Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4801–4803

An improved general method for palladium catalyzed alkenylations and alkynylations of aryl halides under microwave conditions

Andrea Togninelli, Harsukh Gevariya, Maddalena Alongi and Maurizio Botta*

Dipartimento Farmaco ChimicoTecnologico, Università degli Studi di Siena, Via Aldo Moro-53100 Siena, Italy

Received 14 March 2007; revised 4 May 2007; accepted 15 May 2007
Available online 18 May 2007

Abstract—Palladium catalyzed facile method for alkenylation and alkynylation of arylhalides in good to excellent yield under microwave condition is reported.

In the history of organic chemistry, carbon–carbon bond formation has always been one of the most useful and fundamental reactions.[1] A significant research is being done and reviews detail the progress of the metal catalyzed C–C bond formation. A variety of transition metal mediated C–C coupling reactions like Sonogashira[2] and Heck coupling,[3] often known as Mizoroki–Heck reaction, provided a powerful tool for C–C bond formation. Unlike Heck coupling, palladium–copper catalyzed reaction typically known as Sonogashira coupling is carried out in the presence of catalytic amount of palladium and Cu(I) to form a C–C bond.[4] However, drawback of this reaction is the dimerization of terminal alkyne, forming corresponding diyne as a byproduct.[2a–5] CuI in the presence of excess base plays an important role in oxidative homocoupling of terminal alkynes,[6] limiting the original Sonogashira coupling conditions. However, many modified Palladium catalysts have been discovered in order to overcome this difficulty.[7] Pal et al.[8] published a regioselective copper free Palladium catalyzed coupling using DMF as the solvent. Santelli and co-workers[9] used new ligand 'Tedicyp' to get a stable palladium catalyst. To the best of our knowledge, very few reports on the coupling of aryl halides and α–β unsaturated aldehydes and alcohols have been published, mainly due to the polymerization of starting material. Attempts have been made for arylation of acrolein by using $LiPdCl_3$[3a] and a phase transfer catalyst (PTC).[10] However, masking of aldehydes and alcohols could be the best way to overcome the polymerization. Recently Cacchi and co-workers[11] reported a multicomponent palladium catalyzed coupling of aryl iodides and bromides with acrolein diethyl acetal to get cinnamaldehydes. Instead of aryl halides, dimethyl phenyl silanol can also react with acrolein in the presence of stoichiometric amount of $Pd(OAc)_2$ to afford cinnamaldehydes. Ishii[12] very recently reported a Pd catalyzed direct coupling of benzene with acrylates using molybdovanado phosphoric acid (HPMoV) to suppress the polymerization. Attempts[13] have also been made to synthesize cinnamaldehydes by using the same catalyst by reacting benzene with acrolein. However, suppressing the polymerization could not be achieved, resulting in partial success in obtaining the desired cinnamaldehydes. Although substantial improvements in reaction conditions have been done in all methods mentioned above to achieve desired C–C coupling, factors such as variable amounts of different types of palladium catalysts, oxidative homocoupling, polymerization as well as undesired byproducts show that the process still needs further improvement in reaction conditions. In the past few years, heating and driving chemical reactions by microwave (MW) energy has been an increasingly popular theme in the scientific community. The main benefits of performing reactions under microwave conditions are the significant rate enhancements and the higher product yields that can be frequently observed.[14] Reaction rate improvement could be explained considering the higher and more rapid temperature homogeneity reached employing MW than using conventional

Keywords: Alkenylation; Alkynylation; Palladium catalyzed; Microwave-assisted synthesis.
* Corresponding author. Tel.: +390577234306; fax: +39577234333; e-mail: botta@unisi.it

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.086

heating sources.[15] In MW assisted reactions molecules are directly kinetically/thermally activated, conversely in conventional heating methods vessel is heated and this then transfers the heat by convection.[16]

As an extension of our ongoing efforts towards the development of new *S*-DABO derivatives and in view of more extensive functionalizations of the sulphur atom on the thiopyrimidinone scaffold (via a microwave assisted Mitsunobu reaction), the synthesis of several cinnamaldehydes and phenylpropynyl alcohols was performed (Fig. 1).

