# An Acid-Catalysed Hydroamination Approach to Isoindolines

Laura Henderson,[a] David W. Knight,*[a] Andrew C. Williams[b]

[a] School of Chemistry, Cardiff University, Main College, Park Place, Cardiff, CF10 3AT, UK
Fax +44(29)20874030; E-mail: knightdw@cf.ac.uk

[b] Eli Lilly and Co. Ltd., The Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK

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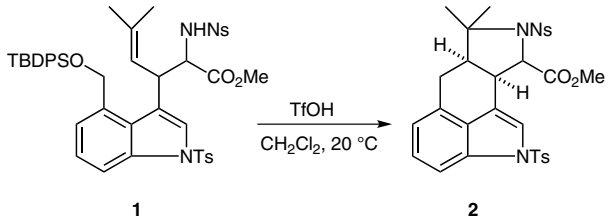
**Abstract:** Acid-catalysed intramolecular hydroaminations of 2-alkenylarylethylamine derivatives lead smoothly to isoindolines via benzylic carbenium ion generation.

**Key words:** cyclisation, sulfonamides, heterocycles, hydroamination, isoindolines

In our recently reported synthesis of the indole alkaloid α-cyclopiazonic acid,[1] a central key step was an acid-catalysed cascade cyclisation of the indole-4-methanol **1** which resulted in isolation of an excellent yield of the hoped-for tetracyclic derivative **2** (Scheme 1).

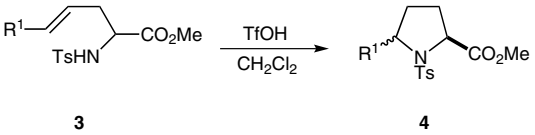



1 2

**Scheme 1** A cascade cyclisation in the synthesis of α-cyclopiazonic acid

We assumed that the mechanism of the cascade was the obvious one: protonation of the pendant oxygen, loss of the silyloxy group as the silanol, resulting in formation of a benzylic carbenium ion, and cascade cyclisation with generation of an intermediate tertiary aliphatic carbenium ion which is finally trapped by the sulfonamide function. In the light of this, we speculated whether similar but somewhat simpler cyclisations onto benzylic carbenium ions would be equally facile. Suitable benzylic carbenium ions could be generated by alkene protonation, as was used in our initial model studies, which demonstrated the viability of this methodology in the synthesis of pyrrolidines [e.g., **4**] from alkenyl sulfonamides **3** by exposure to triflic acid (Scheme 2).[2]

Such methodology has the potential to be applied to the elaboration of a variety of other saturated and semisaturated nitrogen-based heteroaromatic systems in what, overall, is an acid-catalysed alkene hydroamination reaction.[3]

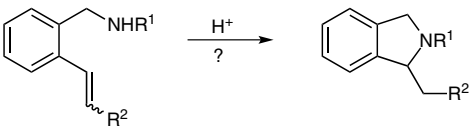



3 4

**Scheme 2** Initial model reactions

Herein, we wish to report our initial findings in this projected series of ideas, which has led to a new and relatively simple approach to the synthesis of substituted isoindolines.

Reducing the cascade sequence shown in Scheme 1 to a simpler form results in the idea of making isoindolines **6**[4] by cyclisation of 2-alkenyl-benzylamine derivatives **5**. Specifically, this would feature sequential alkene protonation and trapping of the resulting benzylic carbenium ion by the pendant amine nitrogen (Scheme 3). Our initial research had revealed that if the amine group in related cyclisation precursors was derivatised as either a sulfonamide or an acid-stable carbamate, then such cyclisations under acidic conditions were indeed viable and did not simply result in complete protonation of the amine group, as might be expected. Such cyclisations leading to pyrrolidines (Scheme 2) were indeed very efficient, especially when using the super acid trifluoromethanesulfonic (triflic) acid to protonate the alkene group.[2]




5 6

**Scheme 3** The proposed new approach to isoindolines

However, an immediate concern was that partial protonation of the modified amine function NHR1, which we anticipated would either be a sulfonamide or an acid-stable carbamate, rather than the alkene group in the precursors **5** could lead to the ammonium salts **7** and thence to loss of the former and nonproductive generation of an alternative benzylic carbenium ion **8** (Scheme 4).

In addition, nonregioselective cyclisation of the modified amine group onto either end of the pendant alkene could lead to mixtures of products. In the event, all of these concerns proved to be unfounded. The results obtained thus far are summarized in Table 1.

