

## Facile synthesis of functionalized 4-aminopyridines

Nagatoshi Nishiwaki,\* Mayumi Azuma, Mina Tamura, Kazushige Hori, Yasuo Tohda and Masahiro Ariga\*

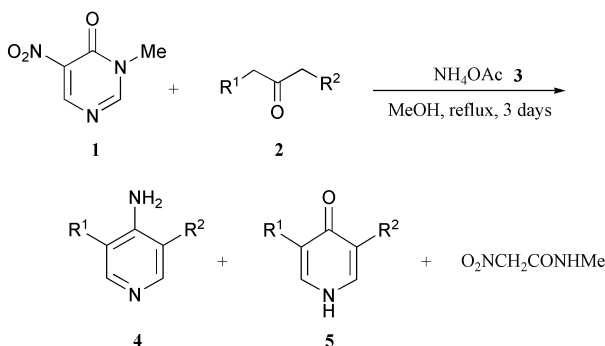
*Department of Chemistry, Osaka Kyoiku University, Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan. E-mail: ariga@cc.osaka-kyoiku.ac.jp; Fax: 81-729-78-3399; Tel: 81-729-78-3398**Received (in Cambridge, UK) 7th June 2002, Accepted 9th August 2002**First published as an Advance Article on the web 23rd August 2002*

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,<sup>1</sup> and their derivatives behave as NAD analogs.<sup>2</sup> 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.<sup>3</sup> Although some preparative procedures for functionalized 4APs have been established, multistep reactions and troublesome experimental manipulations are necessary.<sup>4</sup> Furthermore functionalized 4AP has high possibility being a key compound for design of new medicines since 4AP plays an important role in neuroscience.<sup>5</sup> Hence, development of a facile preparative method for title compounds is one of significant projects.

In our course of study on the ring transformation,<sup>6,7</sup> 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**)<sup>†</sup> 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 (Scheme 1).

To a solution of pyrimidinone **1** (155 mg, 1 mmol) in methanol (20 cm<sup>3</sup>), were added ethyl 3-oxobutanoate (**2a**, 0.25 cm<sup>3</sup>, 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**)<sup>8</sup> 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 a different method,<sup>7</sup> is intact under the same conditions, introduction of an 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.

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

Other oxobutanoates **2b–d** also gave the 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  $\beta$ -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**. By contrast, tricarbonyl compounds **2j,k** only furnish difunctionalized 4-pyridones **5j,k** without formation of 3,5-difunctionalized 4APs **4j,k** (runs 10 and 11).