A novel class of *S*-DABO derivatives was synthesized as non-nucleoside reverse transcriptase inhibitors (NNRTIs).[17] Starting from previous work reported by Cacchi and co-workers,[11] some interesting results were obtained by slightly modifying the original procedure. The previously reported process is high yielding and involves multi component reagents like $^{n}Bu_4NOAc$, KCl and K_2CO_3. Nevertheless the PTCs are often highly hygroscopic and our attempt of using wet PTC failed to get the desired cinnamaldehydes, showing the limitation of the process. We report here a very straightforward and general method for the synthesis of palladium catalyzed C–C coupling using $Pd(OAc)_2$, K_2CO_3, protected alkenes or alkynes and aryl halides in DMF to yield aryl alkenes or aryl alkynes, respectively, in very good yield with hardly any side reactions. Differently from Cacchi's procedure, due to the strong microwave absorbing capacity of palladium and being encouraged to transfer the synthesis in microwave, we found that the hygroscopic $^{n}Bu_4NOAc$ (PTC) is not required in the presence of highly polar solvent (DMF) and KCl is not required as well in the presence of a base (K_2CO_3) (Scheme 1).

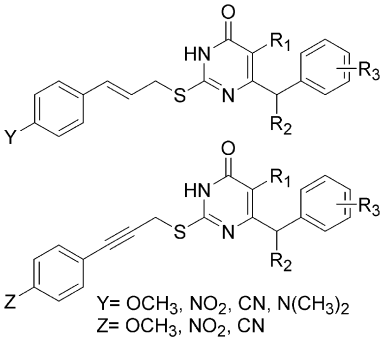
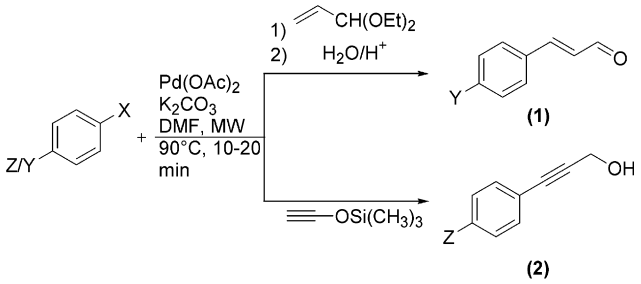


Figure 1.



Scheme 1.

Table 1. Synthesized derivatives **1**(**a**–**i**) and **2**(**a**–**c**)

Entry	Aryl halide	MW cycles (10 min)	Yield (%)
1a	C_6H_5–I	1	87
1b	*p*-MeO–C_6H_4–I	2	83
1c	*p*-O_2N–C_6H_4–I	1	76
1d	*p*-$(CH_3)_2N$–C_6H_4–Br	2	81
1e	*p*-CN–C_6H_4–I	1	69
1f	*p*-EtOOC–C_6H_4–I	1	94
1g	*p*-C_6H_5–C_6H_4–I	2	79
1h	*p*-Cl–C_6H_4–Br	1	87
1i	*p*-C_6H_5CO–C_6H_4–I	2	73
2a	*p*-MeO–C_6H_4–I	1	87
2b	*p*-O_2N–C_6H_4–I	1	89
2c	*p*-CN–C_6H_4–I	1	95

To the best of our knowledge a very few reports have been published that comprise alkene as well as alkyne aryl C–C bond formation under microwave conditions.[18] Further more, our process is also applicable for the generation of aryl alkenes as well as aryl alkynes without the use of CuI. The improved method is a cost effective and robust general method of synthesis for C–C bond formation in very short reaction times. Substituted aryl alkenals and aryl alkynols were prepared in a straightforward fashion using microwave reactor (MW) allowing the desired compound to be obtained in good yields. Moreover, the conventional mode of heating takes around 1.5–8.0 h to complete the reaction while in the MW reactor the reactions could be completed in 10–20 min.[19]

As reported in Table 1 many important functional groups are well tolerated. By taking into account the numbers of cycles, different electron donating groups need two 10 min microwave irradiation cycles, while only one cycle is required for strong electron withdrawing groups.

