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Annulation of Ketones with Vinamidinium Hexafluorophosphate Salts: An Efficient Preparation of Trisubstituted Pyridines

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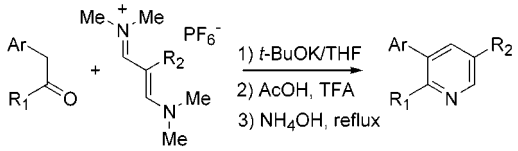
ABSTRACT

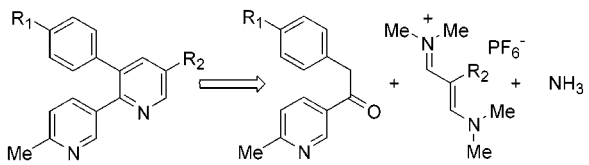


α-Aryl ketones react with vinamidinium hexafluorophosphate salts to give access to the corresponding 3-arylpyridines. The annulation reactions proceed in good to excellent yields with vinamidinium salts containing electron-withdrawing groups at the β-position (R_2). The reaction was applied to the preparation of the COX-2 specific inhibitor 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine (1), as well as a series of analogues.

The recent discovery of a specific cyclooxygenase isozyme, expressed principally in inflammatory tissue and referred to as COX-2 isozyme,[1] prompted several groups to search for inhibitors of COX-2 that would show potent antiinflammatory properties without the gastric ulceration side effects associated with nonselective COX-1/COX-2 NSAIDS.[2,3] Recently, Merck has investigated a series of 2-pyridyl-3-(4-methylsulfonyl)phenylpyridines as orally active COX-2 specific inhibitors.[3] An increase in COX-2 inhibition and specificity was observed with introduction of a substituent at the C-5 position of the central pyridine. 5-Chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine (**1**) was identified as a very potent COX-2 specific inhibitor that may provide therapeutically useful alternatives to traditional NSAIDS with a greater GI safety profile.[3]

We envisioned that the class of compounds represented by **1** may be assembled by construction of the central pyridine ring (Scheme 1). This disconnection would lead to

Scheme 1



1 R_1=SO_2Me, R_2=Cl **2** R_1=SO_2Me **3** R_2=Cl

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a readily available ketosulfone **2**, a 1,5-diazapentadienium salt **3** (vinamidinium salt) as a three-carbon electrophile, and ammonia.

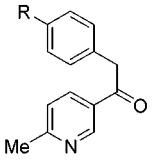
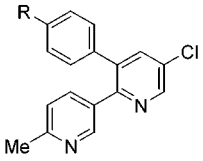
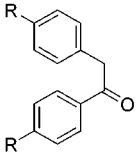
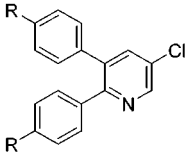
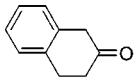
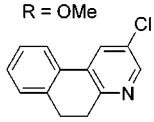
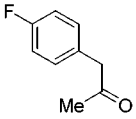
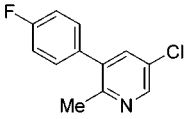
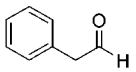
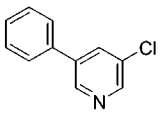
Vinamidinium species, mainly as their perchlorate salts, have been used in synthesis since the mid-1960s for the preparation of nitrogen-containing heterocycles such as pyrroles and pyrimidines.[4] Although pyridines have been prepared by the reaction of β-aminocrotononitriles or β-aminocrotonates with vinyloguous iminium salts,[5] the direct transformation of ketones to pyridines using vinamidinium salts as annulating reagents has not been reported. Carbonyl enolates are known to add to vinamidinium salts to produce dienaminones,[6] and enolates of substituted aryl methyl ketones are alkylated by vinamidinium salts.[7] In the latter case the formation of pyridine rings was achieved in a three-step process in 36−46% yield via the formation of the corresponding pyrylium salts and reaction with ammonium acetate.[7] We recently reported the preparation of several β-substituted vinamidinium hexafluorophosphate salts in good yields by reacting the corresponding acetic acids or acetyl chlorides with phosphorus oxychloride in DMF at 70 °C followed by quenching in aqueous HPF_6.[8] The use of hexafluorophosphate as the counterion resulted in thermally stable salts that were not prone to hydrolysis upon exposure to air. We now report that these salts are suitable three-carbon synthons that react with α-aryl ketone enolates to form 2,5-disubstituted-3-arylpyridines in fair to excellent yields.

