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N-Vinylpyridinium tetrafluoroborate salts as reagents for the stereoselective and regioselective synthesis of symmetrical (2*E*,4*E*)-1,6-dioxo-2,4-dienes

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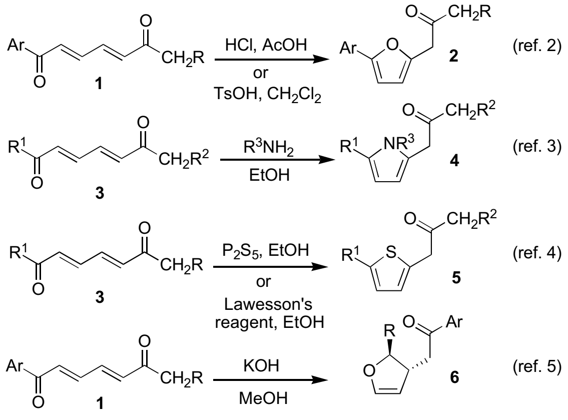
ABSTRACT

We had previously demonstrated the utility of *N*-vinylpyridinium tetrafluoroborate salts as novel electrophilic coupling partners in Pd(0)-catalyzed Suzuki cross-coupling reactions with aryl and vinyl boronic acids. We now report that these crystalline, air-stable, and non-hygroscopic salts are also useful reagents for the synthesis of symmetrical (2*E*,4*E*)-1,6-dioxo-2,4-dienes (diene diones), which in turn are valuable starting materials for the synthesis of various five-membered heterocycles. The optimization of reaction conditions and the scope and limitations of the reductive dimerization are discussed.

The ready availability of variously substituted aromatic heterocycles continues to be an important problem in organic chemistry. In connection with a program of research involving library development with novel chemotypes based on our recently reported indole aryne cycloaddition chemistry,[1] we required an efficient and general route to di-substituted, five-membered ring aromatic heterocycles.

A potentially attractive avenue for the synthesis of the desired cycloaddition partners involves the use of 1,6-dioxo-2,4-dienes (diene diones), as shown in Scheme 1.[2–5] Treatment of diene diones with the appropriate reagents and reaction conditions leads to the formation of furans **2**,[2] pyrroles **4**,[3] or thiophenes **5**,[4] as well as dihydrofurans **6**.[5] However, a review of the literature revealed that there are only ad hoc methods for the synthesis of the requisite 1,6-dioxo-2,4-dienes.[6–11]



Scheme 1. Use of (2*E*,4*E*)-1,6-dioxo-2,4-dienes to form aromatic and other heterocycles.

Most of these methods have significant drawbacks or limitations that detract from their widespread adoption. These include the use of toxic reagents,[6,7] the requirement of harsh reaction conditions,[7] the presence of unstable intermediates,[8] or the involvement of several steps.[9] Several of these methods suffer additionally in that they either give low yields of the diene dione product or result in mixtures of olefinic regio- and stereoisomers.[10,11]

Recently, we showed that *N*-vinylpyridinium tetrafluoroborate salts represent an attractive alternative to vinyl halides and triflates in the Pd(0)-catalyzed Suzuki cross-coupling reaction with aryl boronic acids (Scheme 2).[12] The only other reported use of these salts is that of a dienophile (Jung's dienophile) in the Diels–Alder reaction.[13–15] During the course of our investigation into the application of these salts in the Suzuki reaction, we observed that merely changing the phosphine ligand from PCy$_3$ to PPh$_3$ in **11** suppressed almost entirely the cross-coupling event and gave instead in good yield the symmetrical 1,6-dioxo-2,4-diene **12**, presumably via reductive dimerization.

We now report that this one-step, microwave-assisted (heated) process represents the first general and practical method for the synthesis of symmetrical, isomerically pure 1,6-dioxo-2,4-dienes. The *N*-vinylpyridinium tetrafluoroborate salts used in the present study are prepared in one-step from the addition of pyridinium tetrafluoroborate to various ynones[14] to afford crystalline, non-hygroscopic, and indefinitely air-stable components. Besides the foregoing advantages over the corresponding β-haloenones, the salts have the additional feature of being appreciably soluble in many common organic solvents.

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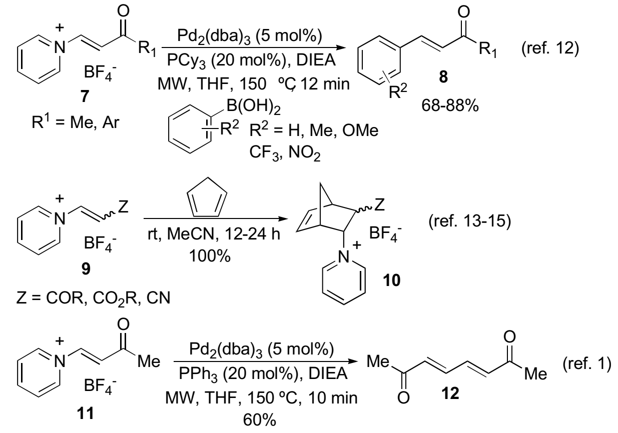
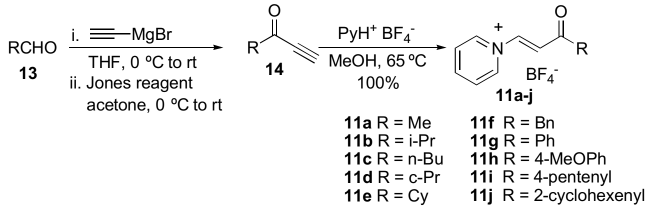


Scheme 2. Applications for *N*-vinylpyridinium tetrafluoroborate salts.