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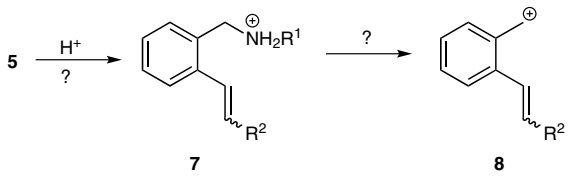
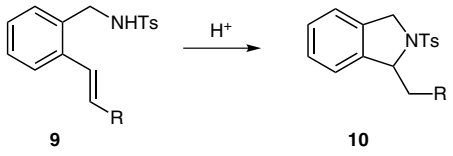



**Scheme 4** A possible alternative pathway

**Table 1** Acid-Catalysed Cyclisations of 2-Alkenylphenyl Sulfonamides **9** to the Isoindolines **10**



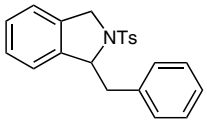
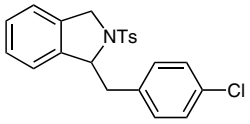
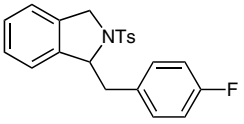
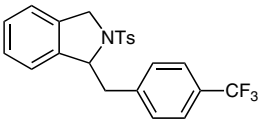
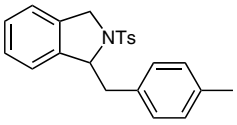
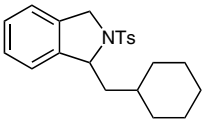
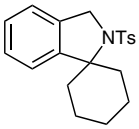
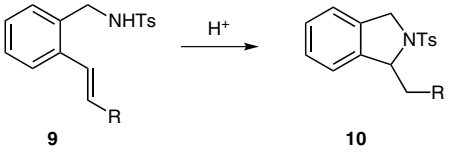
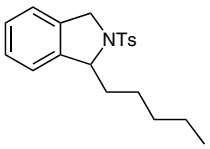

| Entry | Product **10** | Acid | Time (h) | Temp (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **10a** | TfOH | 24 | 0 | 98 |
| | | concd $H_2SO_4$ | 48 | 20 | 92 |
| 2 |  **10b** | TfOH | 24 | 40 | 81 |
| | | concd $H_2SO_4$ | 48 | 40 | 70 |
| 3 |  **10c** | TfOH | 24 | 40 | 84 |
| | | concd $H_2SO_4$ | 24 | 40 | 73 |
| 4 |  **10d** | TfOH | 24 | 40 | 71 |
| | | concd $H_2SO_4$ | 24 | 40 | 67 |
| 5 |  **10e** | TfOH | 24 | 40 | 86 |
| | | concd $H_2SO_4$ | 24 | 40 | 67 |
| 6 |  **10f** | TfOH | 2 | 40 | 93 |
| | | concd $H_2SO_4$ | 4 | 40 | 100 |
| 7 |  **10g** | TfOH | 6 | 0 | 70 |
| | | concd $H_2SO_4$ | 24 | 0 | 78 |

**Table 1** Acid-Catalysed Cyclisations of 2-Alkenylphenyl Sulfonamides **9** to the Isoindolines **10** (continued)




| Entry | Product **10** | Acid | Time (h) | Temp (°C) | Yield (%) |
|---|---|---|---|---|---|
| 8 |  **10h** | TfOH | 3 | 40 | 100 |
| | | concd H2SO4 | 3 | 40 | 98 |

All of the precursor sulfonamides **9a**–**h** were prepared using optimized Suzuki–Miyaura couplings[5] between *N*-tosyl-2-bromobenzylamine[6] and the corresponding alkenylboronic acid. This employed a premix of the palladium catalyst [$Pd(OAc)_2$], dtbpf [1,1′-bis(di-*tert*-butylphosphino)ferrocene] as ligand, buffered by excess potassium phosphate in 1:1 aqueous ethanol under microwave heating.

In the first series of trials, we used the original method for the related acid-catalysed pyrrolidine syntheses which consisted of exposing the precursors **9** to 0.5 equivalents of triflic acid as a ca. 3 mM solution in dry dichloromethane for various times and at various temperatures. The progress of the cyclisations was monitored both by TLC and $^1$H NMR spectroscopy. Once completed, the cyclisations were worked up by quenching the acid using excess 2 M aqueous potassium carbonate, separating the dichloromethane layer, which was then dried, filtered through silica gel, and evaporated. The yields quoted in Table 1 refer to products which were pure according to both $^1$H NMR and $^{13}$C NMR spectroscopy.

