INTRAMOLECULAR REISSERT-HENZE REACTION OF ISOXAZOLO[2,3-*a*]PYRIDINIUM SALT; FACILE SYNTHESIS OF FUNCTIONALIZED PHENACYLPYRIDINES FROM ETHYNYLPYRIDINES

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Abstract-Oxidation of 2-(phenylethynyl)pyridine with H_2O_2-AcOH gave isoxazolo[2,3-*a*]pyridinium acetate, which was successively attacked by alcohols in the presence of Na_2CO_3 to afford 6-alkoxy-substituted 2-phenacylpyridines in moderate yields. It was also possible to introduce amino or alkylthio functionality onto the pyridine ring by similar process. The present reaction is a new example of intramolecular Reissert-Henze-type reaction.

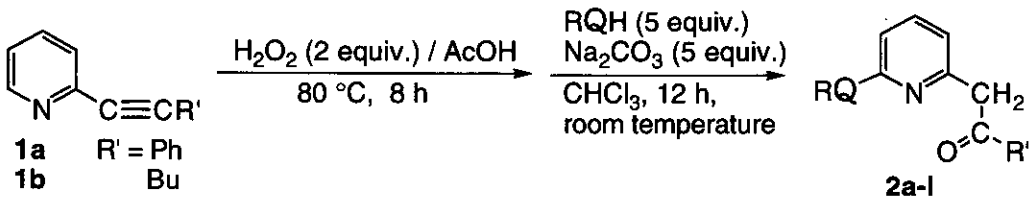
It is well known that enol forms of 2-phenacylpyridines are relatively as stable as keto forms[1] and that they readily form complexes with metals.[2] Based on these properties, 2-phenacylpyridine derivatives are widely utilized as antibacterials and ligands.[3,4] Application as synthetic intermediates for bicyclic pyridines[5,6] or alkaloids[7] are also reported.

2-Phenacylpyridines are generally synthesized by hydration of 2-(phenylethynyl)pyridines[7] or by condensation of 2-picolyllithium with methyl benzoate.[8] Although phenacylpyridines bearing a functional group are considered to have more versatile reactivities and utilities, their efficient synthetic routes are scarcely known. Therefore development of facile approaches to functionalized phenacylpyridines is strongly desirable.

We recently reported a novel synthesis of 2-ethynylpyridines[9] and their transformation into various bicyclic pyrido compounds.[5,10,11] In order to increase the synthetic utility of ethynylpyridines, oxidation was investigated to prepare ethynylpyridine *N*-oxides, which would enable further functionalization.[9] While 4-ethynylated pyridine *N*-oxide is readily obtained by oxidation of 4-ethynylpyridine,[12] there is no report on the synthesis of the 2-ethynylated analog to our best of knowledge. In this paper, we describe the interesting feature of oxidation of 2-(phenylethynyl)pyridine with H_2O_2-AcOH and the synthetic application of this reaction involving a novel intramolecular Reissert-Henze-type reaction.

Oxidation of 2-(phenylethynyl)pyridine (**1a**) with *m*-chloroperbenzoic acid, $NaWO_4$, or *t*-BuOOH gave no definite products, the starting material being recovered. However, transformation of **1a** into unidentified products was apparently observed in the oxidation with H_2O_2 in AcOH, and 6-methoxy-2-phenacylpyridine (**2a**)[13] was isolated upon treatment of the reaction mixture with MeOH in the presence of Na_2CO_3. It was found that phenacylpyridines having a sterically hindered alkoxy group were also obtained by this process. In all cases, competitive reaction with H_2O proceeded to give 6-phenacylpyridin-2(1*H*)-one in 20-30 % yields.

