Tetrahedron Letters 49 (2008) 7294–7298

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-free Sonogashira coupling in amine–water solvent mixtures

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ARTICLE INFO

Article history:
Received 25 July 2008
Revised 30 September 2008
Accepted 8 October 2008
Available online 14 October 2008

Keywords:
Cross-coupling
Acetylenes
Sonogashira reaction
Palladium

ABSTRACT

Extensive study of different amine–water solvent mixtures was carried out for copper free Sonogashira coupling of aryl iodides. The influence of the palladium sources, ligands, amine–water ratio and further additives was also evaluated. Application of *sec*-butylamine–water mixture proved to be an excellent medium for rapid and efficient coupling of aryl-iodides at ambient temperature in the presence of $PdCl_2(PPh_3)_2$ as catalyst.

The palladium-catalyzed Sonogashira cross-coupling reaction[1] between aryl-halides and terminal acetylenes serves as a powerful method for the preparation of internal acetylenes,[2] heterocycles[3] and natural products.[4] Since its discovery by Sonogashira[5] in 1975, several modifications have been reported including variation of the ligands, palladium sources, solvents and bases in order to perform the coupling reactions more efficiently with aryl iodides,[6] bromides[7] and chlorides.[8] The presence of the copper co-catalyst facilitates the coupling reaction by the in situ generation of copper acetylide, but it can also induce a Glaser-type oxidative homocoupling[9] of the terminal acetylene to yield a diyne. Focusing on the suppression of the formation of this undesired side product, several copper-free versions of the palladium-catalyzed Sonogashira coupling have been developed.[10]

Mechanistic studies[11] of the copper-free version of the Sonogashira coupling have shown that the polarity and hydrogen bonding ability of the solvents are important in accelerating the reaction by stabilizing the ionic intermediates of the catalytic cycle, whereas steric bulk decreases the stabilizing ability of the solvent.[12] Another important factor is the strength of the base, which plays an important role in the deprotonation of the terminal acetylene during the process.

Considering the aforementioned facts, we envisaged that the use of amines as solvent and base under aqueous conditions would influence the efficiency of the copper-free coupling. We examined the applicability of different types of amine–water mixtures for the copper-free Sonogashira coupling of aryl iodides with terminal acetylenes at ambient temperature. We envisaged that water as co-solvent would not only accelerate the reaction due to its high polarity and hydrogen bonding ability, but would also serve as an environment friendly solvent for the reaction.[13] Our extensive studies also deal with the choice of palladium source and the ligands for this key transformation.

Initially, several amines as solvent were tested for the Sonogashira coupling of phenyl iodide and phenylacetylene under aqueous and copper-free conditions. We chose the stable and easily accessible $PdCl_2(PPh_3)_2$ complex as catalyst.

While, acyclic tertiary amines (Table 1, entries 1–5) showed no activity at all, the application of DABCO (entry 6) showed increased activity. Although DABCO is a weaker base, compared to other tertiary amines, its less bulky character could be responsible for its higher activity. Among the secondary dialkyl amines, diisopropylamine (DIPA, entry 13) proved to be an excellent base as full conversion was observed after 90 min at 25 °C in DIPA–water 1:1 mixture. In dialkyl amines such as Et_2NH and Pr_2NH (entries 7 and 8), the reaction was slower compared to DIPA. The presence of amines bearing larger alkyl groups (Bu_2NH, $^iBu_2NH$, Hex_2NH and Cy_2NH) resulted in dramatic changes in the catalytic activity (entries 9–12), and no significant coupling was observed with these bases. Whilst the reaction is facilitated in the presence of cyclic secondary amines such as pyrrolidine, *N*-methylpiperazine and 2,2,6,6-tetramethylpiperidine (entries 14–16), morpholine and 1-methylimidazole (entries 17 and 18) were not applicable at all.

