Synthesis of 1-(1-Arylvinyl)pyridin-2(*1H*)-ones from Ketones and 2-Fluoropyridine

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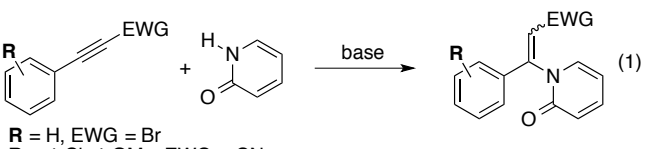
Abstract: Pyridone skeletons are found in numerous biologically active molecules and pharmaceuticals. 1-(1-Arylvinyl)pyridin-2(*1H*)-ones are synthetic intermediates derived from the enamide moiety, and only few examples of the synthesis of 1-(1-arylvinyl)-2-pyridones have been reported. In this work, a simple and efficient procedure for the synthesis of *N*-vinyl-substituted pyridones from ketones and 2-fluoropyridine in the presence of trifluoromethane sulfonic anhydride, followed by base treatment is described. Various ketones with electron-donating or -withdrawing groups at the benzene rings can be used in this reaction. A preliminary mechanistic study indicates that it is not very likely that both vinyl triflates and vinyl cations play major roles as intermediates in this transformation. The thus obtained pyridones can be subsequently transformed via C–H arylation and radical alkylation reactions.

Pyridone, i.e., pyridin-2(*1H*)-one, skeletons exist in numerous biologically active molecules and pharmaceuticals. [1] The development of efficient synthetic methods for the straightforward construction of this structural motif has thus received considerable interest from the synthetic community, and several synthetic routes to *N*-substituted pyridones have been reported.[2] Although 1-(1-arylvinyl)pyridin-2(*1H*)-ones are useful synthetic intermediates derived from the enamide moiety, only few examples of the synthesis of 1-(1-arylvinyl)-2-pyridones have been reported.[3] Undheim and co-workers have reported the reaction of 1-bromophenylacetylene with the sodium salt of 2-pyridinone (eq. 1).[4] Rao *et al.* have reported the nucleophilic addition to cyano-substituted aryl alkynes leading to 1-(1-arylvinyl)-2-pyridones.[5]

On the other hand, 2-halopydinium salts are easily converted into 2-pyridones.[6,7,8] Due to the toxicity of 2-chloropyridine,[9] the development of efficient synthetic routes to vinyl-2-fluoropyridinium salts are highly desirable in order to construct 1-(1-arylvinyl)-2-pyridones. However, the synthesis of 1-(1-arylvinyl)-pyridinium salts is still limited. Relles has reported the synthesis of vinyl pyridinium salts from electron-rich acetophenones with $SOCl_2$ using pyridine as the solvent (eq. 2).[10] Novella and Alvarez-Builla have checked the generality of Relles's work.[11] Substrates with electron-donating groups (e.g., 4-OMe) afford polymers, while substrates with electron-withdrawing groups (e.g., 4-F) do not afford vinyl pyridinium salts. Recently, Zhao and co-workers have reported the synthesis of vinyl pyridinium salts from styrenes with fluoropyridinium salts in the presence of an organoselenium catalyst (eq. 3).[12] Very recently, Majireck has reported the pyridination of alkynes in the presence of TfOH (eq. 4). However, this system is limited to alkynes that contain electron-donating groups such as OMe,[13] and pyridinium salts were not observed using phenylacetylene.

