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Diels-Alder Reactions of 1,2,4-Triazines with Cyclic Vinyl Ethers

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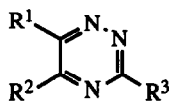
Abstract: The Diels-Alder reaction of 1,2,4-triazines with cyclic vinyl ethers leads to a range of substituted pyridines with hydroxyalkyl and oxoalkyl side chains With dihydrofuran the aromatization of the 1:1 adduct is inhibited by conformational factors and this allows 2:1 adducts to be isolated. Different regioselectivity is observed in the 2:1 adducts formed from ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1f** and from ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1b**. An X-ray crystal structure of the 2: 1 adduct **5** formed from 2,3-dihydrofuran and **1b** is reported.

Introduction.

The inverse electron demand Diels-Alder reactions of 1,2,4-triazines have been widely studied in recent years both as intermolecular and as intramolecular cycloadditions,[1] but there is still scope for extending the method as a route to new pyridines. Acyclic vinyl ethers add to 1,2,4-triazines to give cycloadducts which cannot be isolated but which undergo nitrogen elimination and aromatization to yield pyridines.[1c,2] However, no work has been reported using cyclic vinyl ethers. We decided to explore the Diels-Alder reaction of a range of 1,2,4-triazines **1** with some cyclic vinyl ethers **2** as a route to new pyridines with functionalized side chains.

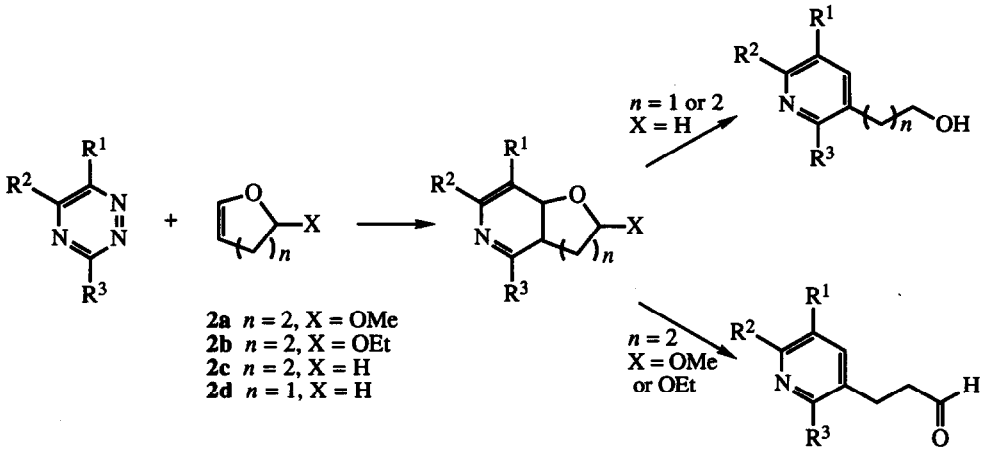


1a $R^1 = R^2 = CO_2Et$, $R^3 = NH_2$
1b $R^1 = R^2 = Ph$, $R^3 = CO_2Et$
1c $R^1 = R^2 = CO_2Et$, $R^3 = NHCOMe$
1d $R^1 = R^2 = CO_2Et$, $R^3 = Me$
1e $R^1 = R^2 = R^3 = CO_2Et$
1f $R^1 = H$, $R^2 = Ph$, $R^3 = CO_2Et$

Cycloaddition Reactions.

In our initial experiments we tried to effect the cycloaddition of the 1,2,4-triazines **1a–1e** with the cyclic vinyl ethers using relatively mild conditions. A solution in chloroform of the 1,2,4-triazine and the dienophile was heated under reflux until no further change was observed. These conditions enabled the reaction to take

place with the more electrophilic 1,2,4-triazines and cyclic vinyl ethers. The reaction follows the course outlined in Scheme 1.

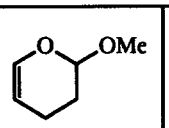
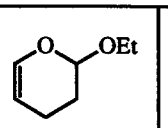
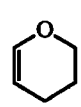
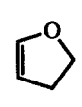


Scheme 1

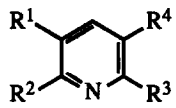
The adduct derived from the 1,2,4-triazine and the vinyl ether eliminates nitrogen, this being followed by the opening of the saturated furan or pyran ring to generate the pyridine. In such a way we obtain pyridines having a side chain which is determined by the structure of the cyclic vinyl ether. This allows for the possibility of introducing side chains bearing a terminal primary alcohol or a formyl function.

The reactivity observed is significantly affected both by the nature of the 1,2,4-triazine substituents and by the structure of the dienophile. As is shown in Table 1, a 1,2,4-triazine activated by the presence of three electron attracting ethoxycarbonyl substituents (**1e**) gives pyridines in high yield with any of the selected enol ethers. The 1,2,4-triazine with two ethoxycarbonyl and one methyl group (**1d**) also reacts with 2,3-dihydrofuran **2d** and with 3,4-dihydro-2*H*-pyran **2c**, but not with the substituted derivatives **2a** and **2b**. The 1,2,4-triazine with only one ethoxycarbonyl and two phenyl substituents (**1b**) reacted only with 2,3-dihydrofuran.

Table 1. Reactions of 1,2,4-Triazines **1** with Cyclic Enol Ethers in Chloroform

Triazine				
1a	n.r.[a]	n.r.	n.r.	n.r.
1b	n.r.	n.r.	n.r.	**3a'**, 55%
1c	n.r.	n.r.	n.r.	**3b'**, 67%
1d	n.r.	n.r.	**3d'**, 38%	**3c'**, 80%
1e	**3g**, 61%	**3g**, 80%	**3f**, 80%	**3e**, 80%

