SYNTHESIS OF ISOXAZOLO[5,4-b]PYRIDINES AND ISOXAZOLO[5,4-d]PYRIMIDINES FROM 5-AMINOISOXAZOLES

Hiroshi Yamanaka* and Takao Sakamoto

Pharmaceutical Institute, Tohoku University

Aobayama, Sendai 980, Japan

Akira Shiozawa

Research Laboratories of Pharmaceutical Division,

Nippon Kayaku Co., 3-31, Shimo, Kitaku, Tokyo 115, Japan

3-Phenyl-4-formyl-5-aminoisoxazole (III) was synthesized by the Vilsmeier reaction of 3-phenyl-5-aminoisoxazole (I) via a stable intermediate, 3-phenyl-4-formyl-5-dimethylaminomethyleneaminoisoxazole (III). Condensation of III with β-keto acids and amidine derivatives afforded isoxazolo[5,4-b]pyridines and isoxazolo[5,4-d]pyrimidines, respectively.

The compounds containing the ring system of isoxazolo[5,4-b]pyridine were frequently prepared by the reaction of 5-aminoisoxazoles with β-dicarbonyl compounds. For instance Abignente et al.[1] reported that 3-methyl-5-aminoisoxazole reacted with 1,1,3,3-tetraethoxypropane to give 3-methylisoxazolo[5,4-b]-

pyridine, and Markillie et al.[2] reported the synthesis of 3,4,6-trimethylisoxazolo[5,4-b]pyridine.

However, few work on the synthesis of isoxazolo[5,4-b]-pyridine derivatives by means of the Friedländer reaction was described in literatures. In this paper, we wish to report the preparation of 3-phenyl-4-formyl-5-aminoisoxazole (III) and the formation of condensed isoxazole ring systems.

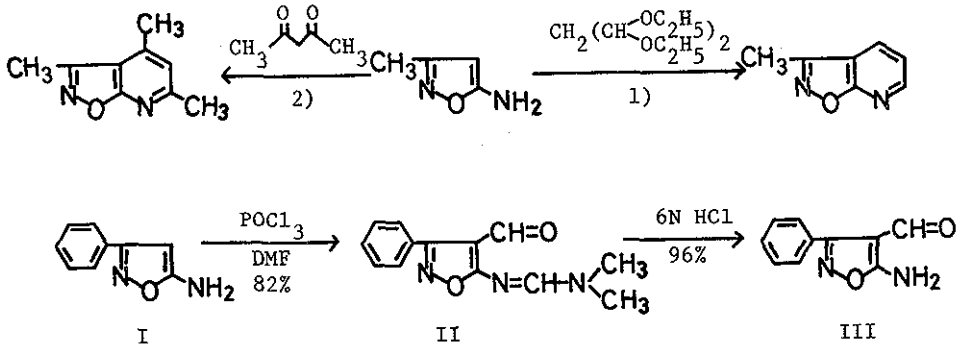


Chart 1

When I was heated with the Vilsmeier reagent ($POCl_3$ + DMF)[3] at 70° for 20 hr, pale yellow needles, $C_{13}H_{13}O_2N_3$ (II), mp 120-121°, were obtained in 82% yield. The IR spectrum ($CHCl_3$) of II showed absorption bands at 1675, 1635, 1590 and 1570 cm^{-1}. The NMR spectrum ($CDCl_3$) of II exhibited signals at δ 3.11 (6H, s), δ 7.25-7.57 (3H, m), δ 7.65-7.93 (2H, m), δ 8.57 (1H, s) and δ 9.82 (1H, s). No signal due to the isoxazole ring proton was observed. These spectral data suggested II to contain a formyl group along with a dimethylaminomethyleneamino group on the isoxazole ring. Hydrolysis of II with 6N HCl at room temperature quantitatively afforded 3-phenyl-4-formyl-5-aminoisoxazole,

$C_{10}H_8O_2N_2$ (III), mp 125-126°, whose spectral data [IR$\nu_{max}^{CHCl_3}$ cm^{-1}, 3350, 3360, 1668, 1609 and 1593; NMR δ($CDCl_3$), 6.60-7.32 (2H, broad), 7.32-8.00 (5H, m), and 9.66 (1H, s)] are in accordance with the structure III.

At first the reaction of III with β-dicarbonyl compounds was investigated. According to the usual manner of the Friedländer reaction[4] III was treated in boiling acetic acid for an appropriate period with such compounds as ethyl acetoacetate, acetylacetone, ethyl cyanoacetate and malononitrile to give isoxazolo[5,4-b]pyridine derivatives (IVa-d). The melting points, yields and spectral data of IVa-d were as follows:

3-phenyl-5-ethoxycarbonyl-6-methylisoxazolo[5,4-b]pyridine (IVa); mp 123-124°; 42%; IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1617; NMR δ($CDCl_3$): 1.43 (3H, t, J=7.1Hz), 2.97 (3H, s), 4.44 (2H, q, J=7.1Hz), 7.38-7.76 (3H, m), 7.76-8.14 (2H, m), 8.81 (1H, s).