Table 1

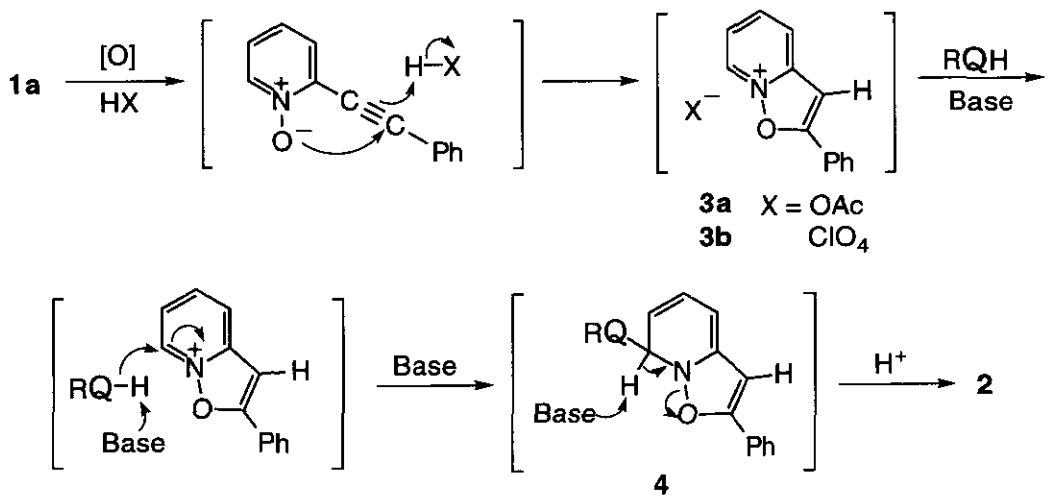


RQH	R'	Product	Yield (%)[a]	RQH	R'	Product	Yield (%)[a]
MeOH	Ph	**2a**	62	$(CH_2OH)_2$	Ph	**2g**	32
EtOH	"	**2b**	60	PrSH	"	**2h**	41
i-PrOH	"	**2c**	49	$PrNH_2$	"	**2i**	0[b]
t-BuOH	"	**2d**	50	*t*-$BuNH_2$	"	**2j**	8[b]
$AcCH_2OH$	"	**2e**	47	*i*-Pr_2NH	"	**2k**	15[b]
Allyl-OH	"	**2f**	15	MeOH	Bu	**2l**	59

a) isolated yield b) Na_2CO_3 was not added.

The present reaction was applicable to alcohols having a functional group such as CH_3CO, CH_2=CH and OH. A propylthio group was introduced when PrSH was employed in place of an alcohol. Although $PrNH_2$ yielded only a complicated mixture of products, *i*-Pr_2NH and *t*-$BuNH_2$, somewhat bulky amines, gave aminated phenacylpyridines (**2j**) and (**2k**) though in low yields. Furthermore, both substitution with methoxy group and hydration of the ethynyl group proceeded similarly with 2-(1-hexynyl)pyridine (**1b**) (Table 1).[15]

Scheme 1



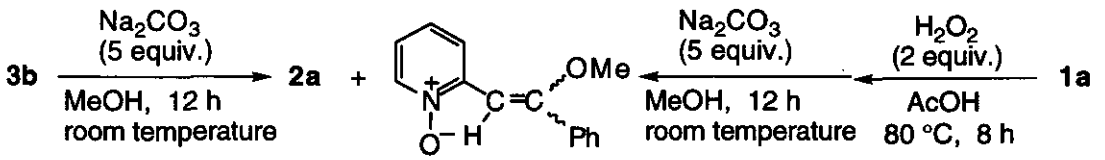
Although attempts to isolate the intermediate of the oxidation of **1a** were unsuccessful, the ^{13}C nmr spectral examination of the reaction mixture of **1a** with H_2O_2 [in $CDCl_3$ / AcOH (1 / 1)] indicated that the isoxazolopyridinium acetate (**3a**)[16] was formed; the spectrum of **3a** was closely similar to that of enol form of 2-phenacylpyridine.[17] Addition of $HClO_4$ to the reaction mixture gave 2-phenylisoxazolopyridinium perchlorate (**3b**)[18] as white precipitates in 75 % yield (Scheme 1). It was revealed that the initially formed *N*-oxide spontaneously converts to an isoxazolopyridinium salt (**3a**). Thus the *N*-oxide has never been isolated. Only a few reports on isoxazolo[2,3-*a*]pyridinium skeleton are available,[18,19] and the present reaction provides a novel synthetic method of this class of compounds.

Consecutively, nucleophilic attack of an alcohol at the 6-position of **3** leads to the adduct (**4**) which readily undergoes aromatization through the N-O bond fission to furnish 6-alkoxy-2-phenacylpyridine (**2**). The

reaction is accelerated by a good leaving group in the molecule itself and provides a new example of intramolecular Reissert-Henze-type reaction (Scheme 1).