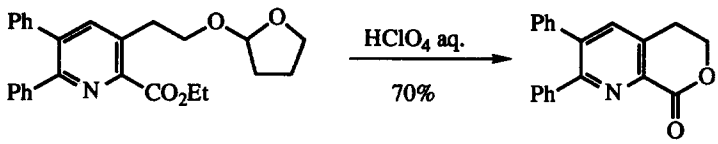
[a] n.r. = no reaction



3a $R^1 = R^2 = Ph$, $R^3 = CO_2Et$, $R^4 = CH_2CH_2OH$
3a' $R^1 = R^2 = Ph$, $R^3 = CO_2Et$, $R^4 = CH_2CH_2O(C_4H_7O)$
3b $R^1 = R^2 = CO_2Et$, $R^3 = NHCOMe$, $R^4 = CH_2CH_2OH$
3b' $R^1 = R^2 = CO_2Et$, $R^3 = NHCOMe$, $R^4 = CH_2CH_2O(C_4H_7O)$
3c $R^1 = R^2 = CO_2Et$, $R^3 = Me$, $R^4 = CH_2CH_2OH$
3c' $R^1 = R^2 = CO_2Et$, $R^3 = Me$, $R^4 = CH_2CH_2O(C_4H_7O)$
3d $R^1 = R^2 = CO_2Et$, $R^3 = Me$, $R^4 = CH_2CH_2CH_2OH$
3d' $R^1 = R^2 = CO_2Et$, $R^3 = Me$, $R^4 = CH_2CH_2CH_2O(C_5H_9O)$
3e $R^1 = R^2 = R^3 = CO_2Et$, $R^4 = CH_2CH_2OH$
3f $R^1 = R^2 = R^3 = CO_2Et$, $R^4 = CH_2CH_2CH_2OH$
3f' $R^1 = R^2 = R^3 = CO_2Et$, $R^4 = CH_2CH_2CH_2O(C_5H_9O)$
3g $R^1 = R^2 = R^3 = CO_2Et$, $R^4 = CH_2CH_2CHO$
3h $R^1 = R^2 = Ph$, $R^3 = CO_2Et$, $R^4 = Me$
3i $R^1 = R^2 = Ph$, $R^3 = CO_2Et$, $R^4 = CH_2CH_2CH_2OH$
3i' $R^1 = R^2 = Ph$, $R^3 = CO_2Et$, $R^4 = CH_2CH_2CH_2O(C_5H_9O)$

The 1,2,4-triazine having two ethoxycarbonyl and one amino substituents (**1a**) is not reactive enough to be attacked by any of the vinyl ethers used in these experiments. Several unsuccessful attempts were made to bring about a reaction of diethyl 3-amino-1,2,4-triazine-5,6-carboxylate **1a** with 2,3-dihydrofuran **2d**, including the use of higher pressure and temperature, different solvents, neat reagents and acid catalysts. A strategy which proved successful in this case was the acylation of the amino group of this 1,2,4-triazine **1a** which made the ring electron deficient enough to give the corresponding pyridine **3b'** in good yield (67%).

In some experiments leading to the primary alcohols **3a** to **3d** the products were initially isolated as acetals **3a'** to **3d'** formed by reaction of the terminal hydroxyl group with the dienophile present in excess. However, the unprotected pyridines were easily obtained by deprotection promoted by aqueous hydrochloric acid or perchloric acid. In one case such a deprotection procedure led to a different result. On treating the protected pyridine **3a'** dissolved in chloroform and in the presence of water with an excess of perchloric acid an intramolecular cyclization occurred with formation of the lactone **4** in good yield (70%) (Scheme 2). The synthesis of this lactone has previously been reported by an intramolecular Diels-Alder reaction of but-3-ynyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate.[3] Our procedure provides a convenient alternative route to **4**.

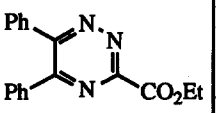
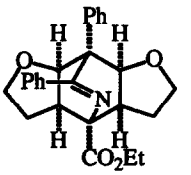
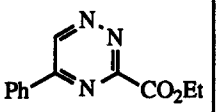
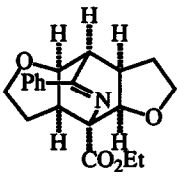


4

Scheme 2

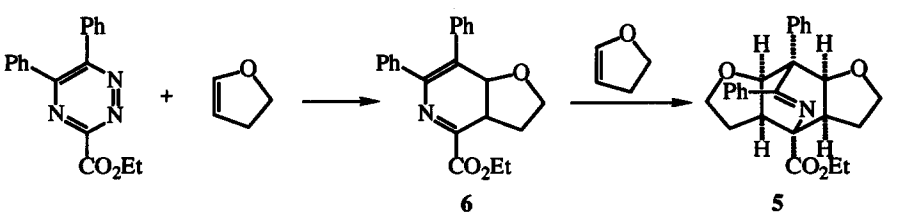
In attempts to widen the applicability of the Diels-Alder reaction of 1,2,4-triazines with cyclic enol ethers we tried to promote the cycloaddition by heating neat mixtures of the reagents in a sealed tube. Under these conditions the cycloaddition of ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1b** with 2,3-dihydrofuran (0.1 g 1,2,4-triazine in 1 ml 2,3-dihydrofuran) led to the formation of a new major product together with the corresponding pyridine **3a'** (9%) (Table 2). When the same reaction was carried out in the presence of a smaller amount of 2,3-dihydrofuran (0.1 g 1,2,4-triazine in 0.5 ml 2,3-dihydrofuran) the same major product was still isolated together with the acetal **3a'** (18%).

Table 2. Products of Reactions of 1,2,4-Triazines **1b** and **1f** with 2,3-Dihydropyran in Sealed Tubes[a]

Triazine	Dienophile	Product	Yield
 **1b**		**3a'**  **5**	9% 69%
 **1f**		 **7**	68%

[a] Reaction with **1b** (0.1 g) and dihydrofuran (1.0 ml) carried out at 60 °C for 90 h; reaction with **1f** (0.1 g) and dihydrofuran (2.0 ml) carried out at 80 °C for 72 h.

The major product was identified as the 2:1 adduct **5** by a combination of spectroscopic techniques and by an X-ray crystal structure determination (see below). Unexpectedly, in these sealed tube reactions the major reaction product does not result from aromatization of the intermediate **6**. Instead compound **6** reacts again as a diene in a Diels-Alder reaction with another molecule of 2,3-dihydrofuran (Scheme 3). The determination of the structure of **5** allowed us to deduce that both cycloaddition steps show the same regioselectivity and that the second cycloaddition occurs with *endo* orientation of the enol ether to the convex face of the diene **6**.

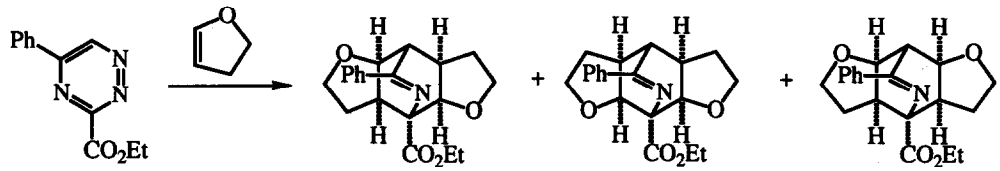


6 **5**

Scheme 3

A 2:1 adduct was also formed in the reaction of ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1f** with 2,3-dihydrofuran in a sealed tube. The analysis of the ^{13}C NMR and ^{1}H NMR spectra of the compound, as described below, allowed us to conclude that it has structure **7** (Table 2). Thus one of the cycloaddition steps has taken place with regioselectivity opposite to that shown by all the other 1,2,4-triazines used in this study. This result is in agreement with the behaviour shown by this 1,2,4-triazine **1f** in cycloadditions with other dienophiles.[4] We therefore suggest that the first cycloaddition step occurs with regioselectivity opposite to that observed with **1b** and that the second step occurs with the same regioselctivity as with **1b.**

In view of this result we then carried out the reaction of ethyl 5-phenyl-1,2,4- triazine-3-carboxylate **1f** with 2,3-dihydrofuran in chloroform. Unexpectedly this led to the formation of the three different 2:1 adducts **7**, **8** and **9** (Scheme 4); no aromatic pyridine derived from a 1:1 adduct was detected. The structures of adducts **8** and **9** were deduced from their ^{1}H NMR spectra as described below. In this reaction it is again apparent that one cycloaddition step occurs predominantly with a regioselectivity opposite to that observed with the other 1,2,4-triazines, although all three possible types of 2:1 adduct resulting from *endo* addition are now present.



