Nickel(0)-Catalyzed Sodium Borohydride Hydrogenolysis of Aromatic Bromides

Shaw-Tao Lin and Jerome A. Roth*

Department of Chemistry, Northern Michigan University, Marquette, Michigan 49855

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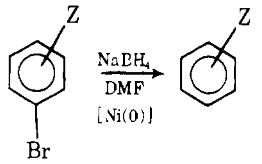
The relatively valuable synthetic process of removing halides from aromatic rings has been traditionally quite difficult. Occasionally this has been done via Grignard reagent or organozinc hydrolysis.[1] More recently, lithium–copper hydride complexes and aluminum hydride systems have been employed.[2,3] Very recently, reports of displacement of halide by $LiAlH_4$–transition metals have appeared.[4] Also, substitution by cyanide, catalyzed by zero-valent transition metals, has been reviewed.[5] We wish to report a simple, mild-conditions variation which does not entail the handling of air-sensitive or pyrophoric compounds and which often gives good yields of hydrogenolysis products.

Results and Discussion

There is no appreciable reaction between $NaBH_4$ and aryl halides under most conditions. However, we have discovered that, in analogy to aromatic cyanation,[5] BH_4^- in the presence of catalytic amounts of tris(triphenylphosphine)nickel(0) [$Ni(0)(Ph_3P)_3$] may serve as a more powerful nucleophilic reagent. A second important condition is that the solvent must be *N,N*-dimethylformamide (DMF), as ethanol, methanol, and THF all proved ineffective for the catalyst preparation or gave poor yields (Table I). The reaction is best performed at about 70 °C, usually under nitrogen. The conversion of the aromatic bromide is usually fair to good after stirring for 3–20 h. The aromatic chlorides also react, but much more slowly (Table I). Similar behavior has been observed for aryl iodides and alkyl halides.[6]



The reaction was found to be first order in nickel complex, but under the catalytic conditions employed for most runs the kinetic expression was found to be pseudo zero order in $NaBH_4$, PPh_3, and Ar–Br through at least the first 50% of the reaction.

A new variation on the preparation of the Ni(0) complex was found to be easy and effective. Instead of employing zinc dust or other potential interferring reagents,[5] $NaBH_4$ was found to effect the reduction of $Ni(Ph_3P)_2Cl_2$ to $Ni(Ph_3P)_3$ by simply adding the $NaBH_4$ to a stirred solution of the Ni(II) complex (plus Ph_3P) in DMF at 70 °C over 30-45 min. Thus, a slight excess of $NaBH_4$ was usually employed to both prepare and maintain the catalyst in the lowest oxidation state and also to serve as the hydrogenolysis reagent. Typical mole ratios are shown in Table II. It should be noted in Table I that nearly identical results were obtained by the two different methods of Ni(0) preparation.

Table I. Reaction Conditions for Ni(0) Dehalogenation

compd	registry no.	temp, °C	reaction time, h	solvent	yield, %
bromobenzene	108-86-1	24	14	THF	3[a]
		55	34	THF	trace[a]
		24	24	DMF	6.6[a]
		50	24	DMF	39[a,b]
		55	18	DMF	36
		55	18	DMF	35
		70	16	DMF	90
		70	1.5	HMPT	59[c]
1,4-dibromobenzene	106-37-6	70	16	DMF	15[d] + 78[e]
1,4-chlorobromobenzene	106-39-8	70	16	DMF	80[f] + 11[e]
chlorobenzene	108-90-7	70	24	DMF	27
α-chlorotoluene	100-44-7	70	0.5	DMF	90[g] + 9.8[h]

[a] Catalyst was prepared by zinc dust method; all others were prepared by $NaBH_4$ method. Ni/ArBr mole ratio of 0.2:4.0 (see Experimental Section). [b] No excess triphenylphosphine was added. [c] Catalyst was difficult to prepare in this solvent. [d] Bromobenzene. [e] Benzene. [f] Chlorobenzene. [g] Toluene. [h] 1,2-Diphenylethane.

Table II. Substituent Effects on Debromination by Ni(0)[a]

compd (Ar–Br)	registry no.	ArH yield, %[b]	log k/k_0[b]	notes
bromobenzene	108-86-1	90.1	0.00	
methyl *p*-bromobenzoate	619-42-1	100	1.85	*c*
p-bromochlorobenzene	108-90-7	80.1 + 10.5	1.03	*d*
p-dibromobenzene	106-37-6	15.3 + 78.4	1.67	*d*
p-bromoanisole	104-92-7	32	−0.35	
p-bromo-*N,N*-dimethylaniline	586-77-6	10.5 + 4.0	−0.29	*c, e*
p-bromobenzonitrile	623-00-7	10 + other products		*f*
p-bromotoluene	106-38-7	7.5	−0.18	
p-bromonitrobenzene	586-78-7	0		*g*
p-bromophenol	106-41-2	0		
p-bromoaniline	106-40-1	0		

