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A highly efficient copper and ligand free protocol for the room temperature Sonogashira reaction

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A mild and efficient catalytic system based on $PdCl_2$ and Na_2SO_4 has been developed for the Sonogashira reaction of aryl iodides at room temperature. The system provides a simple route to obtain polyfunctional alkynes under ligand and copper free conditions. The procedure is equally efficient for aliphatic alkynes and aryl bromides.

Introduction

The Pd-catalyzed Sonogashira reaction of a terminal alkyne with an aryl halide is found to be a reliable tool for the construction of polyfunctional alkynes, which find extensive applications ranging from pharmaceuticals to agrochemicals and in materials chemistry.[1] This method was developed by Sonogashira, Tohda, and Hagihara in 1975 and since its discovery, various modifications have been made to the reaction conditions.[2,3] Initially these reactions were performed in an organic solvent with the concomitant addition of ligand and a Cu-salt as co-catalyst.[2a] Although the addition of copper is advantageous in terms of reaction efficiency, the formation of undesired Glaser type homocoupling from the alkyne is one of the major obstacles associated with this reaction.[4] So to address this issue several other additives were used to maintain the reaction efficiency such as Ag,[5] Zn,[6] Al,[7] Sn,[7] tetrabutyl ammonium salts[8] *etc.* On the other hand ligand plays a key role in the Sonogashira reaction which is generally used to stabilize the active palladium species in the reaction. Among the ligands designed for this reaction significant amount of success have been achieved with phosphine based ligands such as electron rich bulky phosphanes,[9] water soluble phosphanes such as TPPTS and TXPTS,[10] nitrogen based ligands such as *N*-heterocyclic carbenes,[1c,11] oxime palladacycles,[12] amines[13] *etc.* Although complex containing such ligands show excellent reactivity, however in majority of cases principal drawbacks are the availability, stability, and cost of the palladium complexes and related ligands. In addition they also lead to waste disposal which have severe effect on the environment. So regarding the principles of Green chemistry it is the necessity to design catalytic system using cheap and non toxic reagents under mild reaction conditions. Thus the development of a protocol under ligand and copper free condition for Sonogashira reaction is highly desirable. For many years simple inorganic salts are often use are as an activator in different organic transformation.[14] The innocuous nature and rate enhancing effect of these salts makes them a suitable alternate for ligands in the Pd-catalyzed Suzuki–Miyaura cross coupling reaction.[15,16] Recently our group has reported the efficiency of Na_2SO_4 as an activator in the Suzuki–Miyaura cross coupling reaction.[16] In order to extend the scope of this protocol herein we reported the efficiency of same catalytic species in Sonogashira cross coupling reaction of aryl iodides with aryl acetylenes at room temperature.

Results and discussion

The enhancing effect of non-toxic salt particles in Suzuki–Miyaura cross coupling reaction is well known.[16] However to the best of our knowledge; there is no report available on the effect of non-toxic salt particles in Pd catalysed Sonogashira reaction. Therefore we wish to study the effect of different metal salts in the Sonogashira reaction of aryl iodides. For that purpose iodobenzene (0.5 mmol) and phenyl acetylene (0.6 mmol) was considered as model substrate. The preliminary investigation for reaction optimization was performed with 2 mol% of $PdCl_2$ and three equivalent of K_2CO_3 (1.5 mmol) in MeOH (2 mL) at room temperature under aerobic condition. The results obtained are highlighted in Table 1. It was found that $MnCl_2$ has no effect in the cross coupling reaction (Table 1, entry 1). The yield of cross coupling product was slightly increased when $ZnCl_2$ was used as an additive (Table 1, entry 2). Similar observations were also noticed in case of ferrous and ferric salts (Table 1, entries 3 and 4). Then we thought to incorporate alkali metal salts in the reaction. It is interesting to observe that Na_2SO_4 can enhance the efficiency of Sonogashira reaction and