7 **8** **9**

64% 10% 10%

Scheme 4

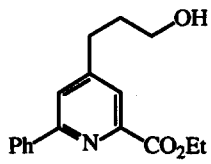
There are some literature examples of the synthesis of 2:1 adducts from 1,2,4-triazines and dienophiles, including dimethyl bicyclo[4.2.2.$0^{2,5}$]deca-3,9-diene-7,8-dicarboxylate, cyclopentene, *cis*-cyclooctene and bicyclo[2.2.1]hept-2-ene, where the aromatization step was known not to be favourable.[2,5] In the cycloaddition of 3-(methylsulfonyl)-1,2,4-triazine with some enamines dihydropyridines were also isolated and this was ascribed to conformational factors which made the elimination step unfavourable.[6] The inhibition of E2 elimination originates from the low value of the torsion angle between the bridging hydrogen and the nitrogen atoms. Similarly, in these dihydrofuran adducts, such as compound **6**, an antiperiplanar orientation cannot be achieved by the bridgehead hydrogen and oxygen substituents and this presumably makes the intermediates sufficiently long lived to allow a second cycloaddition to occur.

The cycloaddition of ethyl 5,6-diphenyl-1,2,4-triazine **1b**, in a sealed tube, with 1-methoxypropene and with 3,4-dihydro-2*H*-pyran was also studied. In both cases the corresponding pyridines were the only products (Table 3) suggesting that the aromatisation step is faster than for compound **6**. In these cases the preferred conformation for E2 elimination can be attained. It is worth noting that the cycloaddition of **1b** with 3,4-dihydro-2*H*-pyran which in this sealed tube reaction gave pyridine **3i** in 48% yield and its acetal **3i'** in 26% yield, was unsuccessful when attempted in chloroform.

A few other sealed tube reactions were carried out (Table 3). The cycloaddition of ethyl 5-phenyl-1,2,4-triazine **1f** with 3,4-dihydro-2*H*-pyran gave the pyridine **10** in 49% yield. Again this is the product having regiochemistry opposite to that shown by the other triazines, the structural assignment being based on the *meta* coupled 3-H and 5-H of the pyridine ring in the NMR spectrum. Diethyl 3-methyl-1,2,4-triazine-5,6-dicarboxylate **1d** reacted with 3,4-dihydro-2*H*-pyran to give the pyridine **3d** in 41% yield. The cycloaddition of triethyl 1,2,4-triazine-3,5,6-tricarboxylate **1e** with 3,4-dihydro-2*H*-pyran and with 3,4-dihydro-2-ethoxy-2*H*-pyran, under these sealed tube conditions, also led to the formation of pyridines **3f'** and **3g**; in no cases were 2:1 adducts formed.

Table 3. Other Reactions of 1,2,4-Triazines with Enol Ethers in Sealed Tubes

Triazine	Dienophile	Pyridine	Yield
1b	3,4-dihydro-2*H*-pyran	**3i** **3i'**	48% 26%
1b	1-methoxypropene	**3h**	10%
1f	3,4-dihydro-2*H*-pyran	**10**	49%
1d	3,4-dihydro-2*H*-pyran	**3d**	41%
1e	3,4-dihydro-2*H*-pyran	**3f'**	76%
1e	3,4-dihydro-2-ethoxy-2*H*-pyran	**3g**	70%



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Determination of Structures of 5, 7, 8 and 9.

The structure of the 2:1 adduct **5** was determined by X ray crystallography; it is illustrated in the Figure. The crystal structure reveals the symmetrical arrangement of the two five membered rings attached to the central bridged ring. The bridging imine function is almost parallel to the C1–C4 axis [bond angles are: C3–C4–N1 108.9(7)°, CC5–C4–N1 110.9(8)°, C2–C1–C11 104.5(7)° and C6–C1–C11 106.7(7)°] but the phenyl substituent attached to C11 is twisted about 40° out of the plane of the C=N bond.

Having established this structure we were able to use NMR data to deduce the structures of the adducts **7**, **8** and **9**. The ^{13}C NMR spectra of compounds **5** and **7** are summarized in Table 4 and distinguishing features of the ^{1}H NMR spectra of all four compounds are shown in Table 5.

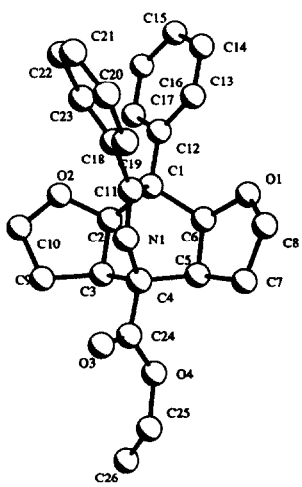
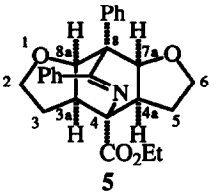
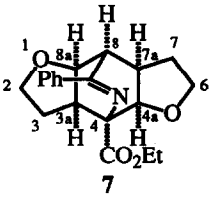


Figure. Structure of compound **5**.

Table 4. ^{13}C NMR spectra of compounds **5** and **7**.[a]

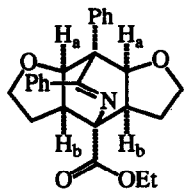
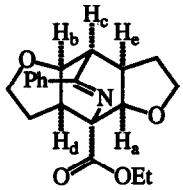
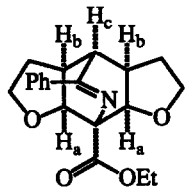
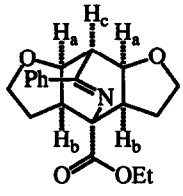
Compound	^{13}C NMR (δ)
 **5**	$C(CH_2CH_3)$ 15.10; C_3 and C_5 29.44; C_{3a} and C_{4a} 48.28; C_8 57.75; C_2 and C_6 62.08; C_4 67.84; $C(CH_2CH_3)$ 68.08; $C_{7a}$and C_{8a} 81.96; C(Ph) 127.28, 127.48, 127.88, 129.11, 131.43, 138.41, 140.11; C(C=O) and C(C=N)169.95, 173.43.
 **7**	$C(CH_2CH_3)$ 14.26; C_3 27.58; C_7 30.23; C_{7a} 38.89; C_{3a} 43.46; C_8 44.48; C_2 60.42; C_6 61.55; $C(CH_2CH_3)$ 68.88; C_4 69.89; C_{8a} 80.57; C_{4a} 82.72; C(Ph)126.90, 128.51, 130.62, 138.44; C(C=O) and C(C=N) 172.44, 175.95.

