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A new method for the synthesis of pyrazolidines.

Faryal Chaudhry,[1] Benson M. Kariuki and David W. Knight*

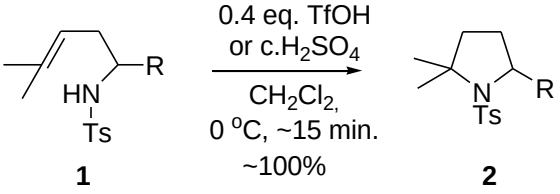
School of Chemistry, Cardiff University, Main College, Park Place, Cardiff, CF10 3AT, UK

Abstract- Fully protected pyrazolidines can be readily obtained by acid-catalysed cyclisations of the corresponding allylic hydrazines by carbenium ion generation using concentrated sulfuric acid in dichloromethane.

Key words: Pyrazolidine; synthesis; acid-catalysed; cyclisation; hydrazines.

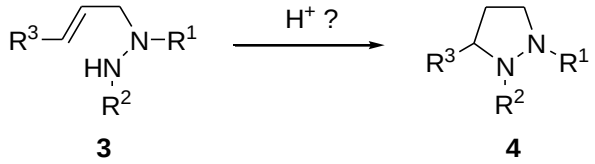
Pyrazoles and their partly and fully reduced derivatives, pyrazolines and pyrazolidines, form an important group of heterocycles, with potentially important contributions to make to drug design by reason of their ability to form strong hydrogen bonds at either or both nitrogen atoms. It is perhaps also significant that Nature does not seem able to form N-N bonds directly and hence such compounds will occupy an entirely non-natural portion of chemical space and hence are likely to continue to play a central role in the discovery of novel pharmaceuticals.[2] Despite the enormous contribution made by heteroaromatic residues, both with and without incorporated nitrogen atoms in a majority of commercial drug structures, it has recently become plain that to achieve a continuation of this success, it would be wise to embrace semi-saturated and fully saturated analogues of such structural features, in order to introduce both greater flexibility and increased three dimensional shape.[2]

Many synthetic routes have been defined for the syntheses of such heterocyclic systems, but quite often these suffer from a lack of regioselectivity, particularly when both C-N bonds are formed effectively simultaneously from a hydrazine and an all-carbon *bis*-electrophile such as a 1,3-dicarbonyl or a conjugated enone.[3] Hence, often it is preferable to assemble such structures using a stepwise approach.[4,5] The inspiration for the present methodology was derived from a possible extension of our finding that unsaturated sulfonamides **1** are readily converted into the corresponding pyrrolidines **2** following exposure to acid,[6] in an intramolecular hydroamination reaction. A particularly rapid and efficient example (Scheme 1) features favourable tertiary carbenium ion generation by protonation of the alkene group in the precursor sulfonamide **1**, which is then trapped by the sulfonamide group to give an essentially quantitative yield of the corresponding pyrrolidines **2**.



Scheme 1. Intramolecular, acid-catalysed hydroamination.

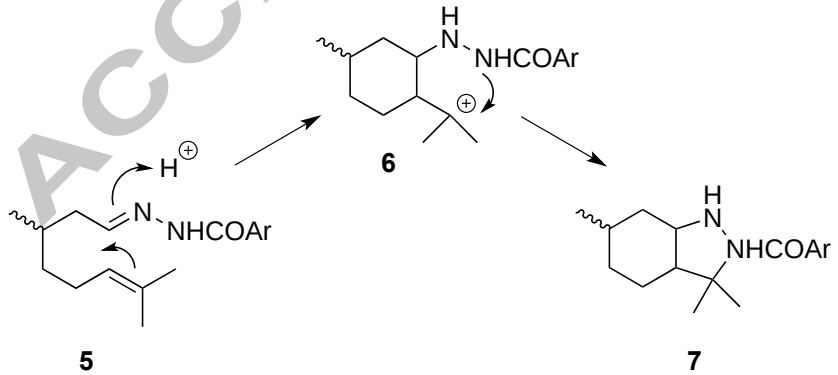
Such cyclisations are quite general and are also successful when secondary carbenium generation is required. The fact that concentrated sulfuric acid can be used in less than stoichiometric quantities gives the method some positive environmental credentials as the only by-product of these usually very clean cyclisations is the sodium or potassium sulfate generated upon mild, basic work-up. Of course, the highly acidic nature of the method will impose some restrictions on future applications; thus far, remote alkenes, alkynes, sulfones, esters and alcohols protected as the corresponding acetates have been found to be stable and not to interfere with such cyclisations. It was against this background that we wondered if such methodology could be extended to include cyclisations of suitably protected allylic hydrazines **3** which, if successful, would result in the definition of a new and perhaps efficient approach to pyrazolidines **4** (Scheme 2).



