# ALKYL 2-[2,2-DISUBSTITUTED ETHENYL]AMINO-3-DIMETHYL-AMINOPROPENOATES IN THE SYNTHESIS OF HETEROCYCLIC SYSTEM. AN ALTERNATIVE METHOD FOR PREPARATION OF 3-AMINO-4*H*-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES

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*Dedicated to Professor Koji Nakanishi, Columbia University, on the occasion of his 75th birthday*

**Abstract** - Substituted 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**6**) were prepared by treatment of 2-aminopyridines (**1**) with alkyl 2-[2,2-disubstituted ethenyl]amino-3-dimethylaminopropenoates (**2**) in which 3-[2,2-disubstituted ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3** - **5**) were formed. The removal of the *N*-protecting group with hydrazine afforded compounds (**6**).

Substituted alkyl 2-acylamino-3-dimethylaminopropenoates as masked α-formyl-α-amino acid derivatives, have been recently found to be versatile reagents in the synthesis of β-aryl-, β-heteroaryl-, β-arylamino-, and β-heteroarylamino acids and their α,β-dehydro analogs.[1] They are frequently intermediates in the synthesis of many heterocyclic systems, such as indolizines, quinolizines, substituted pyranones, benzo- and naphthopyranones, pyrazolopyranones, pyranopyrimidines, azolopyrimidines and azinopyrimidines.[1]

Recently, alkyl 2-[2,2-disubstituted ethenyl]amino-3-dimethylaminopropenoates, such as ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate,[2,3] alkyl 2-[2-benzoyl-2-ethoxycarbonyl-1-ethenyl]amino-3-dimethylaminopropenoate,[4] and methyl 2-[2,2-bis(acetyl)ethenyl]amino-3-dimethylaminopro-

penoate[5] have been synthesized and used as reagents for preparation of many heterocyclic systems, among others also for azolo- and azinopyrimidinones with 2,2-disubstituted 1-ethenylamino group at position 3 of the newly formed pyrimidinone ring[2,5,6] or pyridinone ring.[3,5]

On the other hand, we have observed recently, that 2,2-disubstituted 1-ethenyl, such as 2-benzoyl-2-ethoxycarbonyl-1-ethenyl and 2-benzoylamino-2-methoxycarbonyl-1-ethenyl, groups can be applied as *N*-protecting groups in the synthesis of dehydropeptide derivatives containing *N*-terminal 3-heteroarylamino-2,3-dehydroalanine moiety, since they can be easily removed with hydrazine or hydroxylamine under mild conditions.[7]

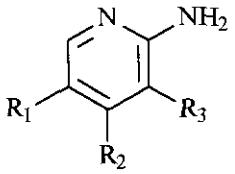
Substituted 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones have been recently studied as candidate fluorescent probes for hypoxic cells in solid tumors.[8] They have been prepared by condensation of substituted 2-aminopyridines with ethoxymethylene(nitro)acetate followed by cyclization in polyphosphoric acid to give substituted 3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. Reduction of the nitro group has been achieved using titanium(III) chloride, with palladium on charcoal in the presence of hydrogen or with cyclohexene by transfer hydrogenation in 53-82% yield[11] and by hydrolysis of benzoylamino group in concentrated hydrochloric acid in yields below 30%.[9]

In this paper, we present, on the basis of above observations, an alternative method for the preparation of 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in two steps, starting by treatment of a pyridine derivative with a reagent for cyclization, containing a protected amino group, followed by a simple removal of the *N*-protecting group.

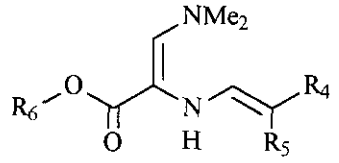
The condensation of the substituted 2-aminopyridines (**1a-d**) with ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate (**2a**), ethyl 2-[2-benzoyl-2-ethoxycarbonyl-1-ethenyl]-amino-3-dimethylaminopropenoate (**2b**) or methyl 2-[2,2-bis(acetyl)ethenyl]amino-3-dimethylaminopropenoate (**2c**) gave 3-[2,2-disubstituted 1-ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3**),[2] (**4**),[6] and (**5**),[5], according to the procedures described earlier (Scheme 1).

The removal of 2,2-disubstituted 1-ethenyl group was easily achieved by treatment of compounds (**3** - **5**) with excess hydrazine hydrate in refluxing ethanol to give 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**6**) in good to excellent yields. The best yields, 86-94%, were obtained when 2-benzoyl-2-ethoxycarbonyl-1-ethenyl was employed as the *N*- protecting group. On the other hand, when 2,2-bis(acetyl)-1-ethenyl group was employed as the *N*-protecting group, the products (**6**) were obtained in analytically pure form, but in lower yields (40-92%). (Scheme 2). The method is therefore advantageous in comparison to reduction of nitro group or hydrolysis of benzoylamino group.