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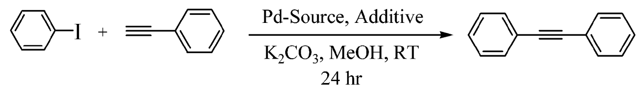
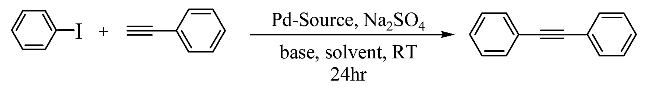
Table 1 Effect of salts on Sonogashira reaction of aryl iodides[a]



Entry	Catalyst (2 mol%)	Additive	Yield[b] (%)
1	$PdCl_2$	$MnCl_2$	54
2	$PdCl_2$	$ZnCl_2$	70
3	$PdCl_2$	$FeSO_4 \cdot 7H_2O$	72
4	$PdCl_2$	$FeCl_3$	76
5	**$PdCl_2$**	**Na_2SO_4**	**91**
6	$PdCl_2$	LiCl	78
7	$PdCl_2$	NaCl	81
8	$PdCl_2$	NaOAc	69
9	$PdCl_2$	—	54
10	$Pd(OAc)_2$	—	56
11	Na_2PdCl_4	—	82
12	$Pd(OAc)_2$	Na_2SO_4	87
13[c]	$PdCl_2$ (1 mol%)	Na_2SO_4	59
14[d]	$PdCl_2$ (1 mol%)	Na_2SO_4	65

[a] Reaction conditions: iodobenzene (0.5 mmol), phenyl acetylene (0.6 mmol); additive (10 mol%), K_2CO_3 (1.5 mmol), MeOH (3 mL) at room temperature unless otherwise noted. [b] Isolated yield. [c] 1 mol% $PdCl_2$ was used. [d] 1 mol% of $PdCl_2$ and 20 mol% of Na_2SO_4 was used.

Table 2 Effect of solvent and base on Sonogashira reaction[a]



Entry	Solvent (3 mL)	Base	Yield[b] (%)
1	MeOH	K_2CO_3	91
2	**EtOH**	**K_2CO_3**	**90**
3	i-PrOH	K_2CO_3	87
4[c]	MeOH : H_2O	K_2CO_3	70
5[d]	EtOH : H_2O	K_2CO_3	79
6	H_2O	K_2CO_3	57
7	DMF	K_2CO_3	80
8	DMSO	K_2CO_3	76
9	PEG-300	K_2CO_3	59
10	CH_3CN	K_2CO_3	68
11	EtOH	Cs_2CO_3	90
12	EtOH	$Na_3PO_4 \cdot 12H_2O$	83
13	EtOH	$NaHCO_3$	69
14	EtOH	KOH	46
15	EtOH	NaOH	39
16	EtOH	Et_3N	68
17[e]	EtOH	K_2CO_3	63
18[f]	EtOH	K_2CO_3	90

[a] Reaction conditions: iodobenzene (0.5 mmol), phenyl acetylene (0.6 mmol); Na_2SO_4 (10 mol%), base (1.5 mmol), solvent (3 mL) at room temperature unless otherwise noted. [b] Isolated yield. [c] 1 : 1 (MeOH : H_2O) was used. [d] 1 : 1 (EtOH : H_2O) was used. [e] 2 equivalent of K_2CO_3 was used. [f] 4 equivalent of base was used.

provide excellent yield of isolated cross coupling product (Table 1, entry 5).

Compared with the efficiency of Na_2SO_4, other alkali metal salts *viz.* LiCl, NaCl and NaOAc showed slightly lower activity (Table 1, entries 6–8). However the yield of the cross coupling product decreased significantly when the reaction was performed in absence of Na_2SO_4 (Table 1, entries 9 & 10) which clearly confirms the role of Na_2SO_4 in the reaction. The use of *in situ* generated complex Na_2PdCl_4 results 82% of isolated cross coupling product (Table 1, entries 11). It is important to mention here that the amount of Glaser type homo-coupling product in case of Na_2SO_4 is minimized to only 1%. A typical reaction with $Pd(OAc)_2$ and Na_2SO_4 results 87% of desired product (Table 1, entries 12). In order to check the effect of amounts of $PdCl_2$ and Na_2SO_4, reactions were performed with various amounts of catalyst and additive. Finally we observed that 2 mol% of $PdCl_2$ was necessary for optimum yield (Table 1, entries 5 *vs.* 13 & 14). Recently $PdCl_2/Na_2SO_4$ system has been found to be very effective for the Suzuki–Miyaura coupling reaction.[16,17] Although the exact role of Na_2SO_4 is not clear, it is believed that the addition of sodium sulfate, could provide soluble *ate* complex of palladium, $Na_2Pd(SO_4)_2$, which is the actual catalytic species.[16,17]