3 **4**

Scheme 2. The idea: would protected hydrazines cyclise?

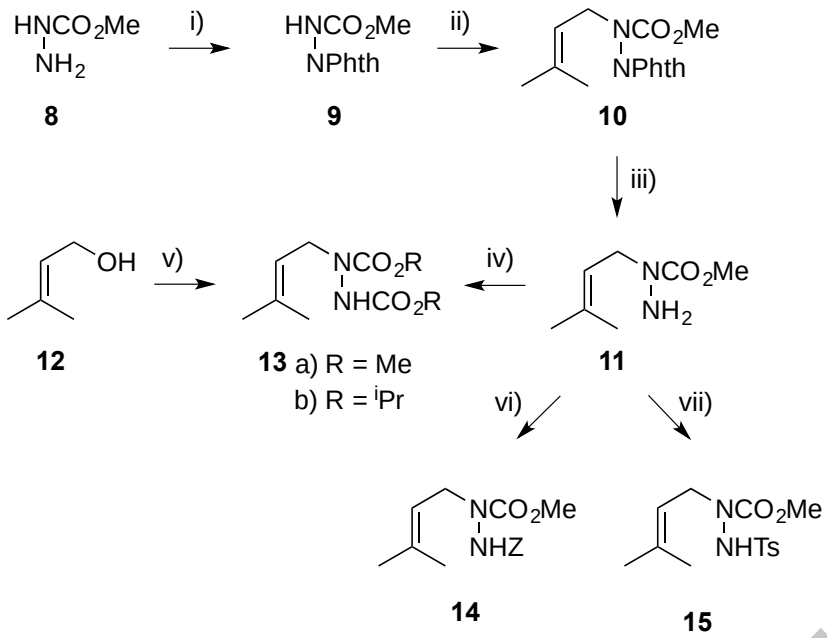
Herein, we report our preliminary results, which show that this idea is indeed viable. A recent report strongly suggested that the methodology shown in Scheme 2 would be successful. In this study, the discovery of novel, two-step cyclisations was described in which the acylhydrazones **5** having a distal prenyl alkene underwent conversion into the annulated pyrazolidines **7** (Scheme 3).[5] A likely mechanism involves imine protonation followed by cyclisation to form a cyclohexane which generates exactly the type of tertiary carbenium ion **6** featured in our pyrrolidine synthesis (Scheme 1), subsequent trapping of which by the newly generated hydrazine leads to the observed products **7**. Of course, as pointed out,[5] alternative mechanisms could well be in operation, but at least a compatibility between such masked hydrazines and an acid-catalysed reaction looked likely.[6]



5 **7**

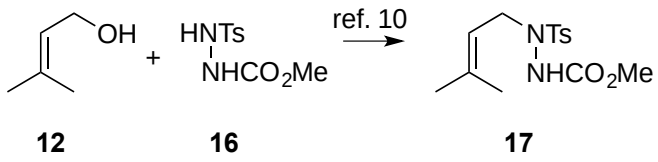
Scheme 3. An acid-catalysed imine cyclisation: possible mechanism.[5]

We relied on the Mitsunobu reaction[7] to obtain suitable substrates for our investigation of the idea shown in Scheme 2, as outlined in Scheme 4.



