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A new method for the synthesis of pyrazolidines

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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.

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 NAN 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.¹ 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.¹

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.² Hence, often it is preferable to assemble such structures using a stepwise approach.^{3,4} 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,⁵ 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**.

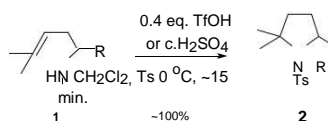
Such cyclisations are quite general and are also successful when secondary carbenium generation is required. The fact that concentrated sulfuric acid can be used in less than stoichiometric quantities gives the method some positive environmental credentials as the only by-product of these usually very 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**).

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**).⁴ A likely mechanism involves imine protonation followed by cyclisation to form a cyclohexane which generates exactly the type of

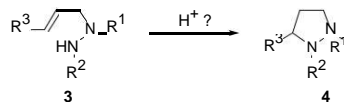
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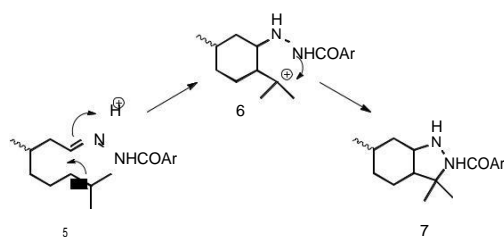
^Y On leave from the Institute of Chemistry, University of the Punjab, Lahore, Pakistan.



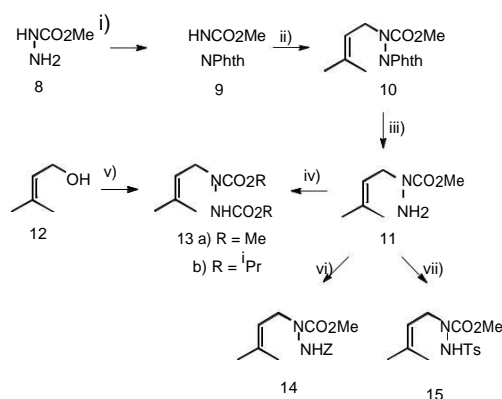
Scheme 1. Intramolecular, acid-catalysed hydroamination.



Scheme 2. Idea: would protected hydrazines cyclise?



Scheme 3. Acid-catalysed imine cyclisation: possible mechanism.⁴

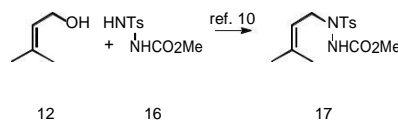


Scheme 4. Starting material synthesis: Reagents and conditions: (i) (a) phthalic anhydride, THF, rt, 0.5 h; (b) DCC, rt, 18 h, add HOAc and Et3N, reflux, 1 h (95%); (ii) Ph3P, THF, 0 °C, DIAD, 0 °C, 0.25 h, alcohol 12, 0 °C, 0.25 h, add hydrazine 9, then rt, 18 h (87%); (iii) MeNHNH2, CH2Cl2, EtOH, 0 °C, 18 h (96%); (iv) K2CO3, Et2O, H2O, amine 11, add ClCO2Me, rt, 2 h (92%); (v) diisopropyl azodicarboxylate, Ph3P, Et2O, rt, 18 h (ca. 50%); (vi) as (iv) with ClCO2Bn (97%); (vii) TsCl, pyridine, CH2Cl2, 0 °C, 18 h (92%).

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,⁴ alternative mechanisms could well be in operation, but at least a compatibility between such masked hydrazines and an acid-catalysed reaction looked likely.⁵

We relied on the Mitsunobu reaction⁶ to obtain suitable sub-strates for our investigation of the idea shown in Scheme 2, as out-lined in Scheme 4.

Starting with methyl carbamate 8, addition to phthalic anhydride followed by carbodiimide-induced cyclisation gave the doubly protected hydrazine 9.⁷ A Mitsunobu coupling of this intermediate with prenyl alcohol 12 then gave fully substituted hydrazine 10, the Ing-Manske 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



Scheme 5. Regioselective Mitsunobu coupling.

