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A General [3 + 2 + 1] Annulation Strategy for the Preparation of Pyridine *N*-Oxides

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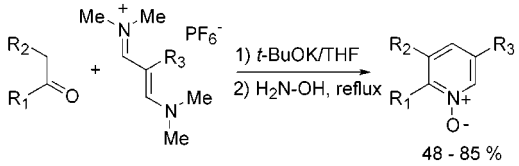
ABSTRACT

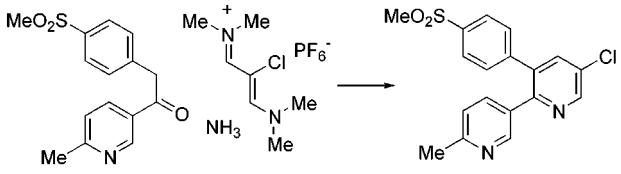


Stabilized ketone, aldehyde, and ester enolates react with vinamidinium hexafluorophosphate salts and hydroxylamine hydrochloride to give access to the corresponding pyridine *N*-oxides. The annulation reactions proceed in good to excellent yields with vinamidinium salts with a range of *β*-substituents (R_3 = halo, aryl, nitro, trifluoromethyl).

Pyridine *N*-oxides are used as antibacterial, antifungal, and antiseborrheic agents.[1] *N*-Oxides are very often metabolites of pyridine-containing molecules and have been used to determine structure−activity relationships. The most commonly used method for the preparation of these compounds relies on oxidation of the parent pyridines.[2] Cyclization of nitroaromatics and oximes are also well-established methods for preparation of fused pyridine *N*-oxides.[3] Other less general methods include reaction of pyrrilium salts or dienones with hydroxylamine.[4] *N*-Oxides are useful synthetic intermediates since they exhibit different reactivity and regioselectivity than the parent pyridine.

The Cox-2 specific inhibitor *Etoricoxib* can be assembled very efficiently in a single step from ketone **1**, the vinamidinium salt **2**, and ammonia in a [3 + 2 + 1] annulation reaction (Scheme 1).[5] The vinamidinium salts, which are readily available from acetic acids, may contain a range of functionality.[6]

Scheme 1



1 **2** *Etoricoxib*

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(1) The Merck Index on CD-ROM, v. 12.3, Chapman & Hall, 2000.

(2) For example, see: Coperet, C.; Adolfsson, H.; Khuong, T.-A.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740.

(3) For example, see: (a) Hirota, K.; Nakazawa, Y.; Kitade, Y.; Saijiki, H. *Heterocycles* **1998**, *47*, 871. (b) Wrobel, Z.; Kwast, A.; Makosza, M. *Synthesis* **1993**, *1*, 31. (c) Kusurkar, R. S.; Bhosdale, D. K. *Tetrahedron Lett.* **1991**, *32*, 3199. (d) Nesi, R.; Giomi, D.; Papaleo, S.; Turchi, S.; Dapporto, P.; Paoli, P. *Heterocycles* **1991,** *32*, 1913.

(4) Uncuta, C.; Caproiu, M. R.; Campeanu, V.; Petride, A.; Danila, M. G.; Plaveti, M.; Balaban, A. T. *Tetrahedron* **1998**, *54*, 9747.

(5) Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. *J. Org. Chem.* **2000**, *65*, 8415. Marcoux, J.-F.; Corley, E. G.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339.

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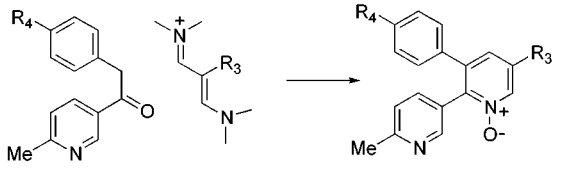
Ammonia is not the only partner that should function as the third component in the [3 + 2 + 1] annulation reaction. For example, the use of hydroxylamine would lead directly to a pyridine *N*-oxide.[7] The use of a primary amine, e.g., methylamine, would lead directly to the *N*-methylpyridinium salt. In this Letter we describe our preliminary results in this area and demonstrate the generality of this [3 + 2 + 1] strategy to access highly functionalized pyridine *N*-oxides.

Initial experiments were performed using ketosulfone **1** and vinamidinium salt **2** (CDT) using the standard reaction conditions. Replacement of ammonia with ~50 wt % aqueous hydroxylamine hydrochloride led to the isolation of the *N*-oxide **3** in 85% yield (Table 1).

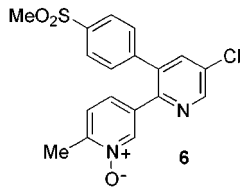
Table 1. Annulation of ketosulfone 1 with *N*,*N*-dimethylvinamidinium hexafluorophosphates[a]



Entry			*N*-oxide	Isolated Yield (%)[a]
1	R_3 = Cl	R_4 = SO_2Me	**3**	85
2	R_3 = NO_2	R_4 = SO_2Me	**4**	52
3	R_3 = Cl	R_4 = SMe	**5**	82

[a] Reactions were conducted in THF using 1.05 equiv of 20 wt % *t*-BuOK/THF and 1.05 equiv of vinamidinium salt.[8]

This result is significant since mCPBA oxidation of *Etoricoxib* led to the exclusive formation of the alternate *N*-oxide regioisomer **6** in 89% isolated yield. *Etoricoxib* also