It was confirmed that phenacylpyridine (**2a**) was obtained from the isolated salt (**3b**) by reaction with Na_2CO_3 in MeOH.[20] In this case, the major product was 2-(α-methoxystyryl)pyridine *N*-oxide (**5**) generated by attack of MeOH on the 2-position of **3**. A similar result was obtained when the reaction mixture from oxidation of **1a** was treated with Na_2CO_3 in MeOH (Scheme 2). These reactions are thought to be effected by contribution of isoxazolopyridinium salt (**3'**) as a resonance form (Scheme 3).

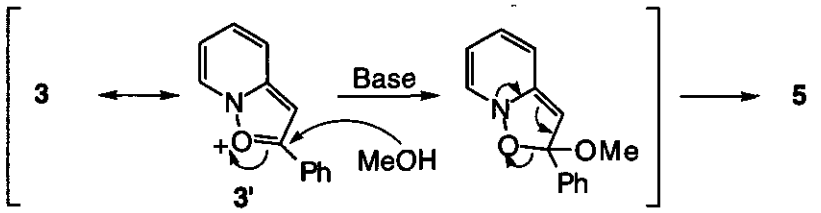
Scheme 2



5 (*E* / *Z* mixture)

	2a	**5**
from **3b**	34 %	66 %
from **1a**	39 %	61 %

Scheme 3



As mentioned so far, 2-phenacylpyridines functionalized at the 6-position were readily prepared by oxidation of 2-(phenylethynyl)pyridines. Further chemical transformations of the obtained phenacylpyridines are under investigation.

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13. After ethynylpyridine (**1a**, 180 mg, 1 mmol) was oxidized by a common method,[14] AcOH was removed in vacuo. To a solution in $CHCl_3$ (18 ml, washed with H_2O before use to exclude the stabilizer, EtOH) of the residue, MeOH (200 μl, 5 mmol), $MgSO_4$ (0.60 g, 5 mmol) and Na_2CO_3 (0.53 g, 5 mmol) were added and stirred (room temperature, 12 h). The insoluble materials were filtered off and the filtrate was concentrated. Extraction of the residue with hexane (20 ml X 3) afforded almost pure phenacylpyridine (**2a**). Purification through a short column (SiO_2) eluted with hexane / AcOEt (98 / 2) gave **2a**[14] (140 mg, 62 %) as pale yellow oil.
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15. All products were isolated and gave satisfactory spectral data. The spectral data of **2a**, for example, are as follows. Ir (neat / cm^{-1}) 3500-3200 (br), 1688, 1640; ^1H nmr (90 MHz, $CDCl_3$) δ 3.86 (s, $3H^k$), 4.03 (s, $3H^e$), 4.37 (s, $2H^k$), 6.06 (s, $1H^e$), 6.4-7.0 (m, $2H^k + 2H^e$), 7.3-7.7 (m, $3H^k + 5H^e$), 7.7-7.9 (m, $1H^k + 1H^e$), 8.0-8.2 (m, $2H^k$), 14.8-15.2 (br, $1H^e$), (H^k and H^e refer to proton(s) of keto and enol forms, respectively); ^{13}C nmr (23 MHz, $CDCl_3$ / ppm) keto form: 199.2, 163.7, 152.8, 138.8, 136.8, 132.9, 128.8, 128.3, 116.4, 108.6, 53.1, 48.0, enol form: 161.8, 160.4, 156.0, 139.5, 135.9, 129.1, 128.2, 125.2, 114.0, 106.3, 95.7, 53.4; ms (EI) *m / z* 227 (M^+, 4), 105 (100), 77 (58).

16. **3a**; ^{13}C nmr (23 MHz, $CDCl_3$ / ppm) 164.7, 145.2, 139.0, 132.7, 130.5, 129.0, 126.5, 122.5, 121.6, 120.9, 98.2, 56.7, 17.6. In the ^{1}H nmr (90 MHz, $CDCl_3$), a doublet signal (J = 7.1 Hz) was observed at δ 9.78.

17. Enol form of 2-phenacylpyridine; ^{13}C nmr (23 MHz, $CDCl_3$ / ppm) 155.3, 149.8, 144.3, 137.1, 129.6, 129.3, 128.9, 128.3, 121.6, 118.4, 94.2.

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20. MeOH was used as the solvent in place of $CHCl_3$ because of low solubility of **3b**.

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