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Novel syntheses of the amino-1,2,4-triazine GW356194: identification of a synthesis amenable to scale up

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Abstract—New syntheses of the amino-1,2,4-triazine, GW356194 have been developed to improve on existing methodology. The use of different amidrazones in cyclisations with α-keto and α-amido carbonyl compounds as the key step for the synthesis of the 1,2,4-triazine core was evaluated and the results are presented here.

Lamotrigine **3**, a sodium channel blocker (Fig. 1), is the active component of Lamictal® and is in clinical use as an anticonvulsant therapy. As part of a programme to identify other potential sodium channel blockers for the treatment of disorders of the central nervous system, the 5-amino-1,2,4-triazine, GW356194 **4** was discovered.[1]

The synthesis of Lamotrigine involves the condensation/cyclisation of aminoguanidine **2** with the acylnitrile **1**. Unfortunately, condensation of the corresponding trichlorobenzoylnitrile with amidrazones results in poor 1,2,4-triazine formation with acylation being the main reaction pathway. Therefore, during the lead optimisation phase it was necessary to use a stepwise synthesis of GW356194 **4** (Scheme 1). Thus, condensation of the methylthiosemicarbazide HI salt **6** with the primary ketoamide **5**, followed by dehydration using phosphoryl chloride gave **8**. Subsequent photolytic isomerisation and concurrent thermally mediated cyclisation gave amino-1,2,4-triazine **9**. The SMe group was then removed by oxidation to the sulfone and sodium borohydride mediated reduction.[1]

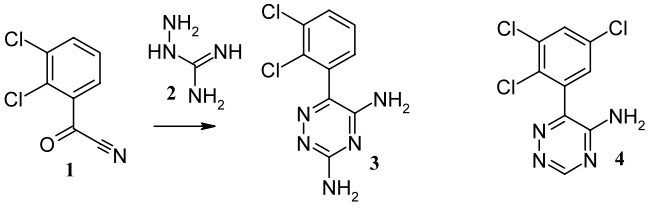

Figure 1.

It was decided that the initial synthesis would not be viable in the long term and therefore we initiated a programme to identify alternative routes for scale up and manufacture of GW356194. The synthesis of 1,2,4-triazines has been extensively reviewed.[2] These heterocycles are often derived from 1,2,4-triazinones, accessible via condensation of amidrazones[3] with α-keto acids, amides and esters and so we envisaged that these would be key intermediates in the synthesis of GW356194.

Initially we found that the low yield in the condensation of **5** with **6** was due to the formation of the 1,2,4-triazinone **10** as a side product.[4] Further investigation of this reaction demonstrated that reaction of **5** and **6** under isomerising conditions gave smooth conversion to **10** in 91% yield. The 1,2,4-triazinone **10** could also be converted to amino-1,2,4-triazine **9** using standard chlorination/amination methodology (Scheme 1). This result encouraged us to consider the use of other 1,2,4-triazinones as key intermediates for the synthesis of GW356194 **4**.

The most direct approach to GW356194 **4**, via the 1,2,4-triazinone **13** (Scheme 2) was investigated initially. We anticipated that the 1,2,4-triazine core of this molecule could be produced by reacting the readily available amidrazones **12**, **15** and **21** with the α-keto

