Efficient Preparation of 2-Pyridylpyridines Using β-*N*,*N*-Dialkylated Aminoacroleins or their Equivalent as Vinadinium Tetrafluoroborate

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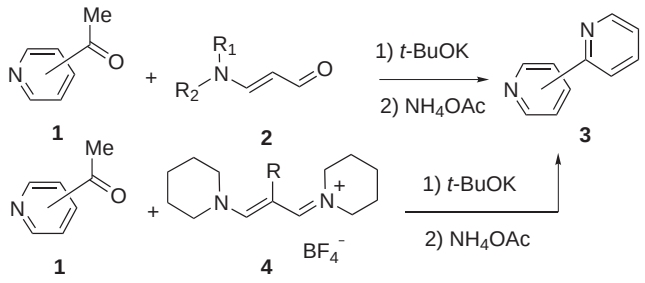
(Received February 17, 2005; CL-050214)

Efficient synthetic procedure for 2-pyridylpyridines using β-*N*,*N*-dialkylated aminoacroleins or their equivalent as dipiperidyl vinadinium tetrafluoroborate is described.

2-Pyridylpyridine derivatives have been well known as fundamental building blocks of some potent drugs[1–3] and as ligands in coordination chemistry.[4] Since the initial use of Ullmann reaction for the 2,4′-bipyridine synthesis,[5] various synthetic procedures for 2-pyridylpyridine derivatives have been developed containing Suzuki–Miyaura coupling reactions of pyridylboronic acid and halopyridines,[6] aza-Diels–Alder methodology from triazine precursors and 2,5-norbornadiene,[7] and the novel ionic annulation reaction using 2-acetylpyridine and vinamidinium hexafluorophosphate salt containing Cl group at the β-position.[8] We have studied the more effective synthetic method and developed two new processes for producing 2-pyridylpyridine derivatives, which we present herein. Our general method is revealed in Scheme 1.

At the first step, we established the new procedure starting from ω-acetylpyridine **1** and several malonaldehyde equivalents **2**, the results of which are summarized in Table 1.[9] In Run 1, Michael reaction of 4-acetylpyridine **1a** with acrolein **2a** and the subsequent annulation provided the desired 2,4′-bipyridine **3a** in 51.2% yield. Similarly, when 3-(1′-piperidino)acrolein **2b** was used, the yield of **3a** went up to 68.2% (Run 2). In the case of commercially available 2-methyl-3-(*N*,*N*-dimethylamino)acrolein **2c**, 5-methyl-2,4′-bipyridine **3b** was obtained in 64.7% yield (Run 3). Analogously, the reaction of acetophenone **5** and **2b** led to formation of 2-phenylpyridine **6** in 37.0% yield (Run 4). Naturally, every product had a high purity (>99.9% from HPLC).

Furthermore, we examined the reactivity of the ionic vinadinium salts which have been reported that electron withdrawing groups at the β-position is essential to produce the corresponding 2-pyridine derivatives in good yield.[8] We selected dipiperidyl vinadinium salts **4** as an equivalent synthetically to the *N*,*N*-disubstituted aminoacrolein **2**, expecting the higher efficiency as the initial Michael reaction acceptor. The salt **4a** was prepared newly as a pale yellow powder by treatment of (3-phenylamino-2-propenylidene)phenylammonium chloride[10] and piperidine in MeOH under reflux for 1 h, removal of the solvent by heating to 100 °C, and then conversion of the counter ion to BF_4^- for the preparation of stable salts against moisture by addition of 42% HBF_4 in MeOH–H_2O (1:13) in 65–70% total yield. The salts having a methyl group (**4b**), a phenyl group (**4c**), and a chloro atom (**4d**) at the β-position were also prepared from corresponding (3-phenylamino-2-propenylidene)phenylammonium chloride. The results of the ionic annulation reaction using **4** with acetylpyridines were shown in Table 2. Our procedure provides the general and smooth annulation reaction with the unsubstituted methinium salt **4a** (Runs 1, 2, and 3) as well as substituted salts **4b** (Run 4), **4c** (Run 5), and **4d** (Run 6) in fairly good yields, being versatile as the general construction of various 2-pyridylpyridines.[11]



Scheme 1. Our general reaction scheme.