Although the application of primary amines is not common in Sonogashira cross-coupling reactions, we continued our examination with these bases. We have found that the coupling reaction takes place very rapidly in the presence of primary amines (entries 20–25). After 90 min reaction time, all of the iodobenzene was consumed at 25 °C, and the desired diphenylacetylene was formed as the only product. Surprisingly, isopropylamine (entry 19) had a

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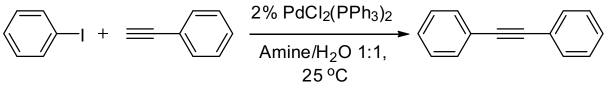
doi:10.1016/j.tetlet.2008.10.037

Table 1
Examination of different amine–water 1:1 solvent mixtures for the copper-free Sonogashira coupling of PhI and phenylacetylene[a]



Entry	Amine	Conversion after 30 min[b] (%)	Entry	Amine	Conversion after 30 min[b] (%)
1	DIPEA	0	14	Pyrrolidine	33
2	TEA	6	15	*N*-Methylpiperazine	47
3	Cy_2NMe	0	16	2,2,6,6-Tetramethylpiperidine	36
4	Bu_3N	0	17	Morpholine	0
5	Pr_3N	0	18	1-Methylimidazole	0
6	DABCO	34	19	$^{i}PrNH_2$	4
7	Et_2NH	9	20	$PrNH_2$	75 (86)
8	Pr_2NH	30	21	$BuNH_2$	65
9	Bu_2NH	0	22	$^{s}BuNH_2$	72 (99)
10	$^{i}Bu_2NH$	0	23	$^{i}BuNH_2$	54
11	Hex_2NH	0	24	$^{t}BuNH_2$	62 (93)
12	Cy_2NH	7	25	$CyNH_2$	64 (96)
13	DIPA	63 (84)			

[a] 0.5 mmol aryl iodide, 0.75 mmol acetylene, 2% $PdCl_2(PPh_3)_2$, 250 μL amine, 250 μL water, 25 °C.
[b] GC conversions after 30 min, isolated yields after 90 min in parentheses.

deleterious effect on the conversion, in comparison to the other primary amines and DIPA.

We have also ran some reactions on preparative scale. As *sec*-butylamine–water 1:1 mixture gave the highest isolated yield (Table 1, entry 22), we chose this medium for further examinations.

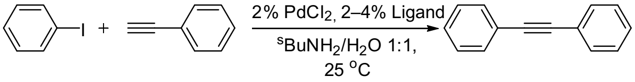
It is well known that the electronic and steric properties of the applied ligands have a strong effect on the reactivity of catalytic systems, we therefore studied the influence of ligands and palladium sources on the Sonogashira coupling.

Ligand screening was achieved in the presence of $PdCl_2$. Without any ligand, we were not able to detect any coupling product in the reaction mixture after 45 min (Table 2, entry 1). Addition of a bulky *ortho*-biphenyl type ligand or tricyclohexylphosphine (entries 2 and 3) did not result in significant conversions. Low conversions were also observed with other sterically demanding ligands such as tri-1-naphthyl-, tri-(*o*-tolyl) and tris(2,4,6-trimethylphenyl)phosphine (entries 5, 6 and 8). Probably, these ligands are not able to coordinate to the palladium in the presence of excess amine due to steric hindrance. Application of the preformed chloro complexes of tricyclohexylphosphine and *tri*(*o*-tolyl)phosphine was also not effective (entries 4 and 7), which could be the consequence of fast ligand dissociation and ligand exchange with the primary amine.

