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Microwave-Assisted Palladium-Catalyzed Heterogeneous Vinylation of 2(1*H*)-Pyridones

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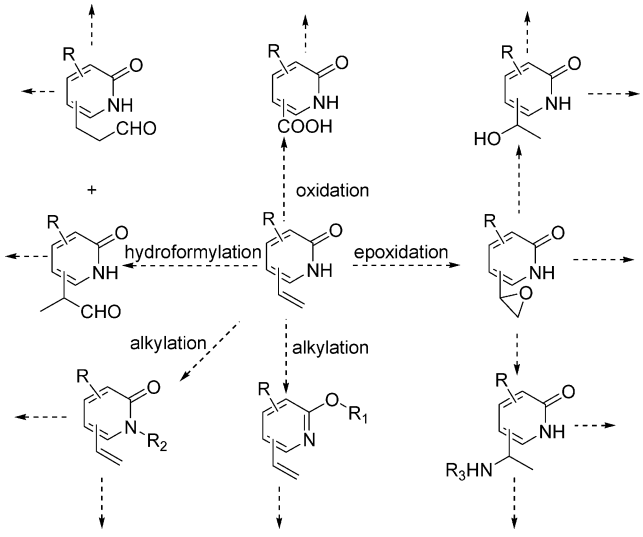
A mild and efficient microwave-assisted vinylation of 2(1*H*)-pyridones has been developed using potassium vinyltrifluoroborate with palladium on carbon as the catalyst. Various vinylating agents, Pd sources and solvents have been screened.

The vast number of bioactive natural products and drugs based on the 2(1*H*)-pyridone ring system exemplifies the importance of this class of compounds.[1] Functionalized 2(1*H*)-pyridones have been used as versatile intermediates in the synthesis of a wide range of nitrogen-containing heterocycles, such as pyridine, piperidine, quinolizidine, and indolizidine alkaloids.[2]

Vinylated 2(1*H*)-pyridones are extremely interesting as they can be easily converted into various key intermediates for the synthesis of various natural products[3] and pharmaceuticals[4] via reduction (hydrogenation, hydroboration, hydrosilylation etc.), oxidation (epoxidation, aziridination, dihydroxylation, halogenation, etc.), hydroamination, hydration, hydroformylation, cycloaddition etc.[5] (Scheme 1).

Although several methods are described for the synthesis of various functionalized 2(1*H*)-pyridones,[6] however many of the established approaches are still severely limited in their use by the lack of generality, the harsh reaction conditions involved, or the multistep procedures required.

Transition-metal-catalyzed couplings with vinylmetallic donors are extremely attractive methods for the introduction of a vinyl group into aromatic and heteroaromatic systems. Among possible vinylmetallics, tin (Stille coupling), silicon (Hiyama coupling) and boron (Suzuki coupling) derivatives are frequently used donors for such cross-couplings because of their tolerance towards a broad range of functional groups.[7] The majority of investigations employing these transition-metal-catalyzed reactions have focused on aromatic and heteroaromatic systems.[7,8] However, to the best of our knowledge, aromatic imidate systems have never been applied in this regard. Therefore, we have elaborated a novel and convenient method for the vinylation of 2(1*H*)-pyridones.



Scheme 1. Vinylated 2(1*H*)-pyridones as versatile synthons for synthesis of various bioactive derivatives.

At the outset, the Pd-catalyzed Stille[9] cross-coupling of 6-chloro-3-nitro-2(1*H*)-pyridone (**1**) as aromatic imidate system with vinyltributyltin (**2**)[10] in the presence of $Pd(PPh_3)_4$ was examined. When a mixture of 6-chloro-3-nitro-2(1*H*)-pyridone (**1**) with 1.1 equiv. of vinyltributyltin in the presence of 5 mol-% of $Pd(PPh_3)_4$ in toluene was re-

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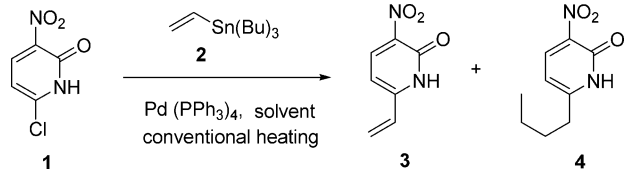
fluxed for 48 h, reaction took place and the desired vinylated product **3** was obtained in 23% yield along with 12% of the butylated product **4** next to the starting material (Scheme 2). However, when the same reaction was performed in refluxing dioxane for 48 h, % product yield ratio changed to 9:6. Other investigated catalytic systems [$Pd_2(dba)_3$/(tBu)$_3$P, (η^3-$C_3H_5PdCl)_2$ and $PdCl_2(PPh_3)$] were ineffective in both refluxing toluene or dioxane, whereas $Pd(OAc)_2$/PPh_3 in boiling toluene for 48 h yielded the vinylated product **3** in 12% yield along with 7% of the butylated product **4**, next to the unreacted starting material (Scheme 2).



