Tetrahedron Letters 50 (2009) 204–207

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Convenient copper- and solvent-free Sonogashira-type alkynylation of aryl iodides and bromides using Pd EnCat™

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ARTICLE INFO

Article history:
Received 15 September 2008
Revised 21 October 2008
Accepted 24 October 2008
Available online 31 October 2008

Keywords:
Pd EnCat™
Sonogashira-type alkynylations
Supported catalysts
Copper-free
Solvent less
Microwave

ABSTRACT

A straightforward methodology is described for the copper- and solvent-free alkynylations of aryl iodides and bromides using 0.1–0.01 mol % of Pd as Pd EnCat™ 40 or TPP30. High yielding reactions can be achieved under aerobic conditions for a variety of activated and deactivated aryl iodides; a few examples with aryl bromides are also described. Microwave irradiation is able to enhance yields and rates of these reactions.

The palladium-catalyzed alkynylation of aryl or alkenyl halides has become the most important method to prepare arylalkynes and conjugated enynes,[1] precursors for natural products, bioactive compounds, and pharmaceuticals,[2] as well as molecular electronics and polymers.[3] The typical Sonogashira protocol, usually carried out under an inert atmosphere, employs an organic solvent (such as benzene, DMF, THF), a Pd(0)/CuI catalytic system, and at least a stoichiometric amount of a base.[4] Recently, significant improvements to this protocol were obtained by using, for instance, aqueous media,[5] ionic liquids,[5a,6] special catalyst ligands,[1a–c,7] and/or microwave irradiation.[8] The most important modifications involved the elimination of CuI,[1a,b,9] which, besides being a potential contaminant and a reagent difficult to remove, can cause drawbacks,[10] mainly the formation of homocoupling by-products of the terminal alkyne.[10c,11] However, it must be said, most of the reported copper-free alkynylations were carried out homogeneously in the presence of organic solvents (or a large excess of an amine base), thus diminishing the environmental and economic advantages of the process. In particular, the use of homogeneous Pd catalysts, even though it can allow lower loadings of Pd and more efficient alkynylations,[1,7] it makes separation, recovery, and recycling of the catalysts tedious or impossible and can result in significant palladium contaminations of the products. On the other hand, as the use of heterogeneous catalysts in Sonogashira-type reactions could offer advantages in terms of low palladium contamination and even of recycling, several heterogeneous catalytic systems have also been reported for these alkynylations.[1a,b,12] There is still the need, however, for efficient and easily available heterogeneous catalysts that are air and moisture stable and applicable to a wide range of Sonogashira-type reactions without copper co-catalysis.

Recently, the commercially available Pd EnCat™ catalysts have been described as giving low Pd leaching and as being easily removed and recycled.[13] These catalysts consist of Pd(II) acetate microencapsulated in a polyurea matrix (the commercial product contains 0.37–0.44 mmol/g of Pd), are air and moisture stable and can be easily removed by filtration. They were successfully employed in several C–C bond formation reactions, notably Suzuki, Heck, and Stille cross-couplings.[13,14] As for Sonogashira-type alkynylations, until 2007, no specific studies on Pd EnCat catalysis were reported and, furthermore, only two isolated examples of efficient reactions were described.[15] More recently, in his intriguing review on EnCat catalysts and microwave heating, Pitts describes and compares two interesting cases of microwave-assisted Pd EnCat/CuI co-catalyzed Sonogashira reactions, but for these neither experimental details nor bibliographic references are reported.[13a]

Herein, we report on the use of Pd EnCat catalysts as Pd(0) precursors in the copper-free alkynylation protocol of a series of substituted aryl iodides and bromides.

As model substrates for optimizing our reaction conditions, we chose phenylacetylene, **1a**, and 2-iodoaniline, **2a**, a 'difficult' aryl iodide being deactivated and *ortho*-substituted by a free amino group. The main results of our first attempts are summarized in Table 1.