Scheme 1



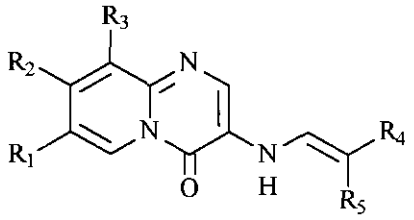
**1**



**2**

| 1 | R1 | R2 | R3 |
|---|---|---|---|
| **a** | H | H | H |
| **b** | H | Me | H |
| **c** | Cl | H | H |
| **d** | H | H | OH |

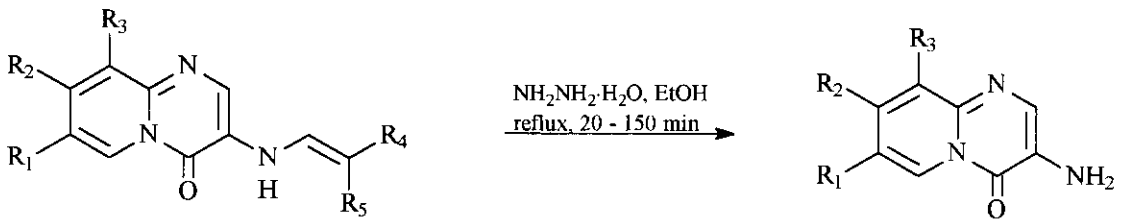
| 2 | R6 | R4 | R5 |
|---|---|---|---|
| **a** | Et | COOEt | COOEt |
| **b** | Et | COOEt | COPh |
| **c** | Me | COMe | COMe |



**3-5**

| 3-5 | R1 | R2 | R3 | R4 | R5 | Yield(%) | Reference |
|---|---|---|---|---|---|---|---|
| **3a** | H | H | H | COOEt | COOEt | 45 | 2 |
| **3b** | H | Me | H | COOEt | COOEt | 62 | 2 |
| **3c** | Cl | H | H | COOEt | COOEt | 57 | 2 |
| **3d** | H | H | OH | COOEt | COOEt | 36 | This Paper |
| **4a** | H | H | H | COOEt | COPh | 39 | 6 |
| **4b** | H | Me | H | COOEt | COPh | 67 | 6 |
| **4c** | Cl | H | H | COOEt | COPh | 50 | 6 |
| **4d** | H | H | OH | COOEt | COPh | 64 | 6 |
| **5a** | H | H | H | COMe | COMe | 26 | 5 |
| **5b** | H | Me | H | COMe | COMe | 17 | 5 |
| **5c** | Cl | H | H | COMe | COMe | 35 | 5 |

Scheme 2




**3-5** **6**

| 6 | R1 | R2 | R3 | Yield from 3 | Yield from 4 | Yield from 5 | Yield from Lit. 11 |
|---|---|---|---|---|---|---|---|
| **a** | H | H | H | 66 | 94 | 40 | 59 |
| **b** | H | Me | H | 96 | 91 | 92 | 53 |
| **c** | Cl | H | H | 64 | 89 | 55 | 72 |
| **d** | H | H | OH | 97 | 86 | | 82 |

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The $^1$H NMR spectra were obtained on a Bruker Avance 300 DPX spectrometer with TMS as the internal standard, IR spectra on a Perkin-Elmer 1310 instrument, MS spectra on an Autospeck Q spectrometer and microanalyses for C, H and N on a Perkin-Elmer Analyser 2400.

The following compounds were prepared according to the procedures described in literature: **2a**,[2] **2b**,[4] **2c**,[5] **3a-c**,[2] **4a-d**,[6] **5a-c**.[5]

**3-[2,2-Bis(ethoxycarbonyl)vinyl]amino-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (3d).** To a solution of 2-amino-3-hydroxypyridine (**1d**) (0.165 g, 1.5 mmol) in acetic acid (5 mL) ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate (**2a**) (0.492 g, 1.5 mmol) was added and the mixture was heated under reflux for 3 h. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 $F_{254}$, 0.2 mm, E. Merck, and chloroform/methanol, 25:1 as solvent). After reaction was completed,

acetic acid was evaporated *in vacuo* and the solid residue recrystallized from a mixture of ethanol and toluene to give **3d** in 38% yield (0.198 g), mp 174-177°. $^1$H NMR (DMSO-$d_6$): δ 1.26, 1.28 (2t, $CH_2CH_3$ x 2), 4.15, 4.28 (2q, $CH_2CH_3$ x 2), 7.16 (dd, $H_8$), 7.26 (dd, $H_7$), 8.49 (dd, $H_6$), 8.70 (s, $H_2$), 8.71 (d, CHNH), 10.90 (d, CHNH), $J_{CH2CH3}$ = 6.8 Hz, $J_{CHNH}$ = 13.9 Hz, $J_{H6H7}$ = 6.9 Hz, $J_{H7H8}$ = 7.5 Hz, $J_{H6H8}$ = 1.1 Hz. *Anal.* Calcd for $C_{16}H_{17}N_3O_6$: C, 55.33; H, 4.93; N, 12.10. Found: C, 55.73; H, 4.97; N, 12.28.

