Episulfonium ion-mediated cyclic peptide and triazine synthesis†

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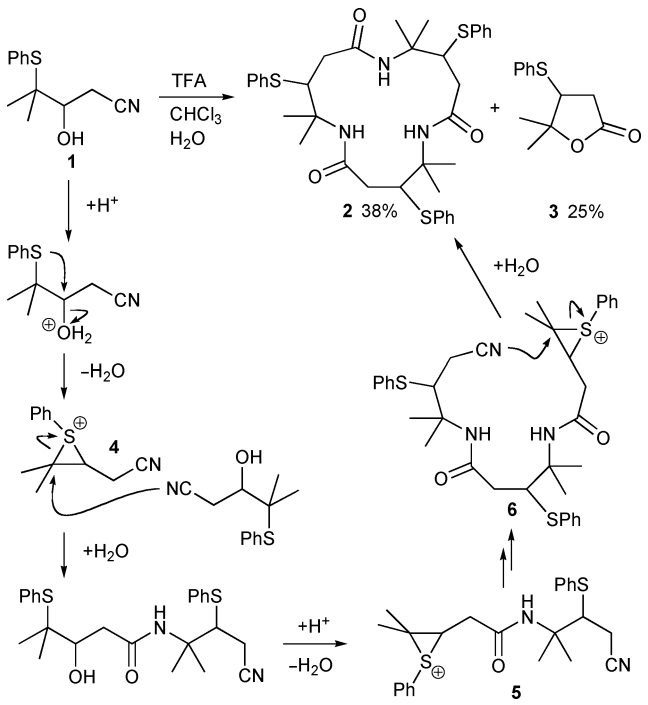
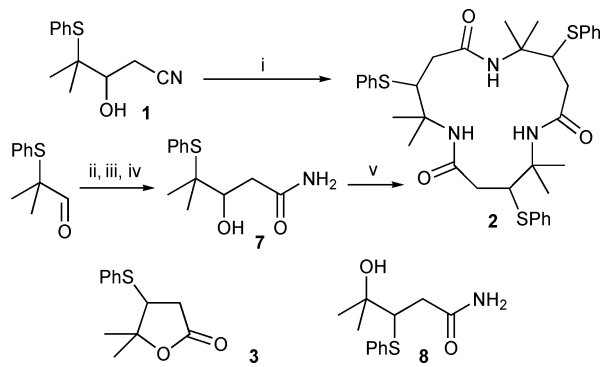
The product of an episulfonium ion-mediated cyclotrimerisation, previously reported as being a 15-membered ring trilactam, has now been shown to be a 1,3,5-triazine. Smaller medium-ring bilactams have, however, been synthesised from linear precursors using the sulfur-based methodology.

We have previously reported that the reaction of hydroxynitrile **1** in acidic conditions produced a trimer with the proposed structure of the 15-membered ring trilactam **2** (Scheme 1).[1] It was assumed that the nitrile starting material was dimerising and then cyclotrimerising *via* intermolecular capture of episulfonium ions,[1] producing secondary amides in a Ritter-type reaction. We considered that the simple intramolecular Ritter reactions of the monomer **4** and dimer **5** episulfonium ions, giving 5- and 10-membered rings respectively, were too strained and that the large-ring trimer cyclisation of episulfonium ion **6** was relatively fast compared with polymerisation. Lactone[2] **3** was thought to be the product of simple nitrile hydrolysis followed by episulfonium-mediated lactone ring closure. We now report further investigations that establish the correct structure for this trimer which is not a macrocyclic trilactam.



Scheme 1

This extremely interesting, and yet surprising, result prompted our continuing investigation of this process. Here, we report that after screening of the reaction solvent and the concentrations of acid catalyst and starting nitrile **1**, the trimer (assumed at the time to be macrocycle **2**) could be synthesised without the addition of water in an optimised yield of 63% (Scheme 2). We sought to improve this yield further by using primary amide **7** as starting material instead of the nitrile **1**. We hoped that the amide nitrogen would act as an intermolecular nucleophile initiating an oligomerisation in an analogous fashion to nitrile **1**. Amide **7** was synthesised *via* aldol reaction and, after the screening of reaction conditions, gave the same trimer product with acid catalysis, but this time in excellent yield (Scheme 2). In incomplete trimerisations of both nitrile **1** and amide **7**, isomeric amide **8** and lactone **3** could be isolated.