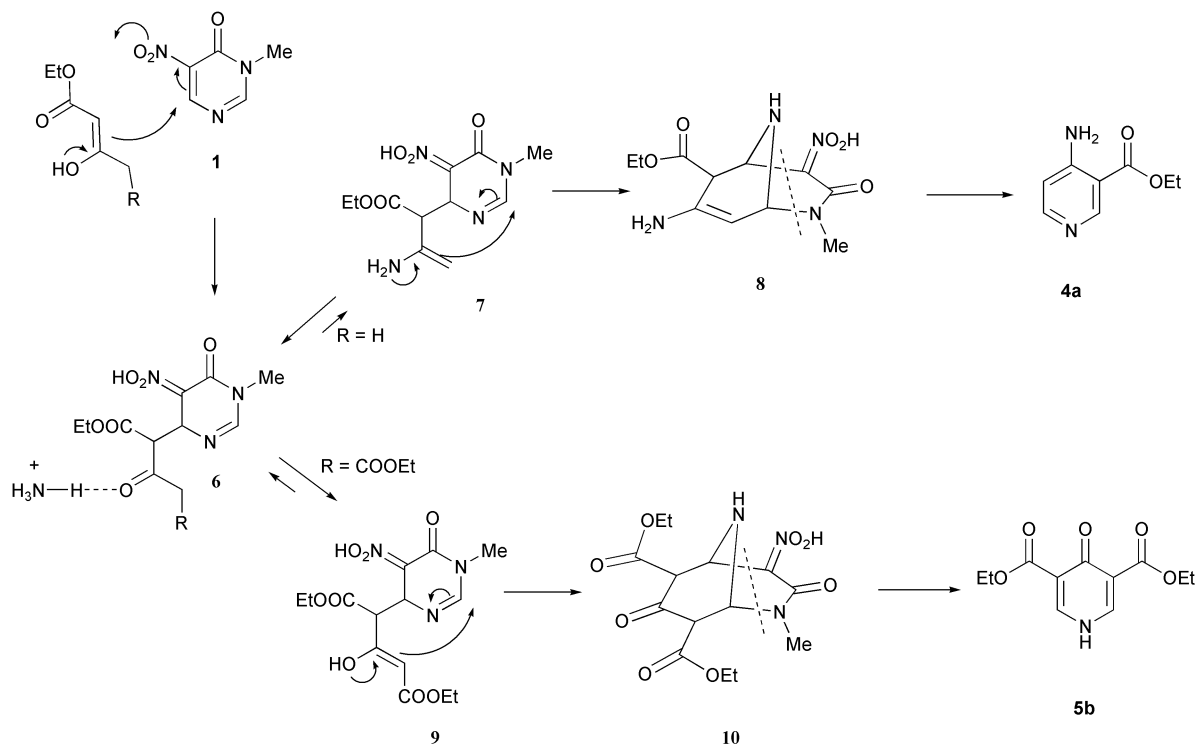
A plausible mechanism for this reaction is proposed in Scheme 2. This reaction is initiated with nucleophilic addition of the enol form of **2** to the electron-deficient 6-position of nitropyrimidinone **1**. The ketone carbonyl group in the adduct **6** is converted to the amino group by ammonium salt **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 ketones instead of active methylene compounds. Actually, the reaction of pyrimidinone **1** with 2-hexanone **2l** under the same conditions gave three types 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**<sup>6</sup> (Scheme 3). Since the pentanoyl group in the adduct intermediate **6'** shows less electrophilicity than the carbonyl group of **6** in Scheme 2,

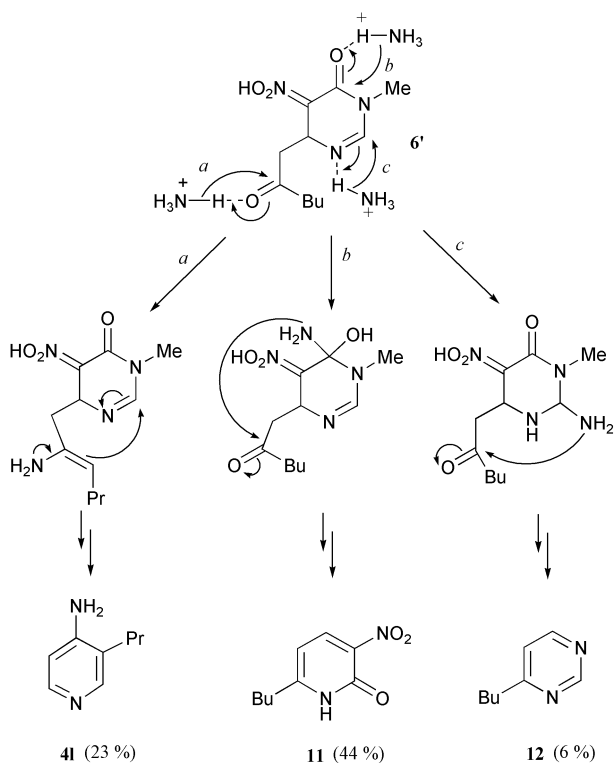
Table 1 Reactions of pyrimidinone **1** with active methylene compounds

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

<sup>a</sup> 2-Pentyl.



Scheme 2 A plausible reaction mechanism.



Scheme 3 Three products in the reaction of **1** with 2-hexanone **21**.

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 pathways is necessary, the present reaction is found to be applicable to aliphatic ketones affording alkylated 4AP.

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

## Notes and references

† Nitropyrimidinone **1** is readily prepared from 2-thiouracil by reduction,<sup>9</sup> methylation<sup>9</sup> and nitration<sup>10</sup> in 43% overall yield.

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