**General procedure for removing of *N*-protecting group in compounds (3-5):** To fused pyrimidine (**3-5**) (1 mmol) excess 80% hydrazine hydrate (1:2 - 1:10 molar ratio) in ethanol (4-5 mL) was added. The mixture was heated under reflux for 20 - 150 min. After that, solution was evaporated to one half of the initial volume and cooled until precipitate was formed. The precipitate was collected by filtration and washed with ethanol and/or recrystallized from an appropriate solvent to give **6**.

**3-Amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6a).** This compound was prepared from **3a** (0.331 g, 1 mmol) with 80% hydrazine hydrate (312 mg, 1:5 molar ratio), reflux for 150 min, in 66% yield; from **4a** (0.362 g, 1 mmol) with 80% hydrazine hydrate (625 mg, 1:10 molar ratio), reflux for 20 min, in 94% yield; from **5a** (0.271 g, 1 mmol) with 80% hydrazine hydrate (125 mg, 1:2 molar ratio), reflux for 60 min, in 40% yield; mp 176-178° (from ethanol), (lit.,[9]: 180-182°); $^1$H NMR (DMSO-$d_6$): δ 5.18 (s, $NH_2$), 7.10 (ddd, $H_7$), 7.40-7.52 (m, $H_8$, $H_9$), 7.91 (s, $H_2$), 8.73 (ddd, $H_6$), $J_{H6H7}$ =7.3 Hz, $J_{H8H9}$ =9.0 Hz, $J_{H7H8}$ =5.6 Hz, $J_{H6H8}$ =1.1 Hz, $J_{H7H9}$ = 2.2 Hz, $J_{H6H9}$ =0.6 Hz.

**3-Amino-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6b).** This compound was prepared from **3b** (0.345 g, 1 mmol) with 80% hydrazine hydrate (312 mg, 1:5 molar ratio), reflux for 150 min, in 96% yield; from **4b** (0.377 g, 1 mmol) with 80% hydrazine hydrate (625 mg, 1:10 molar ratio), reflux for 20 min in 91%; from **5b** (0.285 g, 1 mmol) with 80% hydrazine hydrate (125 mg, 1:2 molar ratio), reflux for 60 min, in 92% yield; mp 225-226° (from ethanol), (lit.,[10]: 215-225°); $^1$H NMR (DMSO-$d_6$): δ 2.34 (s, 8-Me), 5.01 (s, $NH_2$), 6.97 (dd, $H_7$), 7.26 (d, $H_9$), 7.86 (s, $H_2$), 8.66 (d, $H_6$), $J_{H6H7}$ = 7.2 Hz, $J_{H7H9}$ = 1.9 Hz.

**3-Amino-7-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6c).** This compound was prepared from **3c** (0.366 g, 1 mmol) with 80% hydrazine hydrate (312 mg , 1:5 molar ratio), reflux for 150 min, in 64% yield; from **4c** (0.398 g, 1 mmol) with 80% hydrazine hydrate (625 mg, 1:10 molar ratio), reflux for 20 min, in 89% yield; from **5c** (0.306 g, 1 mmol) with 80% hydrazine hydrate (125 mg, 1:2 molar ratio), reflux for 60 min, in 55% yield; mp 192-193° (from methanol), (lit.,[11]: 189-190°); $^1$H NMR (DMSO-$d_6$): δ 5.42 (s, $NH_2$), 7.43 (dd, $H_8$), 7.49 (dd, $H_9$), 7.89 (s, $H_2$), 8.72 (dd, $H_6$), $J_{H8H9}$ = 9.6 Hz, $J_{H8H6}$ = 2.2 Hz, $J_{H6H9}$ = 0.5 Hz.

**3-Amino-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6d).** This compound was prepared from **3d** (0.347 g, 1 mmol) with 80% hydrazine hydrate (312 mg, 1:5 molar ratio), reflux for 150 min, in 97% yield; from **4d** (0.473 g, 1 mmol) with 80% hydrazine hydrate (625 mg, 1:10 molar ratio), reflux for 20 min, in 86% yield; mp 218-220° (from methanol), (lit.,[11]: 213-215°); $^1$H NMR (DMSO-d$_6$): δ 3.98 (s, 9-OH), 5.12 (s, $NH_2$), 6.67 (dd, $H_8$), 6.95 (dd, $H_7$), 7.88 (s, $H_2$), 8.22 (dd, 1H, $H_6$), $J_{H6H7}$ = 7.4 Hz, $J_{H7H8}$ = 7.5 Hz, $J_{H6H8}$ = 1.1 Hz.

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