Scheme 2 *Reagents and conditions*: i) TFA–hexanes (1 : 5 v/v), 60 °C 63%; ii) EtOAc, LDA, THF, 48%; iii) KOH, H_2O, MeOH, 98%; iv) DCC, NHS, THF; then NH_3, H_2O, 92%; v) TFA–toluene (1 : 10 v/v), 40 °C, 92%. NHS = *N*-hydroxysuccinimide.

The formation of the same sized ring by the ring closure of both nitrile and amide nucleophiles seemed unlikely and prompted analysis of the crude reaction products from both reactions by ^{1}H NMR spectroscopy. The similarity in the reactions was explained by the identification of a common intermediate from both nitrile and amide substrates in less complete reactions. The intermediate, imidate **9** (Scheme 3) has a similar ^{1}H NMR spectrum to that of lactone **3** (Scheme 1). The mechanism of formation of the imidate from the amide was a simple capture of the episulfonium ion by the acyl oxygen. The β-hydroxy group of the nitrile **1** can migrate to the γ-position *via* episulfonium ion **4** and add to the nitrile with acid catalysis to give the imidate. The nitrogen of imidate **9** was potentially a better nucleophile than the nitrogens of either the

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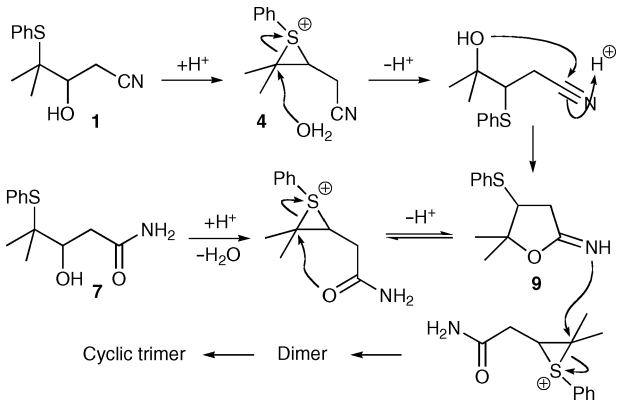
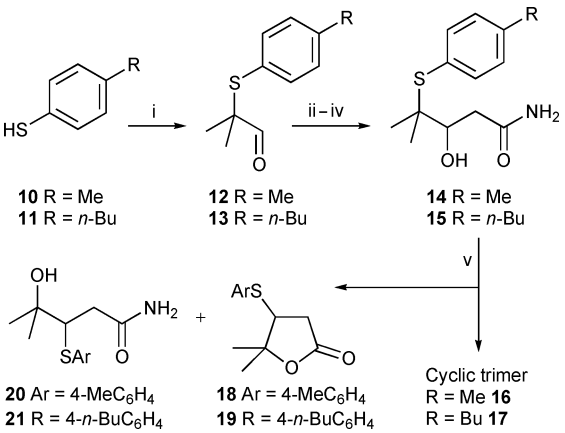


Scheme 3

primary amide or nitrile, and may provide a common route to a linear trimer that can then cyclise to give the proposed macrocycle (Scheme 3). Lactone **3** is a simple hydrolysis product of the imidate and is generally the major by-product in unoptimised reactions.

Further investigations sought to discover why the trimer, rather than say the dimer, tetramer or polymer, is the major product. In fact, no other cyclic oligomers could be identified in the reaction product mixture.

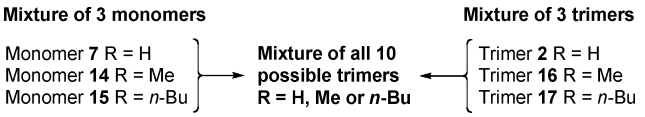
It seemed possible that the oligomerisation and ring closure were reversible, as for other nitrogen ring closures,[3] and the trimer product was significantly more stable than the alternative products in the equilibrating system. To test the reversibility of the imidate trimerisation, a three-way cross-over experiment was designed to discover whether or not the individual units of the cyclic trimer could exchange between different trimer molecules under the reaction conditions. Two trimers with labelled monomer units, differentiated by alkyl group substitution on the phenyl rings, were synthesised. Differently substituted arylsulfanyl amides **14** and **15** were synthesised from 4-methyl- and 4-butyl-benzenethiols **10** and **11** *via* aldehydes[4] **12** and **13** (Scheme 4). Amides **14** and **15** were independently treated with TFA in toluene, as for amide **7**, producing trimethyl- and tributyl-substituted trimers **16** and **17** respectively, which were originally thought to be macrocyclic