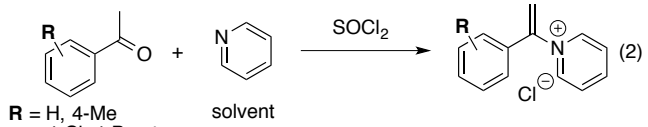
Trifluoromethanesulfonic anhydride (Tf_2O) is a highly electrophilic reagent,[14] and its reactions with ketones and base furnish vinyl triflates.[15] Yields can often be improved when using sterically hindered non-nucleophilic bases such as 2,6-di-(*t*-butyl)-4-methylpyridine (DTBMP), [16] albeit that the latter is relatively expensive. During our study on vinyl triflates,[17] we obtained *N*-vinyl-substituted pyridinium salts from acetophenones with Tf_2O in the presence of 2-fluoropyridine[18] as a mild nucleophilic base. Subsequent treatment of the resulting pyridinium salts under basic conditions furnished 1-(1-arylvinyl)pyridin-2(*1H*)-ones (eq. 5). Herein, we describe the synthesis of 1-(1-arylvinyl)pyridin-2(*1H*)-ones from acetophenones that contain electron-donating or -withdrawing groups at the benzene ring.

Undheim **1979**, Rao **1989**



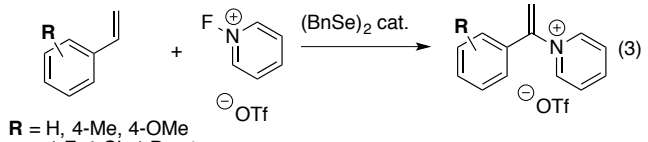
R = H, EWG = Br
R = 4-Cl, 4-OMe, EWG = CN

Relles **1973** and Novella **1985**



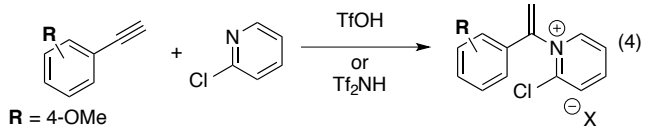
R = H, 4-Me
4-Cl, 4-Br, etc.
solvent

Zhao **2017**



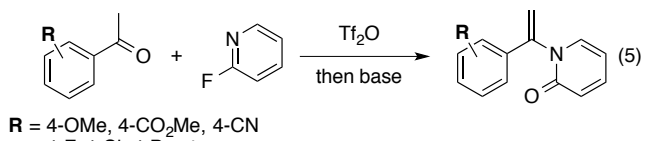
R = H, 4-Me, 4-OMe
4-F, 4-Cl, 4-Br, etc.

Majireck **2019**



R = 4-OMe

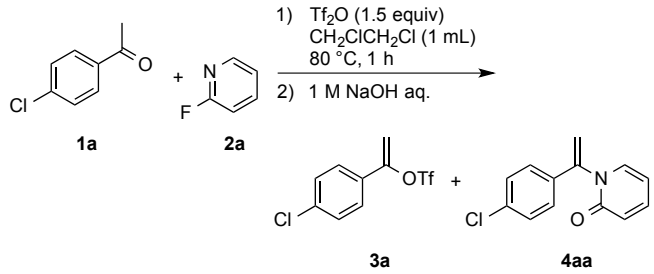
This Work



R = 4-OMe, 4-CO_2Me, 4-CN
4-F, 4-Cl, 4-Br, etc.

For our initial study, we chose 4'-chloroacetophenone (**1a**) as a model substrate (Table 1). When a CH_2ClCH_2Cl solution of **1a**, 2-fluoropyridine (**2a**) (1.0 equiv), and Tf_2O (1.5 equiv) was stirred for 1 h at 80 °C, and subsequently treated with NaOH aq., vinyl triflate **3a** was obtained in 92% yield together with vinyl pyridone **4aa** in 4% yield (Table 1, entry 1). Increasing the amount of **2a** to e.g. 3.0 equiv resulted in the formation of **4aa** in 79% yield after column chromatography on silica gel (entry 3).

Table 1. Initial Study

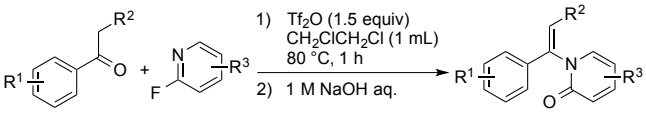


entry	**2a** (equiv)	conv. of **1a** [a]	**3a** [a]	**4aa** [a,b]
1	1.0	97%	92%	4%
2	2.0	86%	42%	53%
3	3.0	99%	5%	93% (79%)

[a] Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [b] The isolated product yield, after flash column chromatography on SiO_2, is given in parentheses.