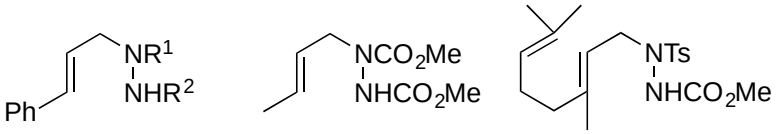
Scheme 4. Starting material synthesis: *Reagents and conditions:* i) a) phthalic anhydride, THF, rt, 0.5 h; b) DCC, rt, 18 h, add HOAc and Et_3N, reflux, 1 h (95%); ii) Ph_3P, THF, 0 °C, DIAD, 0 °C, 0.25 h, alcohol **12**, 0 °C, 0.25 h, add hydrazine **9**, then rt, 18 h (87%); iii) $MeNHNH_2$, CH_2Cl_2, EtOH, 0 °C-rt, 18 h (96%); iv) K_2CO_3, Et_2O, H_2O, amine **11**, add $ClCO_2Me$, rt, 2 h (92%); v) diisopropyl azodicarboxylate, Ph_3P, Et_2O, rt, 18 h (*ca*. 50%); vi) as iv) with $ClCO_2Bn$ (97%); vii) TsCl, pyridine, CH_2Cl_2, 0-20 °C, 18 h (92%).

Starting with methyl carbazate **8**, addition to phthalic anhydride followed by carbodiimide-induced cyclisation gave the doubly protected hydrazine **9**.[8] A Mitsunobu coupling of this intermediate with prenyl alcohol **12** then gave fully substituted hydrazine **10**, Ing-Mansk deprotection of which led to the free amine **11**. Coupling of this with a chloroformate or tosyl chloride then gave precursors **13a**, **14** and **15** in generally excellent yields. More directly, prenyl alcohol **12** was converted into the symmetrically protected hydrazine **13** by a "half-Mitsunobu" wherein no additional nucleophile is added; the hydrazine by-product plays this role.[9] Although more rapid, this direct method never gave much above a 50% yield after careful chromatography and hence the lengthier route was preferred. It did however provide useful structural confirmation of the assigned structures **13** and others. The isomer **17** of the mixed carbamate-sulfonamide protected hydrazine **15** was prepared by a direct, regioselective Mitsunobu alkylation of alcohol **12**.[10]



Scheme 5: Regioselective Mitsunobu coupling.

The methods shown in Scheme 4 were also used to prepare representative phenyl- **18a-c** and a methyl-substituted hydrazine **19** along with the geranyl derivative **20** using cinnamyl, crotyl and geranyl alcohols respectively, in similarly good yields (Figure 1).



18 a) $R^1 = R^2 = CO_2Me$ **19** **20**
b) $R^1 = CO_2Me$; $R^2 = Ts$
c) $R^1 = Ts$; $R^2 = CO_2Me$

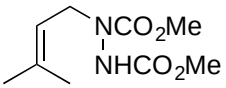
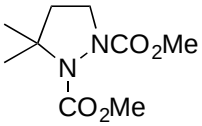
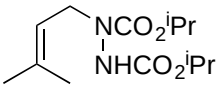
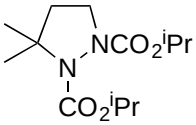
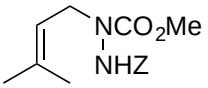
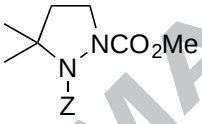
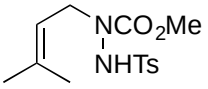
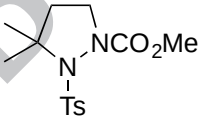
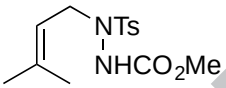
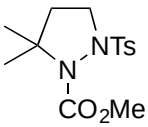
Figure 1. Hydrazines from cinnamyl, crotyl and geranyl alcohols.

In general, the precursors **13-15** and **17-20** were readily purified by column chromatography and subsequently characterized by the usual criteria. However, line broadening was usually evident in both ^1H and ^{13}C NMR spectra, due to restricted rotation. For example, at 400 MHz in $CDCl_3$, the symmetrically protected prenylated hydrazine **13a** showed a pair of broad resonances for the NH group (δ_H 6.6 and 6.8) in a ratio of *ca*. 2:1 but, when combined, integrating accurately for one proton, together with an indistinct methylene resonance centred at δ_H 4.04 and one sharp and one slightly broadened methoxy resonances at δ_H 3.65 and 3.63. Similarly, in the ^{13}C NMR spectrum, while the two allylic methyl groups and one of the methoxy groups appeared as very sharp resonances, the alkene methine (:CH) was slightly broadened and all remaining resonances were very broad. In practise, once such features became familiar, these served as highly characteristic patterns enabling identification of such products.