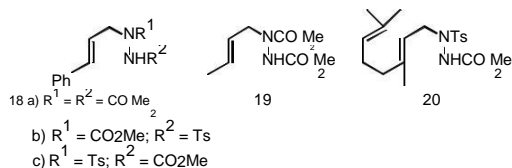


Figure 1. Hydrazines from cinnamyl, crotyl and geranyl alcohols.

symmetrically protected hydrazine 13 by a \hat{O} half-Mitsunobu \hat{O} wherein no additional nucleophile is added; the hydrazine by-product plays this role.⁸ 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 (Scheme 5).⁹

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

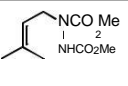

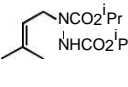

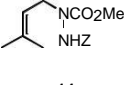

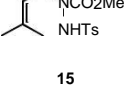

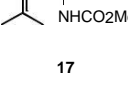

In general, the precursors 13D15 and 17D20 were readily purified by column chromatography and subsequently characterised by the usual criteria. However, line broadening was usually evident in both ¹H and ¹³C NMR spectra, due to restricted rotation. For example, at 400 MHz in CDCl₃, the symmetrically 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 ¹³C NMR spectrum, whilst the two allylic methyl groups and one of the methoxy groups appeared as very sharp res-

onances, the alkene methine (δ _C) was slightly broadened and all remaining resonances were very broad. In practice, once such features became familiar, these served as highly characteristic patterns enabling identification of such products.

Our initial attempts to carry out the cyclisation summarised 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.⁵ Sulfuric acid is poorly soluble in dichloromethane, the most suitable solvent for such chemistry so far identified,¹⁰ and hence may react in a quite different manner with freely soluble triflic acid.¹¹

We were pleased to find that stirring the methoxycarbonyl-protected hydrazine 13a with 0.5 equiv of concentrated sulfuric acid in dichloromethane¹¹ at ambient temperature overnight resulted in complete disappearance of the starting 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 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 (MgSO₄) and evaporated.

Table 1
Acid-catalysed cyclisations of hydrazines 13D15 and 17

Precursor	Conditions	Product	Yield
 13a	0.5 eq c.H ₂ SO ₄ 20 LC, CH ₂ Cl ₂ 18 h 0.5 eq c.H ₂ SO ₄ 40 LC, CH ₂ Cl ₂ 3 h 0.5 eq TfOH 0 LC, CH ₂ Cl ₂ 2 h	 21	95% 93% 97%
 13b	0.5 eq c.H ₂ SO ₄ 20 LC, CH ₂ Cl ₂ 22 h 0.5 eq c.H ₂ SO ₄ 40 LC, CH ₂ Cl ₂ 3 h	 22	94% 93%
 14	0.5 eq c.H ₂ SO ₄ 40 LC, CH ₂ Cl ₂ 3 h	 23	96%
 15	0.5 eq c.H ₂ SO ₄ 0 LC, CH ₂ Cl ₂ 1 h	 24	98%
 17	0.5 eq c.H ₂ SO ₄ 0 LC, CH ₂ Cl ₂ <1 h	 25	94%

Under more vigorous conditions than these, or if the triboic 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-isopropoxy carbonyl 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 LC to give an equally 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 LC. In the case of substrate 15, a lower pK_a of the N-H bond to be broken may be responsible,⁹ whilst in the latter example, perhaps greater steric compression due to the tosyl group assists the conversion to pyrazolidine 25. Overall, the reaction conditions are commensurate with the intermediacy of a tertiary carbenium ion and are relatively close to our previous observations.⁵

Structural proof of the products was straightforward, although there were a few unexpected characteristics. Disappearance of

