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# Ultrasound-Promoted Coupling of Aryl and Heteroaryl Halides in the Presence of Lithium Wire

## Formation of Dimeric and Dehalogenated Products

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**Summary.** Although sonochemical reactions of bromobenzene and of 2-, 3- and 4-halogenopyridines with lithium wire in *THF* solution yield the expected dimers, considerable dehalogenation also occurs, as monitored by $^{13}$C-NMR spectroscopy. A pathway for the unusual formation of 4,4′-bipyridyl from the 2-halogenopyridines is proposed. No dimers were detected from the reactions with 2-bromo-4-methylquinoline and 7-bromo-2,4-dimethylquinoline. The synthetic potential of their alternative facile sonochemical dehalogenation is propounded.

**Keywords.** Ultrasound; Sonochemistry; Bipyridines; $^{13}$C-NMR Spectroscopy.

**Ultraschallunterstützte Kupplung von Aryl- und Hetarylhalogeniden in Gegenwart von Lithiumdraht. Die Bildung von dimeren und dehalogenierten Produkten**

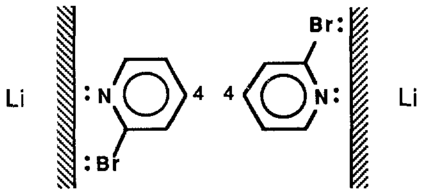
**Zusammenfassung.** Obwohl die Ultraschall-Reaktionen von Brombenzol und 2-, 3- und 4-Halogenpyridinen mit Lithiumdraht in *THF* die erwarteten Dimeren ergeben, tritt auch ein beträchtliches Ausmaß an Dehalogenierung ein. Es wird ein möglicher Mechanismus für die ungewöhnliche Bildung von 4,4′-Bipyridyl aus 2-Halogenpyridin vorgeschlagen. Aus den Reaktionen von 2-Brom-4-methylchinolin und 7-Brom-2,4-dimethylchinolin resultierten keine dimeren Produkte. Das synthetische Potential der sonochemischen Dehalogenierung wird diskutiert.

## Introduction

The application of ultrasound to facilitate organic reactions has recently attracted considerable interest [1 – 4]. Biphenyl may be obtained from bromobenzene **1** in 70% yield through a Wurtz-type sonochemical coupling with lithium wire in *THF* solution [5, 6]. We recently reported [7] a preliminary study of the application of the above reaction to some heteroaryl halides, the products being identified by $^{13}$C-NMR spectroscopy [8]. From 2-bromopyridine **2** an unexpected mixture of bipyridyles was obtained whilst with 3-bromopyridine **4** only minimal formation of the dimer resulted, the main reaction being debromination.

## Results and Discussion

We have now had an opportunity to perform further experiments utilising a new ultrasonic bath and clean lithium metal, in place of the elderly tarnished material employed previously, the results are shown in Table 1. With 3-bromopyridine (**4**) the extent of reaction increased (32% **4** remained compared with 75% previously [7]), but there was considerable debromination to give pyridine; whilst with 4-chloropyridine **5** very little conversion to the dimer occurred. The most interesting reaction was with the 2-halopyridines **2** and **3**, to give a mixture of dimers, viz. 2,2′-bipyridyl and 4,4′-bipyridyl (**6**). Previously [7] debromination was not observed with **2**, and a minute proportion of 2,4′-bipyridyl was tentatively identified. The formation of the dimer **6** bonded through a position different to that previously occupied by the original halogen substituent in a Wurtz-type reaction is particularly unusual [9]. It is evident from Table 1 that as the reaction of **2** progressed (4 hour versus 10 hour sonication period) the proportion of pyridine diminished whilst that of 4,4′-bipyridyl (**6**) increased. Since it is known [10] that pyridine reacts with lithium in *THF* solution to give **6** via the pyridine radical anion, it would appear that this dimer did not result *directly* from an isomeric Wurtz-type reaction but was instead produced from the dehalogenated product. However, it should be noted that no **6** was detected in the reaction with **4** in which a significant quantity of pyridine was found, moreover the reaction with **5** furnished very little **6**. Hence the unique formation of **6** from the 2-halopyridines suggests that this is not a simple process involving "free" pyridine as such. It is proposed that an organometallic species formed at the metal surface by bonding involving *both* the nitrogen and halogen lone pairs is a probable intermediate:



Since the extent of dehalogenation experienced in the present work was extensive, it was considered that the reaction with bromobenzene (**1**), which has been reported [6] to give an *isolated* yield of 57−71% of biphenyl, could also feature this pathway. Direct analysis of the reaction product by $^{13}$C-NMR spectroscopy did indeed indicate the presence of 25% benzene (see Table 1). In view of this finding it is suggested that for a suitable introductory undergraduate sonochemical experiment as introduced by Lash and Berry [6], that *para*-bromotoluene (5) be substituted for **1**, and the work-up performed in a well ventilated fume cupboard.

