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Facile synthesis of functionalized 4-aminopyridines

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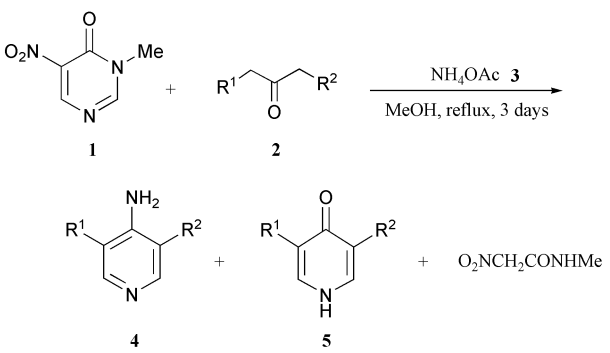
Received (in Cambridge, UK) 7th June 2002, Accepted 9th August 2002
First published as an Advance Article on the web 23rd August 2002

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,[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.

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 (Scheme 1).

To a solution of pyrimidinone **1** (155 mg, 1 mmol) in methanol (20 cm^3), were added ethyl 3-oxobutanoate (**2a**, 0.25 cm^3, 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 a different method,[7] 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 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**. 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**.

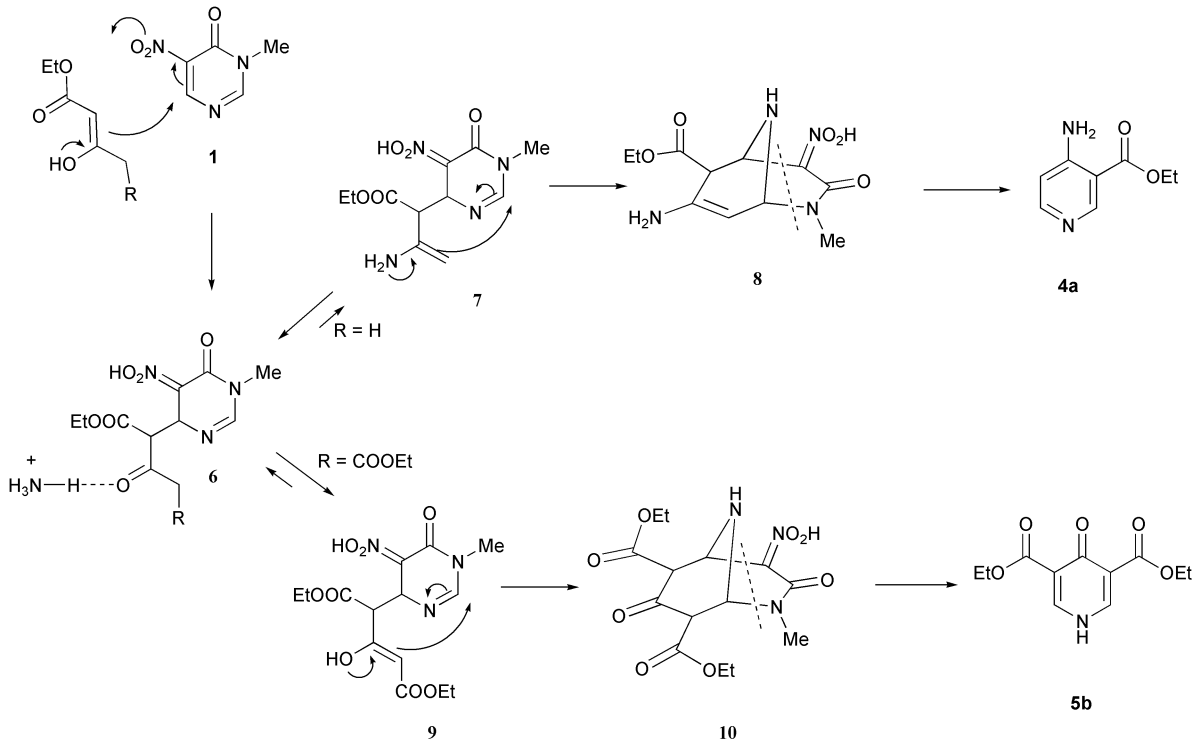
On the basis of the mechanism shown in Scheme 2, it seems to be possible to employ aliphatic ketones instead of active methylene compounds. Actually, the reaction of pyrimidinone **1** with 2-hexanone **2l** under the same conditions gave three types of ring transformed products. 4-Amino-3-propylpyridine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

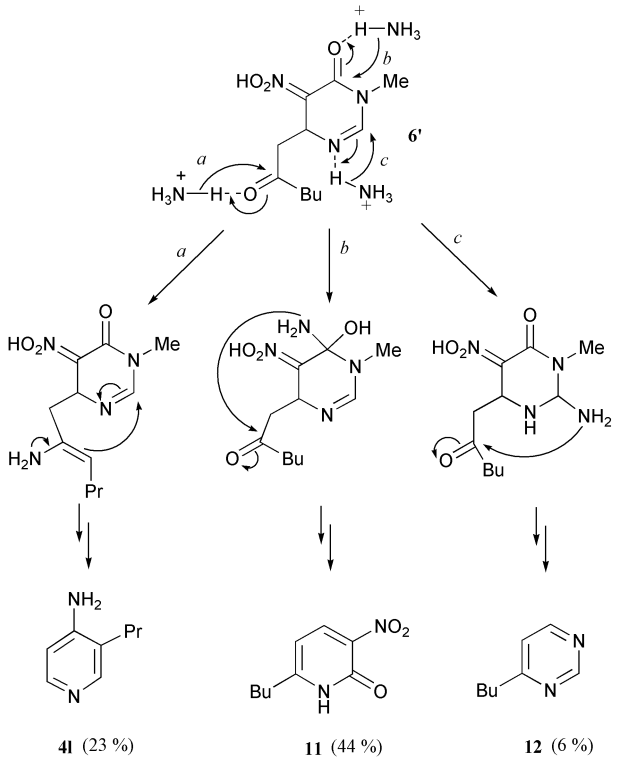
Run	R^1	R^2		**4**	**5**
1	H	COOEt	**a**	97	0
2	H	COOMe	**b**	87	0
3	H	COOPr	**c**	57	7
4	H	COOPent[a]	**d**	81	12
5	Me	COOMe	**e**	97	0
6	MeO	COOMe	**f**	97	0
7	H	$CONH_2$	**g**	31	0
8	H	Cl	**h**	17	0
9	H	COMe	**i**	0	0
10	COMe	COMe	**j**	0	45
11	COOEt	COOEt	**k**	0	88

[a] 2-Pentyl.

DOI: 10.1039/b205510d



Scheme 2 A plausible reaction mechanism.



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

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 pathes 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,[9] methylation[9] and nitration[10] in 43% overall yield.

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