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A CONVENIENT SYNTHESIS OF 2-FUNCTIONALIZED PYRROLO[2,3-*d*]PYRIDO[1,2-*a*]PYRIMIDINES[#]

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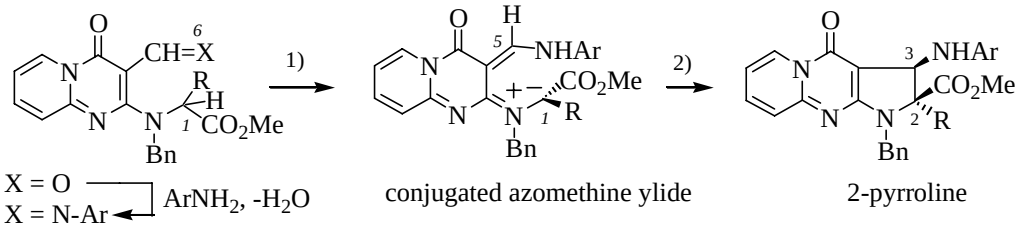
[#] *Dedicated to Professor Steven M. Weinreb in celebration of his 65th birthday and his many outstanding contributions to synthetic organic chemistry.*

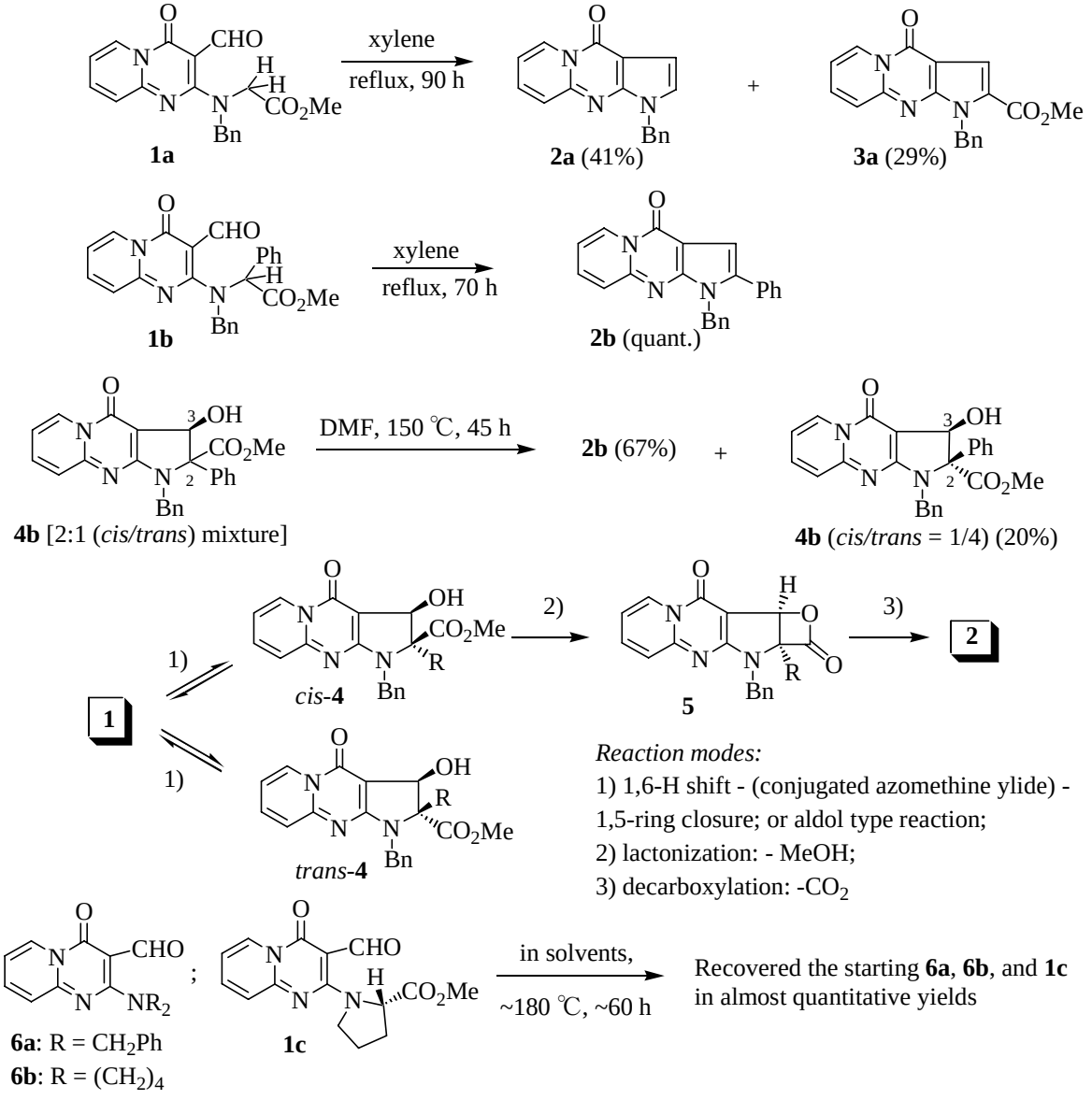
Abstract – The thermal reaction of *N*-benzyl-*N*-{3-formyl-4-oxo-4*H*- pyrido[1,2-*a*]-pyrimidin-2-yl}amino esters (**1**) provides 2-substituted pyrrolo[2.3-*d*]pyrido[1,2-*a*]-pyrimidin-4(1*H*)-ones (**2**) effectively. Therein, the lactonization and consecutive decarboxylation of the initially formed methyl 2-substituted 1,2,3,4-dihydro-3-hydroxy-4-oxopyrrolo[2.3-*d*]pyrido[1,2-*a*]pyrimidine-2-carboxylates (**4**) is proposed for the formation of **2**.