3-phenyl-5-acetyl-6-methylisoxazolo[5,4-b]pyridine (IVb); mp 140-141°; 44%; IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1618; NMR δ($CDCl_3$): 2.68 (3H, s), 2.87 (3H, s), 7.38-7.70 (3H, m), 7.70-8.03 (2H, m), 8.52 (1H, s).

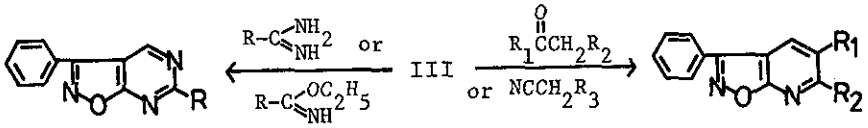
3-phenyl-5-ethoxycarbonyl-6-aminoisoxazolo[5,4-b]pyridine (IVc); mp 158-159°, 27%; IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 3522, 3365, 1700, 1630; NMR δ (CF_3CO_2H): 1.50 (3H, t, J=7.2Hz), 4.60 (2H, q, J=7.2Hz), 7.50-8.10 (5H, m), 9.24 (1H, s).

3-phenyl-5-cyano-6-aminoisoxazolo[5,4-b]pyridine (IVd); mp 218-219°; 17.3%; IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 3350, 2220, 1664, 1632; NMR δ(CF_3CO_2H): 7.33-8.00 (5H, m), 8.63 (1H, s).

The scope and limitations of this reaction were further

examined by using amidine derivatives instead of β-dicarbonyl compounds, under basic conditions. When III was warmed in ethanol with an equimolar amount of formamidine acetate in the presence of sodium ethoxide, 3-phenylisoxazolo[5,4-d]pyrimidine (Va) was obtained in 62% yield. [NMR δ($CDCl_3$): 7.36-7.73 (3H, m), 7.73-8.13 (2H, m), 9.16 (1H, s), 9.40 (1H, s)]. On treatment with free base of ethyl acetimidate, III was convered to 3-phenyl-6-methyl-isoxazolo[5,4-b]pyrimidine, $C_{12}H_9ON_3$ (Vb), mp 147-148° in 82% yield. The NMR spectrum of Vb [δ(CF_3COOH): 3.32 (3H, s), 7.55-7.86 (3H, m), 7.86-8.15 (2H, m), 9.80 (1H, s)] was in full agreement of the structure. Similarly 3,6-diphenyl- (Vc), mp 162-163° (62%) and 3-phenyl-6-amino-isoxazolo[5,4-d]pyrimidine (Vd), mp 251-252° (67%), were obtained from the reaction of III with ethyl benzimidate and guanidine hydrochloride, respectively.

It is well known that the treatment of quinazoline with organic peracid gives rise to 4-quinazolone instead of desired



Va-d

R=H (Va)

$R=CH_3$ (Vb)

$R=C_6H_5$ (Vc)

$R=NH_2$ (Vd)

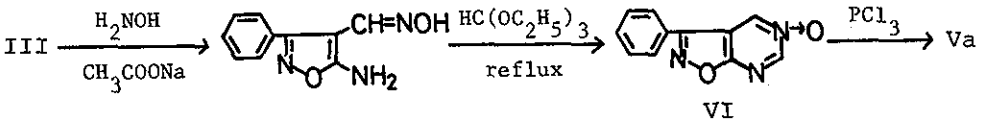
IVa-d

$R_1=COOC_2H_5$, $R_2=CH_3$ (IVa)

$R_1=COCH_3$, $R_2=CH_3$ (IVb)

$R_1=COOC_2H_5$, $R_2=NH_2$ (IVc)

$R_1=CN$, $R_2=NH_2$ (IVd)



VI

Chart 2

quinazoline N-oxide,[5] and that quinazoline 3-oxide was obtained from the condensation of *o*-aminobenzaldoxime with ethyl orthoformate.[5] Thus 3-phenyl-5-aminoisoxazole-4-aldoxime, mp 188-189°, which was prepared according to the usual method, was heated with excess ethyl orthoformate to afford yellow leaflets (VI) $C_{11}H_7O_2N_3$, mp 223-224° in 45% yield [IR(KBr), 1246 cm^{-1}]. The product obtained from the reduction of VI with phosphorous trichloride in chloroform, was identical with Va in every respect, which proved VI to be 3-phenylisoxazolo[5,4-b]pyrimidine 5-oxide.

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