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A ONE-STEP SYNTHESIS OF AZETO[3,2-d]ISOXAZOLINE

Takushi Kurihara* and Masanobu Mori

Osaka College of Pharmacy, 2-10-65, Kawai, Matsubara, Osaka, 580, Japan

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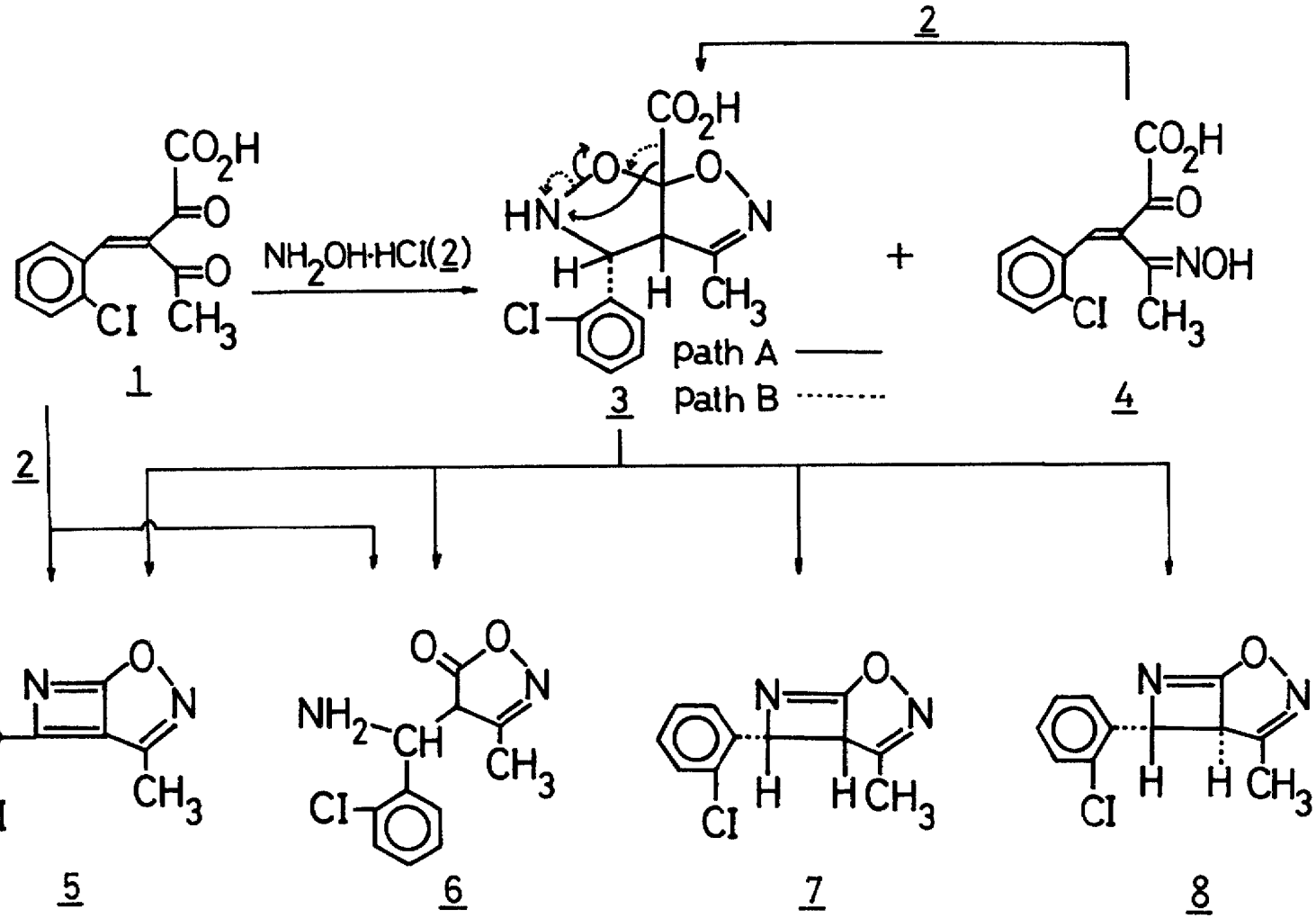
It has been known that the acylpyruvic acid esters react with hydroxylamine to give the isoxazoles[1] or β-aminocrotonic acid esters to give pyridin-3,5-dicarboxylic acid esters[2]. On the continuation of our works upon the reactivity of α,β-unsaturated β-diketones[3], we have recently reported the synthesis of 3-benzylideneacylpyruvic acids such as 1[4]. In the present communication, we wish to report a novel one-step synthesis and the formation mechanism of the azeto[3,2-d]isoxazoline(5), which have hitherto been unknown, by the reaction of 1 with hydroxylamine hydrochloride(2).

Refluxing an acetic acid solution of 1 with two equivalents amount of 2, followed by chromatographic separation, afforded 3-methyl-4-(*o*-chlorophenyl)-azeto[3,2-d]isoxazoline(5) in 43% yield and 3-methyl-4-(α-amino-*o*-chlorophenyl)-5-isoxazolone(6) in 5% yield. The structural assignments to them were accomplished by the following data :

Compound 5 : colorless needles; mp 70-71°(from ligroin); IR ν_{max}^{KBr} 2250 (vs)[5], 1620(s) and 1600(s) cm^{-1}; UV λ_{max}^{EtOH} 262 nm(log ε 4.01); NMR($CDCl_3$) δ 2.52(3H, s, C_3-CH_3) and 7.40-7.70(4H, m, aromatic protons); mass spectrum m/e 218(M^+). *Anal.* Calcd. for $C_{11}H_7N_2OCl$: C, 60.42; H, 3.22; N, 12.81. Found : C, 60.58; H, 3.00; N, 12.79.

