BECKMANN REARRANGEMENT OF 4,5,6-TRISUBSTITUTED 3-ACETYLPYRIDIN-2-ONE OXIMES

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Abstract - Beckmann rearrangement of 4,5,6-trisubstituted 3-acetylpyridin-2-one oximes took place, involving equilibrium between the methyl-*syn* and -*anti* forms, to give exclusively 4,5,6-trisubstituted 3-acetylaminopyridin-2-ones in satisfactory yields.

There have been reported many methods concerning with syntheses of substituted aminopyridines,[1] including the Beckmann rearrangement of pyridyl ketoxime. Previously it was shown that 4,5,6-trisubstituted 3-acetylpyridin-2-ones are readily accessible by simple ring transformation[2] of 2-substituted 6-methyl-1,3-oxazin-4-ones, which are prepared from diketene and appropriate imidates.[3] We wish to report the Beckmann rearrangement of 4,5,6-trisubstituted 3-acetylpyridin-2-one oximes, providing a new method for preparation of 4,5,6-trisubstituted 3-amiopyridin-2-ones.

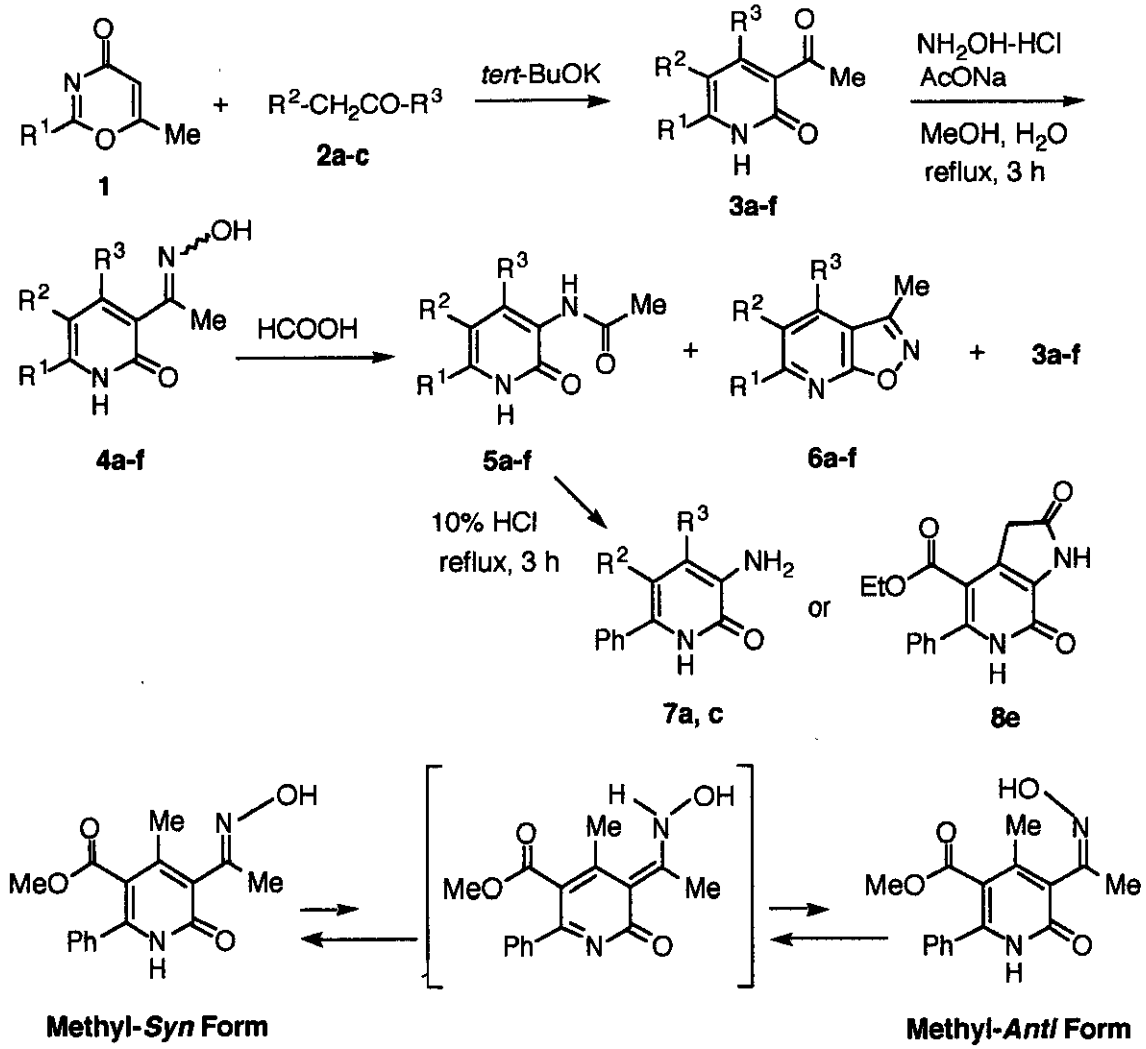
4,5,6-Trisubstituted 3-acetylpyridin-2-ones (**3a-f**) were synthesized by the ring transformation of 2-substituted 6-methyl-1,3-oxazin-4-ones (**1**) with active methylene compounds such as ethyl acetoacetate (**2a**), ethyl benzoylacetate (**2b**), and diethyl acetonedicarboxylate (**2c**) according to the procedure previously reported.[2]