[a] Attached proton test (APT) experiments, decoupled spectra and off-resonance decoupled spectra were used to determine the assignment.

Conclusions.

The Diels-Alder reaction of 1,2,4-triazines with cyclic vinyl ethers gives primary adducts which easily eliminate nitrogen. In most cases this is followed by an easy opening of the oxygen heterocycle, leading to the formation of a diversity of substituted pyridines from easily available starting materials. The reaction has some limitations. 1,2,4-Triazines with enough electron attracting groups are required in order to produce adducts with any of the cyclic enol ethers. Less activated 1,2,4-triazines do not react with all the dienophiles, although it is possible in some cases to make them react under more vigorous (sealed tube) conditions. The opening of the oxygen heterocycle which leads to the aromatization generating the pyridines is also subjected to some limitations. Ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1b** and ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1f** preferentially give 2:1 adducts with 2,3-dihydrofuran. The triazine **1b** only does so in the sealed tube reaction conditions, whereas for **1f** addition of the second dienophile is favoured relative to the aromatization to pyridine even in chloroform solution. The structure of the 2:1 adduct **5** formed from the triazine **1b** shows that both cycloaddition steps take place with the same regioselectivity whereas that of the major 2:1 adduct **7** from the triazine **1f** shows that the two steps show opposite regioselectivity. As in earlier examples, the regioselectivity of this and other cycloadditions to the triazine **1f** is opposite to that observed with the other triazines studied. The striking reversal of regioselectivity of the cycloaddition reactions of triazines **1b** and **1f**, which differ only by the presence of an extra phenyl substituent in **1b**, is not easily explained by simple steric or electronic arguments.

Table 5. ^{1}H NMR Spectra of Compounds **5**, **7**, **8**, and **9**

2:1 Adduct	^{1}H NMR (δ in ppm and J in Hz)	2:1 Adduct	^{1}H NMR (δ in ppm and J in Hz)
 **5**	H_b 3.07, ddd H_a 4.44, d, J_{ab} = 8.45	 **7**	H_e 2.61, approx.dddd H_d 2.86, approx. ddd H_c 3.88, t, $J_{cb} = J_{ce}$ = 3.0 H_b 4.23, dd, J_{bd} = 8.7 and J_{bc} = 3.0 H_a 4.53, d, J_{ae} = 8.5
 **8**	H_b 2.64, m H_c 3.76, t, J_{cb} = 2.65 H_a 4.58, d, J_{ab} = 8.6	 **9**	H_b 2.87, approx. dd, further split H_c 4.08, t, J_{ca} = 2.9 H_a 4.33, dd, J_{ac} = 2.9 and J_{ab} = 8.6

EXPERIMENTAL

General

^{1}H NMR spectra were recorded on a Bruker ACE200 spectrometer operating at 200MHz or on a Bruker AMX400 instrument operating at 400 MHz. The solvent is deuteriochloroform except where indicated otherwise. Signals are singlets where no multiplicity is shown. Mass spectra were recorded under electron impact at 70 meV or under chemical ionisation (NH_3) on a VG Micromass 7070E instrument. M.p.'s were recorded on a Reichert hot stage. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

1,2,4-Triazines

The following triazines were prepared by literature procedures: ethyl 5,6-diphenyl-1,2,4-triazine-5,6-dicarboxylate **1b**,[7] diethyl 3-methyl-1,2,4-triazine-5,6-dicarboxylate **1d**,[8] triethyl 1,2,4-triazine-3,5,6-tricarboxylate **1e**[9] and ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1f**.[10]

Diethyl 3-acetamido-1,2,4-triazine-5,6-dicarboxylate **1c**. To a solution of aminoguanidine hydrogen carbonate (1.0 g, 7.3 mmol) in water (60 ml) diethyl dioxosuccinate (1.48 g, 7.3 mmol) was added The solution was stirred at room temperature for 23 h. The aqueous solution was extracted with chloroform and the organic solvent was evaporated off, leaving diethyl 3-amino-1,2,4-triazine-5,6-dicarboxylate **1a** (1.31 g, 54%) as a yellow solid, m.p. 118–120 °C; δ 1.38 (6 H, t), 4.38 (4 H, q) and 6.26 (2 H, bs). Diethyl 3-amino-1,2,4-triazine-5,6-dicarboxylate (1.13 g, 4.7 mmol) was dissolved in dry THF (10 ml), under argon, acetic anhydride (1.2 g, 11 mmol) and anhydrous sodium carbonate (1.2 g, 11.3 mmol) were added. The mixture was heated at 70 °C for 91 h. The solution was diluted with water and the aqueous phase was extracted with chloroform. The organic phase was washed with saturated aqueous sodium hydrogencarbonate and the chloroform was evaporated off. To the crude product ether was added and the mixture was filtered, leaving the *triazine* **1c** (0.5 g). The ether was evaporated off and the residue was purified by flash chromatography [hexane-ethyl acetate (1:1)]. This gave a further amount of the *triazine* **1c** (0.17 g, total yield 37 %), m.p. 133-134 °C (from ether) (Found: C, 46.9; H, 5.0; N, 19.8. $C_{11}H_{14}N_4O_5$ requires C, 46.8; H, 5.0; N, 19.8 %); δ 1.5 (6 H, m), 2.4 (3 H) and 4.4 (4 H, m); *m/z* 282 (M^+, 17%), 237 (7), 184 (22), 165 (17) and 43 (100).