Our initial attempts to carry out the cyclisation summarized in Scheme 2 were focussed on the precursor **13a** as it should be amongst the easiest to convert into a tertiary carbenium ion and also contained robust, acid-resistant protecting groups. Catalysis of the desired cyclisation using two contrasting acids, concentrated sulfuric and trifluoromethanesulfonic (triflic) acid, was examined.[6] Sulfuric acid is poorly soluble in dichloromethane, the most suitable solvent for such chemistry so far identified,[11] and hence may react in a quite different manner to freely soluble triflic acid.[12]

We were pleased to find that stirring the methoxycarbonyl-protected hydrazine **13a** with 0.5 equivalent of concentrated sulfuric acid in dichloromethane[12] at ambient temperature overnight resulted in complete disappearance of the staring material and isolation of a single product **21** in excellent yield. Similar excellent yields were also obtained but more rapidly by gently refluxing the reaction mixture for three hours or by using triflic acid, when the cyclisation occurred at ice temperature in around two hours. In all cases, work-up was simple: the acid was neutralised using saturated aqueous potassium carbonate and the separated organic layer washed with water then dried ($MgSO_4$) and evaporated.

Table 1. Acid-catalysed cyclisations of hydrazines **13**-**15** and **17**.

Precursor	Conditions	Product	Yield
 **13a**	0.5 eq. $c.H_2SO_4$ 20 °C, CH_2Cl_2, 18 h	 **21**	95%
	0.5 eq. $c.H_2SO_4$ 40 °C, CH_2Cl_2, 3 h		93%
	0.5 eq. TfOH 0 °C, CH_2Cl_2, 2 h		97%
 **13b**	0.5 eq. $c.H_2SO_4$ 20 °C, CH_2Cl_2, 22 h	 **22**	94%
	0.5 eq. $c.H_2SO_4$ 40 °C, CH_2Cl_2, 3 h		93%
 **14**	0.5 eq. $c.H_2SO_4$ 40 °C, CH_2Cl_2, 3 h	 **23**	96%
 **15**	0.5 eq. $c.H_2SO_4$ 0 °C, CH_2Cl_2, 1 h	 **24**	98%
 **17**	0.5 eq. $c.H_2SO_4$ 0 °C, CH_2Cl_2, <1 h	 **25**	94%

Under more vigorous conditions than these, or if the triflic acid was wet, variable loss of the protecting groups was evident from NMR spectra of the crude products. The pattern was much the same with cyclisations of the related *bis*-isopropyloxycarbonyl derivative **13b**, which was converted into the pyrazolidine **22** under similar conditions. Somewhat to our surprise, the benzyloxycarbonyl (Z) group also survived heating to 40 °C to give an equallly good yield of the pyrazolidine **23** (Table 1). Exchanging one of the carbamate groups for a sulfonamide function accelerated the cyclisations, both examples of which (**15** → **24** and **17** → **25**) proceeded rapidly at 0 °C. In the case of substrate **15**, a lower pK_a of the N-H bond to be broken may be responsible,[10] while in the latter example, perhaps greater steric compression due to the tosyl group assists the conversion to pyrazolidine **25**. Overall, the reaction conditions are comsensurate with the intermediacy of a tertiary carbenium ion and are relatively close to our previous observations.[6]