Although tricyclic pyrrolo[2,3-*d*]pyrido[1,2-*a*]pyrimidine system has been unknown yet, only its analogs, 2,3-dihydropyrrolo[2,3-*d*]pyrido[1,2-*a*]pyrimidin-4(1*H*)-one, was prepared by a novel cyclization reaction. In a previous paper,[1] we reported a stereoselective pyrroline-ring formation through the electrocyclization of conjugated azomethine ylides at the periphery of pyrido[1,2-*a*]pyrimidin-4(1*H*)-one system; the thermal reaction of *N*-benzyl-*N*-{3-(*N*-substituted imino)methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl}amino ester, obtained from the reaction of aldehyde esters with primary amine, provided 2,3-dihydropyrrolo[2,3-*d*]pyrido[1,2-*a*]pyrimidin-4(1*H*)-ones effectively and stereoselectively. Therein, the [1,6] shift of the proton on the carbon adjacent to the amino nitrogen generated a conjugated azomethine ylide and its successive 1,5-electrocyclic ring-closure was proposed (Scheme 1).



Scheme 1. *Reaction modes*: 1) 1,6-H shift (8π): antarafacial; 2) 1,5-ring closure (6π): disrotatory

To elucidate the scope of the cyclization reaction and apply it to preparing condensed nitrogen-heterocycles, we examined the thermal behavior of the starting amino esters. A solution of amino ester (**1a**) (R = H) in xylene was heated at reflux for 90 h to give two pyrrole derivatives (**2a** and **3a**) in 41% and 29% yield, respectively.[2] The latter (**3a**) corresponds to the product of Fischer-Fink reaction,[3] while the major (**2a**) would be formed by elimination of methanol and carbon dioxide from the initially formed β-hydroxyester (**4a**) in the Fischer-Fink reaction (Scheme 2). This proposed pathway was supported by the similar reaction of amino ester (**1b**) (R = Ph); a solution of **1b** in xylene was refluxed for 70 h gave 2-phenylpyrrolo[2,3-*d*]pyrido-[1,2-*a*]pyrimidin-4(1*H*)-one (**2b**) quantitatively. In the course of the preparation of **1b**, β-hydroxyester (**4b**)[4] (*cis*:*trans* = 2/1 mixture) was obtained as a by-product. The isolated **4b** (*cis*/*trans* = 2/1 mixture) was heated in DMF at 150 °C for 45 h gave **2b** and unreacted **4b** (*cis/trans* = 1/4) in 67% and 20% yield, respectively. These findings suggest that thermal reaction of amino ester (**1**) would give the β-hydroxyester (**4**) as a mixture of *cis*- and *trans*-isomer, only *cis*-**4** of which was lactonized and decarboxylated to give the final product, pyrrole derivative (**2**) (Scheme 2).[5]

