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-α]pyrimidine-2,4(1H, 3H)-diones (Ia, Ib and Ic) under mild reflux with excess potassium pyrosulfite (K₂S₂O₅) 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) in mp > 320°C for all to separate (52%, 60%, and 48%). To our knowledge, the reaction seems to be the first example in which K₂S₂O₅ was successfully introduced into preparative organic chemistry. Treatment of Ia with sodium

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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. 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**

Re refluxing Ia in DMF while introducing dry ammonia for 4 hr yielded 5-amino-1,3-dimethyl-7-phenylpyrido[4,5-d]pyrimidine-2,4(1H, 3H)-dione (IIb) (mp 260°) (70%), which was deaminated into IIa by treatment with sodium nitrite in hydrochloric acid. Similarly, 299° refluxing Ia with benzylamine and aniline in DMF afforded 5-benzylamino- (IV) (mp (75%) and 5-anilino-1,3-dimethyl-7-phenylpyrido[4,5-d]pyrimidine-2,4(1H, 3H)-dione (V) (mp >320°) (55%).

![Chart 1](image)

The following mechanism through the o-aminonitrile 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](image)

2) Satisfactory analytical and spectral data were obtained for all products.
subsequent Dimroth rearrangement of an imino intermediate. However the formation of benzoylamineiminonitrile (VI) \textit{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\textdegree) (a mixture of \textit{cis}- and \textit{trans}-isomer (about 1:1) by nuclear magnetic resonance spectroscopy) (62\%), which was readily converted into the pyrimidine derivative (mp\textgreater 300\textdegree) (VII) by treatment with dry hydrogen chloride in ethanol in quantitative yield.

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