JOC*Note*

Copper- and Ligand-Free Sonogashira Reaction Catalyzed by Pd(0) Nanoparticles at Ambient Conditions under Ultrasound Irradiation

Atul R. Gholap,[†] K. Venkatesan,[†] Renu Pasricha,[‡] Thomas Daniel,[†] Rajgopal J. Lahoti,[†] and Kumar V. Srinivasan*,[†]

Organic Chemistry; Technology Division, and Centre for Material Characterization, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune - 411 008, India

kvsri@dalton.ncl.res.in

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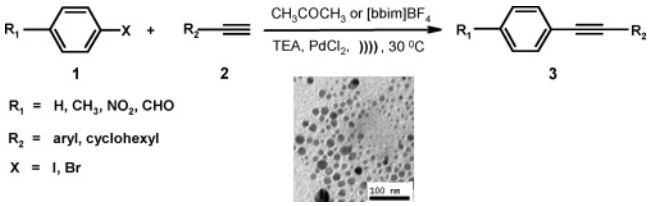

The Sonogashira reaction proceeds at ambient temperature (30 °C) in acetone or room-temperature ionic liquid, 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF_4), as solvent under ultrasound irradiation to give enhanced reaction rates, excellent chemoselectivity, and high yields in the absence of a copper cocatalyst and a phosphine ligand. TEM analysis showed the formation of stable, crystalline, and polydispersed Pd(0) nanoparticles as catalyst for the reaction.

The Sonogashira coupling, a palladium−copper-catalyzed reaction of aryl halides and terminal acetylenes, is a powerful method for the formation of substituted acetylenes.[1] This reaction is frequently utilized as a key step in natural product chemistry[2] and for the synthesis of acetylene compounds which are potentially useful in optoelectronic applications.[3] Since its introduction in 1975, the reaction has been well studied, making use of a variety of ligands and copper salts as cocatalysts.[4] However, the copper salts used as cocatalysts can also induce Glaser-type homocoupling[5] of the alkynes to the corresponding symmetrical diyne via., the copper acetylide formed. To avoid this, copper- and phosphine-free Sonogashira reactions have been developed in recent times resulting in excellent chemoselectivity.[6,7] Extensive research continues to push the limits of this methodology to more and more facile procedures wherein attempts may be made to practice this reaction at ambient temperature without the use of a copper cocatalyst and a ligand. Herein, we report for the first time a copper- and ligand-free Sonogashira reaction at ambient temperature under ultrasound irradiation in a molecular solvent such as acetone as well as a room-temperature ionic liquid (IL), 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF_4), in excellent chemoselectivity with considerably enhanced reaction rates through the formation of stable and crystalline clusters of zerovalent Pd nanoparticles.

The sonochemical reactions were carried out in a thermostated (30 ± 1 °C) ultrasonic cleaning bath of frequency 50 kHz in an inert atmosphere of argon. A variety of aryl halides consisting of substituted iodo- and bromobenzenes were reacted with terminal acetylenic compounds in the absence of any added copper cocatalyst

* Corresponding author. Tel: +91-20-25889089. Fax: +91-20-25893614.
† Organic Chemistry; Technology Division.
‡ Centre for Material Characterization.

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TABLE 1. Synthesis of Diacetylene Derivatives 3

