Pergamon

Tetrahedron Letters 40 (1999) 227–230

TETRAHEDRON
LETTERS

Tailoring Aqueous Solvents for Organic Reactions: Heck Coupling Reactions in High Temperature Water

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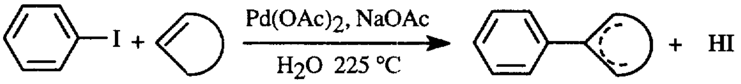
Received 21 August 1998; revised 22 October 1998; accepted 23 October 1998

Abstract: High temperature water is demonstrated to be an effective solvent for Heck coupling reactions of aromatic halides with cyclic alkenes without the addition of co-solvents or specialized ligands. Reactions in the presence of LiCl and quaternary ammonium salts indicate that the reaction takes place in the aqueous phase. © 1998 Elsevier Science Ltd. All rights reserved.

There is a growing understanding of the potential benefits provided by "green" processes - reactions which reduce manufacturing emissions and by-products.[1] This awareness creates new incentives for extending synthetic organic reactions into the aqueous environment. This report describes the use of high temperature water (pressurized aqueous reactions above 100 °C) as *a novel solvent replacement option* for traditional Heck reactions. At high temperatures and pressures, the physical constants of water change dramatically from those at ambient conditions,[2,3] creating opportunities for new chemistry and for simplification of catalyst / product separation. The dielectric constant of hot, compressed water reduces from 80 at ambient conditions to 31 at 225 °C. Around the critical point, the dielectric constant finally drops precipitously to about 6, $T_c = 373$ °C, $P_c = 221$ bar.[2,3] These changes make high temperature water, HTW, a unique moderate-polarity solvent alternative for organic reactions without requiring co-solvents or specialized ligands.

The Heck coupling reaction is one of the most powerful tools for creating carbon-carbon bonds.[4] In the present work, coupling reactions of substituted iodobenzenes with a variety of cyclic alkenes have been explored in compressed liquid water at 225 °C at pressures between 100-200 bar without added ligands, or co-solvents. Most reactions were run without supplementary salts, although LiCl and *n*-Bu_4NCl were added to some reactions to investigate the mechanism. These chemical systems were similar to those developed by Larock at modest temperatures (25-80 °C) with reaction times on the order of days in dimethylformamide, DMF.[5]



In order to extend Heck chemistry into water, important solubility barriers must be overcome. Two variables are available for modification: either the reagents or the environment must be altered. Beletskaya and coworkers elegantly matched the properties of the chemical substrates to the polarity of the aqueous environment,[6] but this technique is limited to water-soluble substrates. Another approach is to solubilize the palladium catalyst by using water-soluble phosphine ligands.[7] A wide variety of substituted phosphines have been developed, although these are rarely used in neat water.[8] The second route to extending Heck reactions into water is to increase the solubility of organics by the use of additives such as quaternary ammonium salts alone[9] or with co-solvents such as DMF in high ratios with water,[10-12] or by

PII: S0040-4039(98)02323-5

taking advantage of the physical changes that occur in HTW. Herein, the decreased dielectric constant of water at 225 °C, ~31 at 100 bar, is used to dissolve the organic components.[3]

Our studies focused on the coupling of cyclic alkenes (5–8 carbons) with iodobenzenes in HTW. Electron donating and electron withdrawing substituents on the iodobenzene were chosen to examine the effect of arene-ring electron density on the coupling reactions. All the results are summarized in Table I. Reactors, 12 ml 316 stainless steel, were loaded with 6 mol % $Pd(OAc)_2$, 1 mmol iodobenzene, 5 mmol alkene, 3 mmol NaOAc, and a shaker ball to insure agitation, then sealed and heated at 225 °C for 20 min.[13] Added salts are noted in Table I. The water loading was set at 10.1 g to generate a homogeneous aqueous compressed phase.[3,14] All products were identified by GC/MS. Quantitation was performed with GC by adding naphthalene as an internal standard, although external to the reactions.

Heck reactions with iodobenzene and various cyclic alkenes, ring size 5 - 8, yielded significant conversion to the desired product, 17-54 % based on conversion of iodobenzene (entries 1-6). The HTW conditions were successful for a variety of unactivated cyclic alkenes. The products were surprisingly similar to those found in typical organic solvents.[5] In the HTW systems, longer reaction times led to scrambling of the double bond ring position and product degradation. Interestingly, larger ring sizes (entries 5-6) reacted more quickly and generated more of the desired product than the smaller ring systems (entries 1-2). This trend differs from that seen in DMF at room temperature where the order was cyclopentene>cyclooctene>cycloheptene>cyclohexene with reaction times on the order of several days.[5]