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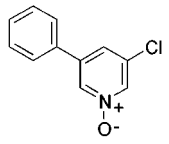

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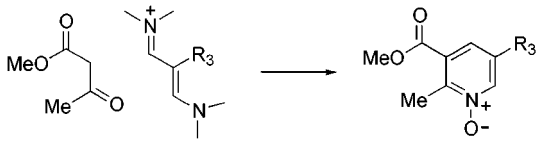
undergoes oxidation at the same site in vitro.[9] Attempted reaction using the DABCO-promoted reaction conditions failed for ketosulfone and CDT, for reasons that we still do not fully understand. The reaction is however quite general, and a range of vinamidinium salts were successfully employed as exemplified by the use of the nitro-vinamidinium salt which gave the *N*-oxide in 52% unoptimized yield. The use of the ketosulfide (entry 3) nicely illustrates the principle of direct access to substrates inaccessible via oxidation chemistry.

Aldehydes also took part in the reaction when KHMDS was used to accomplish enolization and acetic acid/ TFA was used to promote elimination. Phenylacetaldehyde led to the desired *N*-oxide **7** in 61% yield.

The scope of the reaction was studied by reacting a range of enolates and substituted vinamidinium salts (Table 2).

Table 2. Annulation of MAA with vinamidinium salts[a]

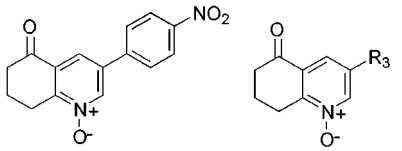


Entry		*N*-oxide	Isolated Yield (%)[a]
1	R_3 = Cl	**8**	78
2	R_3 = Ph	**9**	71
3	R_3 = 4-F-C_6H_4	**10**	76

[a] Reactions were conducted in THF using 1.05 equiv of 20 wt % *t*-BuOK/THF, 1.00 equiv of DABCO, and 1.05 equiv of vinamidinium salt.[10]

In these cases DABCO was used in the reaction to promote the elimination. Methyl acetoacetate (MAA) was reacted as a representative ketoester. The chloride **8** was isolated in an unoptimized 78% yield. The phenyl **9** and 4-fluorophenyl **10** *N*-oxides were isolated in 71% and 76% yields, respectively.

Cyclohexanedione reacted smoothly with the 4-nitrophenyl vinamidinium salt to give the azatetralone derivative **11** in 70% yield. The nitrovinamidinium salt behaved similarly and gave the nitroazatetralone **12** in 72% yield. The trifluoromethylazatetralone **13** was prepared in 45% yield.



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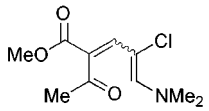
12 R_3 = NO_2
13 R_3 = CF_3



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(7) For a related reaction to form 2-aminopyridine *N*-oxides in two steps using a vinamidinium salt and malonitrile, see: Hagen, V.; Jansch, H.-J. *J. Prakt. Chem.* **1990**, *332*, 748.

(8) **General experimental procedure for the annulation of ketosulfone:** 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 for 45 min, and ~50 wt % aqueous hydroxylamine hydrochloride (50 mmol) was added. The resulting dark solution was heated at reflux for 5 h, and then the organic phase was concentrated under reduced pressure. The residue was directly purified by chromatography on silica gel. All final products were characterized by ^1H and ^{13}C NMR and LC/MS.

The mechanism involves attack on the intermediate dienone **14** in the case of MAA.[11] On the basis of analogy with the reaction of ammonia with **14**, hydroxylamine attacks at the δ carbon rather than at the carbonyl. The resulting hydroxylamine dienone adduct undergoes cyclization and elimination of water to form the pyridine *N*-oxide.

In conclusion, stabilized enolates react with 2-substituted vinamidinium salts to give the pyridine *N*-oxides with high regioselectivity in good to excellent yields. Further work is in progress to expand the scope of the annulation reaction to include other nucleophiles.

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

OL006831R

(9) Chauret, N.; Yergey, J. A.; Brideau, C.; Friesen, R. W.; Mancini, J.; Riendeau, D.; Scheigetz, J.; Silva, J.; Styhler, A.; Trimble, L. A.; Nicoll-Griffith. D. A. Submitted for publication.

(10) **General procedure for the reaction of MAA:** To a solution of MAA (25 mmol) in dry THF (50 mL) at room temperature was added dropwise a 20 wt % solution of *t*-BuOK in THF (26.3 mmol). The solution was stirred at room temperature for 15 min, and then DABCO (25 mmol) and the vinamidinium hexafluorophosphate salt (26.3 mmol) were added sequentially. The resulting mixture was stirred at 40−45 °C for 4 h. Hydroxylamine hydrochloride (60−75 mmol) was added in one portion. The resulting dark solution was heated at reflux for 5 h and concentrated under reduced pressure. The residue was directly purified by chromatography on silica gel. All final products were characterized by ^{1}H and ^{13}C NMR and LC/MS.

(11) The intermediate **14** is isolable in the reaction of MAA. C, H, N characterization and spectral data are included in the Supporting Information. For an example of the formation of a pyridine *N*-oxide from a dienone, see: Bruni, F.; Chimichi, S.; Cosimelli, B.; Costanzo, A.; Guerini, G.; Selleri, S. *Heterocycles* **1990**, *31*, 1635.