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# Cyclisation of 3-alkenylpyrido[1,2-*a*]pyrimidines to furo[2,3-*d*]pyrido[1,2-*a*]pyrimidines

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**Abstract**—3-Alkenylpyrido[1,2-*a*]pyrimidines react under mild conditions to give novel tricyclic furo[2,3-*d*]pyrido[1,2-*a*]pyrimidines in high yields. The cyclisation takes place in the presence of an acid catalyst. The product yield is affected by the type and the strength of the acid used. Exceptionally high yields were obtained when an organic acid like trifluoromethanesulfonic acid and trifluoroacetic acid were used. On the other hand, sulfuric acid gave the best results of the inorganic acids examined.


Furo[2,3-*d*]pyrido[1,2-*a*]pyrimidines are novel tricyclic pyrimidine derivatives and were synthesised for the first time from 3-alkenylpyrido[1,2-*a*]pyrimidines in our earlier research work.[1,2] The thermal reaction of alkylidenemalonate esters **2** with 2-aminopyridines gave 3-(2-alkenyl)pyrido[1,2-*a*]pyrimidines **3** in good yields.[1] An interesting outcome of our earlier work is the cyclisation of the 3-(2-alkenyl)pyrido[1,2-*a*]pyrimidines **3** in trifluoroacetic acid/dichloromethane in which formation of 4*H*-5,6-dihydrofuro[2,3-*d*]pyrido[1,2-*a*]-pyrimidines **4**, was observed in good yields (Fig. 1). Because the cyclisation yield was sufficiently high in the solvent system used, no further study was carried out. However, this reaction is quite attractive for the synthesis of novel tricyclic pyrido[1,2-*a*]pyrimidine derivatives and of some biologically important bicyclic furans.[3–6] Therefore, the effect of different parameters on the formation of 4*H*-5,6-dihydrofuro[2,3-*d*]pyrido[1,2-*a*]-pyrimidines **4** needed to be investigated, particularly the type and the strength of the acid catalyst, preferably to avoid the use of expensive and toxic trifluoroacetic acid.

We now report that the type of acid reagent is very important in order to obtain high yields. Two examples, 2-hydroxy-8-methyl-3-(2-methyl-1-propenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **3a** and 2-hydroxy-8-methyl-3-(2-phenyl-1-propenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **3b**, were used in cyclisation experiments.[1,2,7] Several organic and inorganic acids were used for the cyclisation reaction and the results are given in Table 1. A stronger acid catalyst is required for high yields of cyclic products. No cyclisation occured when a carboxylic acid, such as acetic, malonic or oxalic acid was used. In contrast, good yields of furopyridopyrimidines were obtained in the presence of stronger carboxylic acids, e.g. trifluoroacetic acid.[1,2] Trifluoromethanesulfonic acid gave quantitative yields (entries 1, 3, and 4), but *p*-toluenesulfonic acid did not produce cyclic products in good yields.

Aqueous inorganic acids, such as concentrated HCl and HBr led to simultaneous cleavage of the pyrimidine ring of the substrate and product during the cyclisation process, and did not give cyclic products in

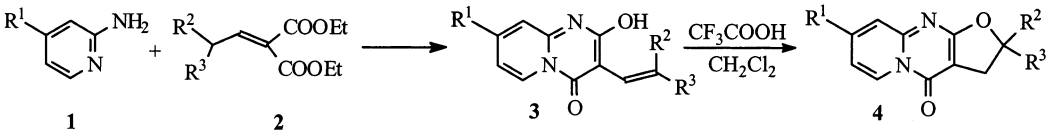


**Figure 1.** Synthesis of furo[2,3-*d*]pyrido[1,2-*a*]pyrimidines **4**.

*Keywords*: cyclisation; furopyridopyrimidines; pyridopyrimidines.
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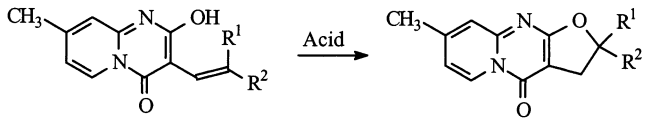
**Table 1.** Cyclisation of 3-(2-alkenyl)pyrido[1,2-*a*]pyrimidines **3** in the presence of acids