Scheme 2. Vinylation of pyridone **1** under conventional heating.

The application of microwave irradiation is well known for its beneficial effects on transition-metal-catalyzed reactions.[11] This prompted us to investigate the vinylation under microwave irradiation conditions. A series of experiments were performed using dioxane or toluene as solvent under various irradiation conditions (Scheme 2, Table 1). This revealed that performing the reaction at a ceiling temperature of 120 °C with a maximum power of 200 W was most effective in terms of both yield and time. Full conversion was accomplished in 30 min with exclusive formation of the desired vinylated product **3** in 59% yields (Table 1, entry 8) next to some unidentified compound. In all other cases, with the exception of entry 4, the formation of butylated product **4** was observed (Table 1, entries 1–3 and 5–7). Apparently, the high ceiling temperature of 120 °C and maximum power of 200 W are required to suppress the side reactions.

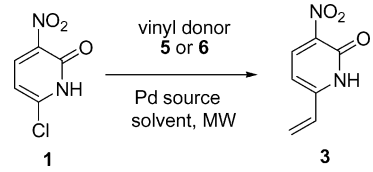
Table 1. Screening of microwave conditions.[a]

Entry	Solvent	Temp/Power [°C/W]	Time[b] [min]	% Yield[c] **3/4**
1	dioxane	100/100	90	33:17
2	dioxane	100/200	60	37:11
3	dioxane	120/100	45	40:7
4	dioxane	120/200	20	37:0
5	toluene	100/100	90	41:13
6	toluene	100/200	60	46:9
7	toluene	120/100	60	53:9
8	toluene	120/200	30	59:0

[a] Reactions were performed on a 0.1 mmol scale of 6-chloro-3-nitro-2(1*H*)-pyridone (**1**) using tributylvinyltin (**2**) (1.1 equiv.) and $Pd(PPh_3)_4$ (5 mol-%). [b] Time taken for full conversion. [c] Isolated yields are given.

Although these results were acceptable, there were still improvements that could be made to render the process more efficient. Recently different research groups have described various vinyl sources based on silicon and boron.[7] Therefore, we investigated vinylsilicon reagents, which offer certain advantages compared to other vinylmetallic for palladium-catalyzed cross-coupling reactions. In particular, organosilicon reagents are nontoxic[12] and the silicon containing byproducts are readily removed by simple workup procedures. Recently, Denmark and co-workers have investigated palladium-catalyzed vinylations with commercially available organosilicon reagents in the presence of inexpensive silanolate activators.[13] For our purpose, we selected commercially available divinyltetramethyldisiloxane (DVDS, **5**) and 1,3,5,7-tetravinyl-1,3,5,7-tetramethylcyclotetrasiloxane (D_4^V, **6**) as potential vinyl donors.[13] When the reactions were carried out for 4 d at room temperature in DMF or for 2 d under reflux in toluene or dioxane with 1.2 equiv. of DVDS (**5**) as vinyl donor in the presence of 5 mol-% of $Pd(dba)_2$ as catalyst, 5 mol-% of PPh_3 as ligand and 2 equiv. of $KOSiMe_3$ as activator, no product formation was observed. However, when the reactions were performed under microwave irradiation at a ceiling temperature of 120 °C and 200 W maximum power in various solvents, a different extent of product formation was observed (Table 2). In order to achieve full conversion different catalysts were screened applying DMF, dioxane or toluene under microwave irradiation (120 °C, 200 W). However, none of the screened conditions led to full conversion (Table 2, Entries 1–6). Even when duplicating the aforementioned conditions with D_4^V (**6**), full conversion was never achieved (Table 2, entries 7–12).