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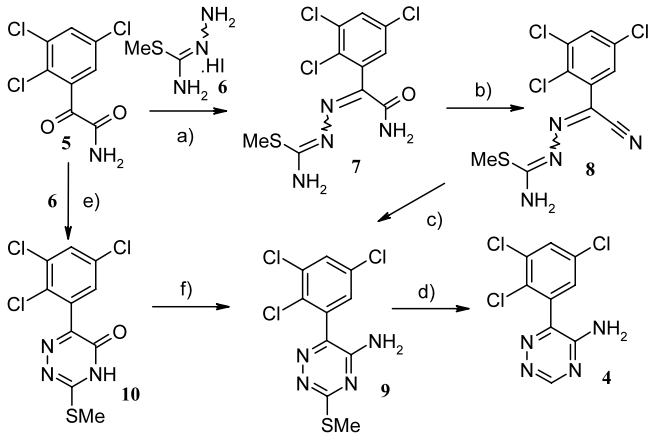
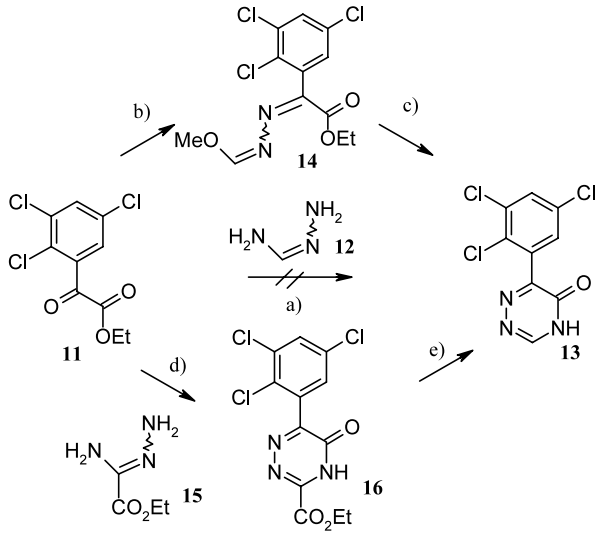


Scheme 1. *Reagents and conditions*: (a) EtOH, reflux, 63%; (b) $(POCl_2)_2O$, 1,4-dioxane, rt, 61%; (c) propan-1-ol, *hv*, 77%; (d) i. *m*CPBA, DMA, EtOAc, ii. $NaBH_4$, EtOH, 63%; (e) EtOH, reflux, *hv*, 91%; (f) i. oxalyl chloride, 1,4-dioxane, ii. NH_3, propan-2-ol, 91%.



Scheme 2. *Reagents and conditions*: (a) EtOH, rt; (b) i. NH_2NH_2, AcOH; ii. $HC(OMe)_3$, $MeSO_3H$; (c) NH_3, EtOH, *hv*, reflux, yields up to 40% (two stages); (d) EtOH, *hv*, reflux, 54%; (e) NaOH, reflux, 81%.

ester **11**, available by acid catalysed ethanolysis of **5**, or one of the α-keto amides **17**, **18**, **19** and **20**, the syntheses of which are described in the preceding paper.[5]

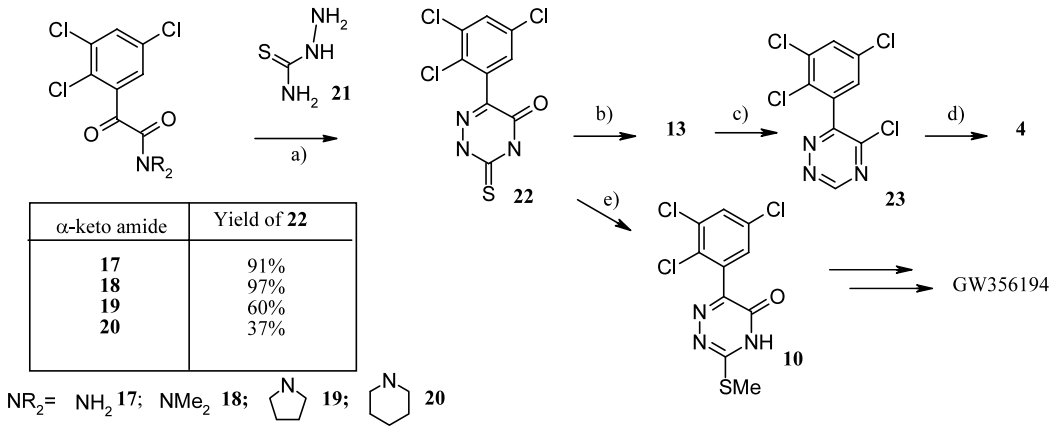
Formamidrazone **12**, formed in situ by the treatment of formamidinium acetate with hydrazine in ethanol,[6] was the amidrazone of choice for the synthesis of **13**, due to potential formation of **13** without the need for further modification. However, despite some success in reacting formamidrazone with methyl benzoylformate, formamidrazone failed to react with the α-keto ester **11**. We assume this is due to increased steric hindrance of the ketone and the instability of formamidrazone. Therefore, we resorted to a stepwise build up of the 1,2,4-triazinone **13** as shown in Scheme 2. Thus, hydrazone formation, followed by formation of iminoether **14** and treatment with ammonia, without isolation, under photolysis conditions gave **13** in moderate yield.