Structural proof of the products was straightforward, although there were a few unexpected characteristics. Disappearance of the resonance for the alkene methine around δ_H 5.2 was the clearest sign of complete reaction. The products all showed similar degrees of resonance broadening due to restricted and/or pseudo-rotation. For example, in the ^{1}H NMR spectrum of the pyrazolidine **13a**, in $CDCl_3$ at 400 MHz and 32 ^{o}C, the two methoxy groups occurred as sharp singlets at δ_H 3.65 and 3.67, while the geminal methyl groups appeared as a sharp single resonance at δ_H 1.41. However, the methylene group remote from nitrogen appeared as a diffuse, broad signal centred on δ_H 1.88 and the two protons of the methylene group adjacent to nitrogen as two diffuse signals centred at δ_H 3.93 and δ_H 3.18. On warming to 50 ^{o}C, the *N*-CH_2 resonances became very broad but the signal due to the other methylene group resolved into a triplet (δ_H 1.87, J = 6.7 Hz). By contrast, when the same sample was used to obtain a ^{13}C proton-decoupled spectrum under the same conditions, all resonances were sharp except for the geminal methyl groups, which appeared as very broadened resonances centred on δ_C 25.3 and 27.4 ppm. Similar effects were observed throughout this series; in many cases, heating the sample in d_6-DMSO produced an even less informative ^{1}H NMR spectrum.

In similar fashion, the mixed carbamate-sulfonamide **24** showed sharp resonances for the tosyl and methoxy groups in its ^{1}H NMR spectrum in $CDCl_3$ at 32 ^{o}C, but separate, broadened resonances for each of the ring protons, centred on δ_H 3.64, 3.43, 1.94 and 1.75 and two broadened singlets for the geminal methyls centred at δ_H 1.61 and 0.97. Once again, all resonances in the ^{13}C spectrum were sharp, except for the methyls which, as in previous examples, appeared as very broadened resonances centred on 24.2 and 28.3 ppm. To be certain of these structural assignments, we carried out an X-ray crystallographic analysis of product **24**, the result of which is shown in Figure 2.[13]

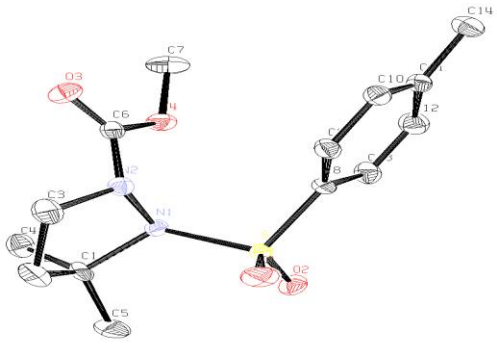
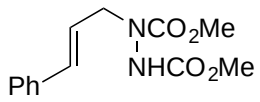
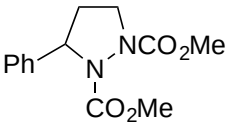
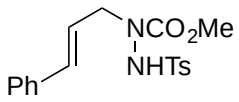
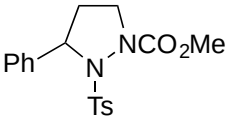
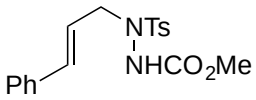
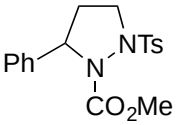
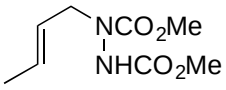
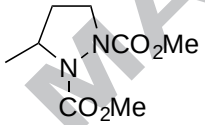
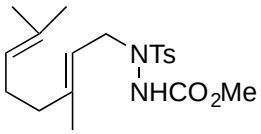
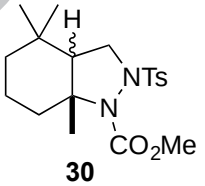


Figure 2. ORTEP diagram of product **24**.

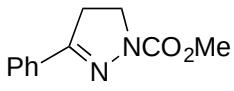
We then continued onto a study of related cyclisations of the less highly substituted substrates **18a-c** and **19**, each of which would give a less stabilised carbenium ion when protonated at the alkene function (Table 2).

In the event, the cyclisations proceeded well under conditions which correlated well with the stability of the intermediate carbenium ion. Using either concentrated sulfuric or triflic acid, cyclisations of the representative cinnamyl derivatives **18a-c** either required heating for 3-6 hours in dichloromethane or a more prolonged reaction time at ambient temperature. At least with these substrates, yields were again excellent.

Table 2. Acid-catalysed cyclisations of hydrazines **18a-c**, **19** and **20**.

