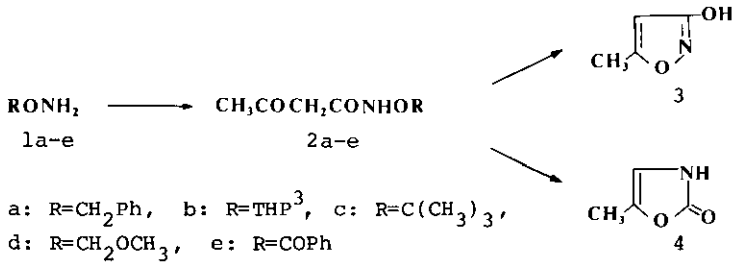
SYNTHESIS OF 3-HYDROXY-5-METHYLISOXAZOLE AND 5-SUBSTITUTED 4-OXAZOLIN-2-ONE

Hiroshi Fukumi*, Kazuhiko Oohata, and Kazuo Takada
Central Research Laboratories*, Odawara Factory, Sankyo Co., Ltd.
1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140, Japan

Abstract -- An improved synthesis of 3-hydroxy-5-methylisoxazole and some rearrangements of O-benzoyl β-keto-propionohydroxamates with the formation of 5-substituted 4-oxazolin-2-one are described.

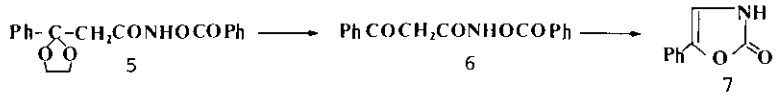
Currently as a plant protecting agent, 3-hydroxy-5-methylisoxazole (3) is widely used in the agricultural field under the commercial name of Tachigaren.[1] Although Kato et al[2] reported the synthesis of 3 by catalytic reduction with palladium charcol by acid treatment of O-benzyl acetoacetohydroxamate (2a), our continuing interest for this compound (3) prompted us here to describe an improved synthesis of 3 and some rearrangement reactions of O-benzoyl β-keto-propionohydroxamates (2e and 6). Our idea for the constructing of molecule (3) is based on the utility of labile leaving groups (OR in 2) under the acidic conditions and the spontaneous ring closure of the generated acetoacetohydroxamic acid to give isoxazole (3) in the same conditions.
The requisite acetoacetohydroxamates (2b-e) were prepared from O-substituted hydroxylamines (1b-e) and diketene in good yields.



The O-substituted acetoacetohydroxamates (2b-d) were treated with acid such as

hydrochloric acid or trifluoroacetic acid to give the expected isoxazole delivate (3). However, 2e (R=COPh) when treated with 2 mole equivalent of sodium ethoxide afforded the crystalline product (4) in 51 % yield, which has the same molecular formula as 3. 4: i.r. (Nujol) 3180, 1735, 1675 cm^{-1}; δ ($CDCl_3$) 2.10 (3H,d, J=1.5), 6.30 (1H,q, J=1.5), 9.7 (1H, br.); m/e 99 (M^+).

It is well known that O-acylhydroxylamines undergo Lossen-rearrangement[4] to give isocyanates on heating or treatment with a base. In our case the same type of rearrangement was thought to occure, and so the structure of the product was assumed to be 5-methyl-4-oxazolin-2-one. The spectral data of the compound 4 was identical in every respect with authentic sample[5]. Futher investigation was made on the synthesis of the 4-oxazolin-2-one derivatives possessing a phenyl group at the 5 position. 5-Phenyl-4-oxazolin-2-one (7) was obtained in 87 % yield by similar treatment of O-benzoyl benzoylacetohydroxamate (6), which was prepared by mild acid treatment of O-benzoyl 3,3-ethylenedioxo-3-phenylpropionohydroxamate (5).

