

Facile Synthesis of Functionalized 4-Aminopyridines

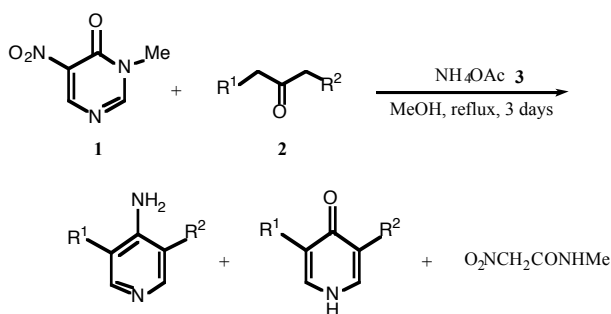
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The title compounds are readily available by ring transformation of nitropyrimidinone with active methylene compounds in the presence of ammonium acetate.

4-Aminopyridine-3-carboxylic acid (4-aminonicotinic acid) and its ester are sometimes found as a partial structure in natural products,¹ and their derivatives behave as NAD analogs.² 4-Aminopyridines (4APs) having a functional group at the vicinal position are also excellent precursors for [c]-fused pyrido compounds such as pyridopyrimidine, imidazopyridine, pyrazolopyridine and naphthyridine, those are widely used for medicines or their synthetic intermediates.³ Although some preparative procedures for functionalized 4APs have been established, multistep reactions and troublesome experimental manipulations are necessary.⁴ Furthermore functionalized 4AP has high possibility being a key compound for design of new medicines since 4AP plays an important role in neuroscience.⁵ Hence, development of a facile preparative method for title compounds is one of significant projects.



Scheme 1 The ring transformation affording 4-aminopyridines **4**.

In our course of study on the ring transformation,^{6,7} 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**)[†] is shown to be a suitable structure for this kind of reaction. The 2- and the 6-positions of **1** are electrophilic and the N3-C4-C5 unit is readily eliminated as nitroacetamide. In the present paper, a new ring transformation yielding functionalized 4APs will be provided.

To a solution of pyrimidinone **1** (155 mg, 1 mmol) in methanol (20 cm³), were added ethyl 3-oxobutanoate (**2a**, 0.25 cm³, 2 mmol) and ammonium acetate **3** (154 mg, 2 mmol), then the mixture was heated under reflux for 3 days. After removal of the solvent, the residue was treated with column chromatography on silica gel to furnish 4-amino-3-ethoxycarbonylpyridine (**4a**)⁸ and *N*-methylnitroacetamide in 97 % and 82 % yields, respectively (Table, run 1). The C2-N1-C6 unit of **1** behaves as the synthetic equivalent of activated diformylamine to compose the C2-N1-C6 unit of **4a**. Additionally, the carbonyl group of **2a** is converted to the amino group. Since 3-ethoxycarbonyl-4-pyridone **5a**, prepared by different method,⁷ is intact under the same conditions, introduction of amino group is not performed after the formation of **5a**. Ammonium ion **3** also causes no change on keto ester **2a**, which indicates enamine of **2a** is not the nucleophile in this reaction.

Table Reactions of pyrimidinone **1** with active methylene compounds.

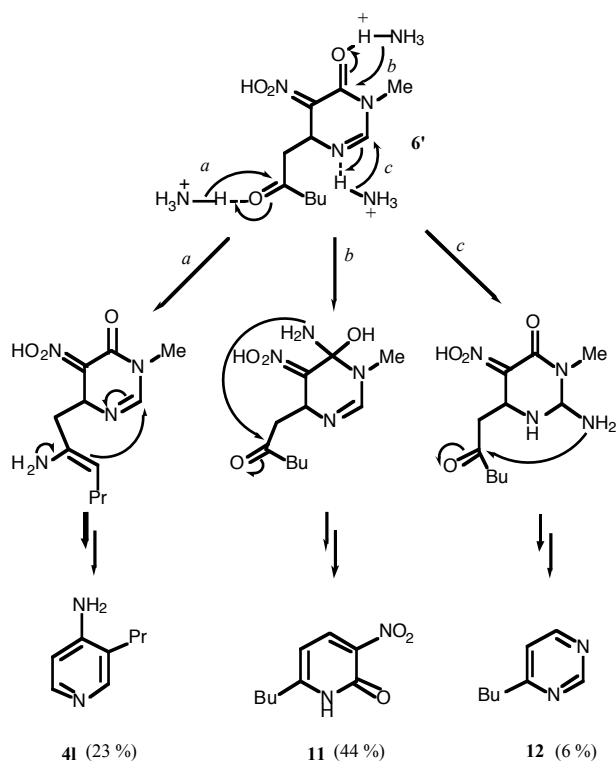
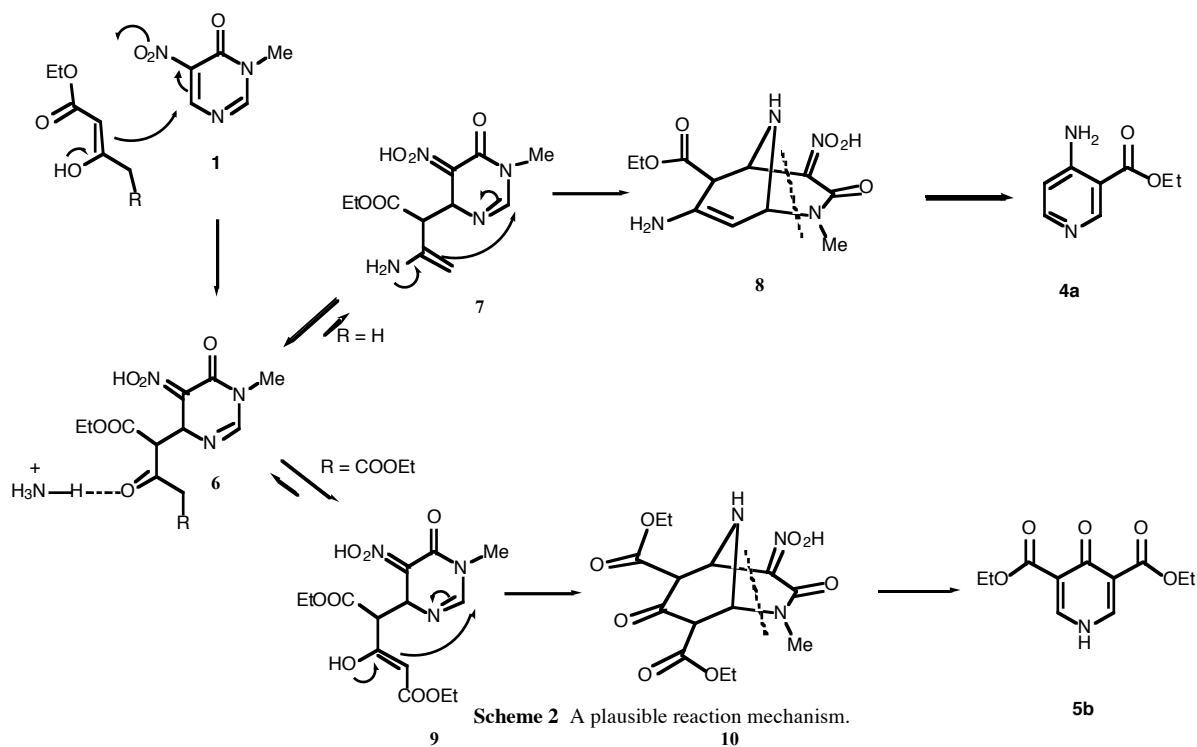
run	R ¹	R ²	4	5	
1	H	COOEt	a	97	0
2	H	COOMe	b	87	0
3	H	COOPr	c	57	7
4	H	COOPent ^a	d	81	12
5	Me	COOMe	e	97	0
6	MeO	COOMe	f	97	0
7	H	CONH ₂	g	31	0
8	H	Cl	h	17	0
9	H	COMe	i	0	0
10	COMe	COMe	j	0	45
11	COOEt	COOEt	k	0	88