Scheme 4 *Reagents and conditions*: i) SO_2Cl_2, Et_3N then $Me_3SiOCH{=}CMe_2$, THF **12** 92%, **13** 79%; ii) EtOAc, LDA, THF; iii) KOH, H_2O, MeOH; iv) DCC, NHS, THF; then NH_3, H_2O, **14** 49%, **15** 41% (over 3 steps); v) TFA–toluene (1 : 10 v/v), 40 °C, **16** 65%, **18** 12%, **20** 15% and **17** 44%, **19** 15%, **21** 30%.

trilactams similar to structure **2**. In each reaction the respective substituted version of lactone **3** and the amides **20** and **21** were also produced as by-products by unwanted imidate hydrolysis.

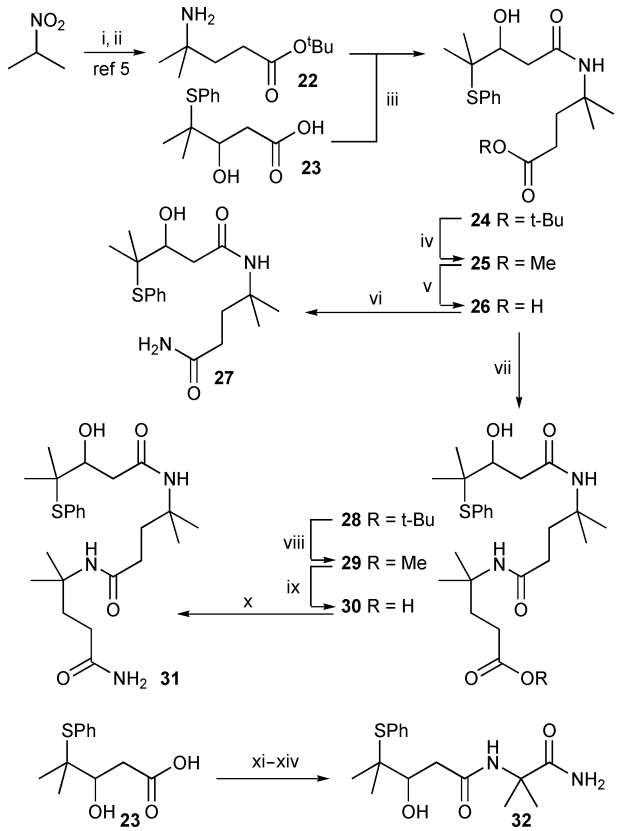
Before the cross-over experiment was performed, a mixture of all of the possible differently alkyl-substituted trimers was independently synthesised by treating a mixture of amides **7**, **14** and **15** with TFA. Analysis of the crude reaction product from this reaction by LCMS identified all ten of the possible trimers from all combinations of hydrogen-, methyl- and butyl-substituted monomers (including trimers with proposed structures **2**, **16** and **17**) by their distinct mass spectra. The key cross-over experiment was then performed: a mixture of 'symmetrical' trimers **2**, **16** and **17** was treated with TFA and the product mixture analysed by LCMS. All ten of the possible trimers were observed, as in the previous experiment, showing that monomer exchange is possible, that the reaction is reversible, and that the synthesis of the trimers is under thermodynamic control (Scheme 5). Simpler experiments involving the mixture of only two starting amides or two trimers were performed and also indicated that the trimerisation is reversible.



