

First Examples of Transition-Metal Free Sonogashira-Type Couplings

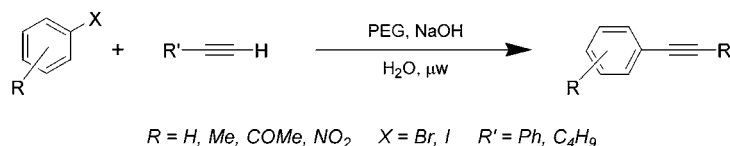
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ABSTRACT



We report here our observation that, using appropriate reaction conditions, the Sonogashira reaction can be performed without the need for transition-metal catalysts. Our approach involves the use of water as a solvent, poly(ethylene glycol) as a phase-transfer agent, and sodium hydroxide as a base. The methodology works, to differing extents, for aryl iodides and bromides.

The Sonogashira reaction (palladium and copper cocatalyzed coupling of terminal alkynes with aryl and vinyl halides) is one of the most widely used C–C bond-forming reactions.¹ It provides an efficient route to aryl alkynes, which are interesting intermediates for the preparation of a variety of target compounds with applications ranging from natural products² and pharmaceuticals³ to molecular organic materials.⁴ Due to the use of the products, the development of new catalytic systems has received considerable attention.

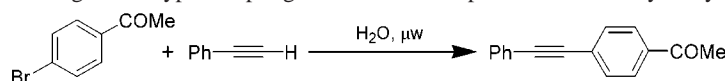
We have recently reported that it is possible to perform the Suzuki coupling reaction (coupling of an aryl halide with an arylboronic acid to yield a biaryl) *without* the need for a transition-metal catalyst.^{5,6} The key to the success of the methodology is the use of water as solvent, a suitable phase-transfer agent, sodium carbonate as a base, and microwave heating. The methodology works well for a range of aryl

bromides and with some aryl iodides. Clearly, we are interested in developing the methodology for use in other reactions. Very recently in the literature there has been an example of a metal-free Heck reaction between styrene and iodobenzene using supercritical water giving a moderate yield of product⁷ and a report of metal-free biaryl ether synthesis through S_NAr -based addition reactions using microwave heating and DMSO as a solvent.⁸ We present here our preliminary findings in the development of our transition-metal free coupling work to the Sonogashira reaction.

Development of a metal-free procedure for the Sonogashira reaction is a particular challenge since it is a traditionally dimetallic-mediated process (palladium and copper required). This being said, there have been a number of recent reports of copper-free approaches to the Sonogashira reaction, most involving the use of an amine, such as piperidine, triethylamine, or pyrrolidine, as a solvent⁹ or in large excess.¹⁰ These methods can also be adapted to use in conjunction with aqueous solvent mixtures by using an ammonium salt as a phase-transfer agent.¹¹ A copper-free coupling of aryl iodides

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Table 1. Transition-Metal Free Sonogashira-Type Coupling of 4-Bromoacetophenone and Phenylacetylene^a

entry	reaction conditions ^b	conversion ^c (%)	product yield ^d (%)
1	1.0 equiv of TBAB, 2.0 mL of H ₂ O, 3.8 equiv of Na ₂ CO ₃ , 60 W, <i>T</i> = 150 °C, hold time 5 min	3	3
2	1.0 equiv of TBAB, 2.0 mL of H ₂ O, 3.8 equiv of Na ₂ CO ₃ , 300 W , <i>T</i> = 170 °C , hold time 5 min	7	7
3	1.0 equiv of TBAB, 2.0 mL of H ₂ O, 2.0 equiv of NaOH , 300 W , <i>T</i> = 170 °C , hold time 5 min	67	33
4	1.0 equiv of TBAB, 2.0 mL of H ₂ O, 2.0 equiv of piperidine , 300 W , <i>T</i> = 170 °C , hold time 5 min	31	17
5	1.0 mL of PEG , 1.0 mL of H₂O , 2.0 equiv of NaOH , 300 W , <i>T</i> = 170 °C , hold time 5 min	85	67
6	1.0 mL of PEG , 1.0 mL of H₂O , 2.0 equiv of NaOH , 300 W , <i>T</i> = 170 °C , hold time 10 min	43	33
7	1.5 mL of PEG , 0.5 mL of H₂O , 2.0 equiv of NaOH , 300 W , <i>T</i> = 170 °C , hold time 5 min	20	14
8	0.5 mL of PEG , 1.5 mL of H₂O , 2.0 equiv of NaOH , 300 W , <i>T</i> = 170 °C , hold time 5 min	14	13
9	1.0 mL of PEG , 1.0 mL of H₂O , 2.0 equiv of NaOH , 300 W , <i>T</i> = 150 °C , hold time 5 min	12	9
10	1.0 mL of PEG , 1.0 mL of H₂O , 2.0 equiv of NaOH , 300 W , <i>T</i> = 160 °C , hold time 5 min	14	11
11	1.0 mL of PEG , 1.0 mL of H₂O , 2.0 equiv of NaOH , 300 W , <i>T</i> = 185 °C , hold time 5 min	53	45

