COMMUNICATION

A novel and regioselective pyridine-ring formation by Lewis acid-induced cyclisation of 2-(*N*-allylbenzylamino)-3-[2,2-bis(ethoxycarbonyl)vinyl]pyrido[1,2-*a*]pyrimidin-4(4*H*)-one

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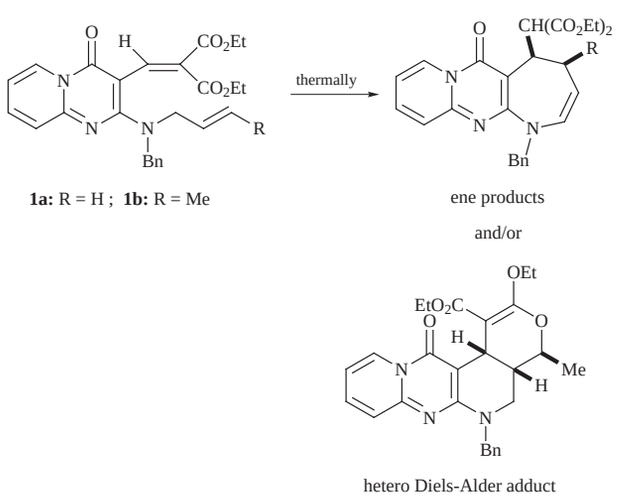
The Lewis acid-induced cyclisation of 2-(*N*-allylbenzylamino)-3-[2,2-bis(ethoxycarbonyl)vinyl]pyrido[1,2-*a*]pyrimidin-4(4*H*)-one 1a, which provides a novel and regioselective synthetic approach to the fused pyridine-ring, is described for the first time.

We have recently been studying the thermal reaction of 2-(alk-2-enyl)amino-3-[2,2-bis(ethoxycarbonyl)vinyl]pyrido[1,2-*a*]-pyrimidin-4(4*H*)-ones **1** and will be reporting elsewhere the resultant ene products and the hetero Diels–Alder adduct.[1] The formation of the latter was due to the [4 + 2] cycloaddition reaction between the α,β-unsaturated ester carbonyl and alk-2-enyl moiety in an inverse electron demand manner (Scheme 1).



Scheme 1

Therefore, we investigated the reaction of 2-(*N*-allylbenzylamino) substrate **1a**[2] in the presence of Lewis acids expecting facile progression of the hetero Diels–Alder reaction.

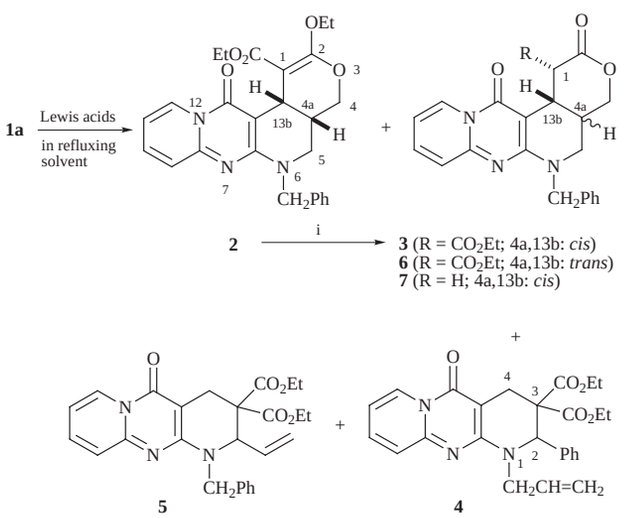
The reaction of **1a** with titanium tetrachloride ($TiCl_4$) in refluxing dichloromethane (DCM) gave a mixture of the hetero Diels–Alder adduct **2** and tetrahydropyran **3**. Almost the same results were obtained in the reaction with ethylaluminium dichloride. Similar reactions utilising zinc dichloride ($ZnCl_2$) or zinc diiodide gave two other products **4** and **5** as an inseparable mixture along with **2** or **3**. The selective formation of **4** and **5** was accomplished by use of diethylaluminium chloride; a *ca.* 1:1 mixture of **4** and **5** was formed in a moderate total yield together with **1a**. Finally, the reaction utilising boron trifluoride–diethyl ether (2.0 equiv.) in refluxing DCM gave only **4** in 76% yield (Scheme 2 and Table 1).