Compound 6 : colorless prisms; mp 259-260°(from methanol)[6]; IR ν_{max}^{KBr} 3400, 1690 and 1625 cm^{-1}; NMR(DMSO-d_6) δ 1.92(3H, s, C_3-CH_3), 3.95(1H, d, J=8 Hz, C_4-H), 5.95(1H, d, J=8 Hz, PhCH).


2
CO2H
O
O
Cl
CH3
1
NH2OH·HCl(2)
CO2H
HN
CO
O
N
H
H
CH3
Cl
3
path A
path B
+
CO2H
O
NOH
Cl
CH3
4
2
N
O
N
Cl
CH3
5
O
O
N
NH2
CH
CH3
Cl
6
N
O
N
H
H
CH3
Cl
7
N
O
N
H
H
CH3
Cl
8

To clarify the formation mechanism of 5, the following reactions were carried out. When a solution of 1 with 2(two equivalents) in acetic acid was heated at 50° for 24 hr, 3-methyl-4-(*o*-chlorophenyl)isoxazolidino[4,5-d]isoxazolin-6a-carboxylic acid(3) was obtained in 57% yield as colorless needles[mp 168-169°(from methanol); IR ν_{max}^{KBr} 1700 cm^{-1}; NMR(DMSO-d_6) δ 1.85(3H, s, C_3-CH_3), 4.77(1H, d, J=10 Hz, C_{3a}-H), 5.95(1H, d, J=10 Hz, C_4-H), and 12.80(1H, bs, NH)], together with 3-(*o*-chlorophenyl)-4-hydroxyiminoacetylpyruvic acid(4) in 7% yield[mp 147-149°(from methanol); IR ν_{max}^{KBr} 3380, 1758, and 1680 cm^{-1}; NMR (DMSO-d_6) δ 2.20(3H, s, CH_3), 6.48(1H, s, vinyl proton), and 11.45(1H, s, OH)]. Treatment of 4 with 2 in acetic acid at 50° gave 3 in 72% yield. Quilico[7] reported the syntheses of 3,4-disubstituted isoxazolo[4,5-d]isoxazoles, but no their tetrahydro derivatives such as 3 were found in literature.

On the other hand, reaction of 1 with 2(two equivalents) in acetic acid at 80° for 24 hr, followed by chromatographic separation and fractional recrystallization, yielded the following four compounds[8] :

Compound 5 (3.5%).

Compound 6 (5%).

3-Methyl-4-(*o*-chlorophenyl)-*cis*-azetino[3,2-d]isoxazoline(7)[9] (10%)[colorless needles; mp 56-57°(from petr. ether); IR ν_{max}^{KBr} 2270(m) cm^{-1}; NMR($CDCl_3$) δ 2.15(3H, s, C_3-CH_3), 3.95(1H, d, J=6 Hz, C_{3a}-H), 6.10(1H, d, J=6 Hz, C_4-H); mass spectrum m/e 220(M^+, 20), 80(100).

3-Methyl-4-(*o*-chlorophenyl)-*trans*-azetino[3,2-d]isoxazoline(8)(16%)[colorless needles; mp 112-114°(from ligroin); IR ν_{max}^{KBr} 2290(m) cm^{-1}; NMR($CDCl_3$) δ 2.20(3H, s, C_3-CH_3), 4.60(1H, d, J=12 Hz, C_{3a}-H), 6.05(1H, d, J=12 Hz, C_4-H); mass spectrum m/e 220(M^+, 16), 80(100).

The reason of the low field shift(0.05 ppm) of C_{3a}-proton of 8 compared to that of 7 will be reasonably explained by the consideration of the anisotropy effect of phenyl ring located at *cis* position.

Similarly, heating of 3 in acetic acid at 80° gave azeto[3,2-d]isoxazoline (5), isoxazolone(6), and azetino[3,2-d]isoxazolines(7 and 8), which were identified with authentic samples in terms of their IR spectra, respectively. Moreover 7 and 8 were derived to 5 by refluxing in acetic acid easily. However attempted

cyclization of 6 under these condition, as well as addition of hydrochloric acid, left 6 unchanged.

Consequently, these results clearly demonstrate that the reaction course of 5 is 1 → 4 → 3 → 7 or 8 → 5 *via* path A and the course of 6 is 1 → 4 → 3 → 6 *via* path B.

Finally it is interesting to note that thermolysis of 3 gave the same results giving the compounds 5, 6, 7, and 8.

References and Notes

1. For a review, see Roderick A. Barnes, "Heterocyclic Compounds", R.C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N.Y. 1975, Vol. 5, p 452; Y. Minami and Y. Suzuki, J. Pharm. Soc. Japan, 95, 815(1975).
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3. T. Kurihara, E. Araya, and T. Sakaguchi, Heterocycles, 3, 543(1975); T. Kurihara, T. Sakaguchi, and H. Hirano, ibid., 3, 633(1975).
4. T. Kurihara and M. Mori, Chem. Pharm. Bull.(Tokyo), submitted.
5. The following abreviations for IR are used : vs = very strong, s = strong, and m = medium.
6. All new compounds gave satisfactory elemental data.
7. A. Quilico, G. Gaudiani, and L. Merlini, Gazz. Chim. ital., 89, 571(1959).
8. No attempts have been undertaken to optimize these yields.
9. The designation of *cis* and *trans* refers to the relationship of hydrogens at C_{3a} and C_4 positions.