Reaction of ethyl oxamidrazonate **15**,[7] with the α-keto ester **11**, under photolysis conditions gave the 1,2,4-triazinone **16** in 54% yield and subsequent decarboxylation in refluxing sodium hydroxide gave **13** in good yield (Scheme 2). Reaction of **15** with α-keto amides was unsuccessful and degradation occurred, we assume that this is because of the larger energy barrier for cyclisation with an amide compared to an ester.

Thiosemicarbazide **21** is a commercially available amidrazone and we envisaged that if the thio-1,2,4-triazinone **22** could be formed, the unwanted thiol could be removed by oxidative elimination to give **13** (Scheme 3).[8] We found that the best conditions for effecting the cyclisation were to treat the α-keto amides **17**, **18**, **19** and **20** with thiosemicarbazide in refluxing sodium hydroxide and the resulting thio-1,2,4-triazinone **22** could be isolated by neutralisation of the reaction mixture. This procedure was a significant improvement on the other methods for 1,2,4-triazinone formation, as the isomerisation of the intermediate hydrazone was mediated by base rather than photolysis. The thio-1,2,4-triazinone **22** could then be treated with aqueous hydrogen peroxide, according to an optimised procedure,[9] to give mixtures of the corresponding sulfinic and sulfonic acids which, on treatment with concentrated HCl, eliminated to give **13** in good yield.

Having developed several syntheses of **13** we needed to effect the final conversion to GW356194 **4**. In stark contrast to the conversion of **10** to **9**, this proved more difficult than first imagined and we found that the chloro-1,2,4-triazine **23** was particularly unstable. However, after screening a large number of chlorinating agents, we were able to form chloro-1,2,4-triazine **23**, using known conditions by treatment of **13** with >2 equiv. PCl_5 in toluene at 90°C.[10] Treatment of the toluene solution of **23** with ammonia in THF gave GW356194 **4** in 40% yield. Significant quantities of polymeric material were formed both in this reaction and also on deviation from the successful chlorinating conditions or on attempted isolation of **23**. This polymerisation is probably due to the increased electrophilicity of the 3 position of the 1,2,4-chlorotriazine and ring opening of the heterocycle after attack in this position.

Despite the success of using 1,2,4-triazinone **13** as an intermediate for the synthesis of GW356194 **4**, we felt that the final chlorination–amination was not robust enough to be practicable on a large scale. Therefore, we decided to see if intermediate **22** could be converted into the SMe-1,2,4-triazinone **10**. Indeed, treatment of **22** with methyl iodide gave **10** in excellent yield and it was decided that this was the approach to GW356194 **4** most amenable to the scale up and manufacture of this compound.



α-keto amide	Yield of **22**
17	91%
18	97%
19	60%
20	37%

NR_2= NH_2 **17**; NMe_2 **18**; **19**; **20**

Scheme 3. *Reagents and conditions*: (a) NaOH, reflux; (b) i. NaOH, EtOH, H_2O_2, ii. cHCl, 75%; (c) PCl_5, toluene 90°C, >95% solution yield; (d) NH_3, THF, toluene, 40%; (e) MeI, NaOH, EtOH, 91%.

In conclusion, we have explored several new approaches to GW356194 **4** and identified an efficient approach, based on the use of thiosemicarbazide as a key building block for the synthesis of the core heterocycle. The robustness of this key reaction has been demonstrated by the scale up of this process for α-keto amides **18** and **19** to produce >100 g of **22**.

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