The structure of **4** was deduced to be 1-allyl-3,3-bis(ethoxycarbonyl)-2-phenyl-1,2,3,4-tetrahydrodipyrido[1,2-*a*:2′,3′-*d*]-pyrimidin-5(5*H*)-one based on its analytical and spectroscopic data;[3] its ^1H and ^{13}C NMR spectra suggested the existence of two ester units and the ^{13}C NMR spectra showed four sp^3-carbon signals [two methylene (δ = 22.4 and 50.1; 4-C and 1-CH_2-CH=), one methine (δ = 61.9; 2-C), and one quaternary carbon (δ = 56.2; 3-C)] besides the ethoxy moiety. The ^1H NMR spectrum of **4** showed the characteristic signal patterns of the *N*-allyl group and one inequivalent methylene (δ = 3.09 and 3.65; 4-H) and one methine proton (δ = 5.24; 2-H), which was coupled with one of the methylene protons (δ = 3.65, J = 2.0 Hz) through a W-coupling. Although **5** could not be isolated in its pure form, the structure of **5** was deduced to be 1-benzyl-3,3-bis(ethoxycarbonyl)-2-vinyl-1,2,3,4-tetrahydrodipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5(5*H*)-one from its spectroscopic data in comparison with **4**.

Table 1 Reaction of **1a** in the presence of Lewis acids

Run	Lewis acid (molar equiv.)	Solvent	*t*/h	Products (Yield: %)[a]
1	$TiCl_4$ (2.0)	DMC	24	**2** (23) **3** (34) **4** and **5** (trace)
2	$ZnCl_2$ (2.0)	Benzene	40	**2** (10) **4** (14) **5** (10) **1a** (38)
3	ZnI_2 (2.0)	Benzene	40	**3** (9) **4** (12) **5** (18) **1a** (22)
4	Et_2AlCl (2.0)	Benzene	20	**4** (24) **5** (20) **1a** (34)
5	$BF_3{\cdot}OEt_2$ (1.0)	DCM	24	**4** (52) **1a** (33)
6	$BF_3{\cdot}OEt_2$ (2.0)	DCM	24	**4** (76) **5** (trace)

[a] Based on isolated products.



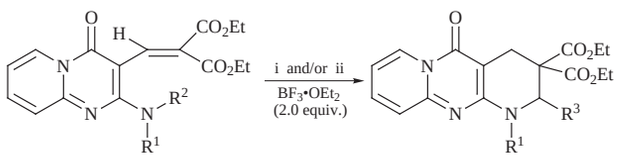
Scheme 2 *Reagents and conditions*: i, cat. HCl, THF, r.t., 18 h, 86%.

The treatment of **2** with Lewis acids (2.0 equiv.) such as $TiCl_4$, $ZnCl_2$ and $BF_3{\cdot}OEt_2$ in DCM gave tetrahydropyrans **3** (*trans*-1,13b isomer) and **6** (*trans*-4a,13b isomer), and **7** along with a mixture of unidentified products, in which no trace of pyridines **4** and **5** could be detected. The ratio of the products **3**, **6** and **7** was dependent on the the Lewis acid utilised. A smooth conversion of **2** into **3** was accomplished by treating **2** with hydrochloric acid in THF (Scheme 2).

The formation of **4** and **5** is due to cyclisation between the α-carbon of the α,β-unsaturated ester and the benzylic and/or

allylic positions of the amino moiety of **1a**. The cyclisation should occur *via* the same intermediate and the regioselectivity should depend upon the nature of the Lewis acids utilised; the best benzylic selectivity was accomplished by use of $BF_3{\cdot}OEt_2$.