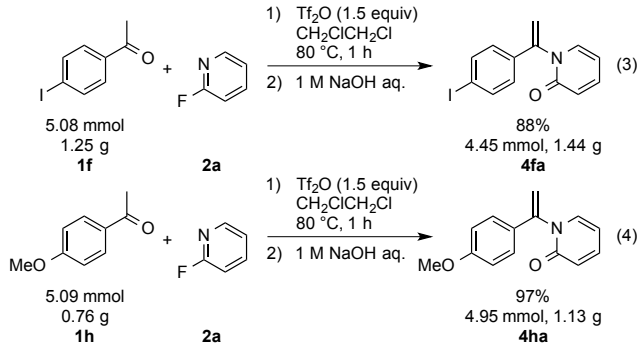
With the optimized conditions (Table 1, entry 3) in hand, we next examined the substrate scope for the synthesis of vinyl pyridones and the results are summarized in Table 2. Halo-substituted acetophenones **1a**–**1f** afforded **4aa**–**4fa** in good yield (entries 1–6). The reaction of acetophenone (**1g**) furnished vinyl pyridone **4ga** in 85% yield (entry 7). *p*-Methoxy-, *o*-methyl-, and *p*-phenyl-substituted acetophenones also worked well (entries 8–10). Substrates with electron-withdrawing groups at the benzene ring (**1k**–**1m**) afforded the corresponding products (**4ka**–**4ma**) in moderate to good yield (entries 11–13). For example, the reaction of 1-(4-(methylsulfonyl)phenyl)ethan-1-one (**1l**) furnished **4la** in 52% yield (entry 12). Increasing the proportion of 4-fluoropyridine (**2a**) to 5 equiv generated vinyl pyridone **4la** in 64% yield (entry 13). 1-(Naphthalen-1-yl)ethan-1-one (**1n**) and 2-(naphthalen-1-yl)ethan-1-one (**1o**) also worked well (entries 16 and 17). The reaction of **1f** and 2-fluoro-4-methylpyridine (**2b**) with Tf_2O gave the corresponding pyridine (**4fb**) in good yield (entry 18). The reaction of 1-(4-chlorophenyl)propan-1-one (**1p**) and 1,2-diphenylethan-1-one (**1q**) afforded the corresponding products with high stereoselectivity in 83% and 60% yield, respectively (entries 19 and 20). The present synthesis of vinyl pyridones can also be carried out on the gram scale, furnishing **4fa** in 88% yield and **4ha** in 97% yield (eq. 3 and 4).

Table 2. Substrate Scope [a]