Our next goal was to identify a suitable solvent which can accelerate the reaction at good rate. A myriad number of aqueous and non-aqueous solvents were examined. The results are listed in Table 2. It has been observed that alcoholic solvents *viz.* MeOH, EtOH and i-PrOH are most suited for the reaction as excellent yield of cross coupling product was obtained in all cases (Table 2, entries 1–3). However, the yield dramatically falls when aqueous alcoholic solvents were used (Table 2, entries 4 & 5). The reaction fails to complete when water was used as a solvent (Table 2, entry 6). On the other hand moderate to good yield were obtained in case of other organic solvents such as DMF, DMSO, PEG-300, MeCN (Table 2, entries 7–10). So we have considered EtOH for further optimization process. Next we thought to examine the effect of bases in the Sonogashira reaction of iodobenzene (0.5 mmol) with phenyl acetylene (0.6 mmol) in presence of 2 mol% $PdCl_2$ with 10 mol% Na_2SO_4 at room temperature. Among the bases tested maximum yield was noted with K_2CO_3 (Table 2, entry 1). Similar yields can be also obtained from Cs_2CO_3 and Na_3PO_4 (Table 2, entries 11 & 12). But considering the cost factor and hygroscopic nature of Cs_2CO_3 and Na_3PO_4, we choose K_2CO_3 for the further optimization process. Whereas, poor yields were recorded with bicarbonate, hydroxide and organic bases (Table 2, entries 13–16). Further optimization confirms that 3 equivalent of K_2CO_3 was optimum for efficient coupling (Table 2, entries 1 *vs.* 17 & 18).

To verify the scope and limitation of the present system we have tested several electronically diverse aryl iodide and aryl acetylene under the optimized condition and the results obtained are highlighted in Table 3. It was noticed that presence of electron donating or withdrawing group at the *para* position of aryl iodide furnishes excellent yield of isolated cross coupling product (Table 3, entries 2–5). The sterically demanding 2-nitroiodobenzne also affords good yield with phenyl acetylene (Table 3, entries 6). The reaction also proceeds well in case of meta substituted electron rich and electron deficient aryl iodides (Table 3, entries 7 & 8). We also investigated the reaction of substituted aryl acetylenes and aliphatic alkynes. In all cases

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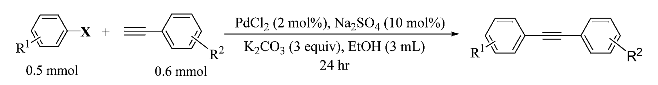
Table 3 Sonogashira coupling of aryl iodides using $PdCl_2/Na_2SO_4$ system[a]



	R_1	R_2	X	Yield[b] (%)
1	H	H	I	91
2	4-Me	H	I	92
3	4-OMe	H	I	86
4	4-NO_2	H	I	99
5	4-$COCH_3$	H	I	97
6	2-NO_2	H	I	91
7	3-NO_2	H	I	95
8	3-Me	H	I	90
9	H	4-Me	I	89
10	4-Me	4-Me	I	90
11	4-NO_2	$C_{10}H_{21}C{\equiv}CH$	I	86
12	4-Me	H	Br	61, 87[c]
13	4-Me	4-Me	Br	81[c]
14	4-OMe	H	Br	65[c], 82[d]
15	4-Me	4-OMe	Br	79[d]
16	4-OMe	4-OMe	Br	50[d]

[a] Reaction conditions: aryl halide (0.5 mmol), aryl/alkyl acetylene (0.6 mmol); Na_2SO_4 (10 mol%), K_2CO_3 (1.5 mmol), EtOH (3 mL) at room temperature unless otherwise noted. Isolated yields. [b] Isolated yields. [c] Reaction conducted at 60 °C. [d] Reaction conducted at 100 °C.

good to acceptable yield of cross coupling product was observed (Table 3, entries 9–11).