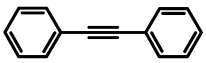
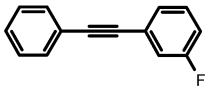
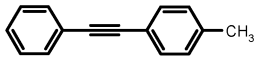
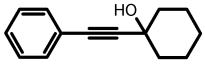
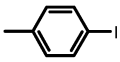
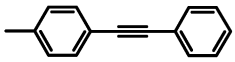
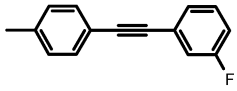
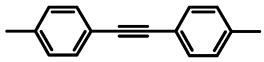
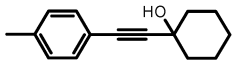
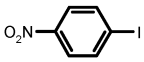
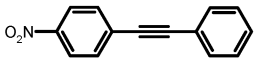
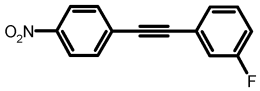
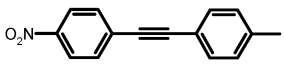
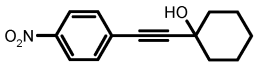
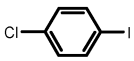
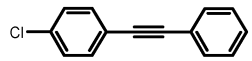
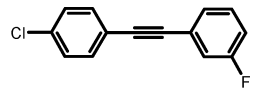
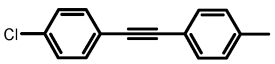
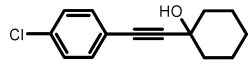
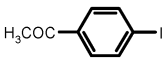
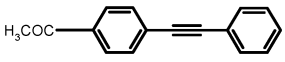
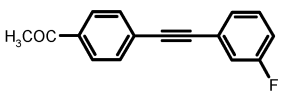
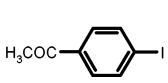
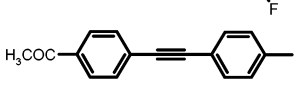
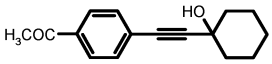
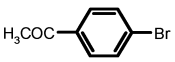
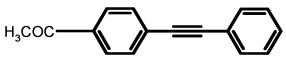
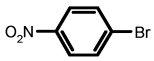
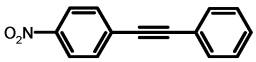
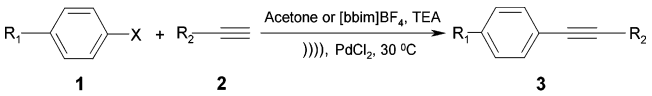
Entry	Aryl halide 1	Acetylene 2	Product 3	Acetone		[bbim]BF_4	
				Reaction time (min)	Yield (%)[a]	Reaction time (h)	Yield (%)[a]
1		1-ethynylbenzene		15	85	2	93
2	1a	3-fluoroethynylbenzene		15	78	2	89
3	1a	4-tolylacetylene		20	75	2	84
4	1a	1-ethynylcyclohexanol		30	65	2.5	78
5		1-ethynylbenzene		20	75	2	85
6*	1b	3-fluoroethynylbenzene		20	72	2	84
7	1b	4-tolylacetylene		35	70	2	80
8*	1b	1-ethynylcyclohexanol		35	68	2.5	74
9		1-ethynylbenzene		15	80	2	89
10*	1c	3-fluoroethynylbenzene		15	78	2	85
11	1c	4-tolylacetylene		25	74	2	80
12*	1c	1-ethynylcyclohexanol		35	68	2.5	72
13		1-ethynylbenzene		15	77	2	88
14*	1d	3-fluoroethynylbenzene		15	72	2	82
15	1d	4-tolylacetylene		20	70	2	80
16*	1d	1-ethynylcyclohexanol		35	66	2.5	72
17		1-ethynylbenzene		15	84	2	90
18*	1e	3-fluoroethynylbenzene		15	80	2	86
19		4-tolylacetylene		15	85	2	95

Table 1 (Continued)

Entry	Aryl halide	Acetylene	Product	Acetone		[bbim]BF_4	
				Reaction time (min)	Yield (%)[a]	Reaction time (h)	Yield (%)[a]
20*	1e	1-ethynylcyclohexanol		15	78	2	89
21	 1f	1-ethynylbenzene		90	65	3	68
22	 1g	1-ethynylbenzene		90	70	3	72

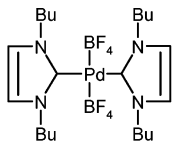
*New compounds. [a] Isolated yields after column chromatography.

SCHEME 1



and phosphine ligands in acetone or the IL [bbim]BF_4 as solvent using $PdCl_2$ as catalyst and triethylamine as base under ultrasonic irradiation (Scheme 1).