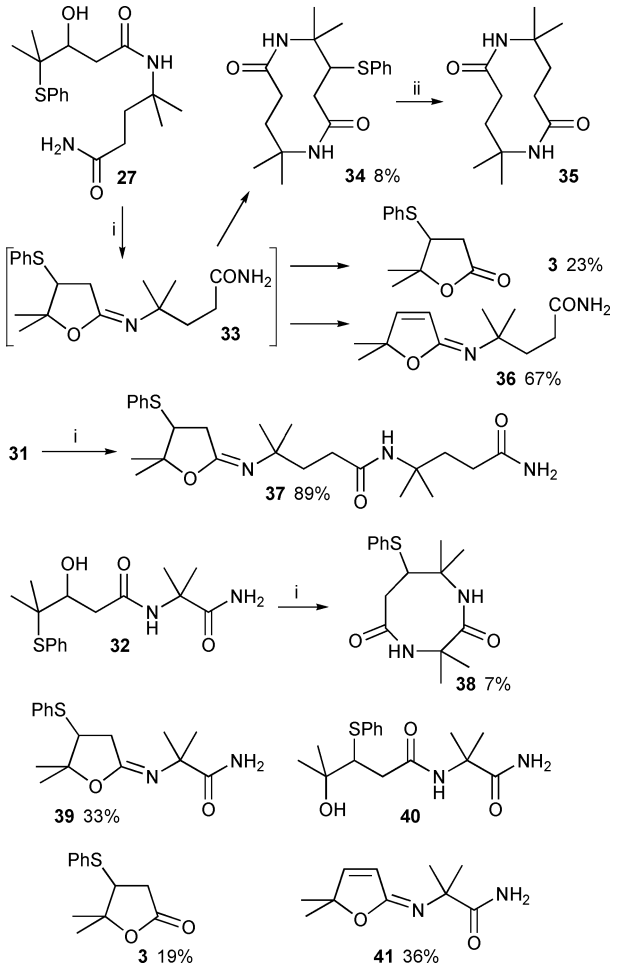
Scheme 5

The ease and selectivity of the synthesis of the ring-forming trimerisation led to consideration of other related macrocyclisation experiments. The first aim for this part of the study was to synthesise and cyclise linear peptides closely related to the possible intermediates in the synthesis of originally proposed macrocyclic trimer **2**. 2-Nitropropane was converted into *tert*-butyl amino-ester[5] **22**, which was coupled onto the hydroxy acid **23**, previously used in the synthesis of amide **7** (Scheme 6). Conversion of the *tert*-butyl ester **24** into the primary amide **27** had to be performed without initiating episulfonium ion generation. Acid-catalysed *trans*-esterification in methanol occurred cleanly, as higher temperatures are usually needed to generate these episulfonium ions in alcohol solvents.[6] Base-mediated saponification of methyl ester **25**, followed by primary amide formation, produced possible 10-membered ring precursor **27**. The coupling of acid **26** to amino-ester **22** led to linear trimer **31**. In addition structurally-related 8-membered ring precursor **32** was synthesised from 2-amino-isobutyric acid (Scheme 6). The secondary amide product of the initial coupling had to be purified from unreacted hydroxy acid **23**, *via* conversion to their methyl esters.

Treatment of linear dimer **27** with TFA in toluene produced 10-membered ring dimer **34** in very low yield, and it could be purified only after desulfurisation with Raney nickel to give bis-lactam[7] **35** (Scheme 7). The other products of the ring closure reaction were the product of benzenethiol elimination (**36**) from the intermediate imidate **33** and lactone **3**. The linear trimer **31** was also treated with acid but the expected 15-membered ring was not formed. The only observed product was the initially formed imidate **37**. Neither the primary nor the secondary amides made a lactam. The failure of the cyclisation of linear trimer **31** was surprising given its similarity to the proposed intermediate in the synthesis of trimer **2** (Scheme 1). It seemed possible, but



Scheme 6 *Reagents and conditions*: i) *tert*-butyl acrylate, DBU, CH_2Cl_2, 95%; ii) H_2, Raney Ni, EtOH, 60%; iii) DCC, HOBt, THF, 79%; iv) MeOH, $SOCl_2$, 69%; v) KOH, H_2O, MeOH, 82%; vi) CDI, HOBt, THF then NH_3, H_2O, 72%; vii) DCC, HOBt, THF then **22**, 67%; viii) HCl, MeOH, 62%; ix) KOH, H_2O, MeOH, 74%; x) CDI, HOBt, THF then NH_3, H_2O, 63%; xi) DCC, HOBt, THF then $H_2NC(CH_3)_2CO_2H$, H_2O; xii) HCl, MeOH; xiii) KOH, H_2O, MeOH; xiv) CDI, HOBt, THF then NH_3, H_2O, 22% (from **23**).