In the presence of tri(2-furyl)phosphine, the reaction was almost complete in 90 min (entry 9), and triaryl phosphines bearing both electron-withdrawing and electron-donating groups at the *para* position showed similar activity (entries 10 and 11). Although the electronic properties of the *para* substituted phosphines did not affect the catalytic activity significantly, more electron deficient phosphines such as tris-(3,5-bis-trifluoromethyl)-phosphine led to the coupling reaction occurring at a lower rate, which is supposedly due to the decreased coordinating ability of the ligand. The highest conversions were observed by adding triphenylphosphine either separate from $PdCl_2$ or in complexed form ($PdCl_2(PPh_3)_2$) (entries 13 and 14). Although reducing the catalyst loading to 1 mol % and 0.5 mol % gave lower reaction rates, the reactions were complete in 2 and 4 h, respectively (entries 15 and 16). The reaction also takes place with almost the same efficiency under aerobic conditions with the same palladium complex (entry 17).

Bidentate ligands with $PdCl_2$ have also showed appreciable activities (entries 18–22); however, the conversions were lower compared to those with triaryl phoshines.

Table 2
Ligand screening experiments[a]



Entry	Palladium cat.	Ligand	Conversion[b] (%)	Entry	Palladium cat.	Ligand	Conversion[b] (%)
1	$PdCl_2$	–	0	13	$PdCl_2$	PPh_3	79
2	$PdCl_2$	^{t}Bu-XPhos	0	14	$PdCl_2(PPh_3)_2$	–	86
3	$PdCl_2$	Cy_3P	0	15	1 mol % $PdCl_2(PPh_3)_2$	–	62
4	$PdCl_2(PCy_3)_2$	–	0	16	0.5 mol % $PdCl_2(PPh_3)_2$	–	32
5	$PdCl_2$	(1-Naphthyl)$_3$P	0	17	$PdCl_2(PPh_3)_2$	–	71 (94)[c]
6	$PdCl_2$	(*o*-Tolyl)$_3$P	0	18	$PdCl_2$	BINAP[d]	2
7	$PdCl_2$(*o*-Me-PPh_3)$_2$	–	0	19	$PdCl_2$	Xanthphos[d]	12
8	$PdCl_2$	(Mesityl)$_3$P	0	20	$PdCl_2$	dppe[d]	15
9	$PdCl_2$	(2-Furyl)$_3$P	75	21	$PdCl_2$	dppp[d]	23
10	$PdCl_2$	(4-Fluorophenyl)$_3$P	68	22	$PdCl_2$	dppb[d]	22
11	$PdCl_2$	(4-Methoxyphenyl)$_3$P	65	23	$Pd(OAc)_2$	PPh_3	70
12	$PdCl_2$	(3,5-Bis-trifluoromethyl)$_3$P	20	24	$Pd_2(dba)_3$	PPh_3	3

[a] 0.5 mmol aryl iodide, 0.75 mmol acetylene, 4 mol % palladium, 4 mol % ligand, 250 μL $^{s}BuNH_2$, 250 μL water, 25 °C
[b] GC conversions after 45 min.
[c] Reaction was performed in the presence of air, isolated yield in parentheses.
[d] 2 mol % of ligand was used.

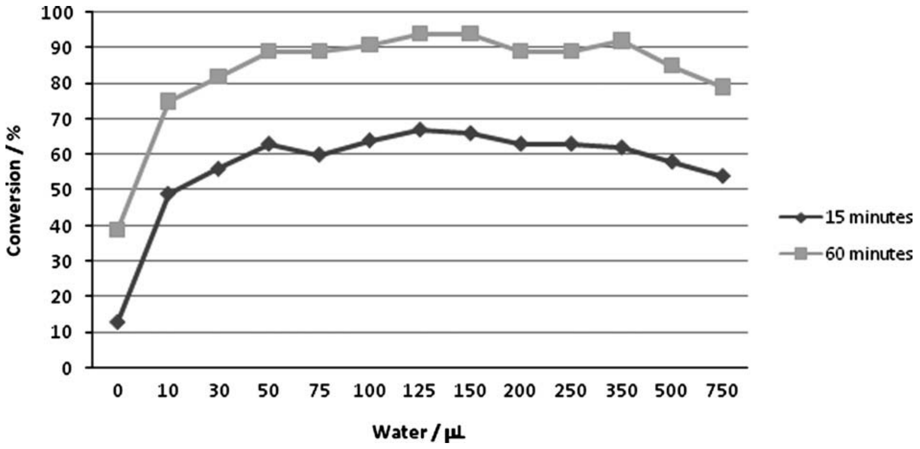


Figure 1. Conversions of the coupling of iodobenzene with phenylacetylene as a function of the amount of water in 250 µL of *sec*-butylamine.