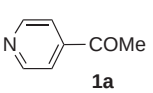
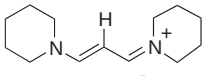
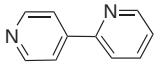
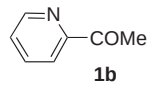
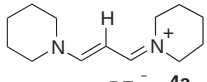
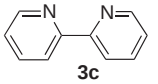
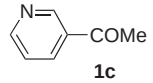
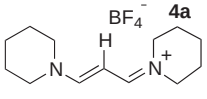
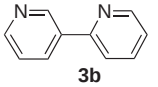
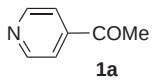
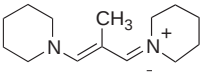
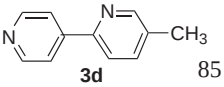
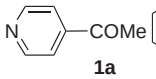
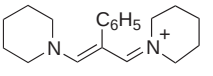
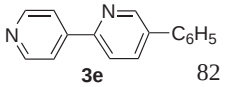
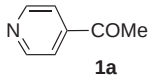
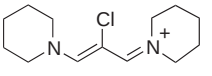
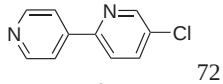
Table 1. The preparation of 2-pyridylpyridines using β-*N*,*N*-dialkylated aminoacroleins as malonaldehyde equivalents[a]

Run	Ketone	Aminoacrolein	Product[b]	Yield/%[c]
1	**1a**	**2a**	**3a**	51.2
2	**1a**	**2b**	**3a**	68.2
3	**1a**	**2c**	**3b**	64.7
4	**5**	**2b**	**6**	37.0

[a]The typical reaction procedure is as follows; *t*-BuOK (1 equiv.) was added to a THF solution of methyl ketone (1 equiv.) and aminoacrolein (1.05 equiv.), and the mixture was stirred at 40 °C for 10 min. Then, NH_4OAc (6 equiv.) and AcOH (6 equiv.) were added and the mixture was heated to 90 °C for 3 h by removing THF gradually to give the desired product. [b]The structure of the product was identified by IR, NMR, and MS spectrometry. [c]Yield based on the starting methyl ketone.

In summary, we developed the new two valuable procedures for the synthesis of 2-pyridylpyridine derivatives. Noticeably, both of them do not require any expensive special catalysts and special equipment, do not cause environmental problems, and could be operated on an industrial scale.

Table 2. The preparation of 2-pyridylpyridines using dipiperidyl vinamidinium tetrafluoroborate as a malonaldehyde equivaent[a]

Run	Ketone	Dipiperidylvinamidinium salt	Product[b]	Yield/%[c]
1	 **1a**	 BF_4^- **4a**	 **3a**	88
2	 **1b**	 BF_4^- **4a**	 **3c**	65[d]
3	 **1c**	 BF_4^- **4a**	 **3b**	80
4	 **1a**	 BF_4^- **4b**	 **3d**	85
5	 **1a**	 BF_4^- **4c**	 **3e**	82
6	 **1a**	 BF_4^- **4d**	 **3f**	72

[a]The typical reaction procedure is as follows; methyl ketone (1 equiv.) was added to a cold solution of *t*-BuOK (1 equiv.) and the mixture was stirred at 0 °C for 15 min. The mixture was added slowly to a suspension of the salt **4** (1.1 equiv.) in THF and the mixture was warmed to rt for 30 min. After addition of NH_4OAc (4 equiv.) and AcOH (4 equiv.), the mixture was stirred at 95 °C for 6 h by removing THF gradually to give the desired product. [b]The structure of the product was identified by 1R, NMR, and MS spectrometry. [c]Yield based on the starting methyl ketone. [d]Yield was only 8% when **1b** and **4a** were mixed first in the absence of *t*-BuOK due to the formation of isoluble complex.

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Published on the web (Advance View) May 21, 2005; DOI 10.1246/cl.2005.834