^a 1 mmol of 4-bromoacetophenone, 1.2 mmol of phenylacetylene. Temperature ramped to that stated and held there for the allotted time. ^b Conditions changed from entry 1 are highlighted in bold. ^c Product conversion. ^d To nearest 1%.

with terminal alkynes has also been reported using an ionic liquid as a solvent.¹² This enables easy separation of the product from the catalyst–ionic liquid system, which could then be reused. An amine- and copper-free methodology for the Sonogashira reaction has also been presented.¹³ A palladacycle catalyst and an additive, tetrabutylammonium acetate, are employed.

As a starting point for the development of our transition-metal-free methodology we chose to study the coupling of 4-bromoacetophenone with phenylacetylene. Optimization data are shown in Table 1. We found that using the same conditions as for our Suzuki-type protocol led to a 3% conversion (Table 1, entry 1). Using a microwave power of 60 W, we ramped the temperature from rt to 150 °C and then held at this temperature for 5 min. Increasing the microwave power to 300 W and the reaction temperature to 170 °C improved the conversion slightly but still was below 10% (Table 1, entry 2).¹⁴ Using this higher microwave power, we investigated the effects on the reaction of changing the base. We found that the use of other group 1 or 2 metal carbonates, hydrogen carbonates, or acetates gave equal or lower conversions as with Na₂CO₃. However, when 2 equiv of sodium hydroxide was used, a conversion of 67% could be obtained (Table 1, entry 3). Although this was a significant improvement, a considerable amount of material was being lost during the course of the reaction. We tried using an organic base, piperidine, but found that this gave poor yields

of product and equally as much material was lost as with the inorganic bases (Table 1, entry 4). Our attention then turned to the phase-transfer agent. Changing this from TBAB to poly(ethylene glycol) (PEG) had a significant effect on the reaction. We were able to obtain an 85% conversion, and the amount of material lost during the reaction was greatly reduced (Table 1, entry 5) but extending the reaction time to 10 min has the effect of destroying product (Table 1, entry 6). We found that the quantity of PEG used in the reaction is of importance. While using 1 mL of PEG and 1 mL of water we obtained an 85% conversion, but if this is varied to make the mixture more or less PEG rich, a significant decrease in product conversion is observed (Table 1, entries 7 and 8). We then investigated the effects of varying the reaction temperature. Running the reaction at 150, 160, or 185 °C all led to significantly lower product conversions indicating that 170 °C is optimum (Table 1, entries 9–11).

To show that the reaction is indeed metal-free, we have used new glassware, apparatus, and reagents and analyzed the entire crude product mixture for palladium and copper content. We found that there was no palladium or copper in the product mixture to the level of detection of the analysis apparatus.¹⁵ These data, and the fact that the reaction is reproducible, argue against catalytic metal contaminants.

With our optimized reaction conditions in hand (Table 1, entry 4), we screened a range of aryl bromides and iodides in the coupling reaction with phenylacetylene. All the reactions have been performed in air and without degassing the water prior to use and with a 1:1.2 stoichiometric ratio of aryl halide to alkyne. The results are shown in Table 2. The first point to note is that the aryl iodides give better yields of product as compared to the corresponding bromides. This is interesting in the light of our results with the transition-metal free Suzuki-type coupling where the opposite

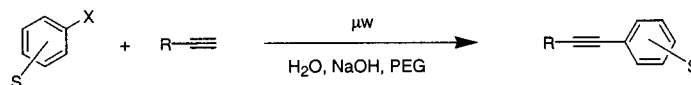
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(14) It should be noted that the power input does not remain the same throughout the reaction period. The power stated is used to take the reaction mixture to the desired temperature, and then bursts of lower power are used to maintain this temperature. This is done automatically by the apparatus. Therefore, in effect, the temperature is maintained only for the reaction time.

