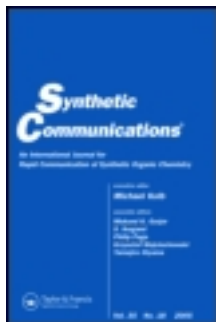


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Ullmann Reaction of Picryl Bromide in the Presence of Ultrasound

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ULLMANN REACTION OF PICRYL BROMIDE
IN THE PRESENCE OF ULTRASOUND

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ABSTRACT

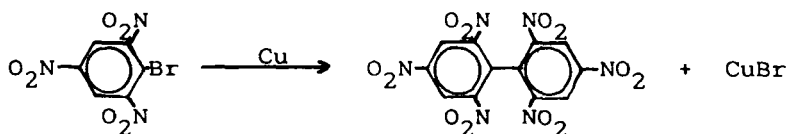
Ultrasonic irradiation was found to promote the Ullmann coupling of picryl bromide at or below room temperature. In the presence of excess copper, a long-lived intermediate is formed that is quenched upon work-up affording variable mixtures of trinitrobenzene and picric acid.

The application of ultrasound in organic synthesis has been the subject of much interest in recent years.¹ It has been found to be especially useful in heterogeneous solid-liquid systems. The collapse of ultrasonically generated cavities at or near a solid surface produces a jet of liquid that impinges on the surface,² eroding it, and thereby exposing a fresh, reactive surface. Subsequent implosions improve mass

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transport by sweeping reactive intermediates and/or products from the solid surface thus increasing reaction rates. Our interest in the synthesis of polynitro polyaryls, and reports on the ultrasonically enhanced Ullmann coupling of 2-iodonitrobenzene,³ prompted our investigation.

The Ullmann reaction, the coupling of aryl halides to biaryls in the presence of copper metal, often requires rather high temperatures, high-boiling solvents, and a large excess of copper, especially with the less reactive aryl bromides and chlorides. When reaction occurs, rapid heat evolution, which is difficult to control, often follows. An obvious benefit of ultrasonic irradiation might be to induce the coupling of unreactive aryl halides at lower temperatures in lower boiling solvents, and with less copper. The Ullmann coupling of picryl bromide to give 2,2',4,4',6,6'-hexanitrobiphenyl was chosen as a model reaction.



Sonications were carried out under a dry nitrogen atmosphere with a 0.5 inch direct probe in a Suslick Cell immersed in an ice/water bath. Initially, four

molar equivalents of copper dust were used since this substrate : copper ratio was found optimum for the ultrasonically enhanced Ullmann coupling of 2-nitroiodobenzene.³ Reactions were run either 1.5 or 0.5 molar in picryl bromide. In cases where thickening of the reaction mixture was a problem, the reactions were run at 0.5 molar concentration only. Sonication was applied in one second pulses at one second intervals, in order to avoid overheating the reaction mixture, until picryl bromide was no longer detected by TLC. Sonication time in subsequent discussion indicates the time of actual sonication. Preliminary experiments indicated that picryl chloride, representative of the more readily available polynitroaryl chlorides, was quite unreactive even with sonication. Picryl bromide, however, responded readily to sonication and was studied in more detail.

Our initial efforts to couple picryl bromide in nitrobenzene gave low yields of the expected hexanitrobiphenyl (HNBP) and significant amounts of trinitrobenzene (TNB) and picric acid (PiOH). Indeed, in a survey of possible solvents, trinitrobenzene and picric acid were the only products except when the reaction was carried out in nitrobenzene or nitromethane in which cases the expected biphenyl was a minor product (Table 1). The reduction of aryl halides

Table 1. Solvent Effects on Product Distribution in the Ultrasound Assisted Ullmann Reaction of Picryl Bromide^a

Entry	Solvent ^b	Picryl Bromide (mol/L)	Sonication Time (min)	HMBP	% Yield ^c TNB	PhOH
1	PhNO ₂	1.5	9	27 ^d	51 ^d	trace ^d
2	PhNO ₂	0.5	10	6	57	10
3	MeNO ₂	0.5	8	4	25	67
4	THF	1.5	12	0	19	49
5	THF	0.5	6	0	11	63
6	PhMe	1.5	4	0	44	31
7	PhMe	0.5	8	0	12	71
8	PhH	0.5	8	0	49	39
9	PhMe ₂	0.5	8	0	70	26
10	TCE	0.5	28	No Reaction		

^aFour molar equivalents of copper dust were used.^bPhNO₂ = nitrobenzene,THF = tetrahydrofuran, PhMe = toluene, PhMe₂ = xylenes, TCE = tetrachloroethylene,and MeNO₂ = nitromethane. ^cYields determined by ¹H NMR analysis except where noted.^dIsolated yields.