Pyridones (**3a-f**) were led almost quantitatively to the corresponding oximes (**4a-f**) by a general procedure[4] using hydroxylamine hydrochloride and sodium acetate. The ^{1}H-nmr spectral examination showed that each oxime consists of both methyl-*syn* and -*anti* isomers[5] as expected.

This paper is dedicated to the late Professor Yoshio Ban.

However, we found that the Beckmann rearrangement of oxime mixtures (**4**) thus obtained afforded only the 3-acetamidopyridines (**5a-f**) arisen from the *syn* isomers (**4a-f-*syn***), *N*-methylnicotinamide derived from anti isomer being not isolated.

For example, when a solution of **4a** in formic acid was heated under reflux for 3 h, amide (**5a**) was exclusively formed in high yield accompanied with small amounts of isoxazolo[5,4-*b*]pyridine (**6a**) and **3a** (Scheme). It was further found the amide (**5a**) was produced by the rearrangement not only of the isolated methyl-*syn* isomer but also of the methyl-*anti* isomer.



Scheme

The formation[6] of amide (**5a**) suggested that the rearrangement occurred involving the precedent isomerism of the *syn* isomer to the *anti* isomer, and was supported by the following evidence; a solution of **4a-*anti*** in CH_2Cl_2-DMSO (10 : 1) was allowed to stand at room temperature for 5 days to give **4a-*syn*** in 47% yield with **4a-*anti*** being recovered in 37% yield, whereas a similar treatment of **4a-*syn*** resulted in recovery of **4a-*syn*** in 79% yield along with isomerized **4a-*anti*** in 2% yield. Such a facile isomerization of the *anti* isomer to the thermodynamically preferable *syn* isomer may be accounted for by the rapid establishment of the equilibrium between the *anti* and *syn* isomers promoted by prototropy as illustrated in Scheme. Hydrolysis of **5** with 10% hydrochloric acid furnished 3-aminopyridin-2-ones (**7**) in good yields, whereas similar hydrolysis of **5e** caused simultaneous ring closure leading to bicyclic **8e**.

In conclusion, the reactions described above would offer advantage to synthesis of this type of substituted 3-aminopyridin-2-ones. Further investigations on the rearrangement and the isomerization in details are in progress.[7]

Table

Oxazine	R^1	**2**	R^2	R^3	**3**	Yield(%)	**4**	Yield(%)	Yield(%)		
									5	**6**	**3**
1a	Ph	**2a**	COOMe	Me	**3a**	86	**4a**	84	84	2	3.2
1b	*p*-FC_6H_4	**2a**	COOMe	Me	**3b**	84	**4b**	78	68	1.4	2
1a	Ph	**2b**	COOEt	Ph	**3c**	78	**4c**	76	72	5	15
1c	*p*-BrC_6H_4	**2b**	COOEt	Ph	**3d**	76	**4d**	72	81	1.2	7
1a	Ph	**2c**	COOEt	CH_2COOEt	**3e**	88	**4e**	82	78	—	4.1
1d	*p*-ClC_6H_4	**2c**	COOEt	CH_2COOEt	**3f**	89	**4f**	82	82	—	6

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5. Determination of methyl-*syn* and -*anti* configuration was carried out on the basis of the chemical shift of methyl proton signal due to the acetohydroximoyl moiety. In general, methyl proton signals due to *syn* form of the acetohydroximoyl moiety appear at lower field than those of *anti* form. See, T. Kato and Y. Goto, *Yakugaku Zasshi*, 1965, **85**, 451; Further assignment of the configuration was achieved by comparison of ^{13}C-nmr of respective methyl derivatives of **4** which were derived in order to improve the solubility. See, E. Hawkes, K. Herwig, and D. Roberts, *J. Org. Chem.*, 1974, **39**, 1017.
6. Landsbury and Mancuso reported that Beckmann rearrangement of oximes of various 1-indanone and α-tetralone derivatives occurred to afford preferentially the aryl migrated product together with small amount of the alkyl migrated product. See, *Tetrahedron Lett.*, **1965**, 2445.
7. All new compounds show spectroscopic (ir, ^{1}H-nmr, ms) and combustion analysis data fully consistent with their proposed structures.

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