**3a** : $R^1$=$R^2$=$CH_3$
**3b** : $R^1$=Ph, $R^2$=$CH_3$

**4a** : $R^1$=$R^2$=$CH_3$
**4b** : $R^1$=Ph, $R^2$=$CH_3$

| Entry | Substrate (mmol) | Acid catalyst (mL/mmol) | Solvent (mL) | Temp. (°C) | Time (h) | Yield[a] **4**[8] (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** (1) | $CF_3SO_3H$ (1.0 mL) | $CHCl_3$ (10) | 20 | 14 | 100 |
| 2 | **3a** (2) | $CF_3SO_3H$ (0.7 mL) | $CHCl_3$ (7) | 20 | 4 | 62 |
| 3 | **3a** (1) | $CF_3SO_3H$ (0.7 mL) | $CHCl_3$ (5) | 20 | 17 | 100 |
| 4 | **3a** (1) | $CF_3SO_3H$ (0.5 mL) | $CHCl_3$ (5) | 20 | 5 | 100 |
| 5 | **3a** (1) | $CH_3COOH$ (3 mL) | $CHCl_3$ (3) | 20 | 48 | –[b] |
| 6 | **3a** (1) | $CF_3COOH$ (2 mL) | $CH_2Cl_2$ (4) | 20 | 12 | 90 |
| 7 | **3a** (1) | 35% HCl (3 mL) | $CHCl_3$ (5) | 20 | 24 | 40 |
| 8 | **3a** (1) | HCl gas (10 mmol) | $CHCl_3$ (5) | 20 | 4 | –[b] |
| 9 | **3a** (1) | HCl gas (10 mmol) | $CH_3COOH$ (5) | 20 | 24 | –[b] |
| 10 | **3a** (1) | HCl gas (10 mmol) | DMF (7) | 20 | 5 | –[b] |
| 11 | **3a** (1) | TosOH (10 mmol) | $CHCl_3$ (5) | 20 | 3 | –[b] |
| 12 | **3a** (1) | $H_2SO_4$ (0.4 mL) | $CHCl_3$ (5) | 20 | 4 | 50 |
| 13 | **3a** (1) | $H_2SO_4$ (1.0 mL) | $CHCl_3$ (5) | 20 | 1 | 80 |
| 14 | **3a** (1) | $H_2SO_4$ (2.0 mL) | $CHCl_3$ (5) | 20 | 4 | 98 |
| 15 | **3b** (1) | $H_2SO_4$ (0.8 mL) | $CHCl_3$ (5) | 20 | 0.25 | 85 |
| 16 | **3b** (1) | $H_2SO_4$ (1.2 mL) | $CHCl_3$ (6) | 20 | 3.5 | 96 |
| 17 | **3b** (2) | $H_2SO_4$ (2.0 mL) | $CHCl_3$ (10) | 20 | 0.35 | 80 |

[a] Isolated cyclic product yields.
[b] A mixture of cyclic product, starting material and decomposition products was obtained.

yields greater than 40%. Anhydrous HCl gas was dissolved in some polar solvents ($CHCl_3$, MeCN, DMF, $CH_3COOH$) and used for cyclisation, however, only low yields of the furopyridopyrimidine derivatives were obtained.