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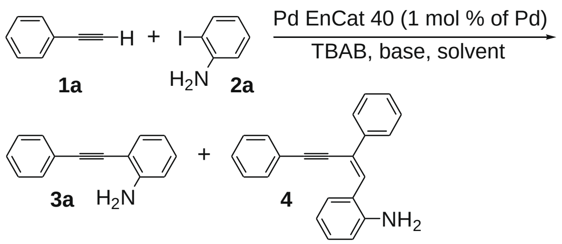
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.130

Table 1
Copper-free Sonogashira first attempts



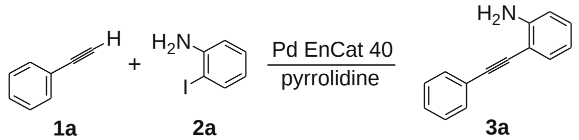
Entry	Base/equiv	Solvent	Temperature (°C)/time (h)	Yield[a] (%)/ product	Ratio **3a**:**4**[b]
1	Pyrrolidine/2	H_2O	85/1.5	64/**3a**	85:15
2	Pyrrolidine/2	H_2O/CH_3CN[c]	75/2.5	72/**3a**	92:8
3	Et_3N/2	H_2O	100/22	n.d.[d]	28:72
4	${}^{i}Pr_2EtN$/2	H_2O	85/22	39/**4**	8:92

[a] Isolated yields.
[b] Ratios were calculated by ^1H NMR.
[c] Without TBAB, H_2O/CH_3CN = 15:85.
[d] A 30% of starting **2a** was detected.

In a first instance, we tried this cross-coupling with Pd EnCat 40 (containing 0.4 mmol of Pd/g) by applying 1 mol % of Pd, water as the solvent, 2 equiv of pyrrolidine, 0.5 equiv of tetrabutylammonium bromide (TBAB), and 1.2 equiv of **1a**, following the conditions reported by Nájera and co-workers[15b] for the alkynylation of the more reactive 4-chloroiodobenzene with **1a** (Table 1, entry 1). After 1.5 h of heating at 85 °C the starting material was completely consumed, but the higher molecular weight product **4** was formed along with the desired 2-(phenylethynyl)aniline, **3a** (which was isolated in 64% yield). The by-product **4** was isolated and characterized by means of NMR experiments that allowed to establish its regio- and stereochemistries. A more favorable **3a**/**4** ratio and a better yield can be obtained in the absence of TBAB and using a mixture H_2O/CH_3CN as the solvent (Table 1, entry 2). More interestingly, we also observed that the relative amounts of **3a** and **4** were strongly affected by the nature of the base. When pyrrolidine was used, the major product was **3a**, while with a hindered tertiary base like diisopropylethylamine, **4** was primarily obtained (Table 1, entry 4). By using triethylamine, the reaction failed to reach completion additionally giving mixtures of products **3a** and **4** (Table 1, entry 3).

Further optimization was conducted in order to improve the yield by applying a lower Pd loading and working, under solvent and ligand free conditions, without TBAB and with pyrrolidine as the base. The results we obtained are reported in Table 2 and show that the solvent free conditions allow for the isolation of **3a** in higher yields even with much lower catalyst loadings: 0.2 and 0.1 mol % (Table 2, entries 1–3). The yield drops considerably with 0.01 mol % of Pd (Table 2, entry 4).

Table 2
Optimization of conditions for the solvent free cross-coupling between **2a** and **1a** promoted by Pd EnCat 40 or TPP30



Entry	Pd loading (mol %)	Base	Temperature (°C)/ time (h)	Yield[a] (%)
1	0.2	Pyrrolidine	85/3	83
2	0.1	Pyrrolidine	85/5	77
3	0.1[b]	Pyrrolidine	85/1	73
4	0.01	Pyrrolidine	85/24	40[c]

[a] Isolated yields.
[b] Pd EnCat TPP30 was used.
[c] Starting **2a** was detected.

These results show that Pd EnCat 40 and TPP30 represent efficient catalytic precursors for the alkynylation of **2a**; in addition, our methodology looked so easy and straightforward that we decided to investigate it further and to test it on different aryl halides and alkynes. Therefore, a study was set up by selecting aryl iodides bearing electron-withdrawing and donating groups and a few examples of aryl bromides. The outcomes are summarized in Table 3. A very low catalyst loading (down to 0.01 mol % of Pd) was applied and this ensured a low Pd contamination in the output. Where Pd EnCat 40 gave poorer yields and longer reaction times, more advantageous results were obtained by using the PPh_3-containing Pd EnCat TPP30 as catalytic precursor.