To obtain further understanding of the cyclisation pathway, we examined a similar reaction of some 2-(*N*,*N*-disubstituted amino) substrates. The reaction of 2-(*N*-benzylmethylamino) substrate **8** and 2-dibenzylamino substrate **10** in refluxing DCM or benzene in the presence of $BF_3{\cdot}OEt_2$ gave **9** and **11**, respectively, in good yields. A similar successful cyclisation at the benzylic position was observed in the reaction of 2-[*N*-benzyl-(ethoxycarbonylmethyl)amino] substrates **12** leading to **13** in refluxing benzene utilising $BF_3{\cdot}OEt_2$ in only 24% yield. However, similar cyclization of 2-[*N*-(ethoxycarbonylmethyl)methylamino] **14** and 2-[*N*-(cyanomethyl)methylamino] substrate **15** utilising $BF_3{\cdot}OEt_2$ failed; the starting compounds **14** and **15** were recovered (in refluxing DCM) and mixtures of the decomposed products were formed (in refluxing benzene) as depicted in Scheme 3.

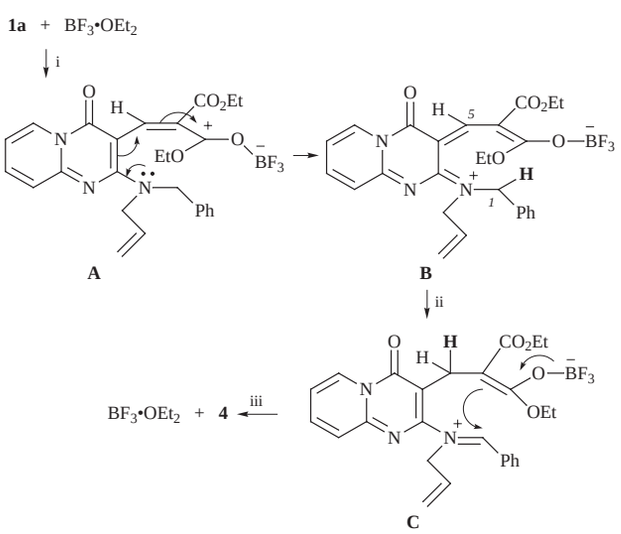


8: R^1 = Me; R^2 = CH_2Ph (i, ii)
10: R^1 = R^2 = CH_2Ph (i)
12: R^1 = CH_2CO_2Et; R^2 = CH_2Ph (ii)
14: R^1 = CH_2CO_2Et; R^2= Me (i; ii)
15: R^1 = CH_2CN; R^2 = Me (i; ii)

9: R^1 = Me; R^3 = Ph (47%; 88%)
11: R^1 = CH_2Ph; R^3 = Ph (78%)
13: R^1 = CH_2CO_2Et; R^3 = Ph (24%)

Scheme 3 *Conditions*: i, DCM, reflux, 18 h; ii, benzene, reflux, 12 h.

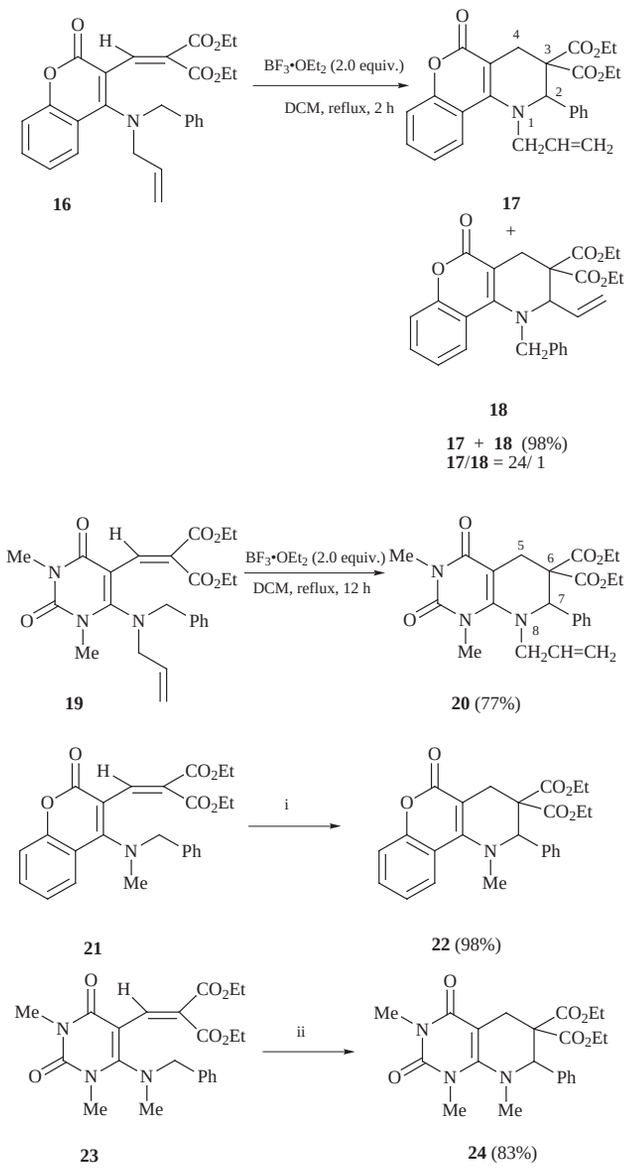
These results suggest that an *N*-benzylideneammonium betaine **C** is rationalised as an intermediate; the coordination of BF_3 with the ester carbonyl oxygen of **1a** gives an iminium betaine **B**, which isomerises to betaine **C**. The nucleophilic attack of the vinyl ether in **C** onto the iminium carbon atom gives tetrahydropyridine **4** (Scheme 4). The hydrogen at the