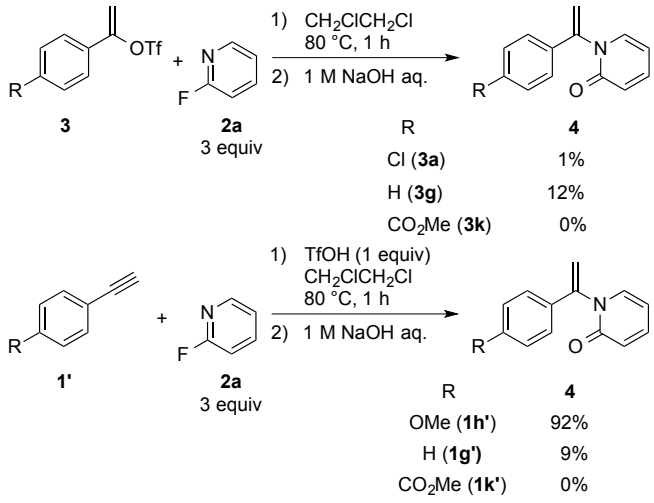
entry	1	2	4	yield [b,c]
1	4-Cl (**1a**)	**2a**	**4aa**	93% (79%)
2	3-Cl (**1b**)	**2a**	**4ba**	77% (66%)
3	2-Cl (**1c**)	**2a**	**4ca**	69% (56%)
4	R^1 = 4-F (**1d**)	**2a**	**4da**	99% (89%)
5	R^1 = 4-Br (**1e**)	**2a**	**4ea**	91% (84%)
6	R^1 = 4-I (**1f**)	**2a**	**4fa**	99% (88%)
7	R^1 = H (**1g**)	**2a**	**4ga**	(85%)
8	R^1 = 4-OMe (**1h**)	**2a**	**4ha**	99% (96%)
9	R^1 = 2-Me (**1i**)	**2a**	**4ia**	(90%)
10	R^1 = 4-Ph (**1j**)	**2a**	**4ja**	99% (98%)
11	R^1 = 4-CO_2Me (**1k**)	**2a**	**4ka**	74% (58%)
12	R^1 = 4-SO_2Me (**1l**)	**2a**	**4la**	(52%)
13	R^1 = 4-CN (**1m**)	**2a**	**4ma**	54% (46%)
14 [d]	R^1 = 4-SO_2Me (**1l**)	**2a**	**4la**	(63%)
15 [d]	R^1 = 4-CN (**1m**)	**2a**	**4ma**	72% (64%)
16	**1n**	**2a**	**4na**	(99%)
17	**1o**	**2a**	**4oa**	90% (92%)
18	**1f**	**2b**	**4fb**	64% (54%)
19	**1p**	**2a**	**4pa**	86% (83%) *Z*/*E* = 85/15 [e]
20	**1q**	**2a**	**4qa**	72% (60%) *Z*/*E* = 88/12 [e]

[a] **1** (0.5 mmol), **2** (1.5 mmol, 3 equiv), Tf_2O (1.5 equiv), CH_2ClCH_2Cl (2 mL), 80 °C, 1 h. [b] Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [c] The isolated product yield, after flash column chromatography on SiO_2, is given in parentheses. [d] **2a** (5 equiv) was used. [e] The stereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.



According to previous work on vinyl triflates by other groups, vinyl triflates that contain electron-donating groups at the *para* position of the benzene ring easily afford vinyl cations, which can be trapped by nucleophiles such as nitriles[19] or sulfoxides.[20] Therefore, we examined the reaction using vinyl triflates **3a**, **3g**, and **3k** or aryl alkynes **1h'**, **1g'**, and **1k'** to gain mechanistic insights. When a CH_2ClCH_2Cl solution of **3a**, **3g**, and **3k** and 2-fluoropyridine was stirred at 80 °C for 1 h, followed by treatment with NaOH aq., the desired product was obtained in 1%, 12%, and 0% yield, respectively. Similar to the result of Majireck *et al.*, エラー! ブックマークが定義されていません。[b] the reaction of aryl alkynes **1g'** and **1k'** with TfOH and 2-fluoropyridine did not afford vinyl pyridones effectively. These results suggest that it is not very likely that both vinyl triflates (**3**) and vinyl cations play major roles as intermediates in this transformation (Scheme 1).

