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Microwave-enhanced Pd(0)/acetic acid catalyzed allylation reactions of *C*, *N*, and *O*-pronucleophiles with alkynes

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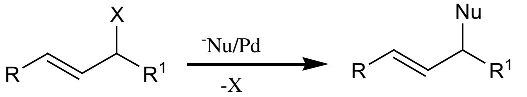
Abstract—An efficient method for the allylation of *C*, *N*, and *O*-nucleophiles with alkynes under solvent-free conditions and by microwave activation is established. The process can be termed as a real eco-chemical process since no waste elements are produced in the reaction, moreover it is solvent free. This technique can also be used for the allylation of dimethyl methylmalonate, which proves inert under the previously reported reaction conditions (refluxing in 1,4-dioxane).

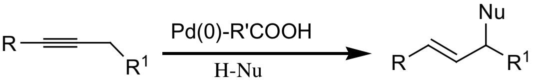
The palladium catalyzed allylation of *C*, *N*, and *O*-nucleophiles is well recognized as one of the most powerful synthetic tools for the construction of C–C and C–X bonds (Eq. 1).[1] However, from the eco-chemical point of view, the method suffers some problems; for instance a stoichiometric amount of base is needed to generate the nucleophiles (Nu^-) and a stoichiometric amount of a leaving group (X^-) is liberated. To solve these problems, we recently reported a novel procedure for the allylation of *C*,[2] *N*,[3] and *O*[4]-pronucleophiles with alkynes, which serves as an alternative to the existing methods, by using a $Pd(PPh_3)_4$/carboxylic acid catalytic system in an organic solvent such as 1,4-dioxane (Eq. 2).[2] Since the products formed in these reactions are via formal addition of pronucleophiles to alkynes, no waste elements are produced. Although the yields and regioselectivities of the reactions were satisfactory, we were not satisfied because a high temperature and long reaction time were drawbacks of the process. Moreover, the use of an organic solvent was unavoidable.

Nowadays, microwave (MW) activation has emerged as a powerful technique as a nonconventional energy source to promote a variety of chemical reactions and has become a very popular and useful technique in organic chemistry.[5] The combination of solvent-free reaction conditions and microwave irradiation leads to significantly reduced reaction times, enhanced conversions, and sometimes, higher selectivity, with several advantages for the eco-friendly approach, termed green chemistry.[6] Herein, we report an efficient method for the allylation of *C*, *N*, and *O*-pronucleophiles with alkynes, using solvent-free conditions under microwave activation (Eq. 2).



(1)

X = OH, OAc, OCO_2R, OTs, OTf, Br/Cl/I, $OP(O)Ph_2$, NR_2



(2)

H-Nu: $HCR^2(EWG)_2$, $H_2C(EWG)_2$, HNR^3_2, HOR^3

As a starting point, we studied the microwave assisted reaction of diethyl malonate with 1-phenyl-1-propyne [Eq. 2, R = Ph, R^1 = H, H–Nu = $H_2C(COOEt)_2$]. Thus a mixture of 1-phenyl-1-propyne **1a** and diethyl malonate **2a** was irradiated in a microwave oven at 500W for 15min in the presence of $Pd(PPh_3)_4$ (5mol%)/acetic acid (20mol%). TLC analysis indicated the presence of the desired product along with unreacted diethyl malonate and 1-phenyl-1-propyne. However, when 700W was used for the above reaction, the yield dramatically increased and **3a** was isolated in 88% yield (Table 1, entry 1). In our earlier observation the same

Keywords: Palladium catalyst; Microwave; Allylation; Pronucleophile; Alkyne; Acetic acid.

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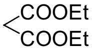
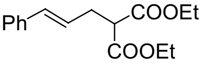
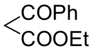
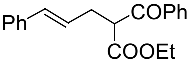
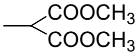
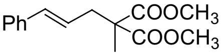
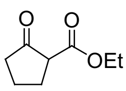
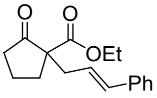
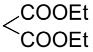
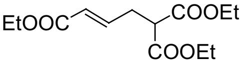
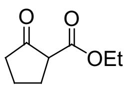
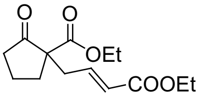
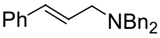
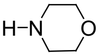
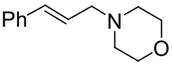
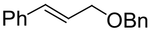
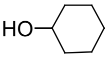
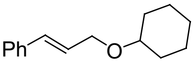
Table 1. Pd(0)/acetic acid catalyzed allylation of *C*-, *N*-, and *O*-nucleophiles with alkynes under MW irradiation[a]