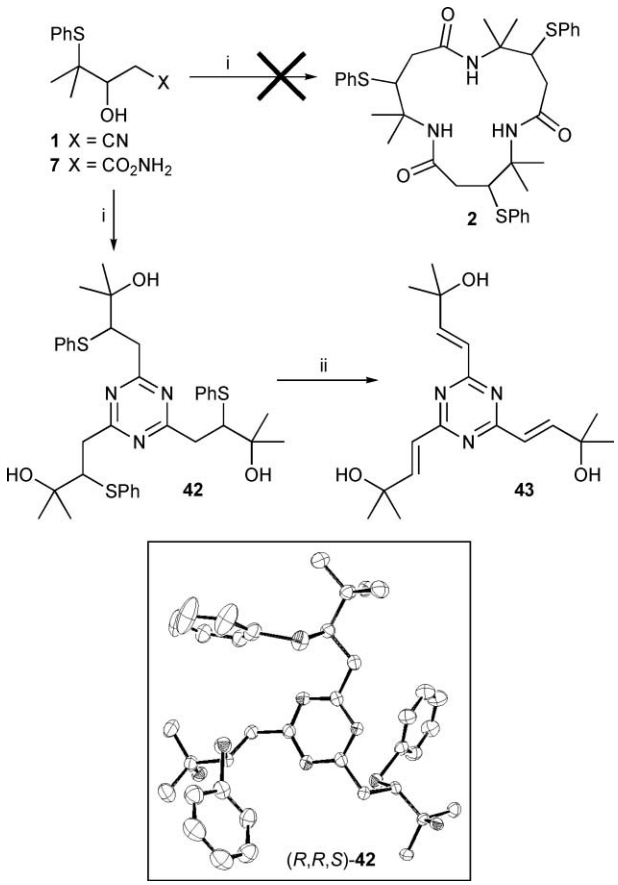
Scheme 7 *Reagents and conditions*: i) TFA–toluene (1 : 10 v/v), 40 °C; ii) Raney Ni, EtOH, 40%.

unlikely, that the two phenylsulfanyl groups missing from amide **31** were responsible for the failure in the cyclisation. Dimer **32** did form some 8-membered ring **38** with acid catalysis, but the major products were the intermediate imidate **39** and its elimination (**41**) and hydrolysis (**3**, **40**) products (Scheme 7).

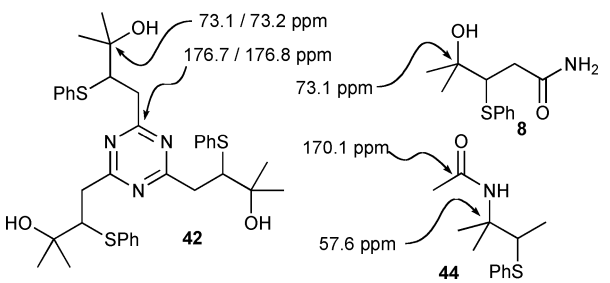
An explanation for the failure of the cyclisation of linear trimer **31** was provided by an attempted *N*-benzylation of the compound we thought was macrocycle **2** with sodium hydride and benzyl bromide. This reaction resulted only in the elimination of three equivalents of benzenethiol and the formation of a symmetrical molecule containing three (*E*)-olefins. X-Ray crystallography of the product (structure not fully reported here) indicated that the eliminated product was triazine **43**, and not a 15-membered ring trilactam (Scheme 8). Therefore the precursor to triazine **43**, previously reported to have the structure trilactam[1] **2**, is the isomeric triazine **42**. Extensive attempts finally yielded crystals of triazine **42** with the quality required for X-ray analysis[8] (Scheme 8). This confirms that the trimers formed in this study, compounds **2**, **16** and **17** as well as all of the 'mixed' compounds formed in the cross-over study, are in fact triazines such as **42**, not trilactams such as macrocycle **2** as previously reported.[1]

Such marked differences between the previously reported and actual structures of the cyclic trimers require explanation. The observed NMR spectra of the trimers is largely consistent with the chemical shifts predicted for the originally proposed trilactam structure **2**. The quaternary ^{13}C NMR resonance at 176 ppm is consistent with that expected for an amide, and the phenylsulfanyl group is bonded to a tertiary carbon (Scheme 9). Both lactam and triazine structures also include similar CH_2 and diastereotopic methyl groups. The remaining quaternary carbon C4 bears an acylated nitrogen in structure **2**, but a hydroxy group in triazine **42**. In the ^{13}C spectrum of the trimer, the chemical shift of the tertiary carbon (73.1 ppm) is more consistent with that of the alcohol **8** than that of the amide[1] **44** (57.6 ppm) (Scheme 9). One additional inconsistency is the strong 1538 cm^{-1} peak in the infra-red spectrum (previously assigned as an amide C=O) which matches that of other 2,4,6-trialkyl triazines[9,10] (*ca.* 1540 cm^{-1}).