In none of the reactions starting material was present at the end of the irradiation cycle(s). Reported low yields could be due to the formation of side products, but these were not isolated because present in very small amount. Acrolein acetals and protected phenyl propargyl alcohol were used to avoid the polymerization problems, in fact, polymerization byproducts were not observed. In all cases, a significant rate-enhancement using MW flash heating as compared to thermal heating was observed.

From a synthetic point, this is a very useful, cost effective and robust general method for the synthesis of various aryl olefins as well as aryl acetylenes that are very useful building blocks in medicinal chemistry, affording the desired products in excellent yields, good purity and reducing the reaction times required by other reported experimental procedures.

Acknowledgement

Support from the European TRIoH Consortium (LSHB-2003-503480) is gratefully acknowledged.

References and notes

1. (a) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874–922; (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770.
2. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470; (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; (c) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: Berlin, 1998; (d) Sonogashira, K. J. *Organomet. Chem.* **2002**, *653*, 46–49.
3. (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526; (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; (c) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320–2322.
4. Bhattacharya, K.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733–8736.
5. (a) Krause, N.; Thorand, S. *J. Org. Chem.* **1998**, *63*, 8551–8553; (b) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr. *Tetrahedron* **2000**, *56*, 5735–5742; (c) Brimble, M. A.; Pavia, G. S.; Stevenson, R. J. *Tetrahedron Lett.* **2002**, *43*, 1735–1738.
6. (a) Rossi, R.; Carpita, A.; Bigelli, C. *Tetrahedron Lett.* **1985**, *26*, 523–526; (b) Kundu, N. G.; Pal, M.; Chowdhury, C. *J. Chem. Res., Synop.* **1993**, 432; (c) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969–1971.
7. Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691–1694.
8. Pal, M.; Parasuraman, K.; Gupta, S.; Yeleswarapu, K. R. *Synlett* **2002**, 1976–1982.
9. Feuerstein, M.; Doucet, M.; Santelli, M. *Tetrahedron Lett.* **2004**, *45*, 1603–1606.
10. Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289.
11. Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777–780.
12. (a) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476–1477; (b) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221–1226.
13. Yamada, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 5471–5474.
14. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
15. Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863–1866.
16. Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66–77.
17. (a) Manuscript, in preparation; (b) Botta, M.; Corelli, F.; Petricci, E.; Radi, M.; Maga, G.; Estè, A. J.; Mai, A. WO2007043094.
18. Maes, B. U. W.; Loones, K. T. J.; Hostyn, S.; Diels, G.; Romboust, G. *Tetrahedron* **2004**, *60*, 11559–11564.
19. Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The reaction was performed in glass vessels (capacity 10 mL) sealed with septum. The pressure was controlled by a load cell connected to the vessel. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. *General procedure for the synthesis of cinnamaldehydes* (**1a**–**i**): To a stirred solution of *p*-substituted iodo/bromobenzene (0.100 g) in dry DMF (2 mL) in a sealed vessel was added acrolein diethyl acetal (3 equiv), K_2CO_3 (1.5 equiv) and $Pd(OAc)_2$ (3 mol %) under Argon atmosphere at room temperature. The reaction mixture was then irradiated at 90 °C for 10 min (in some cases 2 cycles are required, see Table 1). After cooling the reaction mixture was cautiously poured into 2 N HCl aqueous solution and left under magnetic stirring for 10 min. The aqueous layer was then extracted using diethyl ether and the organic layer was dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography using appropriate eluent. *General procedure for the synthesis of phenylpropynyl alcohols* (**2a**–**c**): To a stirred solution of *p*-substituted iodobenzene (0.100 g) in dry DMF (2 mL) in a sealed vessel was added propargyl trimethyloxy silane (3 equiv), K_2CO_3 (1.5 equiv) and $Pd(OAc)_2$ (3 mol %) under Argon atmosphere at room temperature. Then the reaction mixture was irradiated at 90 °C for 10 min. After cooling, distilled out of DMF at 50–55 °C under vacuum. Water was added and the reaction mixture was extracted twice with ethyl acetate, then the organic layer was dried with sodium sulphate and evaporated to dryness under reduced pressure. To the residual mass diethyl ether was added and stirred at room temperature for 45 min. The precipitated pure product was filtered, washed with chilled ether and dried under vacuum.