is a well-known side reaction of the Ullmann reaction but it usually gives only a low yield of the dehalogenated by-product in the absence of a proton source. The formation of picric acid in our experiments appears to be without precedent in the normal Ullmann reaction. While it is not the intent of this report to further illuminate the mechanism of the Ullmann coupling reaction, the observed high yields of trinitrobenzene and picric acid deserve comment. It has been suggested that the dehalogenated by-products are the result of proton abstraction by a reactive intermediate from solvent or even from the starting aryl halide or the coupled product. Reduction of the starting aryl halide has been observed even when the reaction was carried out with no solvent⁴ or with sand as the diluent⁵. Deuterated products were detected when the Ullmann coupling of iodobenzene, 4-iodobiphenyl, and 1-iodonaphthalene was carried out in deuterated benzene or deuterated cyclohexane.⁶ In order to clarify the situation for the ultrasonically promoted reaction of picryl bromide, a mixture of picryl bromide (5.0 mmol) and copper dust (20 mmol) in deuterated nitrobenzene (10 mL) was sonicated until the starting material had been consumed (4 min.). The trinitrobenzene was isolated by dilution of the crude reaction mixture in acetone, filtration, and concentration in vacuo followed by flash

chromatography. Mass spectral analysis showed that no deuterium had been incorporated into the trinitrobenzene thus indicating that no abstraction from solvent had occurred. However, when this reaction was repeated in non-deuterated nitrobenzene and the reaction quenched by stirring the crude reaction mixture at room temperature overnight with a 2:1 mixture of D_2O /acetone- d_6 before work-up, the trinitrobenzene that was isolated was found to contain one deuterium atom. This indicates that under our reaction conditions, a relatively unreactive organocopper intermediate is produced rapidly and is quenched upon work-up to afford the observed mixture of products. Such a scenario may explain the variation in yields of TNB and $PhOH$ that were sometimes observed in duplicate runs.⁹ The above method gives 1,3,5-trinitrobenzene- d_1 in preparatively useful yield and isotopic purity.

The classical Ullmann reaction is carried out in the presence of a large excess of copper. This is undoubtedly necessary due to the relative inactivity of the metal surface. Cleaning of the metal of surface impurities by treatment with iodine⁷ or EDTA⁸ has been reported to activate the metal. Ultrasonic irradiation of the metal has been shown to both reduce the particle size and pit the surface^{3b} of the copper, thereby

increasing the number of active sites. In our experiments, presonication of the copper powder did allow reaction to proceed at temperatures as low as 23°C in the absence of further ultrasonic irradiation, but reaction rates and product yields were lower than with sonication during reaction.

If sonication at room temperature results in a rapid conversion of picryl bromide by excess copper to an organocopper intermediate that is relatively unreactive and is quenched in the work-up, reducing the amount of copper should afford a better opportunity for reaction with picryl bromide. The results of these experiments are shown in Table 2.

Reduction of the amount of copper present in the reaction mixture from four molar equivalents to a mere 10% excess results in a corresponding increase in the yield of HNBP at the expense of TNB and PiOH. This increase is seen clearly in the reactions run in nitrobenzene but is even more dramatic in those run in nitromethane (4% vs. 77%, compare Table 1, entry 3). Further reduction of the amount of copper leads to recovery of starting material and larger proportions of TNB and PiOH. As was expected, reaction times also are observed to generally increase. When the solvent was xylene, however, the reduced amount of copper still

Table 2. Effect of Cu/Substrate Ratio on Product Yields

<u>Entry</u>	<u>Solvent^a</u>	<u>Cu (Equiv.)</u>	<u>Picryl Bromide (mol/L)</u>	<u>Sonication Time (min)</u>	<u>HNPB</u>	<u>% Yield^b INB</u>	<u>PIOH</u>
1	PhNO ₂	4	1.5	9	27 ^c	51 ^c	trace ^c
2	PhNO ₂	2	1.5	8	46	36	trace
3	PhNO ₂	1.1	1.5	16	77	4	9
4	MeNO ₂	1.1	1.5	12	75	6	trace
5	Xylene	1.1	1.5	24 ^d	16	27	22
6	Xylene	1.1	0.5	24 ^d	0	24	27

^aPhNO₂ = nitrobenzene, PhMe₂ = xylenes, and MeNO₂ = nitromethane. ^byields determined by ¹H NMR. ^cIsolated yield. ^d16-18% starting material recovered.

gave primarily TNB and picric acid in a reaction that was markedly slower than in nitrobenzene or nitromethane.