Entry	Alkyne (**1**)	H–Nu (**2**)	MW power (W)	Time (min)	Product (**3**)	Yield (%)[b]
1	$\mathrm{Ph{-}{\equiv}{-}CH_3}$ **1a**	 **2a**	700	15	 **3a**	88
2		 **2b**	500	6	 **3b**	92
3		 **2c**	700	15	 **3c**	76
4		 **2d**	500	7	 **3d**	69
5	$\mathrm{EtOOC{-}{\equiv}{-}CH_3}$ **1b**	 **2a**	500	10	 **3e**	81
6		 **2d**	500	5	 **3f**	78
7	$\mathrm{Ph{-}{\equiv}{-}CH_3}$ **1a**	$HNBn_2$ **2e**	500	10	 **3g**	72
8		 **2f**	500	10	 **3h**	78
9		BnOH **2g**	500	8	 **3i**	88
10		 **2h**	500	8	 **3j**	82

[a] All reactions mixtures were irradiated for the time and power specified in the table.

[b] Isolated yield.

reaction when carried out under reflux in 1,4-dioxane, afforded the product in 92% yield but after a long reaction time (12h). Intrigued with this preliminary result we planned to study the generality of these findings and the results are shown in Table 1.

Treatment of **2b** with 1-phenyl-1-propyne **1a** in the presence of $Pd(PPh_3)_4$ and acetic acid at a power of 500W gave the desired product in 92% yield. Similarly, the reaction of dimethyl methylmalonate **2c** gave the corresponding allylation product **3c**, when treated with **1a** upon microwave irradiation for 15min (entry 3). It should be noted that the reaction of dimethyl methylmalonate **2c** with alkynes gave only a trace amount of the adducts even after heating at 100°C in 1,4-dioxane for a prolonged reaction time under our previously established procedure.[2a] However, under the present reaction conditions, the notorious substrate **2c** gave a good yield of the allylation product. All additional attempts to increase the yield in this reaction, however, proved to be futile. The allylation of cyclic β-keto ester **2d** with **1a** also proceeded giving the product **3d** in 69% yield (entry 4). The alkyne **1b** reacted with **2a** and **2d** giving the corresponding allylation products **3e** and **3f** in good yields (entries 5 and 6). Next, we studied the allylation of *N*- and *O*-nucleophiles with alkynes under these conditions. Thus, 1-phenyl-1-propyne **1a** when treated with amines **2e** and **2f** gave *N*-allyl amines **3g** and **3h** in 72% and 78% yields, respectively (entries 7 and 8). Microwave assisted addition of alcohols **2g** and **2h** to 1-phenyl-1-propyne **1a** gave the allyl ethers **3i** and **3j** in 88% and 82% yields, respectively (entries 9 and 10).

It should be noted that the hydroalkoxylation of alkynes is a slow process and heating for three days was needed in order to obtain good yields of the products under our previously established procedure,[4a] that is heating at 100 °C in 1,4-dioxane. However, significant rate enhancement of the reaction was observed under microwave conditions.

In summary, we have succeeded in developing an efficient method for the allylation of *C*-, *N*-, and *O*-pronucleophiles with alkynes under solvent-free conditions and by microwave activation. Since the process does not need any organic solvents and nothing is liberated from the starting material, the reaction may lead to a method, which solves some environmental problems.

In a typical experiment, diethyl malonate **2a** (0.100 g, 0.624 mmol) was mixed with 1-phenyl-1-propyne **1a** (0.073 g, 0.624 mmol), $Pd(PPh_3)_4$ (0.036 g, 0.031 mmol), and CH_3COOH (0.007 g, 0.125 mmol). The mixture was added to a 5 mL conical flask and was placed in a microwave oven (cooking type, Hitachi MRO-EX3) and irradiated for the time and power as specified in Table 1. On completion of the reaction, the flask was allowed to cool, diluted with diethyl ether and passed through a short silica gel column using diethyl ether as eluent. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/ethyl acetate: 9/1) to give product **3a** as a dense liquid (0.152 g, 88%).

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