The 2-chloro-*N*,*N*-dimethylamino trimethinium hexafluorophosphate salt (**3**)[8] was reacted with ketone **2** in the presence of an equimolar amount of *t*-BuOK in THF and the resulting adduct was quenched in a mixture of acetic acid and TFA. Ring closure of the pyridine ring occurred upon heating at reflux in the presence of an excess of aqueous ammonium hydroxide. The desired COX-2 specific inhibitor 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine (**1**) was obtained as a single regioisomer with an excellent isolated yield of 94% (Table 1, entry 1).[9]

Replacement of the potassium base by sodium *tert*-butoxide or LDA decreased the yields significantly and resulted in the recovery of large quantities of unreacted ketosulfone. This reaction is general and was applied to the preparation of analogues of **1** in excellent yields (entries 2 and 3). α-Aryl acetophenones such as deoxybenzoin, desoxyanisoin, and bis(*p*-methylsulfonyl) deoxybenzoin give access to the corresponding 2,3-diaryl-5-chloropyridines, albeit in lower yields than the corresponding pyridyl ketones. These substrates were highly dependent upon the aromatic substitution (entries 4−6). β-tetralone and *p*-fluorophenyl acetone give access to the corresponding cyclized product in good yields (entries 7 and 8) without formation of the other possible regioisomers as determined by NMR analysis of the crude reaction mixture.

The reaction is not limited to ketones since phenylacetaldehyde reacted in good yield to give 3-phenyl-5-chloropyridine (entry 9).[10]

Table 1. Annulation of Ketones and Aldehydes with *N*,*N*-Dimethyl-2-chlorotrimethinium Hexafluorophosphate (**3**)[a]

Entry	Ketone/Aldehyde	Product	Isolated Yield (%)[b]
			
1	R = SO_2Me	R = SO_2Me	94
2	R = H	R = H	92
3	R = SMe	R = SMe	87
			
4	R = SO_2Me	R = SO_2Me	77
5	R = H	R = H	65
6	R = OMe	R = OMe	38
7			73
8			68
9			80[c]

[a] Unless otherwise noted, all reactions were conducted in THF using 1.05 equiv of 20 wt % *t*-BuOK/THF and 1.05 equiv of vinamidinium salt. For a typical experimental procedure, see footnote 10. [b] Yields refer to the average of at least two isolated yields. Only one regioisomer has been observed by NMR analysis of the crude reaction mixture. [c] A solution of the aldehyde in THF was added dropwise to a suspension of KHMDS at −78 °C and was warmed to rt before the addition of salt **3**.

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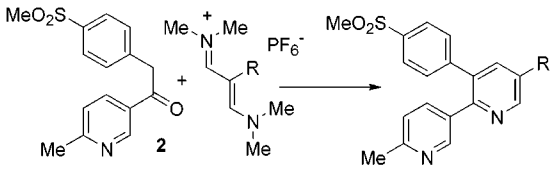
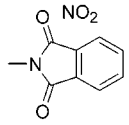
(9) The structure of compound **1** was unambiguously assigned by NMR analysis (COSY, HMBC, HMQC) and by comparison with an authentic sample obtained by a different route (see ref 3a).

(10) **General Experimental Procedure for the Annulation of Ketones.** To a suspension of ketosulfone (25 mmol) in dry THF (50 mL) at 0 °C was added dropwise a 20 wt % solution of *t*-BuOK in THF (26.3 mmol). The yellow slurry was stirred at room temperature for 45 min and the vinamidinium hexafluorophosphate salt (26.3 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 45 min and transferred dropwise with a cannula under nitrogen to a solution of acetic acid (175 mmol) and TFA (20 mmol) in THF (25 mL) at 25−30 °C. The mixture was stirred 45 min and concentrated ammonium hydroxide (15 mL, 250 mmol NH_3) was added in one portion. The resulting dark

The scope of the reaction was studied by reacting various substituted vinamidinium salts with ketosulfone **2** (Table 2).