Reactions in Chloroform

Ethyl 3-[2'-(2"-Tetrahydrofuranyloxy)ethyl)]-5,6-diphenylpyridine-2-carboxylate **3a'**. Ethyl 5,6--diphenyl-1,2,4-triazine-3-carboxylate **1b** (0.4 g, 1.3 mmol) was dissolved in chloroform (20 ml) and 2,3--dihydrofuran **2d** (3 ml, 39.6 mmol) was added After 46 h at reflux, the solvent was evaporated off.and the residue was purified by flash chromatography [hexane, hexane–ethyl acetate (4:1), then hexane–ethyl acetate (3:1)] giving the *pyridine* **3a'** (0.3 g, 55 %) as an oil; $\nu_{max.}$ (cm^{-1}) (neat) 2930, 1725, 1100 and 1040; δ 1.44 (3 H, t), 1.86 (4 H, m), 3.22 (2 H, t), 3.85 (4 H, m), 4.45 (2 H, q), 5.11 (1 H, m), 7.28 (10 H, m) and 7.70 (1 H); δ (^{13}C) 14.14, 23.34, 32.25, 32.51, 61.51, 66.80, 103.74, 127.46, 127.76, 128.26, 129.26, 129.97, 133.35, 137.61, 139.11, 141.74, 147.29, 154.63 and 166.48; *m/z* 417 (M^+, 76%), 346 (12), 317 (97) and 302 (55).

*5,6-Dihydro-2,3-diphenyl-8*H*-pyrano[3,4-b]pyridin-8-one* **4**. Pyridine **3a'** (0.23 g, 0.55 mmol) was dissolved in chloroform (10 ml) and water (5 ml) and perchloric acid (70 %, 5 ml) were added. The solution was stirred at room temperature for 13 h. The solution was diluted with water, extracted with chloroform, the organic layer was separated off, washed with aqueous sodium hydrogen carbonate and the organic layer was evaporated. The residue was purified by flash chromatography [hexane–ethyl acetate (3:1), hexane–ethyl acetate (1:1), then ethyl acetate] giving the lactone **4** (0.115 g, 70 %) as a colourless solid, m.p. 220–221 °C (from ethyl ether-acetone) (lit.,[3] m.p. 220-222 °C) (Found C, 79.8; H, 5.0; N, 4.5. Calc. for $C_{20}H_{15}NO_2$: C, 79.7; H, 5.0; N, 4.7 %); $\nu_{max.}$ (cm^{-1}) (KBr) 1736, 1109 and 769; δ 3.21 (2 H, t), 4.63 (2 H, t), 7.26 (10 H, m) and 7.67 (1 H); δ (^{13}C) 27.26, 66.83, 127.99, 128.12, 128.35, 129.34, 130.12, 134.33, 138.08, 138.57, 138.77, 140.31, 141.13, 158.18 and 162.77; *m/z* 301 (M^+, 47 %), 300 (100), 254 (34) and 120 (4).

Diethyl 3-(2'-hydroxy)ethyl-2-methylpyridine-5,6-dicarboxylate **3c**. Diethyl 3-methyl-1,2,4-triazine-5,6-dicarboxylate **1d** (0.3 g, 1.25 mmol) was dissolved in chloroform (10 ml) and 2,3-dihydrofuran (0.38 ml, 5 mmol). was added. The solution was heated at reflux for 48 h. After adding 1 ml (13.22 mmol) of 2,3-dihydrofuran the solution was further heated for another 96 h. The solvent was evaporated and the residue was purified by flash chromatography [hexane–ethyl acetate (3:1), then hexane–ethyl acetate (1:1)] giving a product which was formulated as the pyridine **3c'** (0.351 g, 80%) as an oil; δ 1.37 (3 H, t), 1.40 (3 H, t), 1.80–2.00 (4 H, m), 2.62 (3 H), 2.93 (2 H, t), 3.63–3.67 (1 H, m), 3.80–4.00 (3 H, m), 4.36 (2 H, q), 4.44 (2 H, q), 5.08–5.10 (1 H, m) and 8.00 (1 H, s, 4-H of pyridine); δ (^{13}C) 14.05, 14.11, 23.43, 32.40, 32.57, 61.72, 62.07, 65.66, 67.13, 103.98, 123.21, 134.56, 138.18, 149.05, 160.74, 165.41 and 166.97; *m/z* 351 (M^+, 1.7%), 251 (26) and 71 (100). Pyridine **3c'** (0.108 g, 0.31 mmol) was dissolved in chloroform (2 ml) and perchloric acid (70%, 0.05 ml) was added dropwise. The solution was stired at room temperature for 15 minutes. The solution was diluted with water and the aqueous phase was extracted with chloroform. The

organic phase was washed with saturated aqueous solution of sodium hydrogen carbonate and the chloroform was evaporated off. The crude product was purified by flash chromatography [hexane-ethyl acetate (1:1), then ethyl acetate], giving the pyridine **3c** (0.06 g, 68%) as an oil; δ 1.33 (3 H, t), 1.38 (3 H, t), 2.58 (3 H, s), 2.88 (2 H, t), 3.83 (2H, t), 4.26 (2 H, q), 4.34 (2 H, q) and 7.80 (1 H). The compound was not characterised further.

Diethyl 2-methyl-3-(3'-hydroxy)propylpyridine-5,6-dicarboxylate **3d.** Diethyl 3-methyl-1,2,4-triazine-5,6-carboxylate **1d** (0.15 g, 0.62 mmol) was dissolved in chloroform (10 ml) and 3,4-dihydro-2*H*-pyran (0.23 ml, 2.5 mmol) was added. The solution was heated at reflux for 120 h. After adding 0.67 ml (7.44 mmol) of 3,4-dihydro-2*H*-pyran the solution was further heated for another 45 h. The solvent was evaporated and the residue was purified by flash chromatography [hexane–ethyl acetate (1:1)] giving the pyridine **3d'** (0.09 g, 38%) as an oil; $\nu_{max.}$ (cm^{-1}) (neat) 2986, 1751, 1267 and 1016; δ 1.16–2.13 (6 H, m), 1.43 (3 H, t), 1.49 (3 H, t), 3.0 (3 H), 3.90–4.10 (8 H, m), 4.40 (2 H, q), 4.46 (2 H, q), 4.92–4.96 (1 H, m) and 7.70 (1 H, s). Pyridine **3d'** (0.11 g, 0.31 mmol) was dissolved in chloroform (2 ml) and perchloric acid (70%, 0.05 ml) was added dropwise. The solution was stired at room temperature for 12 h. The solution was diluted with water and the aqueous phase was extracted with chloroform. The organic phase was washed with saturated aqueous sodium hydrogen carbonate and the chloroform was evaporated off. The crude product was purified by flash chromatography [hexane–ethyl acetate (1:1)] giving the pyridine **3d** (0.062 g, 68%) as an oil; δ 1.35 (6 H, m), 2.03 (2 H, m), 2.58 (3 H), 2.76 (2 H, t), 3.62 (2H, t), 4.3 (4 H, m) and 7.8 (1 H). The pyridine was further characterised as its acetate, which was prepared as follows: compound **3d** (0.5 g, 1.48 mmol) was dissolved in acetic anhydride (5 ml) and the solution was heated under reflux for 12 h. The solution was diluted with water and the aqueous phase was extracted with chloroform. The organic phase was washed with saturated aqueous solution of sodium hydrogencarbonate and the chloroform was evaporated off. The crude product was purified by flash chromatography [hexane-ethyl acetate (3:1)], giving the *diethyl 2-methyl-3-(3'-acetoxy)propylpyridine-5,6-dicarboxylate* (0.49 g, 87.5%) as an oil; δ 1.30 (3 H, t), 1.35 (3 H, t), 1.85–2.00 (2 H, m), 2.58 (3 H, s), 2.76 (2 H, t), 4.03 (2 H, t), 4.25 (2 H, q), 4.33 (2 H, q) and 7.87 (1 H, s); *m/z* 337.1526 (M^+, 6%) ($C_{17}H_{23}NO_6$ requires M, 337.1525).