In the case of acetone, the products were isolated by evaporation of the solvent followed by extraction with 10% ethyl acetate in petroleum ether (bp 60−80 °C) and filtration through a Celite bed to separate the Pd catalyst. The Pd catalyst in the form of Pd(0) nanoparticles was difficult to recover and recycle. However, from the point of view of ease of recovery and recycle of the expensive Pd catalyst, the reactions were performed in the IL [bbim]-BF_4. In this case, the products were selectively extracted with 10% ethyl acetate in petroleum ether leaving behind the Pd catalyst in the form of Pd(0) nanoparticles as a solution in IL. As reported previously,[8a,b] the complete formation of a Pd−biscarbene complex (A) takes place during the reaction in [bbim]BF_4 as solvent. This complex (A) formed "in situ" was selectively extracted into chloroform separating it from the ionic liquid medium, purified by column chromatography, and completely characterized. The complex (A) under the sonochemical conditions gives rise to the stable, crystalline, and polydispersed Pd(0) nanoparticles as the catalyst for the reaction.



Pd-biscarbene complex [A]

(8) (a) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun*. **2001**, 1544. (b) Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616. (c) Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371.

TABLE 2. Reuse of Catalyst System for Synthesis of Diphenylacetylene (entry1)

entry	1	2	3	4	5
yield (%)	93	91	89	88	85

In all cases, pure products were isolated by subjecting the organic layer to column chromatography and characterized by mp, spectral, and elemental analyses. The results are recorded in Table 1.

As is evident, the ultrasound-assisted Sonogashira reaction proceeds smoothly at ambient temperature even in the absence of copper cocatalyst and phosphine ligands to afford the products in excellent isolated yields. The reactions were significantly faster in acetone as the reaction medium (15−90 min) as compared to those in the IL (2−3 h). However, the reactions in the IL afforded the products in relatively higher yields with the added advantage of the recyclability of both catalyst and the reaction medium. The IL consisting of the Pd catalyst was recycled five times for the reaction of iodobenzene with ethynylbenzene. The results are recorded in Table 2. It was observed that the catalyst exhibits only a marginal loss in activity spread over five recycle batches.

It was important to note that no Glaser coupling product even in traces could be observed for all the reactions involving iodobenzenes. However, in the case of less reactive bromobenzenes, the homocoupled product arising out of the terminal acetylene was formed to an extent of 6−7%. The extent of formation of Glaser coupling product was determined by GC analysis. It can be observed that the process tolerates both electron-donating and electron-withdrawing substituents in the aryl halides as well as terminal acetylenes.

A Pd(0) species stabilized by ligands is proposed to be involved in the catalytic cycle comprising of oxidative insertion, trans-metalation, and reductive elimination of the Sonogashira reaction. Consequently, the formation of such Pd(0) nanoparticles was investigated in the present work by subjecting the reaction mixture after a successful Sonogashira reaction of iodobenzene with 1-ethynylbenzene in acetone and the IL respectively under the sonochemical conditions for "in situ" TEM analysis. TEM analysis was carried out in a Transmission

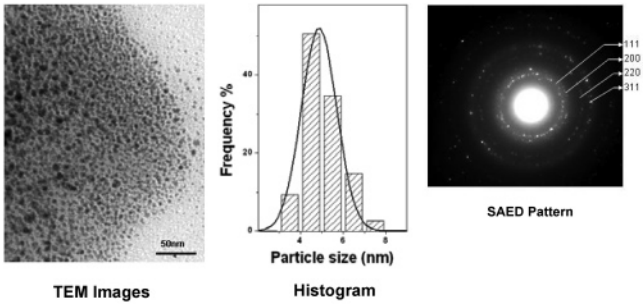


FIGURE 1. TEM measurements in acetone.

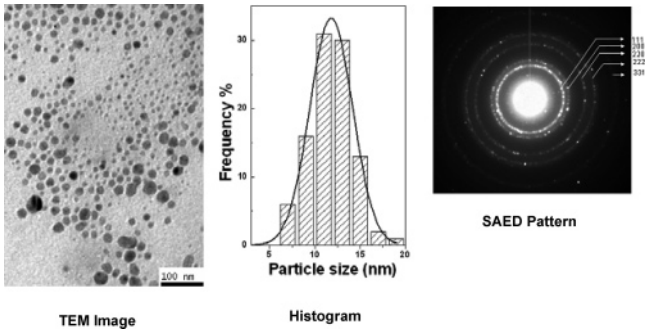


FIGURE 2. TEM measurements in [bbim]BF_4.