The coupling reaction with $Pd(OAc)_2$ as an alternative palladium(II) source under the same conditions also took place and provided a comparable conversion to $PdCl_2$ (entry 23). Surprisingly, $Pd_2(dba)_3$ showed much lower activity than the Pd(II) salts (entry 24).

After finding $PdCl_2(PPh_3)_2$ as a suitable catalyst for the coupling, the influence of the amount of added water on the catalytic activity was studied. First, we ran the Sonogashira coupling of iodobenzene with phenylacetylene in freshly distilled *sec*-butylamine, then the conversions in different amine–water mixtures (250 µL *sec*-butylamine and 2% $PdCl_2(PPh_3)_2$ were present in all the reactions) were compared (see Fig. 1).

After 15 min only 13% conversion was obtained in the absence of water. Even the presence of very small amounts of water caused significantly higher reaction rates. In 10:250 v/v water/amine mixture, 49% conversion was obtained within the same period of time.

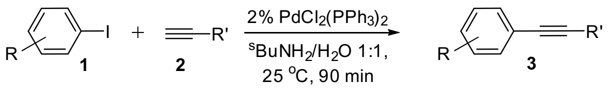
Increasing the water content to 30:250 and 50:250, the conversions were found to be even higher. Further addition of water to the system resulted in smaller effects on the conversion, and the optimal ratio was found to be between 125:250 and 250:250. We also applied a strong inorganic base besides the amines, dissolved in the aqueous phase. In the presence of 1.5 equiv of KOH the reaction took place rapidly, and full conversion was obtained within 30 min at 25 °C.

After these optimization studies, we applied $^sBuNH_2$/water 1:1 mixture and $PdCl_2(PPh_3)_2$ for the copper-free coupling of various aryl iodides and terminal acetylenes to assess the scope of the developed reaction conditions. First, phenylacetylene (**2a**) was reacted with aryl iodides bearing either electron-withdrawing or electron-donating functional groups, to afford the corresponding acetylenes **3a–g** in good isolated yields (Table 3, entries 1–7). Among these substrates, the coupling reaction worked efficiently even in the case of bulky 2-^{i}Pr-iodobenzene (**1d**) (entry 4).

Heteroaromatic systems such as 2-iodopyridine (**1i**), 3-iodopyridine (1 h) and 2-iodothiophene (**1j**) were also coupled successfully with phenylacetylene under the developed conditions (entries 8–10). Coupling of 3-ethynyltoluene (**2b**) as an aromatic acetylene with an electron-donating group yielded the appropriate internal

Table 3

$PdCl_2(PPh_3)_2$ catalyzed Sonogashira coupling of aryl iodides with terminal acetylenes in $^sBuNH_2$/water 1:1 mixture[a]



