and ketones is as follows:

To a stirred suspension of an appropriate aldehyde or ketone (7.5 mmole) and 10% Pd-C (0.350 g) in glacial acetic acid (10 ml), the anhydrous ammonium formate (38 mmole) was added in a single portion under argon. The resulting reaction mixture was stirred at $110^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for 10-30 min. The progress of reaction was monitored by TLC and GC. After completion of the reaction, 50 ml of CHCl_3 was added, and the catalyst was removed by filtration through a celite pad and washed with CHCl_3 (20 ml). The combined organic filtrate was washed with water (20 ml x 2), then with saturated sodium bicarbonate solution (20 ml x 2), and dried over anhydrous Na_2SO_4 . The organic filtrate on evaporation, either under reduced pressure or at normal pressure, afforded the desired product, which was further purified by column chromatography over silica gel using an ethyl acetate-hexane mixture as the mobile phase. The phenolic derivatives were obtained by direct evaporation of filtrate after removal of the catalyst. Characterization data for this new procedure are shown in Table 1.

In most cases, the reaction is over within 10-30 min, however, in the case of 1-benzosuberone(11) and dibenzosuberone(10), reaction did not proceed to completion, and 40-45% of the ketone starting materials were observed on GC analysis [5% methyl silicone oil OV-101, column size 50 cm x 1/8", temperature programmed 50°C (1 min hold) to 280°C (3 min hold) at a rate of $25^{\circ}\text{C}/\text{min}$, helium flow rate 30 ml/min]. Neither increasing the reflux time (30 min to 4 hrs) nor adding an additional amount of ammonium formate changes the product/substrate ratio in the reaction mixture. The reduction of acetophenone was sluggish. After a 30 min reaction time interval, the product/substrate ratio in the reaction mixture was 1/5 observed by GC analysis (as described above, except initial temperature hold time 3 min). However, upon adding an additional amount of HCO_2NH_4 and increasing the reaction time up to 4 hr, the product/substrate ratio changed to 55/44. In the case of benzaldehyde, 15% toluene, 34% benzyl alcohol (retention time 4.9 min) and 60% high boiling byproduct (retention time 8.9 min) were observed in the reaction mixture after 20 min at 85°C . Prolonging the reaction time slowly increases the concentration of toluene (Table 1) with reduction of benzyl alcohol. This important observation provides evidence that reduction of aldehydes and ketones to hydrocarbons proceeds via the alcohol intermediate, which is further confirmed by our finding that diphenylmethanol is rapidly converted to diphenylmethane under the experimental conditions reported here. The poor yield of toluene may be due to its low boiling point.

These results demonstrate a rapid, mild and selective reduction of a wide variety of aromatic aldehydes and ketones to methylene derivatives under moderate reaction conditions and can be an attractive alternative for Wolff-Kishner or Clemmensen reduction, provided other functionalities such as nitro or halo substituents are not present in the substrate, since these groups are readily reduced or displaced¹⁷⁻¹⁸. We have found, however, this procedure is not applicable for reduction of conjugated olefinic carbonyl groups, as

evidenced by the reduction of the double bond of debenzylideneacetone(12) to diphenethyl ketone in preference to the carbonyl group. It should also be noted in Table 1 that this procedure is useful for the synthesis of 2,4-dimethoxyethylbenzene, which is a key intermediate in the synthesis of Eticlopride¹⁹, a selective dopamine D₂-receptor antagonist.

Acknowledgement: We thank Professor Richard E. Ehrenkaufner for helpful discussions. This work was supported by Radiology, Duke University Medical Center

References

*To whom correspondence should be addressed

1. S. Ram and L. D. Spicer; Tetrahedron Letters, 28, 515 (1987)
2. S. Ram and L. D. Spicer, Synthetic Commun., 17, 415 (1987)
3. E. Vedejs; Org. React., 22, 401 (1975), E.L. Martin, Org. React. 1, 155 (1942)
4. D. Todd, Org. React., 4, 378 (1948)
5. J. Blackwell and W.J. Hickinbottom, J. Chem. Soc., 1405 (1961).
6. G.W. Gribble, W.J. Kelly and S.E. Emery; Synthesis, 763 (1978)
7. J.L. Fry, M. Orfanopoulos, M.G. Adlington, W.P. Dittman and S.B. Silverman, J. Org. Chem. 43, 374 (1978)
8. C.T. West, S.J. Donnelly, D.A. Kooistra, M.P. Doyle; J. Org. Chem., 38, 2675 (1973)
9. D.N. Kursanov, Z.N. Parnes and N.M. Loim; Synthesis, 633 (1974)
10. C. Bradsher and F. Vingiello, J. Org. Chem., 13, 786 (1948).
11. R. Reimschneider and H. Kassahn; Ber., 92, 1705 (1959)
12. R.L. Augustine; Catalytic Hydrogenation, Dekker, New York (1965)
13. G. Brieger, T.J. Nestruck and T.H. Fu; J. Org. Chem., 44, 1876 (1979)
14. G. Brieger and T.H. Fu; J. Chem. Soc. Chem. Commun., 757 (1976)
15. S. Ram and R.E. Ehrenkaufner, Synthesis, 91, (1988)
16. M.L. Moore, Org. React., 5, 301 (1941)
17. S. Ram and R.E. Ehrenkaufner, Tetrahedron Letters, 25, 3415 (1984).
18. M.K. Anwer and A.F. Spatola; Tetrahedron Letters, 26, 1381 (1985)
19. T. dePaulis, Y. Kumar, L. Johansson, S. Ramsby, H. Hall, M. Sallemark, K. Angeby-Moller and S.-O. Ogren, J. Med. Chem., 29, 61 (1986)

(Received in USA 28 March 1988)