Table 2. Annulation of (2-Methyl-5-pyridinyl 4-Methylsulfonylbenzyl Ketone (**2**) with Substituted *N*,*N*-Dimethylaminovinamidinium Hexafluorophosphates[a]



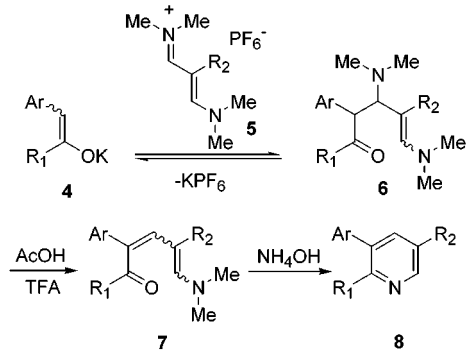
Entry	R=	Assay Yield (%)[b]	Isolated Yield (%)[c]
1	Cl	96	94
2	Br	78	73
3	I	25	12[d]
4	CF_3	75	69
5		45	29[e]
6		30	21[e]

[a] Unless otherwise noted, all reactions were conducted in THF using 1.05 equiv of 20 wt % *t*-BuOK/THF and 1.05 equiv of vinamidinium salt. [b] Assay yield determined by HPLC using an analytically pure sample of the final product as standard. [c] Yields refer to the average of at least two isolated yields. [d] 2.0 equiv of vinamidinium salt was used. [e] 1.5 equiv of vinamidinium salt was used.

The reaction proved to be very sensitive to the nature of the β-substituent. Good to excellent yields are obtained in the case where a strong electron-withdrawing group such as Br or CF_3 is present at the β-position of the vinamidinium species (entries 2 and 4). The good reactivity of the bromo-substituted vinamidinium salt to give the pyridine is noteworthy since it has previously been used to brominate ketone enolates.[11] The 3-bromo substituted pyridines are interesting substrates since they can be further functionalized via metal-catalyzed carbon−carbon bond-forming reactions. Surprisingly, the nitro-substituted salt gave a moderate yield for reasons that are still unclear (entry 5). Lower yields were obtained with the weaker electron-withdrawing iodide (entry 3). The phthaloyl group also behaved poorly (entry 6). The reaction failed in the cases where R is a neutral, electron-rich or electron-poor substituted aryl group (R = Ph, *p*-$MeOC_6H_4$ and *p*-$O_2N{-}C_6H_4$). In these examples, and in the case of the parent vinamidinium (R = H), the starting ketosulfone was recovered.

Although all of the intermediates have not been characterized, the following observations have been made. The potassium enolate of ketones adds reversibly to dimethyliminium salts **5** to form the adduct **6** (Scheme 2). We found

Scheme 2



that the *inverse* addition of the intermediate **6** to a THF solution containing TFA (0.5−1.0 equiv) and an excess of acetic acid (7.0 equiv) induced the irreversible elimination to the conjugated intermediate **7**. The direct addition of AcOH/TFA to the reaction mixture resulted in the regeneration of high amounts of starting ketone formed by retro-addition and protonation of the enolate.

Although the TFA did not prove to be essential for the reaction to proceed, the higher acidity that resulted with TFA significantly increased the yields and led to higher reproducibility. Heating at reflux in the presence of an excess of ammonium hydroxide promotes the cyclization and the formation of the desired pyridine **8**.

In conclusion, α-aryl ketones and aldehydes react with vinamidinium salts to give the corresponding pyridine rings with high regioselectivity in fair to excellent yields. The reaction is dependent upon the nature of the substituent at the β-position of the vinamidinium species. Further work is in progress to expand the scope of the reaction as well as to unambiguously define the intermediates involved.

Supporting Information Available: Characterization data: ^1H and ^{13}C NMR spectra for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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solution was heated at reflux for 5 h and concentrated under reduced pressure. The residue was directly purified by chromatography on silica gel (CH_2Cl_2 or $CHCl_3$/MeOH was used as eluent). All final products were characterized by ^1H, ^{13}C NMR and LC/MS.

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