Scheme 3. Synthesis of *N*-vinylpyridinium salts **11a**–**j**.

To explore the scope and limitations of this procedure, we commenced with a series of commercially available aldehydes having various aliphatic and aromatic groups (Scheme 3). Reaction with 1.5 equiv of ethynylmagnesium bromide (CCMgBr, THF, 0 °C) followed by oxidation with excess Jones reagent (Jones, acetone, 0 °C) afforded the 3-yn-2-ones in good to excellent yields. Reaction with an equivalent of pyridinium tetrafluoroborate in refluxing methanol for up to 12 h gave in each case a quantitative yield of the exclusively trans vinylpyridinium salt.[14]

The original reductive dimerization conditions failed to give acceptable or reproducible yields of diene diones for the remaining vinylpyridinium salts. From our initial efforts at improving the yield for the other substrates, we determined that the use of a 7:3 mixture of THF/water as the solvent proved to be beneficial, and generally resulted in a modest yield improvement. Accordingly, we elected to start with this solvent system using **11** as the test substrate, then to vary the catalyst, ligand, base, solvent, and temperature in an iterative fashion to find the optimum conditions for the remaining compounds.

Our previous experience in the Suzuki cross-coupling study involving *N*-vinylpyridinium salts revealed that the reactions carried out with conventional heating (i.e., reflux) led to prolonged reaction times and usually significantly diminished yields. For this reason, along with the observation that microwave use is becoming common in organic synthesis, we continue to use a focused beam, closed system microwave reactor as the heating method of choice.[16,17]

Table 1 shows the attempted optimization of the catalyst using various palladium sources. The catalyst and ligand combination of $Pd_2(dba)_3$ with PCy_3, while affording a modest yield of the diene dione, was superior to the other entries, and therefore adopted. Also examined were other metals such as nickel(II)iodide and copper(I)iodide, but with these catalysts no homocoupling was observed.

Table 1
Attempted catalyst optimization[a]

Entry	Catalyst	Ligand	Yield (%)
1	$Pd_2(dba)_3$	PPh_3	27
2	$Pd_2(dba)_3$	$AsPh_3$	23
3	$Pd_2(dba)_3$	P-*o*-tol$_3$	26
4	$Pd_2(dba)_3$	dppf	15
5	$Pd_2(dba)_3$	PCy_3	34
6	$PdCl_2[P(tol)_3]_2$	na[b]	27
7	$PdCl_2[PCy_3]_2$	na	24
8	$PdCl_2[PPh_3]_2$	na	32
9	$Pd(dppe)_2$	na	15
10	$Pd(PPh_3)_4$	na	15

[a] Reaction conditions: 5 mol % catalyst, 20 mol % ligand (if applicable), 2.2 equiv DIEA, THF/H_2O (7:3), MW 150 °C, 10 min.
[b] na = not applicable.

Table 2
Solvent optimization[a]

Entry	Solvent	Yield (%)
1	THF	34
2	Acetone	31
3	CH_2Cl_2	35
4	DMF	19
5	MeCN	42
6	MeOH	15
7	MeCN/H_2O (7:3)	21
8	THF/H_2O (7:3)	30

[a] Reaction conditions: 5 mol % $Pd_2(dba)_3$, 20 mol % PCy_3, 2.2 equiv DIEA, MW 150 °C, 10 min.

We next examined the effect of solvent, as shown in Table 2. Acetonitrile (entry 5) was superior to other strongly coordinating (DMF) or weakly coordinating (acetone) polar aprotic solvents, and also showed improved yields compared to weakly polar solvents such as THF or DCM. Interestingly, the use of protic solvents such as water or methanol alone or in pairs is clearly detrimental to the reaction as shown in entries 6, 7, and 8. Accordingly, we employed acetonitrile for the subsequent optimization.

We next examined the choice of base for the reaction, the results of which are summarized in Table 3. In the absence of base (entry 1), no reaction takes place. While Hunig's reagent was used successfully in our earlier homocoupling work, curiously, the addition of other common organic bases, such as triethylamine, pyridine, and 2,6-lutidine, failed to give any diene dione (entries 3–5).