Precursor	Conditions	Product	Yield
 **18a**	0.5 eq. c.H_2SO_4 40 °C, CH_2Cl_2, 6 h 0.5 eq. TfOH 35 °C, CH_2Cl_2, 4 h	 **26**	93% 96%
 **18b**	0.5 eq. c.H_2SO_4 20 °C, CH_2Cl_2, 44 h 0.5 eq. c.H_2SO_4 40 °C, CH_2Cl_2, 3 h	 **27**	87% 79%
 **18c**	0.5 eq. c.H_2SO_4 20 °C, CH_2Cl_2, 40 h	 **28**	95%
 **19**	0.5 eq. c.H_2SO_4 85 °C, $(CH_2)_2Cl_2$, 22 h	 **29**	90%
 **20**	0.5 eq. c.H_2SO_4 0 °C, CH_2Cl_2, 1 h	 **30**	98% [3:2 t/c]

Lengthier reaction times again began to cause loss of the protecting groups. In the case of the NHTs derivative **18b**, 18 hours exposure to c.H_2SO_4 at ambient temperature led to clean conversion but only to an extent of *ca*. 50%. In contrast, under both conditions mentioned in Table 2, formation of an isolable by-product was evident (~25 and 15% respectively), which turned out to be compound **31**, formed by elimination of toluenesulfinic acid. This showed characteristic apparent triplets at δ_H 3.94 and 3.19, along with other consistent features. Similar elimination products were thought to be present in the crude reaction mixtures isolated from reactions of the other two cinnamyl-based precursors but were not isolated and therefore not identified with certainly.



31

Figure 3. The elimination product from **18b**

Predictably, the corresponding crotyl derivative **19** required the much more vigorous conditions of reflux in dichloroethane in order to induce cyclisation. Nevertheless, a decent yield of the hoped-for pyrazolidine **29** was isolated, but once again there was evidence for the loss of protecting groups although no products from this were isolated. The products **26**-**29**, in contrast to the foregoing *gem*-dimethyl derivatives (Table 1), exhibited largely first order NMR spectra, with only minimal line broadening.

A final example featured an attempt to use a cascade cyclisation to form a bicyclic derivative. As this would be a return to the intermediacy of tertiary carbenium ions, it was expected to proceed under much milder conditions. In the event, the geranyl-substituted hydrazine **20** was smoothly converted into a mixture **30** of two separable products, in a ratio of *ca*. 3:2, at 0 °C in under one hour. These were assigned as the *trans*- and *cis*-fused products **32** and **33 (**Fig. 4), on the basis of some rather poor quality nOe evidence.

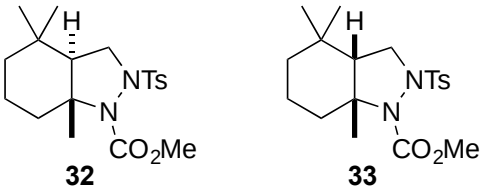


Figure 4. The *trans*- and *cis*-isomers of product **30**.

Fortunately, both were crystalline solids and so X-ray crystallographic analysis was used to confirm these assignments, by measurement of the minor isomer **33**, the resulting ORTEP diagram of which is shown in Figure 5.[14]

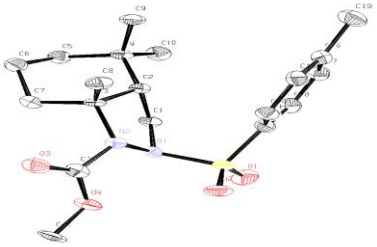


Figure 5. ORTEP diagram of the *cis*-isomer **33**

Some resonances were characteristic of the two isomers in their ^{1}H NMR spectra: in the *trans*-isomer **32**, one of the protons α-to nitrogen appeared as a dd pattern (J = 13.2 and 11.0 Hz) at δ_H 3.22 and a relatively sharp methoxy signal resonating at δ_H 3.63 whereas in the *cis*-isomer **33**, the corresponding protons resonated as an apparent triplet (J = 13.0 Hz) at δ_H 3.09 and a very broadened resonance centred on δ_H 3.40.