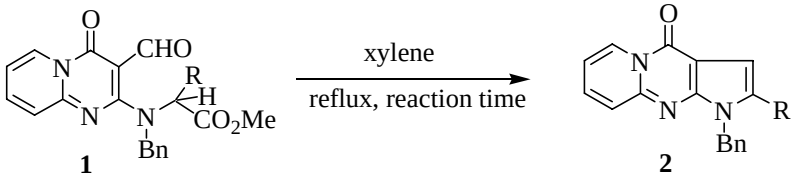


Scheme 2. Thermal ring-closure of amino esters (**1**) to pyrroles (**2**)

The ester group in **1** is essential for this pyrrole-ring formation; *N*,*N*-dibenzylamino (**6a**) and 1-pyrrolidinyl analogs (**6b**) did not undergo the similar cyclization even at more harsh reaction conditions. This means that in the transformation from **1** to **4** the proton on the carbon adjacent to the amino nitrogen is required to be acidic and suggests that, therefore, the reaction process for the transformation does not seem be limited to the1,6-H shift and 1,5-electrocyclization one; an aldol type cyclization process could not be ruled out. On the other hand, the thermal cyclization of cyclic amino ester (**1c**) failed probably due to steric reason.

Although details on the reaction pathway are still unclear, this thermal cyclization reaction should be a novel, facile, and effective preparation method for 2-substituted pyrrolo[2,3-*d*]pyrido[1,2-*a*]pyrimidin-4(1*H*)-one derivatives. So, we examined the similar reaction of other amino esters (**1d-j**); in every case pyrroles (**2d-j**) were formed in good to excellent yields (Table 1). Therein, the substituents (R) at the 2-position in the starting amino esters (**1**) were converted to those at the 2-position of pyrroles (**2**) respectively.

Table 1. Preparation of pyrrolo[2,3-*d*]pyrido[1,2-*a*]pyrimidin-4(1*H*)-ones (**2**) form amino esters (**1**)



Entry	R	Time / h	Product / Yield (%)[a]
4	$PhCH_2$	65	**2d** / 69
5	Me	120	**2e** / 75
6	*i*-Pr	42	**2f** / 88
7	*n*-Pr	90	**2g** / 90
8	*sec*-Bu (*S*)	72	**2h** / 86
9	*i*-Bu	40	**2i** / 96
10	$(CH_2)_2SMe$	45	**2j** / 85

[a] Based on isolated products.

In conclusion, we have reported the facile pyrrole-ring formation through the thermal reaction of *N*-benzyl-*N*-{3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl}amino esters (**1**). This provides an efficient approach toward 2-functionalized pyrrolo[2,3-*d*]pyrido[1,2-*a*]pyrimidin-4(1*H*)-ones (**2**). Further details on the reaction path and investigation on the effect of the heterocyclic system are in progress and will be reported elsewhere.

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1. M. Noguchi, M. Shirai, K. Nakashima, I. Arai, A. Nishida, H. Yamamoto, and A. Kakehi, *Tetrahedron*, 2003, **59**, 4581.