In particular, Pd EnCat 40 gave good to excellent yields with 0.01 mol % of Pd when iodobenzene or aryl iodides bearing electron-withdrawing groups were employed (Table 3, entries 2–6, 16, and 17), whereas electron-rich aryl iodides gave better results with 0.1 mol % of Pd (compare entry 2 with entry 4, Table 2, and entry 8 with entry 9, Table 3). Moreover, Pd EnCat 40 allowed excellent results even with *ortho*-substituted phenylethynes and triisopropylsilylethyne (Table 3, entries 16–19). On the other hand, less reactive *ortho*-substituted iodides afforded higher yields when Pd EnCat TPP30 was used (Table 3, compare entries 10 and 13 with entries 11 and 14); also, 4-bromo-acetophenone, but not bromobenzene, efficiently reacts in the presence of this catalyst (Table 3, entries 20–22).

It is worth noting that all the reactions were carried out without additional solvents, by simply mixing, under aerobic conditions, starting materials, catalytic precursor, and pyrrolidine and by heating to 85 °C for the specified times. No particular attention was paid to the dryness of reagents or equipments.

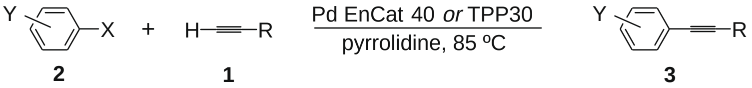
Finally, we studied the effects of microwave irradiation[16] on our alkynylation conditions, by employing a selection of the more difficult aryl halides. Table 4 shows that, with respect to the thermal heating, microwave heating allowed a drastic reduction of reaction times, an enhancement of yields, and a 10-fold reduction of the catalyst loading. In particular, for 2-iodoaniline a comparison reaction was run by applying the same conditions with thermal heating (Table 4, compare entry 1 with entry 2).

In order to verify the level of leaching of palladium in the products, we chose seven of the arylalkynes which we prepared for atomic absorption analyses. All the samples showed Pd contents lower than 6 ppm (the majority between 1 and less than 0.1 ppm), thus confirming the low level of leaching already reported for these catalysts (these results are described more in detail in the Supplementary data).[13–15]

As to preliminary data gathered in recycling procedures, we report on the behavior of Pd EnCat 40 with 4-chloroiodobenzene as the model substrate. A loading of 1 mol % of Pd was applied in all the trials in order to have an amount of catalyst significant to weigh and appreciate any occurring loss. The catalyst was recovered by filtration and recycled up to three times without significant loss of catalytic activity as shown in Table 5.[17]

In summary, Pd EnCat™ catalysts are able to promote conveniently the copper- and solvent-free Sonogashira-type couplings. Our efficient and very simple procedure allows the alkynylation of aryl iodides bearing both electron-withdrawing and electron-donating substituents and of activated aryl bromides and it involves the use of very low catalyst loadings (down to 0.01 mol % of Pd for the most reactive substrates). These conditions are not sensitive to moisture and air, can be enhanced by microwave irradiation and allow for the recovery of products free from significant heavy metal contaminations. The preliminary data gathered in

Table 3
Copper-free Sonogashira-type cross-couplings for different aryl halides and alkynes[a]