Table 2. Screening of vinylsilicon compounds as vinylating agents applying microwave irradiation.[a,b]



Entries	Vinyl donor	Pd source[c]	Solvent	Time[d] [min]	Conv.[e] (%)
1	DVDS (**5**)	$Pd(dba)_2$/PPh_3	DMF	120	0
2		$Pd(dba)_2$/PPh_3	dioxane	60	50
3		$Pd(dba)_2$/PPh_3	toluene	90	20
4		$Pd(PPh_3)_4$	DMF	120	0
5		$Pd(PPh_3)_4$	dioxane	60	50
6		$Pd(PPh_3)_4$	toluene	90	30
7	D_4^V(**6**)	$Pd(dba)_2$/PPh_3	DMF	120	0
8		$Pd(dba)_2$/PPh_3	dioxane	45	70
9		$Pd(dba)_2$/PPh_3	toluene	60	60
10		$Pd(PPh_3)_4$	DMF	120	0
11		$Pd(PPh_3)_4$	dioxane	30	70
12		$Pd(PPh_3)_4$	toluene	45	70

[a] Reactions were performed on a 0.1 mmol scale of 6-chloro-3-nitro-2-(1*H*)pyridone (**1**) under microwave irradiation at a ceiling temperature of 100 °C, and a maximum power of 200 W using **5** or **6** as vinyl donor (1.5 equiv.), $KOSiMe_3$ as activator (2 equiv.), $Pd(dba)_2$ or $Pd(PPh_3)_4$ as Pd source (5 mol-%) in solvent (3 mL). [b] When the same reactions were performed under conventional conditions, no product formation was observed even after 4 d at room temp. or 2 d of reflux. [c] In case of $Pd(dba)_2$ as catalyst, PPh_3 (5 mol-%) was used as additional ligand. [d] Reactions were run until no further conversion was observed by GC. [e] Conversions were determined by GC.

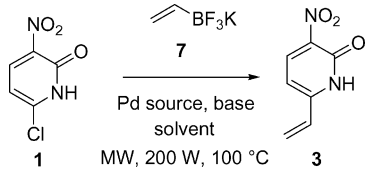
Unfortunately, organosilicon vinyl donors were ineffective for the investigated pyridone system, so we diverted our investigations to organoborane as vinyl donor, and in particular potassium vinyltrifluoroborate (**7**), which appears to be more nucleophilic[14] than other organoboron comounds. Moreover, potassium vinyltrifluoroborate (**7**) has been proven to be a particularly useful boron reagent that is air- and moisture-stable, atom economical, resistant to protodeboronation, thereby allowing stoichiometric quantities of reagent to be used in cross-coupling protocols.[15] Additionally, it is commercially available and numerous methods have been developed for its synthesis which are environmentally sound and byproducts are of low toxicity compared to other organometallic reagents, particularly organostannanes.[15] Recently, different groups have successfully demonstrated the use of microwave irradiation for this kind of cross-couplings applying potassium organotrifluoroborate.[16] Therefore we decided to explore the palladium-catalyzed reaction of 2(1*H*)-pyridones using potassium vinyltrifluoroborate (**7**) under microwave irradiation.

Initially a brief screening of various catalyst systems was performed. Adopting the described procedure, we evaluated the cross-coupling with $PdCl_2/PPh_3$, $Pd(OAc)_2/PPh_3$, $Pd(PPh_3)_4$[17] and Pd/C.[18] The reaction proceeded well and full conversion was achieved in all cases using 2 mol-% of Pd source, 3 equiv. of Cs_2CO_3 as base and THF/H_2O (9:1) as solvent under microwave irradiation at 100 °C and a maximum power of 200 W (Table 3). Although all evaluated Pd sources gave satisfactory results (Table 3, Entries 1–4), we preferred to proceed with the heterogeneous catalytic system (Pd/C) as this is supposed to prevent leaching of Pd and is relatively inexpensive.[19] Several solvent systems were investigated [THF/H_2O (9:1), NMP/H_2O (9:1), NMP, H_2O] (Table 3, Entries 4–7) using 2 mol-% of Pd/C and 3 equiv. Cs_2CO_3 as base. All of them were found to be equally effective and furnished the desired vinylated compound in 67–71% yield within 30–50 min.