Triethyl 3-(2'-hydroxy)ethylpyridine-2,5,6-tricarboxylate **3e.** Triethyl 1,2,4-triazine-3,5,6-tricarboxylate **1e** (0.4 g, 1.34 mmol) was dissolved in chloroform (10 ml) and 2,3-dihydrofuran (0.1 ml, 16.08 mmol) was added. The solution was heated at reflux for 49 h. After evaporation of the solvent the residue was purified by chromatography [ethyl acetate–hexane (2:1)] giving the *pyridine* **3e** (0.35 g, 77%) as a pale yellow solid, m.p. 90-92 °C (from hexane–ether) (Found C, 56.8; H, 6.7; N, 4.5. $C_{16}H_{21}NO_7$ requires C, 56.6; H, 6.2; N, 4.1 %); $\nu_{max.}$ (cm^{-1}) (KBr) 2986, 1730, 1282 and 1194; δ 1.35–1.45 (9 H, m), 3.28 (2 H, t), 4.40–4.45 (6 H, m), 4.63 (2 H, t) and 8.0 (1 H); δ (^{13}C) 13.79, 27.14, 62.34, 62.47, 66.52, 128.84, 137.13, 137.91, 143.84, 151.25, 160.89, 163.89 and 165.08; *m/z* 339 (M^+, 1%), 336 (14), 266 (7.), 249 (31), 220 (93) 177 (46) amd 149 (100).

Triethyl 3-(3'-hydroxy)propylpyridine-2,5,6-tricarboxylate **3f.** Triethyl 1,2,4-triazine-3,5,6-tricarboxylate **1e** (0.2 g, 0.67 mmol) was dissolved in chloroform (10 ml) and 3,4-dihydro-2*H*-pyran (0.6 ml, 8 mmol) was added. The solution was heated at reflux for 49 h. After evaporation of the solvent the residue was purified by flash chromatography [hexane–ethyl acetate (3:1), then hexane–ethyl acetate (1:1)] giving the *pyridine* **3f** (0.189 g, 80%) as an oil; $\nu_{max.}$ (cm^{-1}) (neat) 3439, 2982, 1730 and 1323; δ 1.39 (3 H, t), 1.40 (3 H, t), 1.42 (3 H, t), 1.90–2.05 (2 H, m), 3.02 (2 H, t), 3.65 (2 H, t), 4.40–4.45 (6 H, m) and 7.86 (1 H, s); δ (^{13}C) 13.89,14.01, 28.35, 33.50, 61.12, 62.27, 62.38, 127.74, 139.16, 140.27, 148.29, 150.22, 164.68 and 165.51; *m/z* 353.1468 (M^+, 12%) ($C_{17}H_{23}NO_7$ requires M, 353.1474), 322 (80), 308 (33), 280 (39) 209 (56) and 163 (100).

Triethyl 3-(3'-oxo)propylpyridine-2,5,6-tricarboxylate **3g.** Triethyl 1,2,4-triazine-3.5.6-tricarboxylate **1e** (0.18 g, 0.6 mmol) was dissolved in chloroform (10 ml) and 3,4-dihydro-2-ethoxy-2*H*-pyran (0.33 ml, 2.46 mmol) was added. The solution was heated at reflux for 40 h. After addition of 0.33 ml of 3,4-dihydro-2-ethoxy-2H-pyran the solution was further heated for another 80 h. The solvent was evaporated off and the residue was purified by flash chromatography [hexane–ethyl acetate (3:1), hexane–ethyl acetate (1:1), then ethyl acetate] giving the pyridine **3g** (0.169 g, 80%) as an oil; $\nu_{max.}$ (cm^{-1}) (neat) 2980, 1728, 1275 and 1115; δ 1.37–1.44 (9 H, m), 2.94 (2 H, t,), 3.23 (2 H, t), 4.41–4.47 (6 H, m), 8.21 (1 H) and 9.81 (1 H); δ (^{13}C) 13.55, 13.59, 13.69, 24.60, 44.03, 61.96, 127.35, 137.91, 140.39, 148.36, 149.66, 164.09, 164.66, 165.15 and 199.76; *m/z* 351 (M^+, 2%), 322 (72), 294 (100) and 278 (52). The aldehyde **3g** (0.38 g, 1 mmol) was converted into its *semicarbazone* (90%), a colourless solid, m.p. 120–125 °C (from ethyl acetate-hexane) (Found: C, 52.2; H, 5.7; N, 13.1. $C_{18}H_{24}N_4O_7$ requires C, 52.9; H, 5.9; N, 13.7%).

Diethyl 2-acetamido-3-(2'-hydroxy)ethylpyridine-5,6-dicarboxylate **3b.** Diethyl 3-acetamido-1,2,4-triazine-5,6-dicarboxylate **1c** (0.2 g, 0.7 mmol) was dissolved in chloroform (15 ml) and 2,3-dihydrofuran (1.8 ml, 23.76 mmol) was added. After five days at reflux, the solvent was evaporated and the residue was purified by flash chromatography [hexane-ethyl acetate (1:1)] giving diethyl 2-acetamido-3-[2'-(2"-tetrahydrofuranyloxy)-ethyl]pyridine-5,6-dicarboxylate **3b'** (0.185 g, 67 %) as an oil; δ 1.6–1.42 (6 H, m), 1.92–1.96 (4 H, m), 2.42 (3 H, s), 2.9 (2 H, t), 3.81–3.87 (4 H, m), 4.42–4.46 (4 H, m), 5.06–5.10 (1 H, m), 8.05 (1 H, s) and 9.14 (1 H, bs). The pyridine **3b'** was dissolved in chloroform and treated with 1M HCl. \ Workup by flash chromatography [hexane–ethyl acetate (1:1)] gave the *pyridine* **3b** as a colourless solid, m.p 150–151 °C (from ethyl acetate–ether) (Found: C, 55.4; H, 6.2; N, 8.6. $C_{15}H_{20}N_2O_6$ requires C, 55.6; H, 6.2; N, 8.7 %); $\nu_{max.}$ (cm^{-1}) (KBr) 3429, 3316, 3186, 1747, 1720 and 1278; δ 1.34 (3 H, t), 1.40 (3 H, t), 2.11 (3 H, s), 2.85 (2 H, t), 4.22 (2 H, t), 4.32 (3 H, q), 4.41 (3 H, q), 5.62 (1 H, br s) and 7.88 (1 H, s); *m/z* 324 (M^+, 23 %), 279 (22), 264 (100) and 120 (64).