Scheme 4 *Reactions*: i, coordination of BF_3 with the carbonyl oxygen; ii, 1,5-hydrogen shift; iii, nucleophilic attack to iminium carbon.

α-position to the iminium nitrogen of **B** undergoes a 1,5-shift across the π-electron system and the isomerisation of **B** to **C** seems to be essential for the pyridine-ring formation. Although these consecutive processes seem to follow the "*tert*-amino effect",[4] there is little literature[5] on similar cyclisations induced by Lewis acids, except for the present work.

We next applied this cyclisation to two other heterocyclic systems. The reaction of 4-(*N*-allylbenzylamino)-3-[2,2-bis-(ethoxycarbonyl)vinyl][1]benzopyran-2(2*H*)-one **16** in the presence of $BF_3{\cdot}OEt_2$ also gave a (24 : 1) mixture of **17** and **18** in a good total yield. A similar reaction of 4-(*N*-allylbenzylamino)-1,3-dimethyl-5-[2,2-(ethoxycarbonyl)vinyl]pyrimidine-2,4-(1*H*,3*H*)-dione **19** gave only **20**. To elucidate the generality of this cyclisation, (*N*-benzyl)methylamino substrates **21** and **23** were allowed to react; the reaction of **21** in the presence of $ZnCl_2$ gave **22** quantitatively and the reaction of **23** in the presence of $BF_3{\cdot}OEt_2$ gave **24** in a good yield (Scheme 5).



Scheme 5 *Reagents and conditions*: i, benzene–AcOH (cat.), $ZnCl_2$ (1.0 equiv.), 80 °C, 6 h; ii, DCM, $BF_3{\cdot}OEt_2$ (2.0 equiv.), reflux, 10 h.

In conclusion, the reaction of the titled and related substrates in the presence of Lewis acids gave the fused pyridine derivatives *via* an iminium betaine according to the "*tert*-amino effect".

Experimental

Typical procedure for the reaction of 1a with $BF_3{\cdot}OEt_2$

To a solution of **1a** (0.310 g; 0.66 mmol) in DCM (10 cm^3) was added $BF_3{\cdot}OEt_2$ (0.16 cm^3; 1.3 mmol) and the mixture was refluxed for 24 h. Brine and additional DCM (each 10 cm^3) were added to the mixture and the organic phase separated. The organic layer was dried and evaporated to dryness. Silica gel column chromatography of the residue gave **4** (0.236 g; 76%) with hexane–ethyl acetate (2 : 1) as eluent.

Acknowledgements

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References

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2 In order to prepare selectively the vinyl substrates, modified Knoevenagel reaction conditions [$CH_2(CO_2Et)_2$ (1.1 equiv.), benzene, piperidine (2.0 equiv.), AcOH (2.0 equiv.), reflux, 7–18 h] were employed to afford the desired substrates in 38–72% yields. A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, *J. Am. Chem. Soc.*, 1941, **63**, 3452.
3 All new products in this study were fully characterised by spectroscopic and microanalytical data.
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