We next explored the activity of our present system to the coupling of aryl bromides. However, at room temperature low conversion was observed for 4-bromotolyl (Table 3, entry 12). Hence it was decided to perform the reactions for aryl bromides at high temperature. Aryl bromides having electron donating substituent's *viz.* 4-Me and 4-OMe rendered good yield of isolated cross coupling products (Table 3, entries 12–16).

Conclusion

In summary we have developed a Na_2SO_4 promoted efficient procedure for the Sonogashira cross coupling reaction of aryl iodides with aryl acetylenes at room temperature. The main advantages of the protocol are that it operates at mild condition under ligand and copper free condition. Further the protocol is also suitable for the aliphatic alkynes.

Experimental section

General procedure for the Sonogashira reaction of aryl iodides/aryl bromides

In a 50 mL round bottomed flask aryl halide (0.5 mmol), aryl/alkyl acetylene (0.6 mmol), $PdCl_2$ (2 mol%; 1.77 mg), Na_2SO_4 (10 mol%; 7.1 mg) and K_2CO_3 (1.5 mmol; 207 mg) in 3 mL EtOH was stirred at room temperature under aerobic condition. The progress of the reaction was monitored by TLC. After completion of the reaction the mixture was diluted with H_2O (20 mL) and extracted with diethyl ether (3 × 20 mL). The ether part dried over by Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash chromatography (silica gel, hexane) to give the pure product. Formation of the product was confirmed by comparing FTIR spectra, ^1H NMR spectra, ^{13}C NMR spectra, melting point measurement and high resolution GC-MS with authentic compounds.

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References

1 (*a*) H. S. Nalwa and S. Miyata, *Nonlinear Optics of Organic Molecules and Polymers*, CRC Press, Boca Raton, FL, 1997; (*b*) J. Suffert and R. Ziessel, *Tetrahedron Lett.*, 1991, **32**, 757; (*c*) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874.

2 (*a*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467; (*b*) J. A. Marsden and M. M. Haley, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijre and F. Diederich, Wiley-VCH, Weinheim, Germany, 2nd edn, 2004, pp. 317–394; (*c*) K. Sonogashira, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-I. Negishi, JohnWiley&Sons, Inc., Hoboken, N. J., 2002, vol. 1, pp. 493–529.

3 (*a*) A. Molnar, *Chem. Rev.*, 2011, **111**, 2251; (*b*) H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834; (*c*) R. L. Duncan and J. Macquarrie, *Org. Biomol. Chem.*, 2009, **7**, 1627; (*d*) A. Komaromi and Z. Novak, *Chem. Commun.*, 2008, 4968; (*e*) R. Chinchilla and C. Najera, *Chem. Soc. Rev.*, 2011, **40**, 5084; (*f*) K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46; (*g*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442; (*h*) U. H. F. Bunz, *Chem. Rev.*, 2000, **100**, 1605; (*i*) A. L. K. Shi Shun and R. R. Tykwinski, *Angew. Chem., Int. Ed.*, 2006, **45**, 1034; (*j*) V. Farina, *Adv. Synth. Catal.*, 2004, **346**, 1553.

4 G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054.

5 (*a*) T. Lauterbach, M. Livendahl, A. Rosellon, P. Espinet and A. M. Echavarren, *Org. Lett.*, 2010, **12**, 3006; (*b*) A. Mori, J. Kawashima, T. Shimada, M. Suguro, K. Hirabayashi and Y. Nishihara, *Org. Lett.*, 2000, **2**, 2935; (*c*) M. Zhu, Z. Zhou and R. Chen, *Synthesis*, 2008, 2680; (*d*) Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3199.