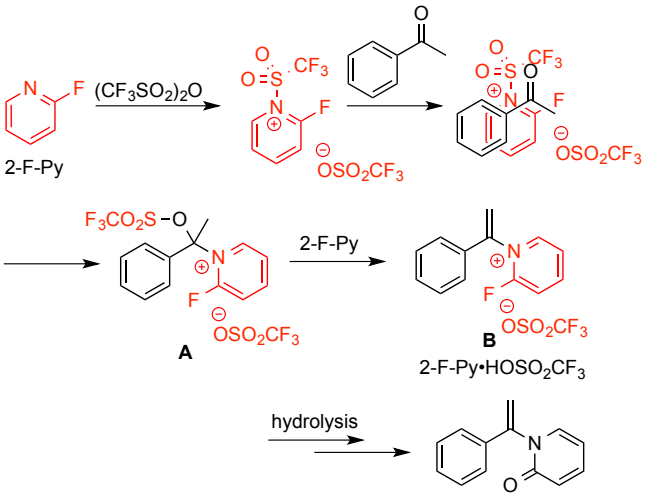
Scheme 1. Control experiments



When a pyridinium salt, which was obtained from treating 2-fluoropyridine (**2a**) with Tf_2O,[18d] in $CDCl_3$ was exposed to acetophenone **1a** (4-Cl) or **1h** (4-OMe) at rt for 1h, the corresponding vinyl pyridinium salts were generated.

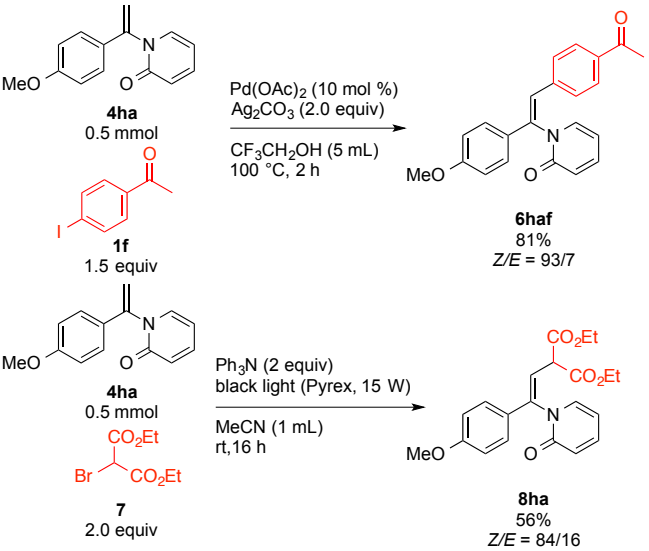
Although the details of the underlying mechanism still remain unclear at this stage, a plausible mechanism is shown in Scheme 2. The generated trifluoromethanesulfonyl pyridinium salt reacts with a ketone via a concerted pathway to give pyridinium intermediate **A**. Another 2-fluoropyridine abstracts a proton to give vinyl pyridinium **B**, which undergoes hydrolysis to furnish the final product. An alternative mechanism is based on Neuhoff's work.[21]The reaction of acetophenone with Tf_2O gives carbocation intermediate, which is trapped by 2-fluoropyridine to afford pyridinium intermediate **A**.

Scheme 2. Plausible reaction mechanism for the synthesis of 1-(1-arylvinyl)pyridin-2(1*H*)-ones from ketones and 2-fluoropyridine



As the products contain enamide moieties, they are amenable to further transformations (Scheme 3). For example, a palladium-catalyzed C–H arylation reaction[22] of **4ha** with aryl iodide **5** forms trisubstituted alkene **6ha** in 81% yield. A black-light-induced Heck-type reaction with bromomalonate furnished the corresponding alkylated product (**8ha**) in 56% yield.

Scheme 3. Subsequent transformation of the obtained vinyl pyridones



In summary, we have developed a synthetic route to vinyl pyridones from acetophenones and 2-fluoropyridine with Tf_2O as an activator. This strategy is characterized by an excellent functional-group tolerance and procedural simplicity. The generated vinyl pyridones are easily transformed via C–H arylation and radical alkylation reactions. Further mechanistic studies are currently in progress and the corresponding results will be reported in due course.

Acknowledgements

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Keywords: Ketones • Vinyl Pyridones • Vinyl Pyridinium • Cations • Tf_2O

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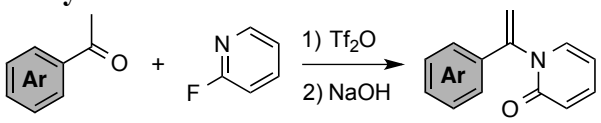

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