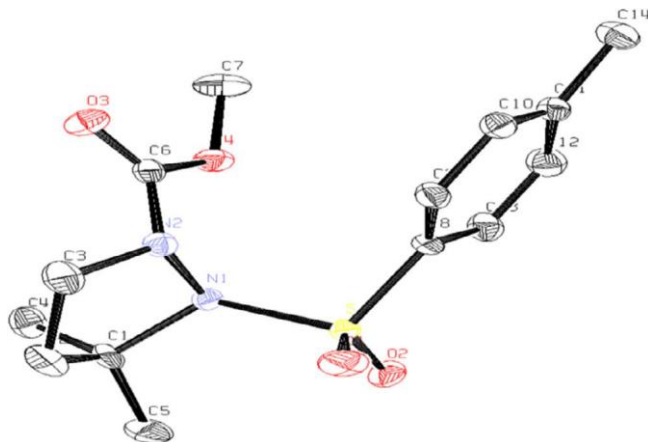


Figure 2. ORTEP diagram of product 24.

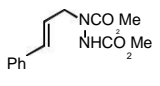
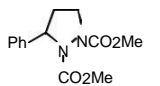
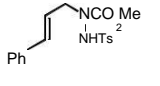
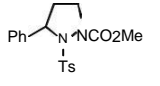
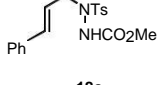
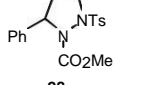
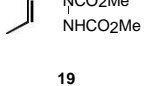
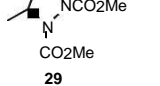
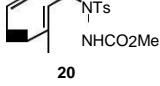
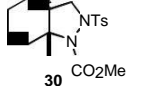
the resonance for the alkene methine around δ_H 5.2 was the clearest sign of complete reaction. The products all showed similar degrees of resonance broadening due to restricted and/or pseudo-rotation. For example, in the ¹H NMR spectrum of the pyrazolidine 13a, in CDCl₃ at 400 MHz and 32 LC, the two methoxy groups occurred as sharp singlets at δ_H 3.65 and 3.67, whilst 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 LC, the N-CH₂ 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 ¹³C 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 d₆-DMSO produced an even less informative ¹H NMR spectrum.

In a similar fashion, the mixed carbamate/sulfonamide 24 showed sharp resonances for the tosyl and methoxy groups in its ¹H NMR spectrum in CDCl₃ at 32 LC, 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 ¹³C 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 2.¹²

We then continued onto a study of related cyclisations of the less highly substituted substrates 18aDc 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 triboic acid, cyclisations of the representative cinnamyl derivatives 18aDc either

Table 2
Acid-catalysed cyclisations of hydrazines 18aDc, 19 and 20

Precursor	Conditions	Product	Yield
 18a	0.5 eq c.H ₂ SO ₄ 40 LC, CH ₂ Cl ₂ 6 h 0.5 eq TfOH 35 LC, CH ₂ Cl ₂ 4 h	 26	93% 96%
 18b	0.5 eq c.H ₂ SO ₄ 20 LC, CH ₂ Cl ₂ 44 h 0.5 eq c.H ₂ SO ₄ 40 LC, CH ₂ Cl ₂ 3 h	 27	87% 79%
 18c	0.5 eq c.H ₂ SO ₄ 20 LC, CH ₂ Cl ₂ 40 h	 28	95%
 19	0.5 eq c.H ₂ SO ₄ 85 LC, CH ₂ Cl ₂ 22 h	 29	90%
 20	0.5 eq c.H ₂ SO ₄ 0 LC, CH ₂ Cl ₂ 1 h	 30	98% [3:2 t/c]

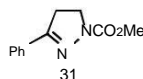


Figure 3. Elimination product from 18b.

required heating for 3D6 h in dichloromethane or a more pro-longed reaction time at ambient temperature. At least with these substrates, yields were again excellent.

Lengthier reaction times again began to cause loss of the pro-TECTING groups. In the case of the NHTs derivative 18b, 18 h expo-SURE to c.H₂SO₄ 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 evi-DENT (5 10%), which turned out to be compound 31, formed by elimination of toluenesulFonic acid. This showed characteristic apparent triplets at dH 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 there-fore not identiFied with certainty (Fig. 3).