(15) No Pd or Cu found down to below 1 ppm of each.

Table 2. Transition-Metal Free Sonogashira-Type Couplings^a

X = Br, I, S = substituent, R = Ph, C₄H₉

entry	aryl halide	alkyne	conv. (%) ^b	yield (%) ^c	entry	aryl halide	alkyne	conv. (%) ^b	yield (%) ^c
1			99	91	9			23	16
2			85	67	10			14	8
3			100	92	11			0	0
4			10	9	12			35	30
5			95	83	13 ^e			49	37
6			68	41	14 ^f			25	13
7			0 ^d	0 ^d	15 ^g			82	78
8			52	43					

^a 1 mmol of aryl halide, 1.2 mmol of phenylacetylene, 2.0 mmol of NaOH, 1 mL of H₂O, 1 mL of PEG. Temperature ramped to 170 °C and held there for the 5 min. ^b Conversion. ^c Isolated yield. ^d Decomposition. ^e Reaction mixture dipped into an oil bath preheated to 170 °C for 6 min. ^f Reaction mixture dipped into an oil bath preheated to 170 °C for 1 h. ^g Reaction run on a 3 mmol scale.

trend was observed. Not surprisingly the substrates need to be stable toward the highly basic reaction conditions when using sodium hydroxide. For example, 4-bromobenzaldehyde is destroyed during the course of the reaction whereas it is not in our metal-free Suzuki-type protocol where less basic sodium carbonate is used.

In an effort to explore the scope of the reaction, we have screened the coupling of representative aryl halides with 1-hexyne (Table 2, entries 9–11). We find that the coupling can be effected but in lower yields than with phenylacetylene. This is not unsurprising in the light of the results in the literature from copper-free protocols which show that aliphatic alkynes are much more difficult to couple as compared to phenylacetylene.

We have also formed a symmetrically disubstituted alkyne by coupling 4-iodotoluene with trimethylsilylacetylene (TMSA). We postulated that, in the basic aqueous medium, the TMSA would be deprotected during the course of the reaction and thus we could effect Sonogashira-type couplings at each end of the acetylinic unit. This is indeed the case,

and we obtain a 30% yield of the desired di-*p*-tolylacetylene product (Table 2, entry 12).

We have explored whether the reaction can be effected using conventional heating. We kept the quantities of substrates, base, PEG, and water exactly the same as in the microwave-heated methodology and performed the reaction in a sealed 10 mL microwave tube. The tube was dipped into an oil bath preheated to 170 °C and held it there for 6 min before removing it and cooling the reaction mixture. An isolated yield of 37% was obtained in the reaction of 4-iodoacetophenone with phenylacetylene (Table 2, entry 13). This cannot be improved even on extension of the reaction time to 1 h; indeed the yield and conversion drop due to competitive decomposition of starting material and product (Table 2, entry 14).

To see if the quantity of starting materials can be scaled up, the reaction of 4-iodoacetophenone and phenylacetylene was repeated on a 3 mmol scale with a product yield of 78% being obtained (Table 2, entry 15). The 3 mmol scale is the largest possible using our sealed 10 mL microwave tubes.

We attribute the lower yield obtained to the fact that we have to use a greater reagents: solvent ratio than in the 1 mmol case in order to keep the quantity of material in the vessel within the optimum working volume of the microwave tube and, as shown in the optimization studies, varying this ratio can effect the yield considerably.

In conclusion, we have shown that it is possible to perform Sonogashira-type couplings of aryl halides and alkynes without the need for a transition-metal catalyst. The reactions are performed in water using sodium hydroxide as a base and PEG as a phase-transfer agent. Work is underway to develop the methodology further, to increase the substrate

scope, to address scale-up issues, and to investigate its mechanism.

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Supporting Information Available: Full experimental details and elemental analysis data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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