

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

Yutaka Yamamoto * and Yoshitaka Ogawa

Tohoku College of Pharmacy, 4-1, Komatsushima 4 chome, Aoba-ku,
Sendai 981, Japan

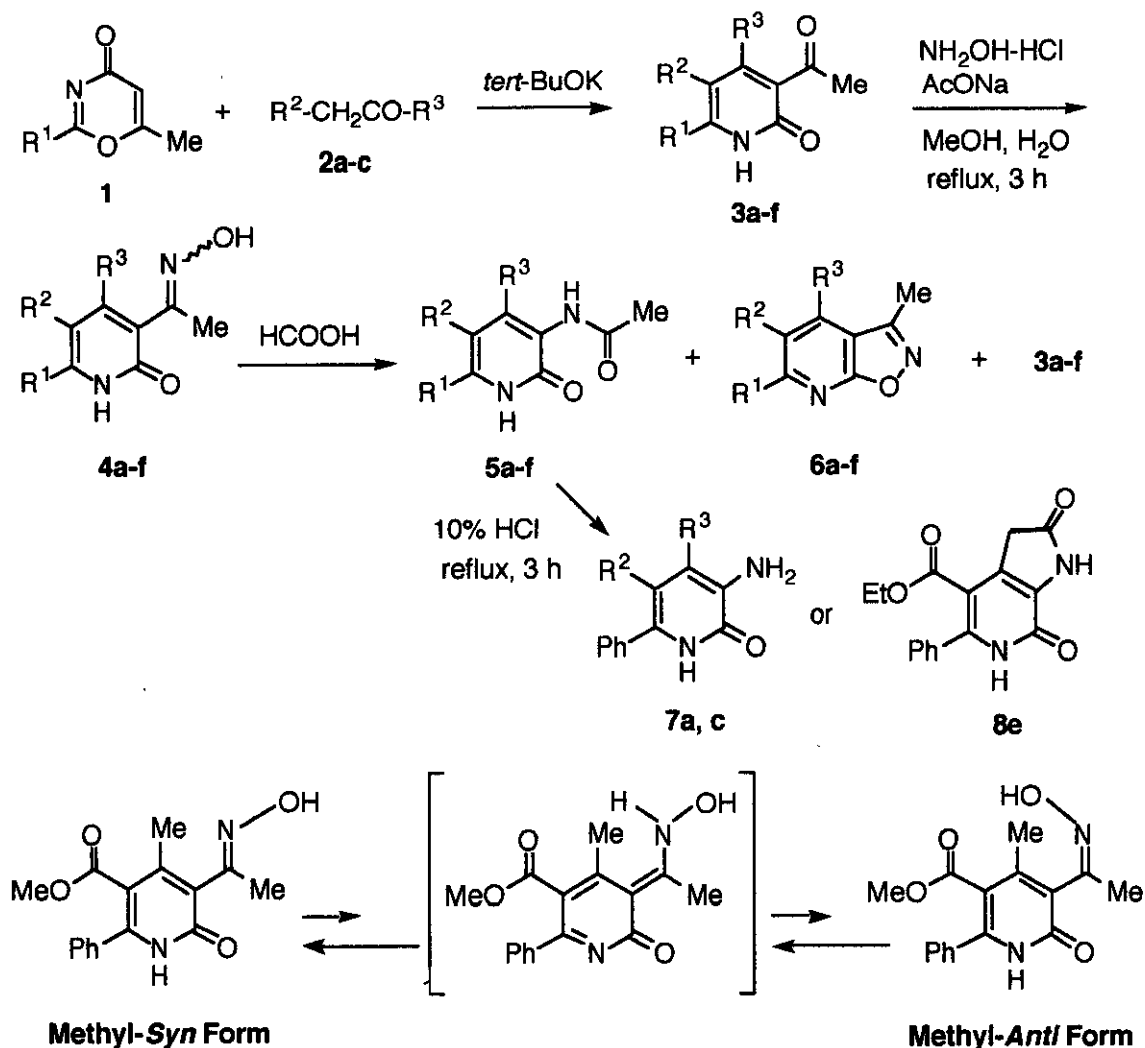
Abstract - Beckmann rearrangement of 4,5,6-trisubstituted 3-acetylpyridin-2-one oximes took place, involving equilibrium between the methyl-*syn* and -*anti* forms, to give exclusively 4,5,6-trisubstituted 3-acetylaminopyridin-2-ones in satisfactory yields.

There have been reported many methods concerning with syntheses of substituted amino-pyridines,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 transformation² 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 procedure⁴ using hydroxylamine hydrochloride and sodium acetate. The ¹H-nmr spectral examination showed that each oxime consists of both methyl-*syn* and -*anti* isomers⁵ as expected.

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 formation⁶ 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 CH₂Cl₂-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	<i>p</i> -FC ₆ H 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	<i>p</i> -BrC ₆ H ₄	2b	COOEt	Ph	3d	76	4d	72	81	1.2	7
1a	Ph	2c	COOEt	CH ₂ COOEt	3e	88	4e	82	78	—	4.1
1d	<i>p</i> -ClC ₆ H ₄	2c	COOEt	CH ₂ COOEt	3f	89	4f	82	82	—	6

REFERENCES AND NOTES

1. a) H. Vorbrüggen, *Adv. Heterocycl. Chem.*, Ed. by A. R. Katritzky, 1990, **49**, 118; b) C. K. McGill and A. Rapa, *Adv. Heterocycl. Chem.*, Ed. by A. R. Katritzky 1988, **44**, 1; c) T. Takemoto, M. Eda, T. Okada, H. Sakashita, S. Matzno, M. Gohda, H. Ebisu, N. Nakamura, C. Fukaya, M. Hihara, M. Eiraku, K. Yamanouchi, and K. Yokoyama, *J. Med. Chem.*, 1994, **37**, 18; d) B. Bohn, N. Heinrich, and H. Vorbrüggen, *Heterocycles*, 1994, **37**, 1731; e) L. Estel, F. Linard, F. Marsis, A. Godard, and G. Quéguiner, *J. Heterocycl. Chem.*, 1989, **26**, 105.

2. a) T. Kato, Y. Yamamoto, and M. Kondo, *Chem. Pharm. Bull.*, 1975, **23**, 1873; b) Y. Yamamoto and Y. Morita, *Chem. Pharm. Bull.*, 1985, **33**, 975; c) Y. Yamamoto, Y. Morita, and O. Ohmukai, *Heterocycles*, 1992, **33**, 515.
3. Y. Yamamoto, Y. Azuma, and K. Miyakawa, *Chem. Pharm. Bull.*, 1978, **26**, 1825.
4. "The Systematic Identification of Organic Compounds," 6 th. ed., ed. by R. L. Shriner, R. C. Fuson, D. Y. Curtin, and T. C. Morrill, John Wiley & Sons, Inc., New York, 1980, pp. 181-182; T. Kato, H. Yamanaka, and H. Hiranuma, *Yakugaku Zasshi*, 1970, **90**, 877.
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, ^1H -nmr, ms) and combustion analysis data fully consistent with their proposed structures.

Received, 18th November, 1994