In contrast to the reaction with the 2-halopyridines, that with 2-bromo-4-methylquinoline resulted in no detectable biquinolyl product. 7-Bromo-2,4-dimethylquinoline was then studied since this compound contains a carbocyclic ring substituted bromine and might therefore behave similarly to **1**, however, in the event an especially clean reaction took place which resulted in quantitative debromination to 2,4-dimethylquinoline.

Although ultrasound therefore appears inappropriate for the synthesis of biquinolyls it does nevertheless represent a valuable technique for the removal of a

**Table 1.** Ultrasound promoted coupling of aryl and heteroaryl halides

$$n\,ArX \xrightarrow[)))]{\text{Li, } THF} Ar_2 + Ar\text{H} + \ldots$$

| Starting material[b] | Reaction period (h) | Unreacted starting material | Reaction product (% composition)[a] | |
|---|---|---|---|---|
| | | | Dimer(s)[b] | Dehalogenated product |
| $C_6H_5Br$ (**1**) | 10 | 5 | 70 | 25 |
| 2-Br*Py* (**2**) | 4 | 34 | 2,2′-*Bipy* 16<br>4,4′-*Bipy* 5 | 45 |
| | 10 | 24 | 2,2′-*Bipy* 34<br>4,4′-*Bipy* 7 | 35 |
| 2-Cl*Py* (**3**) | 10 | 32 | 2,2′-*Bipy* 18<br>4,4′-*Bipy* 4 | 46 |
| 3-Br*Py* (**4**) | 10 | 32 | 9 | 59 |
| 4-Cl*Py* (**5**) | 10 | 64 | 2 | 34 |
| 2-Br-4-*MeQ* | 10 | 25 | – | 75 |
| 7-Br-2,4-$Me_2Q$ | 10 | – | – | 100 |

[a] Determined by $^{13}$C NMR spectroscopy in $CDCl_3$ solution, components identity confirmed by "spiking" with authentic material [8]

[b] *Py* = pyridine, *Bipy* = bipyridyl, *Q* = quinoline

halogen atom present as a protecting group. Thus the facile sonochemical dechlorination of 8-chloro-5-methylquinoline [11], should provide a convenient route to 5-methylquinoline. The alternative traditional synthesis via the Skraup reaction with *meta*-toluidine [12] furnishes a mixture of products with the 5-methyl isomer as the minor component.

Further studies are in progress featuring changes of solvent as well as the use of alternative metals as reactants.

## Experimental

### *Sonochemical Reactions*

Finely chopped lithium wire (0.11 mol) was added to a solution of the aryl/heteroaryl halide (0.1 mol) in dry tetrahydrofuran (25 ml) contained in a 100 ml conical flask fitted with a reflux condenser. The flask was immersed in a Kerry Pulsatron PU 125 ultrasonic cleaning bath and then sonicated (125 watts, 38 KHz) for the required time period (see Table 1). After sonication the flask was thoroughly agitated to produce a uniform consistency. A sample (1 ml) of the supernatant mother liquor was then taken, diluted with $CDCl_3$ (1 ml) and examined by $^{13}$C-NMR spectroscopy (Jeol FX 60, 15 MHz) [8].

*2-Bromo-4-methylquinoline.* M. p. 81 – 2°, lit., m. p. 81 – 81.5° [13]; *picrate*: fine yellow needles from ethanol, m. p. 131 – 2°, found C 42.7, H 2.3, N 12.4, $C_{16}H_{11}BrN_4O_7$ requires C 42.6, H 2.4, N 12.4%.

*7-Bromo-2,4-dimethylquinoline.* M. p. 46 – 7°, lit., m. p. 46 – 7° [14]; *picrate*: microscopic yellow needles from ethanol, m. p. 228 – 30°, found C 43.8, H 2.8, N 11.9, $C_{17}H_{13}BrN_4O_7$ requires C 43.9, H 2.8, N 12.0%.

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