^a 2-Pentyl.

Other oxobutanoates **2b-d** also gave corresponding aminopyridines **4b-d** in good yields (runs 2-4). When the alkoxy group is sterically hindered, small amounts of pyridones **5c** and **5d** are additionally produced. Substrate **2** for this reaction does not require an acetyl group, and keto esters **2e-f** similarly react with pyrimidinone **1** giving 4-aminopyridine-3-carboxylates having a methyl or a methoxy groups at the 5-position (runs 5 and 6). The present reaction is applicable to β-keto amide **2g** and chloroacetone **2h** to enable the introduction of other functional group at the 3-position (runs 7 and 8). 2,4-Pentanedione **2i** is less reactive under the same conditions (run 9). A strong intramolecular hydrogen bond might be a possible reason for the failure of the reaction with **2i**. To the contrary, tricarbonyl compounds **2j-k** only furnish difunctionalized 4-pyridones **5j-k** without formation of 3,5-difunctionalized 4APs **4j-k** (runs 10 and 11).

A plausible mechanism for this reaction is proposed in Scheme 2. This reaction is initiated with nucleophilic addition of the enol form of **2** to the electron-deficient 6-position of nitropyrimidinone **1**. The ketone carbonyl group in the adduct **6** is converted to the amino group by ammonium salt **3**, then the resultant enamine **7** intramolecularly attacks the 2-position to afford a bicyclic intermediate **8**. The elimination of nitroacetamide from **8** leads to 4AP **4**. When **2j** and **2k** are employed as the substrate, the enolization of **6** easily occurs rather than conversion to the enamine, thus 4-pyridone **5** is produced with similar transformation of enol form **9** via bicyclic intermediate **10**. In cases of oxobutanoates **2c** and **2d**, the sterically hindered alkoxy group prevents ammonium salt **3** from approaching to the carbonyl group, which causes both ring transformations to afford small amounts of pyridones **5c-d** in addition to 4APs **4c-d**.

On the basis of the mechanism shown in Scheme 2, it seems to be possible to employ aliphatic ketone instead of active methylene compounds. Actually, the reaction of pyrimidinone **1** with 2-hexanone **2l** under the same conditions gave three kinds of ring transformed products. 4-Amino-3-propylpyridine (**4l**) is isolated in 23 % yield to our expectation, besides 6-butyl-3-nitro-2-pyridone **11** and 4-butylpyrimidine **12**⁶ (Scheme 3). Since the pentanoyl group in the adduct intermediate **6'** shows



less electrophilicity than the carbonyl group of **6** in Scheme 2, other electrophilic sites (2- and 4-positions) competitively react with ammonium salt **3**. When the carbonyl group at the 4-position is aminated, pyridone **11** is formed (route *b*), and amination of the 2-position leads to pyrimidine **12** (route *c*). Although further study on the control of these reaction paths is necessary, the present reaction is found to be applicable to aliphatic ketone affording alkylated 4AP.

In summary, a new ring transformation of nitropyrimidinone **1** is provided. Since this reaction does not need special reagents, conditions and manipulations, it facilitates the preparation of functionalized 4APs.

References and notes

- † Nitropyrimidinone **1** is readily prepared from 2-thiouracil by reduction,⁹ methylation⁹ and nitration¹⁰ in 43 % overall yield.
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