Chart 3

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Faculty of Pharmaceutical Sciences,
Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya

SANSEI NISHIBE
SUEO HISADA
ISAO INAGAKI

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Novel Ring Expansions of Pyrrolo-pyrimidines to Pyrimido-pyrimidines

We report two novel conversions of pyrrolo-pyrimidines into pyrimido-pyrimidines involving reduction-induced and nucleophile-induced ring expansions.

Method A

Stirring 1,3-dimethyl-5-nitroso-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H, 3H)-diones (Ia, Ib and Ic) under mild reflux with excess potassium pyrosulfite ($\text{K}_2\text{S}_2\text{O}_5$) in dimethylformamide (DMF) for 1 hr followed by cooling caused 1,3-dimethyl-5-hydroxy-7-phenylpyrimido[4,5-*d*]pyrimidine-2,4(1H, 3H)-diones (IIa, IIb and IIc)¹⁾ (mp > 320° for all) to separate (52%, 60% and 48%). To our knowledge, the reaction seems to be the first example in which $\text{K}_2\text{S}_2\text{O}_5$ was successfully introduced into preparative organic chemistry. Treatment of Ia with sodium

1) F. Yoneda and M. Higuchi, *Chem. Commun.*, 1972, 402.

dithionite in DMF under the same conditions yielded IIa (34%), whereas this reaction in water gave the usual reduction-product, 5-aminopyrrolo[2,3-*d*]pyrimidinedione.¹⁾ When Ia was refluxed alone in DMF, only a trace of IIa was obtained and almost starting material was recovered.

Treatment of Ia with triphenyl phosphine in DMF under the same conditions also gave IIa (50%). The mother liquid was evaporated into dryness under reduced pressure and the residue was dissolved in chloroform and chromatographed (active alumina, 300 mesh, benzene-ethanol (3:1) eluate) to give triphenylphosphine oxide (76%). From these facts, the ring expansion described above suggests the intermediacy of the nitrene intermediate, which was captured by intramolecular insertion.

Method B

Refluxing Ia in DMF while introducing dry ammonia for 4 hr yielded 5-amino-1,3-dimethyl-7-phenylpyrimido[4,5-*d*]pyrimidine-2,4(1H, 3H)-dione (III)²⁾ (mp 260°) (70%), which was deaminated into IIa by treatment with sodium nitrite in hydrochloric acid. Similarly, 229° refluxing Ia with benzylamine and aniline in DMF afforded 5-benzylamino- (IV) (mp 75%) and 5-anilino-1,3-dimethyl-7-phenylpyrimido[4,5-*d*]pyrimidine-2,4(1H, 3H)-dione (V) (mp >320°) (65%).

Chart 1

The following mechanism through the *o*-amidonitrile intermediate rationalizes this ring expansion. A formal Beckmann type rearrangement would also account directly for the formation of the 5-benzyl-(IV) and 5-anilino-derivative (V) without the need to postulate

Chart 2

2) Satisfactory analytical and spectral data were obtained for all products.

subsequent Dimroth rearrangement of an imino intermediate. However the formation of benzoylaminoethylenitrile (VI) (*vide infra*) from Ia by the action of alkali would eliminate the similar Beckmann process. Namely, refluxing Ia with 40% potassium hydroxide solution in a mixture of ethanol and water (1:1) for 1 hr yielded VI (mp 191°) (a mixture of *cis*- and *trans*-isomer (about 1:1) by nuclear magnetic resonance spectroscopy) (62%), which was readily converted into the pyrimidine derivative (mp > 300°) (VII) by treatment with dry hydrogen chloride in ethanol in quantitative yield.

Faculty of Pharmaceutical Sciences,
Kumamoto University
Oe-honmachi, Kumamoto

FUMIO YONEDA
MASATSUGU HIGUCHI

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