Water offers practical advantages as it is inexpensive, readily available, and non-flammable and it renders the process a "greener" aspect.[20] Also different bases [Cs_2CO_3, Na_2CO_3, K_2CO_3, KOAc] were screened using 2 mol-% of Pd/C as catalyst in water as solvent (Table 3, entries 7–10). Although no significant differences in yield were observed, the reaction proceeded slower when using Na_2CO_3 or K_2CO_3, hence KOAc was the preferred base as it is less expensive than Cs_2CO_3.

Having optimized the protocol, we investigated the vinylation of various 2(1*H*)-pyridone halides. When 4- or 5-iodo-2(1*H*)-pyridone was subjected to vinylation, the reaction proceeded smoothly yielding the desired vinylated products in excellent yields of 84% and 91% in mere 10 min (Table 4, Entries 1 and 2). However, when bromo pyridones were reacted under the aforementioned conditions, full conversion could not be achieved. Switching to NMP/H_2O (8:2) as solvent mixture under the optimized conditions, furnished the desired vinylated products in excellent yields of 78–91% within 20 min (Table 4, Entries 3–4). Attempts to use chloro-2(1*H*)-pyridones for this cross-coupling, other than model compound **1**, were unsuccessful. The reactivity of **1** could probably be ascribed to the activating nitro group in position 3 of the pyridone system.

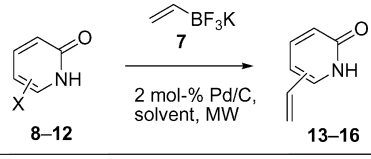
Table 3. Screening of catalyst system and solvent using potassium vinyltrifluoroborate (**7**) as potential vinylating agent under microwave irradiation.[a]



Entries	Pd source	Solvent	Base	Time[b] [min]	% Yield[c]
1	$PdCl_2/PPh_3$	THF/H_2O (9:1)	Cs_2CO_3	50	68
2	$Pd(OAc)_2/PPh_3$	THF/H_2O (9:1)	Cs_2CO_3	30	69
3	$Pd(PPh_3)_4$	THF/H_2O (9:1)	Cs_2CO_3	30	70
4	Pd/C	THF/H_2O (9:1)	Cs_2CO_3	40	67
5	Pd/C	NMP/H_2O (9:1)	Cs_2CO_3	40	69
6	Pd/C	NMP	Cs_2CO_3	30	71
7	Pd/C	H_2O	Cs_2CO_3	30	69
8	Pd/C	H_2O	Na_2CO_3	50	70
9	Pd/C	H_2O	K_2CO_3	50	68
10	Pd/C	H_2O	KOAc	30	70

[a] Reactions were performed on a 0.1 mmol scale of 6-chloro-3-nitro-2-(1*H*)-pyridone (**1**) using potassium vinyltrifluoroborate (**7**) (1.1 equiv.), Pd source (2 mol-%) and 3 equiv. of base at a ceiling temperature of 100 °C and a maximum power of 200 W. [b] Time taken for full conversion. [c] Isolated yields.

Table 4. Evaluation of scope of the vinylation using different 2(1*H*)-pyridones.[a]



Entry	X	Time [min][b]	Solvent	Product	% Yield[c]
1.	5-I	10	H_2O	**13**	91
2.	4-I	10	H_2O	**14**	84
3.	5-Br	20	NMP/H_2O (8:2)	**13**	78[d]
4.	3-Br	20	NMP/H_2O (8:2)	**15**	81[d]

[a] Reactions were performed on a 0.1 mmol scale of 2(*1H*)-pyridone using potassium vinyltrifluoroborate (**7**) (1.1 equiv.), Pd/C (2 mol-%) and 3 equiv. of KOAc under microwave irradiation at a ceiling temperature of 100 °C and a maximum power of 200 W. [b] Time taken for full conversion as indicated by GC. [c] Isolated yields. [d] When H_2O was used as solvent no full conversion was achieved.

In summary, we have developed a novel and heterogeneous, palladium-catalyzed vinylation of 2(1*H*)-pyridones using potassium vinyltrifluoroborate as vinyl donor. This protocol is applicable to various iodo and bromo 2(1*H*)-pyridones. Reactions can be performed in various solvents like H_2O, NMP, THF, or in mixtures of THF/H_2O, NMP/H_2O. This procedure is an interesting complement of the existing Suzuki cross-coupling reaction. It provides a methodology for the synthesis of various compounds derived

from the 2(1*H*)-pyridone ring system. Attempts to use chloropyridone for this cross-coupling are currently under way and will be reported in due course.

Acknowledgments

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