6 A. D. Finke, E. C. Elleby, M. J. Boyd, H. Weissman and J. S. Moore, *J. Org. Chem.*, 2009, **74**, 8897.

7 E.-I. Negishi and L. Anastasia, *Chem. Rev.*, 2003, **103**, 1979.

8 (*a*) C. Najera, J. Gil-Molto, S. Karlstrom and L. R. Falvello, *Org. Lett.*, 2003, **5**, 1451; (*b*) J. Gil-Molto and C. Najera, *Eur. J. Org. Chem.*, 2005, 4073; (*c*) A. Arques, D. Aunon and P. Molina, *Tetrahedron Lett.*, 2004, **45**, 4337; (*d*) D. A. Alonso, C. Najera and M. C. Pacheco, *Tetrahedron Lett.*, 2002, **43**, 9365; (*e*) S. Urgaonkar and J. G. Verkade, *J. Org. Chem.*, 2004, **69**, 5752; (*f*) U. S. Sorensen and E. Pombo-Villar, *Tetrahedron*, 2005, **61**, 2697.

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Published on 01 December 2014. Downloaded on 11/12/2014 13:58:06.

9 (*a*) M. Kosugi, M. Kameyama and T. Migita, *Chem. Lett.*, 1983, 927; (*b*) V. P. W. Bohm and W. A. Herrmann, *Eur. J. Org. Chem.*, 2000, 3679; (*c*) T. Hundertmark, A. F. Littke, S. L. Buchwald and G. C. Fu, *Org. Lett.*, 2000, **2**, 1729; (*d*) C. Yi and R. Hua, *J. Org. Chem.*, 2006, **71**, 2535; (*e*) C. A. Fleckenstein and H. Plenio, *Organometallics*, 2007, **26**, 2758; (*f*) A. C. Fleckensteinab and H. Plenio, *Chem. Soc. Rev.*, 2010, **39**, 694.

10 (*a*) M. Vrabel, R. Pohl, B. Klepetarova, I. Votruba and M. Hocek, *Org. Biomol. Chem.*, 2007, **5**, 2849; (*b*) P. Capek, H. Cahova, R. Pohl, M. Hocek, C. Gloeckner and A. Mark, *Chem.–Eur. J.*, 2007, **13**, 6196; (*c*) L. Kalachova, R. Pohl and M. Hocek, *Synthesis*, 2009, 105; (*d*) R. B. DeVashner, L. R. Moore and K. H. Shaughnessy, *J. Org. Chem.*, 2004, **69**, 7919.

11 (*a*) S. Roy and H. Plenio, *Adv. Synth. Catal.*, 2010, **352**, 1014; (*b*) A. John and P. Ghosh, *Dalton Trans.*, 2010, 7183; (*c*) M. G. Organ, G. A. Chass, D.-C. Fang, A. C. Hopkinson and C. Valente, *Synthesis*, 2008, 2776; (*d*) F.-T. Luo and H.-K. Lo, *J. Organomet. Chem.*, 2011, **696**, 1262.

12 J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527.

13 H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834.

14 (*a*) A. Kumar, *Chem. Rev.*, 2001, **101**, 1; (*b*) T. vom Stein, P. Grande, F. Sibilla, U. Commandeur, R. Fischer, W. Leitner and P. D. de María, *Green Chem.*, 2010, **12**, 1844.

15 B. Zhang, J. Song, H. Liu, J. Shi, J. Ma, H. F. W. Wang, P. Zhang and B. Han, *Green Chem.*, 2014, **16**, 1198.

16 M. Mondal and U. Bora, *Green Chem.*, 2012, **14**, 1873.

17 (*a*) S. Xu, H.-H. Chen, J.-J. Dai and H.-J. Xu, *Org. Lett.*, 2014, **16**, 2306; (*b*) C. Goncalves, C. Favre, P. Feuardant, S. Klein, C. V. Garcia, C. Cecutti, S. T. Roux and E. Vedrenne, *Carbohydr. Polym.*, 2015, **116**, 51; (*c*) G. Zhao, Z. Wang, R. Wang, J. Li, D. Zou and Y. Wu, *Tetrahedron Lett.*, 2014, **55**, 5319.

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