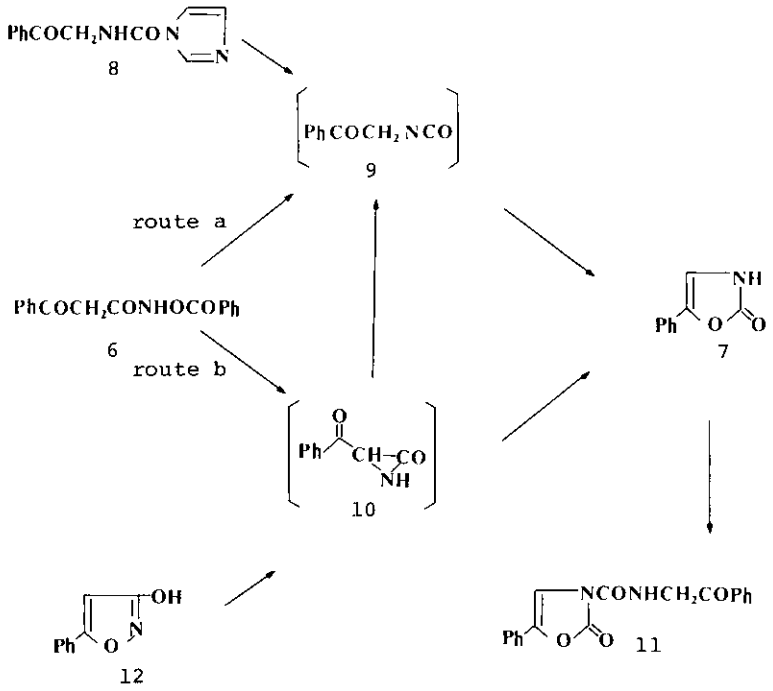


Since there are very little information which is available on the synthesis of 5-substituted 4-oxazolin-2-one, it is noteworthy that 4 and 7 were formed in the reaction of O-benzoyl β-keto-propionohydroxamates.

The reaction mechanism was assumed to be route a (Lossen-rearrangement) or route b (photochemical rearrangement from 12 to 7). Recently, Krieg et al[6] reported that N- phenacyl-1-imidazolecarboxamide (8) cyclized, on heating, to 5-phenyl-4-oxazolin-2-one (7) via isocyanate ketone (9), but they could not obtain N-phenacylcarbamoyl derivative (11). In our case, when less than two mole equivalent of sodium ethoxide or triethylamine was used, the adduct (11) (mp 185-187° (decomp.)) was formed along with 7 from 6. 11: i.r. (Nujol) 3270, 3130,1768, 1724, 1682 cm^{-1}; δ (D_6-DMSO) 4.85 (2H,d, J=5), 7.3-7.8 (8H, m), 7.8-8.1 (3H, m), 8.5 (1H, br., t, J=5); m/e 322 (M^+).

Futhermore compounds 4 and 7 were formed even in aqueous or ethanol solution. Isocyanate intermediate (9) is thought to be plausible, however in our case the reaction conditions are not thermolytic but basic ones, so the another

intermediate involving α-lactam (10) may be existing. Futher experimental study for this reaction mechanism is under investigation.



REFERENCES AND NOTE

1) K. Tomita, Y. Takahi, R. Ishizuka, S. Kamimura, M. Nakagawa, M. Ando, T. Nakanishi, T. Nakamura, and H. Okudaira, Ann. Sankyo Res. Lab., 1973, 25, 1.

2) T. Kato, N. Katagiri, N. Minami, Chem. Pharm. Bull., 1972, 20, 1368.

3) 2-tetrahydropyranyl

4) H. L. Yale, Chem. Revs., 1943, 33, 209; de Mayo, 'Molecular Rearrangements', Part 1, John Wiley & Sons Inc., New York, 1963, p528.

5) M. Nakagawa, T. Nakamura, and K. Tomita, Agr. Biol. Chem., 1974, 38, 2205.

6) B. Krieg and P. Konieczyn, Ann. Chem., 1976, 1862.

Received, 20th July, 1979