The corrected triazine structure **42** is consistent with the number of sets of $CHCH_2$ spin system peak collections observed in the high field ^1H NMR spectrum of the trimer.[1] We previously reported[1] that there were two sets of $CHCH_2$ peaks in the NMR, but closer inspection has revealed a third set of peaks. The intensities of the three peaks occur in the ratio 8 : 4 : 3. As nitrile **1** and amide **7** are racemic, triazine **42** is formed as mixture of diastereoisomers (Scheme 10). One isomer **42a**, with all (*R*)- or all (*S*)-stereocentres, is C_3 symmetric and results in only one set of observable NMR peaks. The (*R*,*R*,*S*)- and (*R*,*S*,*S*)-isomers **42b** produce two spin



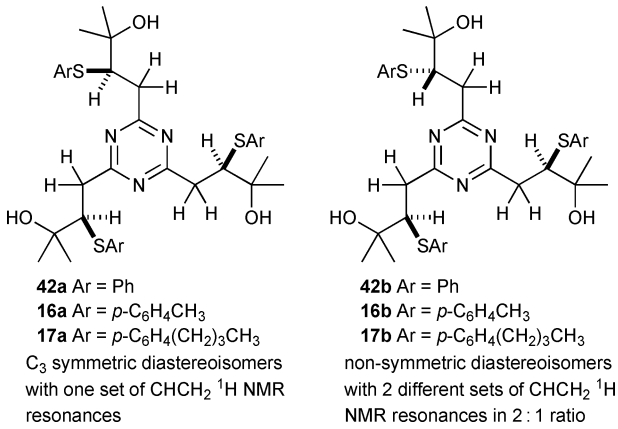
Scheme 8 *Reagents and conditions*: i) TFA–toluene (1 : 10 v/v), 40 °C; ii) NaH, THF >95%. Inset: X-ray crystal structure of one of the stereoisomers of triazine **42** with thermal ellipsoids shown at 50% probability.



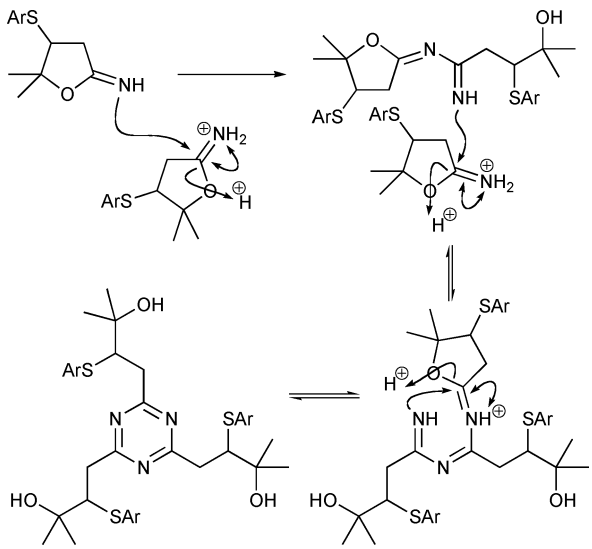
Scheme 9

systems in a 2 : 1 ratio. Owing to the different topology of the cyclo-trilactam, while the C_3 stereoisomer should produce one set of peaks, the (*R*,*R*,*S*)- and (*R*,*S*,*S*)-isomers would produce three sets of peaks. This total of four different $CHCH_2$ spin systems is not observed in a 500 MHz NMR spectrum of the trimerisation product. It should be noted that only the unsymmetrical (*RS*,*RS*,*SR*) diastereoisomer of triazine **42** crystallised from the diastereoisomeric product mixture (Scheme 8).