Entry	Aryl halide **2**		Alkyne **1**	Pd loading (mol %)	Time (h)	Yield[b] (%)
	Y	X	R			
1	2-NH_2	I	C_6H_5	0.1	5	77
2	H	I	C_6H_5	0.01	5	93
3	4-Cl	I	C_6H_5	0.01	3.5	99
4	4-Br	I	C_6H_5	0.01	3	88
5	4-CF_3	I	C_6H_5	0.01	3.5	95
6	4-MeCO	I	C_6H_5	0.01	1	57
7	2-COOMe	I	C_6H_5	0.1[c]	1.5	60
8	4-Me	I	C_6H_5	0.01	24	63
9	4-Me	I	C_6H_5	0.1	3	74
10	2-Me	I	C_6H_5	0.1	5	73
11	2-Me	I	C_6H_5	0.1	1.5	98
12	4-MeO	I	C_6H_5	0.1	3	90
13	2-MeO	I	C_6H_5	0.1	3	64
14	2-MeO	I	C_6H_5	0.1[c]	1.5	99
15	4-NH_2	I	C_6H_5	0.1	3	54
16	H	I	2-$MeOC_6H_4$	0.01	7	61
17	H	I	2-$H_2NC_6H_4$	0.01	2.5	84
18	H	I	2-$H_2NC_6H_4$	0.1	0.5	99
19	H	I	i-Pr_3Si	0.1	4.5	99
20	H	Br	C_6H_5	0.1[c]	20	20
21	H	Br	C_6H_5	1[c]	1	31
22	4-MeCO	Br	C_6H_5	1[c]	0.5	69

[a] Reactions were run in open vessels, using 4 mmol of **2**, 1.5 equiv of **1**, 2 equiv of pyrrolidine (0.67 ml), and the specified amount of Pd as Pd EnCat 40 (1 mg of Pd EnCat 40 for a Pd loading of 0.01 mol % and 10 mg for 0.1 mol % of Pd). The reaction mixtures were heated to 85 °C for the specified time.

[b] Yields of products **3** after chromatographic purification.

[c] Pd EnCat TPP30 was used (10 mg of Pd EnCat TPP30 for a Pd loading of 0.1 mol % and 100 mg for 1 mol % of Pd).

Table 4
Microwaves application[a]

Entry	Aryl halide **2**		Alkyne **1**	Pd loading (mol %)	Temperature (°C)/time (h)	Yield[b] (%)
	Y	X	R			
1	2-NH_2	I	C_6H_5	0.01	100/0.5	95
2	2-NH_2	I	C_6H_5	0.01	100/6.5	42[c]
3	2-MeO	I	C_6H_5	0.01	120/0.5	59
4	H	I	2-$H_2NC_6H_4$	0.01	100/0.5	99
5	H	I	2-$MeOC_6H_4$	0.01	100/0.5	76
6	H	Br	C_6H_5	0.1	100/1	40
7	4-MeCO	Br	C_6H_5	0.1	100/0.5	74

[a] Reactions were run using 4 mmol of **2**, 1.5 equiv of **1**, 2 equiv of pyrrolidine, and the specified amount of Pd as Pd EnCat 40.[16]

[b] Isolated yields of compounds **3**.

[c] Thermal heating was applied. The ratio 2-iodoaniline/product was 85/15 after 30 min at 100 °C, while it was 45/55 after 6.5 h where a complete consumption of phenylacetylene was detected.

Table 5
Preliminary recycling experiments for Pd EnCat 40[17]

Run	Time (min)	Temperature (°C)	Yields[a] (%)
1	30	85	>99
2	30	85	>99
3	40	85	>99

[a] Isolated yields after chromatographic purification.

recycling experiments show a good potential for reusing of Pd EnCat 40, anyway other experiments are ongoing to verify more accurately the possibility of recycling the catalysts under both thermal and microwave heating conditions.

Acknowledgments

We thank Dr. Alessio Ceccarini (Dipartimento di Chimica e Chimica Industriale, Università di Pisa) for atomic absorption analysis and Dr. Paolo Stabile (GlaxoSmithKline, Verona) for the helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.130.

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16. Microwave experiments were performed in 10 ml sealed pressure tubes, using a CEM Explorer reactor; see Supplementary data.
17. *Recycling procedure*: A 10 ml round-bottomed flak was charged with 4-chloroiodobenzene (3 mmol, 0.72 g), phenylacetylene (4.5 mmol, 0.50 ml), pyrrolidine (6 mmol, 0.51 ml), and Pd EnCat 40 (1 mol % Pd, 75 mg). The mixture was stirred at 85 °C for the time specified in Table 5, then cooled to room temperature, diluted with AcOEt (20 ml) and water (20 ml), and filtered through a glass filter (G5). The recovered catalyst was washed upon the filter with AcOEt (2 × 10 ml) and water (2 × 10 ml), dried under vacuum and reused.