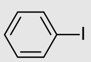
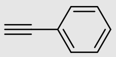
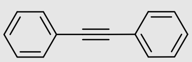
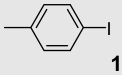
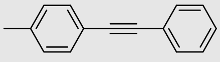
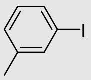
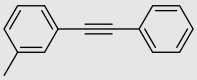
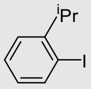
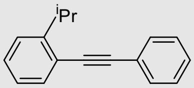
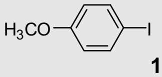
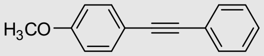
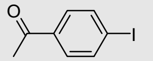
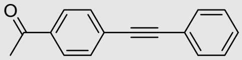
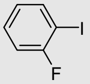
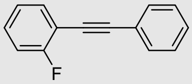
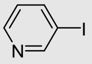
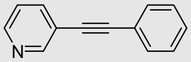
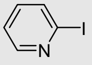
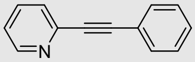
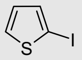
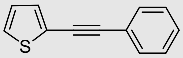
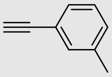
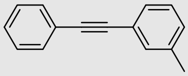
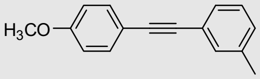
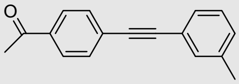
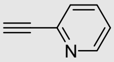
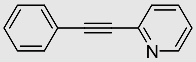
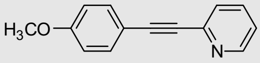
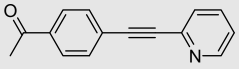
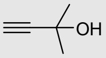
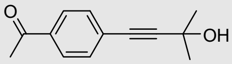
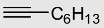
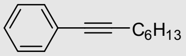
Entry	Aryl Iodide	Alkyne	Product	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	99
2	 **1b**	**2a**	 **3b**	90
3	 **1c**	**2a**	 **3c**	94
4	 **1d**	**2a**	 **3d**	93
5	 **1e**	**2a**	 **3e**	84

Table 3 (*continued*)

Entry	Aryl Iodide	Alkyne	Product	Yield[b] (%)
6	 **1f**	**2a**	 **3f**	87
7	 **1g**	**2a**	 **3g**	96
8	 **1h**	**2a**	 **3h**	94
9	 **1i**	**2a**	 **3i**	92
10	 **1j**	**2a**	 **3j**	88
11	**1a**	 **2b**	 **3c**	95
12	**1e**	**2b**	 **3k**	89
13	**1f**	**2b**	 **3l**	96
14	**1a**	 **2c**	 **3i**	88
15	**1e**	**2c**	 **3m**	87
16	**1f**	**2c**	 **3n**	92
17	**1f**	 **2d**	 **3o**	83[c]
18	**1a**	 **2e**	 **3p**	78[c]

[a] 0.5 mmol aryl iodide, 0.65 mmol acetylene, 2% $PdCl_2(PPh_3)_2$, 250 μL $^{s}BuNH_2$, 250 μL water, 25 °C, 90 min.

[b] Isolated yield.

[c] Reaction was carried out in the presence of 0.75 mmol (1.5 equiv) KOH, 8 h, 25 °C.

acetylenes with electronically diverse aryl iodides in excellent yields (entries 11–13). Efficient couplings were also obtained in the case of iodides **1a, 1e** and **1f** with the electron deficient heterocyclic acetylene 2-ethynylpyridine (**2c**) (entries14–16). For the Sonogashira coupling of aryl iodides with carbinol type[14] and aliphatic acetylenes, the utilization of KOH was found to be necessary in order to accelerate and complete the reaction within 8 h (entries 17 and 18). We have found that the reaction did not reach full conversion in 24 h without the strong inorganic base.

In conclusion, we have explored the applicability of different amines as solvents and bases under aqueous conditions in copper-free Sonogashira coupling. We have established that primary amine–water mixtures are suitable for the efficient coupling at ambient temperature in the presence of 2% $PdCl_2(PPh_3)_2$. We also found that the presence of water promotes the coupling reaction, and the reaction can be accelerated in the presence of KOH. In order to explain the reaction rate accelerating effect of water and the strong base, we are currently pursuing spectroscopic studies in our laboratory. The developed copper-free conditions could serve as a competitive, efficient and practical procedure for the Sonogashira coupling of aryl iodides and terminal acetylenes by offering mild conditions, short reaction times and high yields.

Acknowledgements

The authors thank Professor K. Torkos, Dr. Zs. Eke, Ms. D. Benesóczki, Mr. V. Angyal for providing analytical services, and P. Kele for fruitful discussions and suggestions. The financial support of the Hungarian Scientific Research Fund (OTKA D048657) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.037.

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