[a] All reactions were performed in 10 mL of DMF with 4.0 mmol of Ar–Br, 4.8 mmol of $NaBH_4$, 0.2 mmol of $Ni(II)Cl_2(PPh_3)_2$, and 0.4 mmol of triphenylphosphine at 70 °C for 16 h. [b] Determined by GLC; log k/k_0 values are ±0.06. [c] Determined by NMR. [d] Second yield is benzene. [e] Second yield is *p*-bis(*N,N*-dimethylamino)biphenyl. [f] Three other products were determined by LC: trace of benzylamine plus two others. 100% of *p*-bromobenzonitrile reacted. [g] Determined by LC; main product is *p*-bromoaniline, plus a smaller amount of aniline. 100% of *p*-bromonitrobenzene reacted.

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In addition to hydrogenolysis, hydrogen addition was also observed (as the major reaction) in the case of nitro and (surprisingly) cyano groups. The major products from *p*-bromonitrobenzene and *p*-bromobenzonitrile were *p*-bromoaniline and *p*-bromobenzylamine, respectively. While the cyano group is apparently easy to reduce under these conditions, it is interesting to note that the carbomethoxy group is unaffected (Table II).

Since the variety of yields in Table II indicated an obvious substituent effect, individual rates were measured and compared in a Hammett plot, excluding those which exhibited addition reactions. The slope was found to have a ρ value of +3.38 for the positive σ substitutents ($r = 0.950$), implying a nucleophilic transition state. For *p*-bromo-*N*,*N*-dimethylaniline and the other negative σ substituents, the ρ value is much closer to 0 ($\rho = 0.10$, $r = 0.90$), indicating a different kind of transition state of a much less polar nature (possibly a change of mechanism to form the arylphosphonium salts). Also, the dimeric products noted in Tables I and II suggest aryl radical intermediates. Very similar results have been observed for the nickel(0)-catalyzed cyanation in ethanol.[5]

This reaction may be synthetically useful under relatively simple conditions, provided DMF is used as solvent and in the absence of other easily reduced functional groups, phenols, and unsubstituted anilines.

Experimental Section

Apparatus. Gas chromatography was performed with Varian Aerograph 90-P or 1700 gas chromatographs fitted with thermal conductivity detectors. High-performance liquid chromatography was performed with a Waters instrument fitted with a C_{18} reverse-phase column, using acetonitrile–water (70:30) as mobile phase. NMR spectra were recorded with a Varian A-60D spectrometer.

Materials. *p*-Bromotoluene, *p*-bromochlorobenzene, *p*-bromonitrobenzene, and *p*-bromobenzonitrile were prepared by standard methods modified from ref 7 and purified by recrystallization or vacuum distillation before use. Methyl *p*-bromobenzoate and *p*-bromoanisole were prepared after the procedure of ref 8, *p*-bromophenol after ref 9, and *p*-bromo-*N*,*N*-dimethylaniline after ref 10. *p*-Dibromobenzene and dimethyl sulfoxide were purchased from J. T. Baker and used without further purification. *p*-Bromoaniline was from Eastman Kodak. THF, HMPT, $NaBH_4$, and triphenylphosphine were from Aldrich. The DMF was from Matheson Coleman and Bell and was redistilled before use.

Catalyst Preparations. Bis(triphenylphosphine)nickel(II) was prepared after the method of Venanzi.[11]

The nickel(II) complex was converted to the nickel(0) catalyst by two different methods. (1) After heating 10 mL of DMF to 70 °C under nitrogen gas for 30 min, the nickel(II) complex from above (0.13 g, 0.2 mmol), triphenylphosphine (0.11 g, 0.4 mmol), and zinc dust (0.07 g, 1 mmol) were added. The characteristic deep red color of the tetrakis(triphenylphosphine)nickel(0) was formed within 45–50 min.[12] (2) The same procedure as 1 was used, except that $NaBH_4$ (0.01 g, 0.27 mmol) was substituted for the zinc dust. This method was used for all runs, except those indicated.

General Procedure for Dehalogenation. After preparing the catalyst solution as above, the temperature (70 °C) and nitrogen atmosphere were maintained and the mixture was stirred for 30 min. The aromatic halide (4.0 mmol) was then added, and conditions were maintained for another 30 min. Sodium borohydride (0.37 g, 4.0 mmol) was then added and the mixture stirred at 70 °C for 3–20 h with periodic GLC analysis.

For kinetic runs, a similar procedure was followed. A narrow-neck tube fitted with a rubber septum was first charged with 1 mmol of aromatic halide and then evacuated.[13] Then freshly prepared solutions of Ni(II) complex in DMF (2.5 mL, 0.04 M) and $NaBH_4$ in DMF (2.5 mL, 0.48 M) were also introduced via syringe. The solutions were prepared and mixed in a drybox filled with nitrogen. Once mixed, the tube was filled to 1 atm with nitrogen, removed from the drybox, and emersed in a 50 °C oil bath. Samples were periodically removed via syringe (4 μL) for GLC analysis by direct injection of the reaction mixture; preliminary experiments had demonstrated that no dehalogenation reaction occurrred in the hot GLC injector.

