



Organometallic-type Reactions in Aqueous Media. Wurtz-coupling of Alkyl Halides with Manganese/Cupric Chloride

Jihai Ma, Tak-Hang Chan*

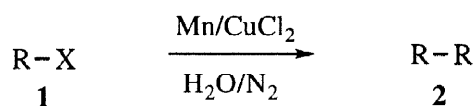
Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

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Abstract: Homo-coupling of alkyl halides in aqueous media can be mediated by manganese/cupric chloride to give the dimerisation products in good yield. Cross-coupling can also be controlled to give the desired product. © 1998 Elsevier Science Ltd. All rights reserved.

The classical Wurtz reaction, involving the coupling of alkyl halides mediated by sodium metal, has found only limited use in organic synthesis.^{1,2} The following factors may have contributed to the limitation: (1) there is the difficulty of working with sodium metal itself which requires careful exclusion of moisture; (2) the reaction gives poor yield with secondary alkyl halides. Coupling of alkyl halides is now generally accomplished by conversion first of one of the alkyl halides to the corresponding Grignard or lithium reagents. This is then followed by coupling with the second alkyl halides, often with some copper salt as the catalyst.² In all cases, anhydrous organic solvents have to be employed to avoid the destruction of the organometallic intermediates.³ Recently, we⁴ and others⁵ have demonstrated that many organometallic-type reactions can be carried out in aqueous media. These reactions offer the advantage of mild reaction conditions, and the practical convenience of obviating the need of handling inflammable and anhydrous organic solvents. The potential advantage in reducing the adverse impact of solvent disposal on the environment provides additional impetus in exploring organic reactions in aqueous media.


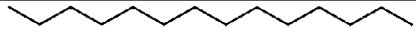
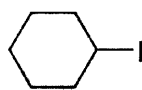
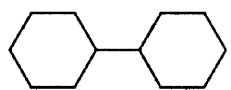
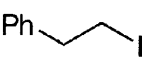
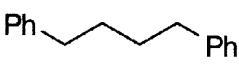
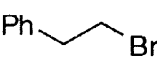
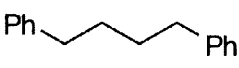
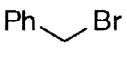
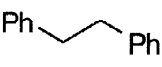
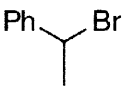
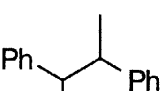
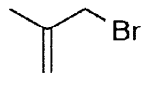
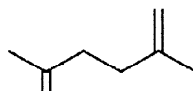
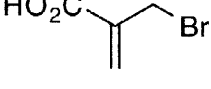
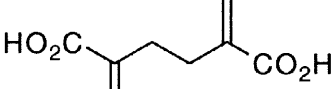
While we have previously reported a single example of the homo-coupling of an allylic halide mediated by zinc in aqueous media,⁶ zinc is not effective in mediating the coupling of simple alkyl halides. Neither, for that matter, are indium,⁷ bismuth⁸ or tin,⁹ the other common metals often used in organometallic reactions in aqueous media. We have found, however, that manganese in conjunction with catalytic quantity of cupric chloride in water are quite effective as the metal system for the Wurtz coupling of alkyl halides.¹⁰



Thus, heptyl iodide (**1a**) was efficiently coupled to the corresponding dimeric hydrocarbon tetradecane (**2a**) in 87% yield (Table 1). The following typical conditions were used. The alkyl halide (1 mmol) and

CuCl_2 (14 mg, 0.1 mmol) were mixed with water (3 mL). Manganese (165 mg, 3 mmol) was added in one portion with stirring under nitrogen. The reaction was left stirring at room temperature for 16 h. The reaction mixture was quenched with hydrochloric acid (1 M, 10 mL) and extracted with ether (2 x 10 mL). The combined ether extract was washed with water and dried over MgSO_4 . The solvent was removed and the residue was generally purified by flash chromatography over silica gel to give the product. In the absence of CuCl_2 , the alkyl halides failed to couple and starting materials were recovered. The reaction has to be carried out under nitrogen otherwise the yield of the coupled product was much lower, possibly due to oxidation of the presumed manganese intermediates by air.