2:1 Adducts 7, 8 and 9 from ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1f** *and 2,3-dihydrofuran*. Ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1f** (0.2 g, 0.87 mmol) was dissolved in chloroform (10 ml) and 2,3-dihydrofuran (2 ml, 26.4 mmol).was added After the reaction mixture had been heated for two days under reflux the solvent was evaporated off. Workup by flash chromatography [hexane–ethyl acetate (3:1), hexane–ethyl acetate (1:1), then ethyl acetate] gave the following (in order of elution): (i) the *2:1 adduct* **9** (0.03 g, 10 %) as an oil; δ (400 MHz) 1.38 (3 H, t), 1.70–1.80 (2 H, m), 1.86–1.95 (2 H, m), 2.84–2.90 (2 H, approx. dd), 3.44–3.50 (2 H, overlapping ddd), 3.67 (2 H, approx. dt, *J* 3.9 and 8.0), 4.08 (1 H, t, *J* 2.9), 4.33 (2 H, dd, *J* 8.6 and 2.9), 4.40 (2 H, q), 7.27–7.43 (3 H, m) and 7.83–7.86 (2 H, m); *m/z* 341.1634 (M^+, 17 %) ($C_{20}H_{23}NO_4$ requires M, 341.1627), 313 (5), 270 (100) and 198 (29); (ii) the *2:1 adduct* **7** (0.19 g, 64 %) as a colourless solid, m.p. 102–104 °C (from hexane–ether) (Found C, 70.2; H, 6.8; N, 3.9. $C_{20}H_{23}NO_4$ requires C, 70.4; H, 6.7; N, 4.1 %). δ (400 MHz) 1.39 (3 H, t), 1.73–1.80 (1 H, m), 1.86–1.95 (2 H, m), 1.98–2.05 (1 H, m), 2.61 (1 H, approx. dddd), 2.86 (1 H, approx. ddd), 3.45–3.55 (3 H, m), 3.63 (1 H, approx. dt), 3.72 (1 H, approx. dt), 3.88 (1 H, t, *J* 3.0), 4.23 (1 H, dd, *J* 8.7 and 3.0), 4.42 (2 H, q), 4.53 (1 H, d, *J* 8.5), 7.41–7.45 (3 H, m) and 7.92–7.94 (2 H, m); δ (^{13}C) 14.26, 27.58, 30.23, 38.89, 43.46, 4.48, 60.42, 61.55, 68.88, 69.89, 80.57, 82.72;, 126.90, 128.51, 130.62, 138.44, 175.95 and 172.44; *m/z* 341 (M^+, 6 %), 270 (100), 197 (34) and 193 (26) and (iii) the *2:1 adduct* **8** (0.03 g, 10 %) as a colourless solid, m.p. 137–139 °C (from hexane–ether) (Found C, 70.3; H, 6.8; N, 4.1. $C_{20}H_{23}NO_4$ requires C, 70.4; H, 6.7; N, 4.1 %); δ (400 MHz) 1.35–1.41 (2 H, m), 1.42 (3 H, t), 1.94–2.03 (2 H, m), 2.62–2.66 (2 H, m), 3.47 (2 H, approx. dq), 3.66–3.72 (2 H, m), 3.76 (1 H, t, *J* 2.65), 4.46 (2 H, q), 4.58 (2 H, d, *J* 8.6), 7.41–7.47 (3 H, m) and 8.01–8.03 (2 H, m); *m/z* 341 (M^+, 23 %), 272 (82), 198 (100), 171 (28) and 115 (25).

Sealed Tube Reactions

Ethyl 5,6-diphenyl-3-methylpyridine-2-carboxylate **3h**. Ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1b** (0.1 g, 0.32 mmol) was dissolved in 1-methoxy-1-propene (2 ml, 22 mmol) and heated, in a sealed tube, at 80-85 °C for 114 h. Workup by flash chromatography [hexane-ethyl acetate (3:1)] gave the *pyridine* **3h** (0.7 g, 10 %) as an oil; $\nu_{max.}$ (cm^{-1}) (neat) 2924, 1740, 1716, 1246 and 700; δ 1.42 (3 H, t), 2.22 (3 H, s), 4.42 (2 H, q), 6.95–7.15 (10 H, m) and 8.02 (1 H, s); *m/z* 317.1399 (M^+, 6 %) ($C_{21}H_{19}NO_2$ requires M, 317.1415), 316 (16), 245 (100) and 178 (18).

Ethyl 5,6-diphenyl-3-(3'-hydroxy)propylpyridine-2-carboxylate **3i**. Ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1b** (0.3 g, 0.96 mmol) was dissolved in 3,4-dihydro-2*H*-pyran (3 ml, 32.6 mmol) and heated, in a sealed tube, at 80 °C for 14 days. Workup by flash chromatography [hexane, hexane-ethyl acetate (3:1), then hexane-ethyl acetate (1:1)] gave (i) the pyridine **3i'** (0.111 g, 26%) as an oil; $\nu_{max.}$ (cm^{-1}) (neat) 2941, 2870, 1724, 1313 and 1219; δ 1.43 (3 H, t), 1.50–1.80 (6 H, m), 1.90–2.20 (2 H, m), 1.95–3.10 (2 H, m), 3.3.42–3.60 (2 H, m), 3.75–3.95 (2H, m), 4.46 (2 H, q), 4.60 (1 H, br s), 7.10–7.35 (8 H, m), 7.37–7.41 (2 H, m) and 7.69 (1 H, s); *m/z* 445 (M^+, 1%), 416 (3), 361 (48), 330 (76), 245 (61) and 85 (100); and (ii) the *pyridine* **3i** (0.167 g, 48%) as a pale yellow solid, m.p. 93–96 °C (from hexane–ether) (Found: C, 76.4; H, 6.4; N, 3.8. $C_{23}H_{23}NO_3$ requires C, 76.4; H, 6.4; N, 3.8%); $\nu_{max.}$ (cm^{-1}) (KBr) 3450, 2932, 1726, 1697 and 1319; δ 1.45 (3 H, t), 1.85–2.10 (2 H, m), 3.03 (2 H, t), 3.74 (2 H, t), 4.45 (2 H, q), 7.00–7.55 (10 H, m) and 7.68 (1 H, s); *m/z* 361 (M^+, 8 %), 330 (12), 314 (100) and 268 (43).