Rate measurements were duplicated at least once each, and reproducibility was ±2% or better. Rates were measured as the decrease in Ar–X concentration via GLC peak area determination. Under catalytic conditions (0.1 M dibromobenzene and 0.005 M Ni(II)), the reaction was found to be first order in Ni complex; by halving the Ni concentration the rate dropped from 5.14×10^{-1} to 2.60×10^{-1} h^{-1}.

Registry No.—$NaBH_4$, 16940-66-2; $Ni(Ph_3P)_2Cl_2$, 14264-16-5; $Ni(Ph_3P)_3$, 25136-46-3.

References and Notes

(1) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley-Interscience, New York, 1967.
(2) S. Masamune, G. S. Bates, and P. E. Georghiou, *J. Am. Chem. Soc.*, **96**, 3686 (1974).
(3) S. Tyrlik and I. Wolvehowicz, *J. Chem. Soc., Chem. Commun.*, 781 (1975).
(4) E. C. Ashby and J. J. Lin, *J. Org. Chem.*, **43**, 1263 (1978).
(5) L. Cassar, S. Ferrara, and M. Foá, *ACS Monogr.*, **No. 132** (1974); also L. Cassar and J. Foá, *J. Organomet. Chem.*, **74**, 75 (1974).
(6) J. A. Roth and S. T. Lin, unpublished results.
(7) A. I. Vogel, "A Textbook of Practical Organic Chemistry", Wiley, 3rd ed., New York, 1956.
(8) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, **21**, 347 (1956).
(9) R. Adams and C. S. Marvel, "Organic Syntheses", Collect. Vol. 1, Wiley, New York, 1941, p 128.
(10) R. F. Borch and A. I. Hassid, *J. Org. Chem.*, **37**, 1673 (1972).
(11) L. M. Venanzi, *J. Chem. Soc.*, 719 (1958).
(12) C. A. Tolman, W. C. Seidel, and D. H. Gerlack, *J. Am. Chem. Soc.*, **94**, 2669 (1972).
(13) D. F. Shriver, "The Manipulation of Air-Sensitive Compounds", McGraw-Hill, New York, 1969.

General, Efficient, One-Step Synthesis of β-Keto Esters

Wendell Wierenga* and Harvey I. Skulnick

Experimental Chemistry Research,

The Upjohn Company, Kalamazoo, Michigan 49001

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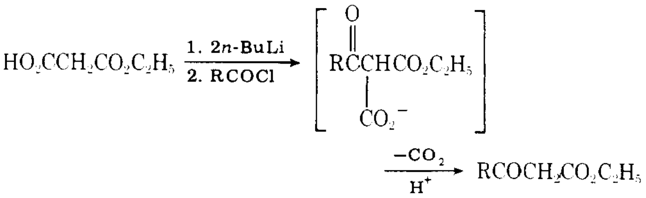
β-Keto esters form a large part of the important class of 1,3-dicarbonyl compounds and, as such, have enjoyed a long history of diverse chemical preparations and use in synthesis. Their popularity is based on several factors, one of which is facile bond formation with the two, differentiable, electrophilic carbonyls and either of the nucleophilic α or γ sp^3 carbons.

As part of a program in our laboratory on pyrimidine chemistry, we needed to exploit these attributes of β-keto esters and, therefore, required an economical and efficient preparation. Although nearly all possible routes of synthesis of β-keto esters have been conceptualized and reduced to practice in specific and general approaches,[1-3] we felt a reasonable incentive for improvement existed in the more pragmatic aspects such as economical availability of starting materials, yields, purifications necessary, competing side reactions, and scale-up requirements.

In 1959 Ireland and Marshall[1b] reported that the magnesium salt of α-substituted malonyl monoesters yielded β-keto esters in 50–70% yields upon reaction with acid chlorides.[1f] We have found that dilithio dianion of monoethyl malonate reacts with acid chlorides to afford β-keto esters directly in excellent yield and without need of further purification.

Treatment of monoethyl malonate[4] in tetrahydrofuran (THF) with 2 equiv of *N*-butyllithium from −30 °C with slow warming to −5 °C yields a heterogeneous solution. The reac-



$$HO_2CCH_2CO_2C_2H_5 \xrightarrow[\text{2. RCOCl}]{\text{1. }2n\text{-BuLi}} \left[R\overset{\overset{\Large O}{\|}}{C}\underset{\underset{\Large CO_2^-}{|}}{C}HCO_2C_2H_5 \right] \xrightarrow[H^+]{-CO_2} RCOCH_2CO_2C_2H_5$$

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