Excellent results were obtained with concentrated sulfuric acid, which led to good to excellent yields of the desired pyrimidine **4** from both **3a** and **3b** (entries 13–17). The presence of water in the system caused hydrolysis of pyrimidine ring in both starting materials and cyclic products. This resulted in formation of ring cleaved by-products and reduced the yield of **4**. The amount of acid catalyst is also an important factor. One or two equivalents of acid were insufficient for the cyclisation, at least a 10-fold excess of acid was required for high yields. The cyclisation process is also affected by the reaction temperature. Most of the experiments were carried out at ambient temperature, which was found to be satisfactory for the cyclisation. In a few cases, reactions at reflux ($CH_2Cl_2$ and $CHCl_3$) were attempted, but unfortunately pyrimidine ring cleavage took place in the substrate and the cyclic product.

Typical procedure: the substrate (200–300 mg, 1 mmol) was dissolved in dichloromethane or chloroform (5 mL) and 1.0–1.5 mL of conc. sulfuric acid was added. The solution was stirred over a period of 3–5 h at room temperature. The resulting dark red solution was evaporated under reduced pressure. The remaining oil was mixed with 5 g of ice-water mixture. The aqueous solution was neutralised with saturated $Na_2CO_3$ and the organic material was extracted with dichloro methane (2×20 mL), dried over $Na_2SO_4$, passed through a small silica gel column (5 g) and evaporated. The remaining solid was pure furopyridopyrimidine.

In summary, the synthesis of novel tricyclic pyrimidine derivatives can be achieved in two steps from alkylidene malonates and aminopyridines. Cyclisation of 3-(2-alkenyl)pyrido[1,2-*a*]pyrimidines was realised in quantitative yields at room temperature using suitable organic and inorganic acids, preferably concentrated sulfuric acid. This successful cyclisation reaction may find important applications in the synthesis of cyclic furan derivatives. An extension of this work is currently under investigation.

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7. 2-Hydroxy-8-methyl-3-(2-methyl-1-propenyl)-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one **4a** and 2-hydroxy-8-methyl-3-(2-phenyl-1-propenyl)-4*H*-pyrido[1,2-*a*] pyrimidin-4-one **4b** were prepared in about 90% yield as described in Refs. 1 and 2. Both compounds gave satisfactory spectroscopic and analytical data similar to that described in Ref. 2.
8. Cyclic products were isolated by flash column chromatography (silica gel 60 and chloroform as eluent). Both compounds **4a**–**b** gave satisfactory spectroscopic and analytical data. **Product 4a**: mp 135–136°C. $\nu_{max}$ (KBr)/cm$^{-1}$ 2969, 1717 (C=O), 1654, 1592, 1498, 1344. $\delta_H$ (400 MHz; $CDCl_3$, TMS) 1.56 (6H, s, two $CH_3$), 2.48 (3H, s, $CH_3$-Py), 3.06 (2H, s, $CH_2$), 6.92 (1H, d, *J* 8, 7-H), 7.28 (1H, s, 9-H), 8.95 (1H, d, *J* 8, 6-H). *m*/*z* 230.1 ($M^+$, 100%, $C_{13}H_{14}N_2O_2$ requires 230.1), 189.1 (21.4), 172.1 (20.6), 144.1 (26.1), 135.1 (42.5), 113.0 (18.1), 92.1 (46.4). **Product 4b**: mp 121–122°C. $\nu_{max}$ (KBr)/cm$^{-1}$ 3069, 3037, 2986, 1708 (C=O), 1651, 1600, 1510, 1491, 1459, 1437, 1375, 1336, 1080, 1054. $\delta_H$ (400 MHz; $CDCl_3$, TMS) 1.8 (3H, s, $CH_3$), 2.45 (3H, s, $CH_3$-Py), 3.35 (1H, d, *J* 15, 5-H), 3.45 (1H, d, *J* 15, 5-H), 6.9 (1H, d, *J* 8, 7-H), 7.2–7.45 (6H, m, 9-H and Ph), 8.9 (1H, d, *J* 8, 6-H). *m*/*z* 292.1, ($M^+$, %100, $C_{18}H_{16}N_2O_2$, requires 292), 189.1 (59), 135.1 (33), 108.1 (24), 92.1 (37).