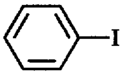
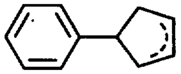
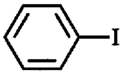
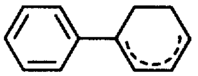
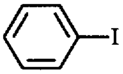
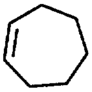
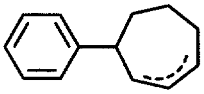
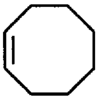
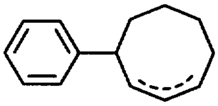
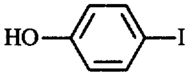
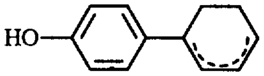
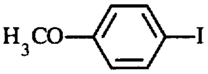
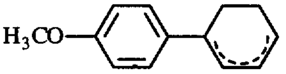
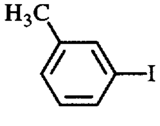
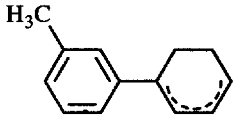
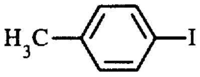
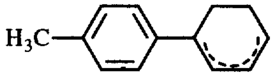
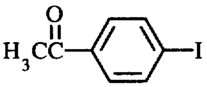
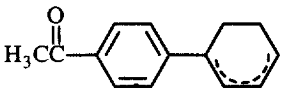
The source of the reactivity trend in HTW is difficult to identify. The rate could be increased by either improved solubility of the reactants in HTW or by additional organic association, hydrophobic acceleration, as described by Breslow.[15] Permissivity (dielectric constant) and hydrophobicity were considered as possible predictors of reactivity. For the cyclic alkenes, permissivities are 2.083 for cyclopentene, 2.218 for cyclohexene, 2.265 for cycloheptene, and 2.306 for cyclooctene.[16] Hydrophobicity calculations, based on the octanol/water partition coefficient, show that hydrophobicity also increases with ring size: 2.251 for cyclopentene, 2.810 for cyclohexene, 3.369 for cycloheptene, and 3.928 for cyclooctene.[17] Both permissivity and hydrophobicity increase with increases in alkene ring size and reactivity, so they could not discriminate between the rate increase due to improved solubility or improved organic association.

Preliminary experiments with salt effects were investigated. LiCl, 0.5-2 M, was added to the coupling reaction of iodobenzene and cyclohexene (entry 3) in an attempt to salt-out the organics from the aqueous phase.[15] The conversion to phenylcyclohexene was significantly *decreased* with a yield between 13-18 % during the 20 min run at 225 °C. There was no significant change in the isomer ratios accompanying the decrease in yield. Inclusion of 1 mmol n-Bu_4NCl (entry 4) significantly increased the yield of the desired product (40%), as well as the major isomer compared to the systems without added salts and with added LiCl. (Table I, entries 2 and 3, respectively.) This observation supports the importance of water involvement in these systems. We expect our reactions to be single phase and are therefore continuing investigations to identify the source of the changes in yield and isomer ratios due to added salts.

The entries 7-11 report the reactivity of substituted iodobenzenes with cyclohexene in HTW. These results illustrate the effect of multiple different and competing trends. As with traditional Heck systems, aromatic halides with substituents which increase the electron density on the iodo-substituted carbon on the benzene ring were deactivated; whereas, decreased electron density on the arene increased the reactivity of the Heck reaction.[4] This trend is visible with strongly electron donating or withdrawing substitutents (entries 7 and 11); however, issues of solubility are superimposed on this trend in the intermediate region (entries 8 –10).

Other researchers have reported Heck reactions in HTW at 260 °C and in supercritical water at 400 °C.[18] Contrary to our studies, arenes with electron donating groups and unactivated alkenes were unreactive. Hexene was found to be completely inert toward coupling under these conditions.[18] It is

Table I. Palladium-Catalyzed Arylation of Cycloalkenes in High Temperature Water

Entry	Aryl Iodide	Cycloalkene	Added Salts	Products	%Yield (ratio)[a]
1			none		17 %
2			none		21 % (8:30:62)
3	"	"	0.5 - 2 M LiCl	"	15 -18% (9:30:60)
4	"	"	1 mmole *n*–Bu_4NCl	"	40 % (67:13:20)
5			none		48 %
6	"		none		54 %
7			none		7 %
8		"	none		24 %
9		"	none		17 %
10		"	none		21 %
11		"	none		32 %

a. Ratio of isomers: 1-phenylcyclohexene: 2-phenylcyclohexene : 3-phenylcyclohexene

possible that some of the differences between these studies are due to differences in water loading. In our work, the water loading was set to create homogeneous, compressed water conditions. If lower water loading is used, multi-phase systems are created: liquid water with dissolved catalyst in equilibrium with vapor-phase water, and vapor-phase organics. The lower reactivity could be traced to the mass transfer problems associated with heterogeneous water systems, aggravated by limited agitation.[19]

In summary, the unusual properties of water under HTW conditions provide a novel method for extending Heck reactions into *neat* water. HTW can be used as an organic solvent alternative without special adaptation of the catalyst or reactants or the addition of quaternary ammonium salts or co-solvents, due to the changes in the physical properties of water under these conditions. Herein, the decreased dielectric constant of water at 225 °C, ~31 at 100 bar, is used to dissolve the organic components.[3] Preliminary results suggest that the reaction proceeds in the aqueous phase; further research in this area is on going.

Acknowledgments: The authors gratefully acknowledge support from the National Science Foundation (CHE-9709224), Research Corporation Cottrell College Science Award, Research Corporation Department Development Award, and the Donors of the Petroleum Research Fund, administered by the American Chemical Society. A. Tinsley thanks the SILO Advisory Council Undergraduate Research Fellowship (SURF) program for support.

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13. CAUTION High-temperature and high-pressure reactions should be approached with reasonable care.
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19. A manuscript describing our experiments on the physical factors affecting HTW reactions is under preparation.