These model studies have therefore established that the cyclisations shown in Scheme 2 are indeed viable, despite the presence of two albeit protected nitrogen atoms. Given due attention to the stability or otherwise of additional substituents, this combination of Mitsunobu coupling or, in the future, other C-N formation

methods and the acid-catalysed cyclisation should provide viable and regiospecific access to many types of pyrazolidines.

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References and notes

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11. When temperatures above 45 °C were required, dichloroethane, b.p. 84 °C, was used. As concentrated sulfuric acid can only be largely suspended in dichloromethane, measuring 'standardized' mixtures was also quite inaccurate.

12. Typically, 0.5 equivalent of acid was used with respect to the precursor hydrazine. Reactions were carried out in anhydrous dichloromethane under dry nitrogen. Triflic acid was measured by syringe and added to the solution. Concentrated sulfuric acid was measured dropwise by glass pipette; typically ~30 mg (two drops) was added to 4 mL of dry dichloromethane.

13. X-ray analysis of pyrazolidine **24:** $C_{14}H_{20}N_2O_4S$, Mr=312.38, Triclinic, *P-1*, *a*=8.2711(4) Å, *b*=9.5914(6) Å, *c*= 10.2058(6) Å, □=106.254(3)°, *β*=95.929(3)°, □=95.034(3)°, *V*=767.33(8) Å^3, *Z*=2, D_X=1.352 Mg m^{-3}, *λ*(Mo Kα)=0.71073 Å, *μ*=0.228 cm^{-1}, *F*(000)=332, *T*=160(2) K, crystal size = 0.30 x 0.30 x 0.12 mm3, Reflections collected = 5124, Independent reflections = 3689, 2555 with Fo > 4□(Fo), R_{int} = 0.0462, Final R1 = 0.0892, wR2 = 0.1832 for I>2sigma(I), and R1 = 0.1267, wR2 = 0.199 for all data. The CIF files have been deposit at Cambridge Crystallographic Deposit Center with registry number CCDC 888756.

In the crystal, the toluene and methyl ester groups adopt a *cis* conformation. The other face of the phenyl ring overlaps partly with a ring from a neighbouring molecule resulting in intermolecular π□π interaction.

14. X-ray analysis of pyrazolidine **33:** $C_{19}H_{28}N_2O_4S$, Mr=380.49, Triclinic, *P-1*, *a*=8.8933(6) Å, *b*=10.0576(6) Å, *c*=11.9571(5) Å, □=73.913(3)°, *β*=73.257(3)°, □=80.234(3)°, *V*=979.36(10) Å^3, *Z*=2, D_X=1.290 Mg m^{-3}, *λ*(Mo Kα)=0.71073 Å, *μ*=0.191 cm^{-1}, *F*(000)=408, *T*=160(2) K, crystal size = 0.35 x 0.25 x 0.09 mm3, Reflections collected = 6520, Independent reflections = 4575, 2410 with Fo > 4□(Fo), R_{int} = 0.0598, Final R1 = 0.0914, wR2 = 0.1806 for I>2sigma(I), and R1 = 0.1887, wR2 = 0.2244 for all data. The CIF files have been deposit at Cambridge Crystallographic Deposit Center with registry number CCDC 888757.

The toluenesulfonyl and methyl ester groups adopt a *trans* conformation in the crystal. The phenyl ring is involved in π□π interactions through partial overlap with a ring from a neighbouring molecule. The closest contact made by the opposite face of the ring is through the tertiary hydrogen, with an intramolecular C-H...ring-centroid interaction of *ca.* 2.7 Å.

E-mail: knightdw@cardiff.ac.uk

[Graphical abstract]

A new method for the synthesis of pyrazolidines

Faryal Chaudhry, Benson M. Kariuki and David W. Knight

Protected allylic hydrazines, prepared using Mitsunobu couplings, can be cyclised efficiently to give good to excellent yields of pyrazolidines using strong acid catalysts.

Key words: Pyrazolidine; synthesis; acid-catalysed; cyclisation; hydrazines.

E-mail: knightdw@cardiff.ac.uk

Highlights.

The synthesis of substituted pyrazolidines using simple, cost-effective methodology.

Catalysis by sulfuric acid.

Secondary benzylic and secondary carbenium ions can also be trapped.

Short approach to generate precursors.

Regiospecific pathway.