In conclusion, ultrasonic irradiation of a mixture of picryl bromide and copper powder at or below room temperature has been shown to result in the formation of 2,2',4,4',6,6'-hexanitrobiphenyl or a trinitrobenzene/picric acid mixture, depending on the solvent and relative amounts of picryl bromide and copper. Higher picryl bromide concentrations in nitrobenzene or nitromethane with a slight molar excess of copper powder promote Ullmann coupling to afford hexanitrobiphenyl. Dilute picryl bromide solutions in aromatic hydrocarbon solvents or THF with large excesses of copper powder promote formation of 1,3,5-trinitrobenzene and picric acid upon work-up in the presence of water. From deuterium labeling experiments it appears that a large excess of copper powder converts picryl bromide relatively rapidly to a long-lived organocopper intermediate that reacts with water upon work-up to give trinitrobenzene; the picric acid observed could be formed from the same intermediate by reaction with air, but this was not fully established in this work.

EXPERIMENTAL

General.- Copper (Venus Natural Copper Fine No. 44F) was dried in vacuo over P_2O_5 at room temperature.

Nitrobenzene was dried over MgSO_4 , distilled under reduced pressure, and stored over CaH_2 . Picryl bromide was recrystallized from 6:5 dichloroethane/hexane. Sonications were carried out under a N_2 atmosphere in a Suslick cell immersed in an ice/water bath. Ultrasound (20 KHz) was generated in one second pulses with one second intervals at 50% output by a Heat Systems-Ultrasonics Sonicator Model W-285 using a 0.5 inch direct immersion horn. All reactions were monitored by TLC (silica gel 60 eluted with 10% ethyl acetate/hexanes). Mass spectra (EI) were determined by the Mass Spectroscopy Facility, Dept. of Chemistry, Cornell University, Ithaca, N.Y.

2,2',4,4',6,6'-Hexanitrobiphenyl.- A mixture of copper powder (0.94g, 14.8 mmol) and picryl bromide (3.95g, 13.5 mmol) in nitrobenzene (9.0 mL) was irradiated until all picryl bromide had been consumed. The reaction was monitored by diluting small aliquots with acetone and analyzing the supernatant by TLC. When the reaction was deemed complete, the tan reaction mixture was diluted in 100 mL of wet (not dried) acetone, filtered, and the solids washed with a small amount of a acetone/20% HCL mixture (ca. 10:1). The combined filtrate and washings were concentrated in vacuo with the nitrobenzene being coevaporated with water to give a tan solid that was triturated with 20% HCl (2 x 5 mL) and water (2 x 5 mL), then dissolved in

acetone, filtered, and concentrated in vacuo to give another tan solid. Recrystallization was carried out by adding acetone, sufficient to effect dissolution, to a suspension of the crude product in 30 mL of toluene, then distilling the solution until the vapor temperature reached 90°C. Cooling to room temperature afforded tan crystals that were filtered and dried in vacuo. The product, hexanitrobiphenyl, was a solvate with 0.25 mol toluene; mp 238-241°C (lit. mp 238°C¹⁰); yield: 1.858g, 4.380 mmol, 65%.

1,3,5-Trinitrobenzene-d₁.— A mixture of copper powder (1.26g, 19.8 mmol) and picryl bromide (1.46g, 5.01 mmol) in nitrobenzene (10 mL) was irradiated until all picryl bromide had been consumed (12 min.). The reaction was monitored by TLC as described above. Upon completion, 3 mL of a 2:1 mixture of D₂O/acetone-d₆ was added and the resulting mixture stirred at room temperature under a N₂ atmosphere overnight. The yellow-black mixture was then filtered and the solids washed well with acetone. The combined filtrate and washings were concentrated in vacuo and the nitrobenzene removed by coevaporation with water. Recrystallization from CCl₄ afforded TNB-d₁ as fine yellow flakes (503mg). Concentration and flash chromatography (15g silical gel 60, 60:19:1 hexanes/dichloromethane/ethyl acetate) gave another 313mg of TNB-d₁ as well as 39mg (0.09 mmol, 4%) of HNBP; total

yield of TNB-d₁: 816mg, 3.81 mmol, 76%. The TNB-d₁ was identified by its mass spectrum as well as the ¹H and ¹³C NMR spectra; the latter were identical with those of non-deuterated TNB (no splitting of ¹H or ¹³C signals observed); MS m/z (relative intensity) 214 (M, 100), 213 (9), 121 (14), 76 (56), 75 (28); MS for TNB m/z (relative intensity) 214 (8), 213 (M, 100), 120 (22), 75 (61), 74 (33).

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