Table 1: Symmetrical coupling of alkyl halides


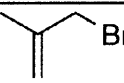
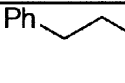
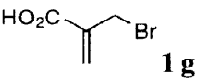
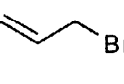
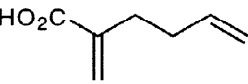
R-X	R-R	Yield (%)
 1a	 2a	87
 1b	 2b	81
 1c	 2c	81
 1c	 2c	52
 1d	 2d	97
 1e	 2e (t/e 1.03/1)	83
 1f	 2f	100
 1g	 2g	95

The reaction worked well with secondary iodides as well. For example, iodocyclohexane (**1b**) was coupled under identical conditions to give the dimeric bicyclohexyl (**2b**) in 81% yield.¹¹ 2-Iodoethylbenzene (**1c**) was coupled to 1,4-diphenylbutane (**2c**) in 81% yield as well. It is interesting to note that, in this particular case, the ubiquitous elimination of 2-iodoethylbenzene under basic conditions to give styrene did not

take place. When 2-bromoethylbenzene was used in place of the iodo compound, the yield of the coupled product **2c** was reduced to 52% under the same reaction conditions. Addition of sodium iodide to the reaction mixture to generate the alkyl iodide in situ did not improve the yield. It appeared that iodine was formed during the reaction conditions instead. On the other hand, benzylic or allylic bromides were found to give good yields of the coupled products. In the coupling of 1-bromoethylbenzene (**1e**) to the corresponding 2,3-diphenylbutane (**2e**), the reaction was found to be not stereoselective, with **2e** having a threo/erythro ratio of 1.03/1.00. 2-Bromomethylpropene (**1f**) was coupled to give the dimer **2f** in quantitative yield. The coupling of α -bromomethylacrylic acid (**1g**), under the aqueous conditions, proceeded efficiently to give the dicarboxylic acid **2g** in excellent yield. This illustrates the advantage of such organometallic reactions in aqueous media in that reactive functional groups such as carboxylic acid appear not to be affected.

Classical cross-coupling of two different halides usually gives a mixture of homo- and cross-coupled products in a statistical ratio. However, by using one of the alkyl halide in excess, it is possible to obtain one of the cross-coupled products in synthetically useful yield, especially if the excess homo-coupled hydrocarbon can be removed readily. Thus, in the coupling of α -bromomethylacrylic acid (**1g**) with allyl bromide in a ratio of 1:4, the product 2-methylene-5-hexenoic acid (**3b**) was obtained in 79% yield (calculated on the basis of **1g**). In this case, the product **3b** can be readily separated from the other major product, 1,5-hexadiene.¹²

Table 2: Cross-coupling of alkyl halides

R-X	Mmol	R'-X	Mmol	Product: R-R'	Yield (%)
	1.0		3.0	 3a	62
 1g	0.25		1.0	 3b	79

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 12. Experimental conditions for the preparation of **3b**: α -Bromomethylacrylic acid (42 mg, 0.25 mmol) and allyl bromide (121 mg, 1 mmol) was dissolved in a mixed solvent of THF (2 mL) and water (2 mL). CuCl_2 (28 mg, 0.2 mmol) was added and followed by manganese (110 mg, 2 mmol) in one portion with stirring under nitrogen. The reaction was carried out at room temperature for 16 hr. The reaction mixture was mixed with hydrochloric acid (1 M, 10 mL) and was extracted with ether (2 x 10 mL). The combined ether layer was washed with water (2 x 10 mL) and dried over MgSO_4 . The solvent was removed and the resulting residue was purified by flash chromatography over silica gel with chloroform as eluent to give the oily product **3b** (25 mg, 79%). $^1\text{H NMR}$ (CDCl_3) δ ppm 2.20-2.50 (m, 4), 4.90-5.10 (m, 2), 5.68 (s, 1), 5.69-5.95 (m, 1), 6.32 (s, 1).