2. Representative procedure:[6] A solution of **1a** (140 mg) in xylene (2 mL) was heated at reflux for 90 h and the solvent was evaporated *in vacuo* to give a residue, which was subjected to a silica-gel column chromatography (hexanes/EtOAc = 2/1) gave **2a** (41%) and **3a** (29%). **2a**: Yellow needles from EtOH; mp 158 °C; ^{1}H NMR ($CDCl_3$): 5.44 (2 H, s, C*H*$_2$Ph), 6.86, 6.93 (each 1 H, each d, *J* = 3.6 Hz, 3- and 2-H), 6.89 (1 H, ddd, *J* = 2.3, 5.6, 7.3 Hz, 7-H), 7.21-7.56 (7 H, ov, 8- and 9-H and Ph-H), 9.02 (1 H, ddd, *J* = 1.0, 2.3, 7.3 Hz, 6-H); ^{13}C NMR($CDCl_3$): 48.0, 102.6, 102.9, 112.0, 124.3, 125.5, 127.2, 127.5, 127.8, 128.8, 132.9, 137.2, 147.4, 148.1, 155.0. *Anal.* Calcd for $C_{17}H_{13}N_3O$ (275.30): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.38; H, 4.91; N, 15.01. **3a**: Known compound.[1]

3. H. Fischer and E. Fink, *Z. physiol. Chem.*, 1944, **280**, 123; H. Fischer and E. Fink, *Z. physiol. Chem.*, 1948, **283**, 152. Also, see: A. Alberrola, L. Calvo, A. Gonzalez-Ortega, A. P. Encabo, and M. C. Sanudo, *Synthesis*, **2001**, 1941 and references cited therein.

4. The reaction of 2-chloro-3-formylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one and *N*-benzylphenylglycine methyl ester in the presence of triethylamine gave the desired **1b** and β-hydroxyester (**4b**) depending on the solvent utilised.[1] Fractional recrystallization of **4b** (*cis/trans* = 2/1 mixture) from ethanol gave only *cis*-**4a** as a pure form. *Cis*-**4a**: colorless crystals; mp 251-252 °C; ^{1}H NMR ($CDCl_3$): 3.57 (3 H, s, CO_2CH_3), 3.71 (1 H, br, OH), 4.55, 4.94 (AB quartett, *J* = 15.8 Hz, C*H*$_2$Ph), 5.66 (1 H, d, *J* = 3.0 Hz, 3-H), 6.98 (1 H, ddd, J = 1.3, 6.9. 8.3 Hz, 7-H), 7.12-7.39 (6 H, ov, 9-H and Ph-H), 7.66 (1H, ddd, *J* = 1.7, 6.9, 8.3 Hz, 8-H), 9.06 (1 H, br dd, *J* = 1.0, 6.9 Hz, 6-H); ^{13}C NMR($CDCl_3$): 47.3, 52.13; 77.7, 80.7, 92.3, 113.4, 124.7, 126.4, 126.5, 127.4, 127.9, 128.5, 128.5, 128.7, 137.5, 137.8, 138.5, 153.9, 154.1, 164.9, 169.6. *Anal.* Calcd for $C_{25}H_{21}N_3O_4$ (427.45): C, 70.25; H, 4.95; N, 9.83. Found: C, 70.48; H, 5.01; N, 10.01. The stereochemistry of *cis*- and *trans*-**4a** was deduced by their ^{1}H NMR data (chemical shifts of 3-H and hydroxyl and methoxy protons) taking account for the anisotropic effects by phenyl and hydroxy groups. *Trans*-**4a**: Selected ^{1}H NMR ($CDCl_3$): 2.21 (1 H, OH), 3.37 (3 H, CO_2CH_3), 6.04 (1 H, 3-H).

5. Lactonization of β-hydroxyester accompanied with decarboxylation has been known as a method for olefin synthesis:W. Adam, J. Baeza, and J.-C. Liu, *J. Am. Chem. Soc.*, 1972, **94**, 2000; W. Adam, G. Martinez, J. Thompson, and F. Yany, *J. Org. Chem.*, 1981, **46**, 3359; T. Tazawa and J. Schwartz, *Organometallics*, 1990, **9**, 3026; W. Oppolzer, C. G. Bochet, and E. Merifield, *Tetrahedron Lett.*, 1994, **35**, 7015; W. R. Dolbier Jr., R. Ocampo, and R. Paredes, *J. Org. Chem.*, 1995, **60**, 5378; I. Marao, B. Lecea, A. Begona, A. Arrieta, and F. P. Cossio, *J. Am. Chem. Soc.*, 1997, **119**, 816 and references cited therein.

6. The general experimental procedures were the same as those reported in lit. 1.