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 26D29, 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 inter-mediacy 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 LC 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.

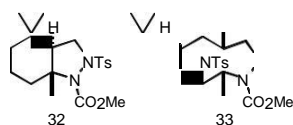
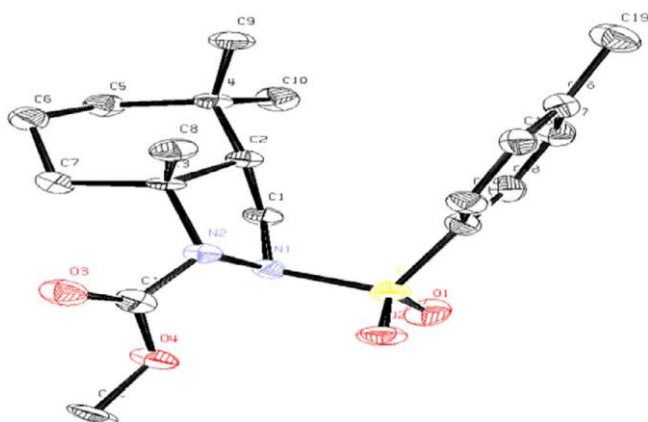


Figure 4. trans- and cis-isomers of product 30.



9. Dunford, D. G.; Chaudhry, F.; Kariuki, B.; Knight, D. W.; Wheeler, R. C. *Tetrahedron Lett.* 2012, 53, 7006D7009, and references therein.
10. When temperatures above 45 °C were required, dichloroethane, bp. 84 °C, was used. As concentrated sulfuric acid can only be largely suspended in dichloromethane, measuring standardized mixtures was also quite inaccurate.
11. Typically, 0.5 equiv of acid was used with respect to the precursor hydrazine. Reactions were carried out in anhydrous dichloromethane under dry nitrogen. Triethylamine 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.
12. X-ray analysis of pyrazolidine 24: C₁₄H₂₀N₂O₄S, Mr = 312.38, *Triclinic, P1*, a = 8.2711(4) Å, b = 9.5914(6) Å, c = 10.2058(6) Å, α = 106.254(3)°, β = 95.929(3)°, γ = 95.034(3)°, V = 767.33(8) Å³, Z = 2, Dx = 1.352 Mg m⁻³, k(Mo Kα) = 0.71073 Å⁻¹, l = 0.228 cm⁻¹, F(0 0 0) = 332, T = 160(2) K, crystal size = 0.30 × 0.30 × 0.12 mm³, Reflections collected = 5124, Independent reflections = 3689, 2555 with F₀ > 4 σ (F₀), R_{int} = 0.0462, Final R1 = 0.0892, wR2 = 0.1832 for I > 2σ(I), and R1 = 0.1267, wR2 = 0.199 for all data. The CIF files have been deposited 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.

13. X-ray analysis of pyrazolidine 33: C₁₉H₂₈N₂O₄S, Mr = 380.49, *Triclinic, P1*, a = 8.8933(6) Å, b = 10.0576(6) Å, c = 11.9571(5) Å, α = 73.913(3)°, β = 73.257(3)°, γ = 80.234(3)°, V = 979.36(10) Å³, Z = 2, Dx = 1.290 Mg m⁻³, k(Mo Kα) = 0.71073 Å⁻¹, l = 0.191 cm⁻¹, F(0 0 0) = 408, T = 160(2) K, crystal size = 0.35 × 0.25 × 0.09 mm³, Reflections collected = 6520, Independent reflections = 4575, 2410 with F₀ > 4 σ (F₀), R_{int} = 0.0598, Final R1 = 0.0914, wR2 = 0.1806 for I > 2σ(I), and R1 = 0.1887, wR2 = 0.2244 for all data. The CIF files have been deposited 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.