The importance of cyclic imidate **9** becomes apparent when it is noted that non-cyclic imidates are used in the acid-catalysed synthesis of triazines.[9,11,12] Imidate **9** trimerises with ring opening rather than loss of a simple alcohol (Scheme 11). The availability of the pendant hydroxy group to add as a nucleophile to the triazine



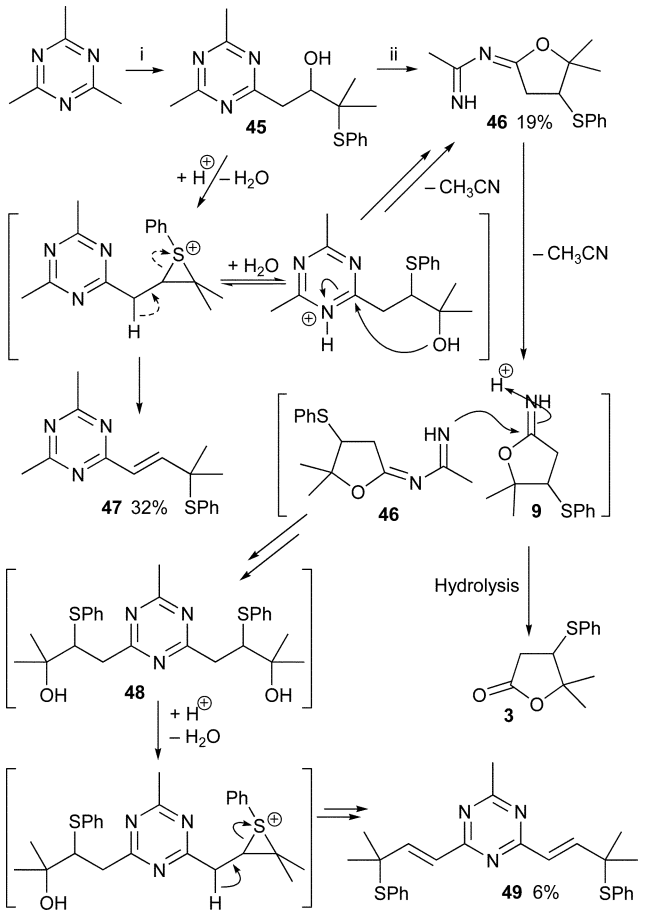
Scheme 10



Scheme 11

ring explains the ready reversibility of the triazine synthesis observed in the cross-over experiments of trimers **42**, **16** and **17**. Substitution of imidates into unsubstituted 1,3,5-triazine, but not trialkyl-triazines, has been reported.[10]

In an attempt to study this intramolecular-hydroxy-faciliated equilibration, alcohol **45** was synthesised from 1,3,5-trimethyl triazine[9] and then subjected to the triazine equilibration conditions used above (Scheme 12). The major products of the reaction were dehydrated starting material **47**, and lactone **3**. The formation of the lactone indicated that imide **9**, formed by opening of the triazine ring, could be an intermediate. The precursor to imide **9**, the amidine **46** formed by the hydroxy-mediated cleavage of acetonitrile from triazine **45**, was also isolated. Such an intermediate has not been isolated from triazine synthesis before and it may have a longer reaction lifetime in this instance as it lacks the additional pendant hydroxy group necessary for the rapid decomposition into two stable cyclic imidates. Most interestingly, the isolation of diene **49** suggests that amidine **46** can react with imide **9** to form a new triazine **48** which dehydrates (Scheme 12).



Scheme 12 *Reagents and conditions*: i) BuLi, $PhSC(Me)_2CHO$, 49%; ii) TFA–toluene (1 : 10 v/v), 40 °C.

In conclusion, we have discovered that the trimer of nitrile **1** is not a cyclic tripeptide but triazine **42**, *via* the sulfur-mediated synthesis of a stable cyclic imidate. This imidate cyclisation is reversible and isolated intermediates have supported the proposed reaction mechanism. This methodology may prove useful for the synthesis of 'dynamic' libraries of aromatic heterocycles, medicinal chemistry intermediates, and molecular scaffolds.[13]

Acknowledgements

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References and notes

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8 Crystal data for **42**. $C_{36}H_{45}N_3O_3S_3 \cdot \frac{1}{2}(H_2O)$, $M = 672.94$, triclinic, space group $P\bar{1}$, $a = 12.2457(2)$, $b = 13.6867(3)$, $c = 22.7701(5)$ Å, $\alpha = 83.977(1)$, $\beta = 80.763(1)$, $\gamma = 75.344(1)°$, $U = 3636.02(13)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.243 mm^{-1}, 39905 reflections measured at 120(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 16301 unique ($R_{int} = 0.088$); $R_1 = 0.071$, $wR_2 = 0.167$ [$I > 2\sigma(I)$]. CCDC reference number 607540. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606882k.
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