Ethyl 6-phenyl-4-(3'-hydroxy)propylpyridine-2-carboxylate **10**. Ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1f** (0.46 g, 2 mmol) was dissolved in 3,4-dihydro-2*H*-pyran (5 ml, 54.3 mmol) and heated, in a sealed tube, at 100 °C for 14 days. Workup by flash chromatography [hexane–ethyl acetate (3:1), then hexane–ethyl acetate (1:1)] gave the *pyridine* **10** (0.28 g, 49 %) as an oil (Found C, 71.3; H, 6.9; N, 4.7. $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.7; N, 4.9%); δ 1.45 (3 H, t), 1.88–2.05 (2 H, m), 2.86 (2 H, t), 3.71 (2 H, t), 4.48 (2 H, q), 7.40–7.55 (3 H, m), 7.73 (1 H, d, *J* 1.6 Hz), 7.91 (1 H, d, *J* 1.6 Hz), and 8.00–8.10 (2 H, m); *m/z* 285 (M^+, 14%), 254 (93), 213 (31), 180 (100) and 169 (64).

Triethyl 3-(3'-oxo)propylpyridine-2,5,6-tricarboxylate **3g**. Triethyl 1,2,4-triazine-3.5.6-tricarboxylic **1e** (0.45 g, 1.5 mmol) was dissolved in 3,4-dihydro-2-ethoxy-2*H*-pyran (4 ml, 29.8 mmol) and heated, in a sealed tube, at 80-85 °C for 5 days. Workup by flash chromatography [hexane-ethyl acetate (3:1), hexane-ethyl acetate (1:1), then ethyl acetate] gave the pyridine **3g** (0.37 g, 70 %) as an oil, which was identified by comparison with the specimen isolated earlier.

Triethyl 3-(3'-hydroxy)propylpyridine-2,5,6-tricarboxylate **3f**. Triethyl 1,2,4--triazine-3,5,6-tricarboxylate **1e** (0.4 g, 1.33 mmol) was dissolved in 3,4-dihydro-2*H*-pyran (4 ml, 43.4 mmol) and heated, in a sealed tube, at 70-75 °C for 4 days. Workup by flash chromatography [hexane-ethyl acetate (3:1), then hexane-ethyl acetate (1:1)] gave the pyridine **3f'** (0.442 g, 76%) as an oil; *m/z* 437 (M^+, 0.3 %), 408 (2), 392 (21), 322 (73), 308 (76) 163 (82) and 81 (5). Pyridine **3f'** (0.17 g, 0.4 mmol) was dissolved in chloroform (5 ml) and perchloric acid (70%, 0.2 ml) was added dropwise. The solution was stired at room temperature for 12 h. The solution was diluted with water and the aqueous phase was extracted with chloroform. The organic phase was washed with saturated aqueous sodium hydrogencarbonate and the chloroform was evaporated off. The crude product was purified by flash chromatography [hexane-ethyl acetate (1:1)], giving the pyridine **3f** (0.113 g, 80%) as an oil, which was identified by comparison with the specimen isolated earlier.

Diethyl 2-methyl-3-(3'-(hydroxy)propylpyridine-5,6-dicarboxylate **3d**. Diethyl 3-methyl-1,2,4-triazine--5,6-carboxylate **1d** (0.14 g, 0.57 mmol) was dissolved in 3,4-dihydro-2*H*-pyran (3 ml, 32.6 mmol) and heated, in a

sealed tube, at 70–75 °C for 14 days. Workup by flash chromatography [hexane–ethyl acetate (1:1)] giving the pyridine **3d** (0.07 g,41%) as an oil, which was identified by comparison with the specimen isolated earlier.

2:1 Adducts **7** *from ethyl 5-phenyl-1,2,4-triazine-3-carboxylate and 2,3-dihydrofuran*. Ethyl 5-phenyl--1,2,4-triazine-3-carboxylate **1f** (0.1 g, 0.435 mmol) was dissolved in 2,3-dihydrofuran (2 ml, 26.4 mmol) and the solution was heated in a sealed tube at 80–85 °C for 3 days. Workup by flash chromatography [hexane–ethyl acetate (3:1), then hexane–ethyl acetate (1:1)] gave the 2:1 adduct **7** (0.1 g, 68 %) as a colourless solid, m.p. 102–104 °C (from hexane–ether), which was identified by comparison with the specimen isolated earlier.

2:1 Adduct **5** *from ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate and 2,3-dihydrofuran*. Ethyl 5,6--diphenyl-1,2,4-triazine-3-carboxylate **1b** (0.1 g, 0.32 mmol) was dissolved in 2,3-dihydrofuran (1 ml, 13.2 mmol) and the solution was heated in a sealed tube at 60 °C for 69 h. Workup by flash chromatography [hexane–ethyl acetate (3:1)] gave the pyridine **3a'** (0.012 g,9 %) as an oil and the 2:1 adduct **5** (0.092 g, 69 %) as a colourless solid, m.p. 188–189 °C (from ethyl acetate-hexane) (Found: C, 75.2; H, 6.4; N, 3.4. $C_{26}H_{27}NO_4$ requires C, 74.8; H, 6.5; N, 3.3 %); δ (400 MHz) 1.38 (3 H, t), 1.85–1.90 (2 H, m), 1.99–2.06 (2 H, m), 3.07 (2 H, approx. ddd), 3.55 (2 H, approx. dq), 3.83–3.88 (2 H, m), 4.42 (2 H, q), 4.44 (2 H, d, *J* 8.45), 7.11–7.22 (8 H, m) and 7.34–7.38 (2 H,m); δ (^{13}C) 15.10, 29.44, 48.28, 57.75, 62.08, 67.84, 68.08, 81.96, 127.28, 127.48, 127.88, 129.11, 131.43, 138.41, 140.11, 169.95 and 173.43; *m/z* 417 (M^+, 100 %), 388 (20), 344 (23), 270 (39) and 105 (45).

Crystal data for $C_{26}H_{27}NO_4$, **5**. M = 417.50, monoclinic, space group $P2_1/n$ (#14), a = 14.254(4), b = 8.062(4), c = 18.580(5) Å, β = 98.34(2)°, V = 2113(1) Å^3, Z = 4, D_c = 1.313 g cm^{-3}, F_{000} = 888, μ (Mo-Ka) = 0.82 cm^{-1}, T = 296 *K*. Number of independent intensities = 2979 from colourless block, 0.300 x 0.250 x 0.200 mm. R = 0.073, R_W = 0.093 for 1280 observed reflections [$I > 4.00\sigma(I)$] and 220 variable parameters.

X-Ray intensity measurements were made using the omega scan technique to a maximum 2Q value of 50.0° on a Rigaku AFC6S diffractometer. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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