Electron Microscope operated at 100 kV with the magnification varying from 100 to 300 k. The sample after appropriate dilution with isopropyl alcohol was directly deposited on carbon coated 400 mesh Cu TEM grids. The TEM measurements for the acetone medium (Figure 1) show the presence of polydispersed Pd(0) nanoparticles of irregular morphology varying in diameter from 3 to 8 nm. For the reaction in the IL medium (Figure 2), TEM measurements show that the particles are almost spherical in shape and the boundaries are clear. They are well dispersed and show the size to be in the range of 10−20 nm. The crystallinity and crystallography of the nanoparticles obtained from both the medium are proved by selected area electron diffraction (SAED) patterns which indicate that the Pd(0) nanoparticles are polycrystalline in nature and can be indexed as face-centered cubic (fcc) crystals from the allowed reflections.

It is important to note that the reaction of 4-iodotoluene with 1-ethynylbenzene in acetone or IL at room temperature under similar conditions but in the absence of ultrasound (silent condition) did not show the formation of any cross-coupled product even after several hours (6 h) of stirring. Moreover, in a blank experiment, Pd(0) nanoparticles were formed by sonicating a mixture of $PdCl_2$ and triethylamine in either acetone or IL, respectively. To this were added the reactants, viz. 4-iodotoluene and 1-ethynylbenzene, and the mixture was stirred for 6 h at ambient temperature under silent conditions. The cross-coupled product 4-(phenylethynyl)toluene was obtained to an extent of 36% and 38% (isolated yields) in acetone and the IL, respectively, as against the 75% and 85% yields obtained in the total sonochemical reaction. This implies that ultrasound not only brings about the formation of highly crystalline, active Pd(0) nanoparticles required for the Sonogashira reaction but also promotes the activity of the catalytic species in the oxidative insertion, trans-metalation, and reductive elimination catalytic cycle of the Sonogashira reaction. This is made possible by the phenomenon of acoustic cavitation generating transient cavitation bubbles of very short lifetimes ($\sim 10^{-9}$ s), the implosive collapse of which under adiabatic conditions gives rise to high temperatures and pressures.[9]

TABLE 3. Synthesis of Diphenylacetylene in Various ILs

entry	ionic liquid	reaction time (h)	yield[a] (%)
1	[bmim]Br	2	89
2	[beim]BF_4	2	90
3	[bpim]Br	2	92
4	[emim]BF_4	2	89
5	[bbim]Cl	2	88
6	[bbim]Br	2	92
7	[bbim]BF_4	2	93
8	[bbim]PF_6	2	90
9	[bbim]ClO_4	2	85

[a] Isolated yields after column chromatography.

It was interesting to ascertain whether this reaction is effective with similar room-temperature ILs belonging to the imidazolium class. Thus, a variety of ILs as shown in Table 3 were screened as solvents for the synthesis of diphenylacetylene under identical sonochemical reaction conditions. It was also observed that all the ionic liquids with varying cations and anions were found to give more or less similar results as shown in Table 3.

In conclusion, the Sonogashira reaction has been achieved in short reaction times, excellent chemoselectivity, and high isolated yields at ambient temperature under ultrasonic irradiation in a molecular solvent as well as a room-temperature ionic liquid even in the absence of a phosphine ligand and copper cocatalysts. For iodobenzenes, no traces of Glaser coupling product were detected, whereas in the case of bromobenzenes the homocoupled product was formed to the extent of 6−7% only. The formation of stable and crystalline Pd(0) nanoparticles under the sonochemical conditions has been shown by TEM measurements. It was ascertained that ultrasound not only generated the Pd(0) nanoparticles as the active catalyst for the reaction but also promoted and enhanced the catalytic activity of this species in the catalytic cycle of the Sonogashira cross-coupling reaction. The short reaction times, excellent chemoselectivity, high isolated yields, and easy workup procedure make this sonochemical methodology an efficient protocol for the rapid synthesis of disubstituted acetylene libraries.

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Supporting Information Available: Representative procedures, TEM measurements, characterization data and ^1H and ^{13}C NMR spectra for all products listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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