However, employing inorganic bases such as lithium carbonate, potassium bicarbonate, or sodium bicarbonate again gave product, with sodium carbonate being the best of these three. This observation stands in contrast to our earlier efforts involving the Suzuki cross-coupling of *N*-vinylpyridinium salts in which poor yields

Table 3
Base optimization[a]

Entry	Base	Yield (%)
1	None	0
2	EtN(*i*-Pr)$_2$	42
3	2,6-Lutidine	0
4	Pyridine	0
5	NEt_3	0
6	Li_2CO_3	27
7	$KHCO_3$	49
8	$NaHCO_3$	56

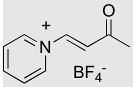
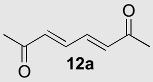
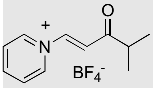
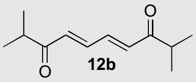
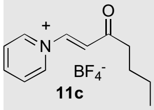
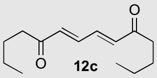
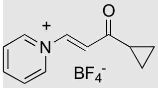
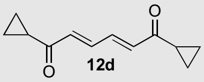
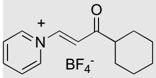
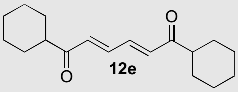
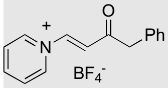
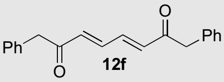
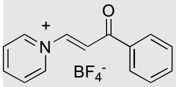
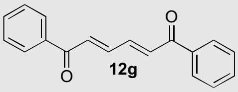
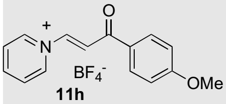
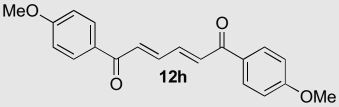
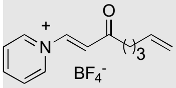
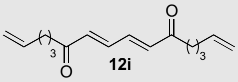
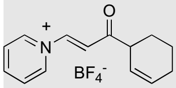
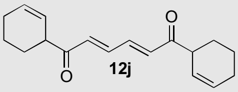
[a] Reaction conditions: 5 mol % $Pd_2(dba)_3$, 20 mol % PCy_3, 2.2 equiv base, MeCN, MW 150 °C, 10 min.

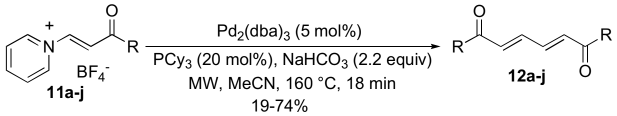
Table 4
Reaction temperature and time optimization[a]

Entry	Temperature (°C)	Time (min)	Yield (%)
1	150	10	56
2	150	20	58
3	170	10	53
4	180	7	51
5	190	5	54
6	160	18	74

[a] Reaction conditions: 5 mol % $Pd_2(dba)_3$, 20 mol % PCy_3, 2.2 equiv $NaHCO_3$, MeCN, MW temperature and time as shown.

Table 5
Yields for the formation of 1,6-dioxo-2,4-dienes **12a–j**

N-Vinylpyridinium salt	1,6-Dioxo-2,4-diene	Yield (%)
 **11a**	 **12a**	74
 **11b**	 **12b**	52
 **11c**	 **12c**	41
 **11d**	 **12d**	61
 **11e**	 **12e**	47
 **11f**	 **12f**	52
 **11g**	 **12g**	31
 **11h**	 **12h**	19
 **11i**	 **12i**	62
 **11j**	 **12j**	65



Scheme 4. Preparation of various 1,6-dioxo-2,4-dienes under optimized homocoupling conditions.

were obtained with inorganic bases, but significantly improved yields were obtained with organic bases.[12]

Finally, we looked into the effect of temperature and reaction time on homodimerization with the catalyst, solvent, and base system developed thus far (Table 4).

The best conditions were achieved by a combination of increased reaction time and slightly increased temperature (entry 6) compared to our original time and temperature profile (entry 1). Increasing the reaction time alone led to only a marginal improvement (entry 2), whereas increasing the temperature beyond 160 °C even for much shorter periods resulted in diminished yields (entries 3–5). The new conditions resulted in a significantly improved yield of the diene dione **12** to 74% from the previously reported 60%.[12]

The other nine *N*-vinylpyridinium salts, **12b–j**, were then subjected to the same optimized homodimerization conditions as shown in Scheme 4. The yields for the reactions are summarized in Table 5.

Overall, the procedure gives fairly uniform and good yields of a wide variety of relatively unhindered diene diones. The exceptions include the aryl-substituted ketone products **11g**, and **11h**, which are themselves relatively unstable and maybe decomposing or reacting further (e.g., as a diene) during the course of the reaction. In spite of this limitation, the reaction seems to be general for alkyl, branched alkyl, cycloalkyl, and olefin-containing alkyl and cycloalkyl groups.

In conclusion, we have discovered a facile and general Pd-(0) catalyzed method for the stereo- and regioselective synthesis of symmetrical alkyl-substituted (2*E*,4*E*)-1,6-dioxo-2,4-dienes which are in turn valuable precursors for substituted heterocyclic systems. This method represents a substantial improvement over previously reported approaches to diene diones. The advantages of the current procedure derive from the fact that it is rapid, it involves only one-step from stable and easily prepared substrates, and it does not rely upon toxic or other reactive or unstable reagents during the preparation. Investigation into the mechanism of this reaction and further efforts to find other applications for *N*-vinylpyridinium salts are underway, and will be reported as developments warrant.

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