We were delighted that the first substrate **9a**, an otherwise unsubstituted stilbene derivative, underwent slow but very clean cyclisation at 0 °C to give an essentially quantitative yield of the hoped-for product **10a**. In all probability, mild heating would deliver a similarly excellent yield in a (much) reduced time. Heating was required for the conversion of the much more electron-deficient substrates **9b**–**d**, but in each case, carrying out the reaction in gently refluxing dichloromethane delivered high yields of the isoindolines **10b**–**d**.[7] Presumably, this type of substituent significantly retards the rate of alkene protonation by reducing its electron density. Quite why the 4-methyl derivative **9e** required similar conditions remains an oddity. None of these or the following products **10** contained any of the alternative six-membered tetrahydroisoquinoline products, which might be formed from the isomeric carbenium ion resulting from protonation at the alternate benzylic centre, followed by addition of the sulfonamide group to the distal end of the alkene.

The conditions required to achieve cyclisations onto aliphatic alkenes were significantly milder, presumably because in such substrates, an extended stilbene chromophore is not ruptured during protonation. Thus, the cyclohexylethenyl derivative **9f** required a much briefer period of reflux to deliver a respectable yield of the expected product **10f**, while the cyclohexenyl analogue **9g** underwent smooth cyclisation at 0 °C to give the *spiro* derivative **10g** presumably because, in this case, the intermediate carbenium ion is tertiary. This is a particularly useful result, as such highly substituted derivatives are not readily accessible using alternative approaches. Finally, a purely aliphatic derivative **10h** was also obtained relatively rapidly as would be expected in the light of the foregoing results.

An irritating drawback with this methodology is that it required triflic acid. Obviously a highly corrosive and also relatively expensive reagent, this has the additional complication of being rather difficult to store and to keep completely anhydrous, meaning that its quantification and indeed its reactivity (anhydrous vs. hydrate) is always a matter of some uncertainty. For these reasons, we chose to determine whether concentrated sulfuric acid[2b] could be used with similar efficacy, as it is so much cheaper and also more easily preserved in an anhydrous state. A disadvantage appeared to be that it is not especially soluble in dichloromethane. This turned out not to be relevant, as shown by the results presented in Table 1. Each of the precursors **9** also underwent smooth cyclisations when exposed to similar amounts of concd $H_2SO_4$ suspended in dichloromethane. In general, such cyclisations were slightly slower and delivered slightly inferior yields. However, it should be kept in mind that the conditions detailed in Table 1 are not completely optimized and that alternative combinations of both time and temperature could be more efficacious in some of the examples.

The present method should find many applications in this area as it is simple and requires only two steps – a robust palladium-catalysed coupling and a cyclisation. Many alternative approaches to isoindolines are known[4] and some are equally efficient and relatively brief but, at the least, the present method does not produce substantial amounts of byproducts and noxious spent reagents and therefore is relatively 'green'. Obviously, a significant concern with a method which employs such strong acids is its compatibility with potentially sensitive functional groups. In our previous work, we have shown that, at least, carboxylic acid methyl and ethyl esters, sulfones, and isolated alkenes survive unmolested. More recently,[8] we have found that acetyloxy groups are especially good at masking alcohol groups which could otherwise interfere with such cyclisations; the highly acidic conditions do not interfere with this type of ester, even when heated. We therefore do not view this as an especially serious drawback.

## Acknowledgment

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## References

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(6) Zhu, M.; Fujita, K.; Yamaguchi, R. *Org. Lett.* **2010**, *12*, 1336.

(7) **Preparation of Isoindolines 10b–d; Typical Procedures: 1-(4-Chlorobenzyl)-2-tosylisoindoline (10b)**
*i*) (*E*)-*N*-[2-(4-Chlorostyryl)benzyl]-4-methylbenzenesulfonamide **9b** (95 mg, 0.238 mmol, 1.0 equiv) was dissolved in dry dichloromethane (10 ml), to which was added TfOH (0.20 ml, 0.119 mmol, 0.5 equiv). The resulting solution was heated to 40 °C for 24 h, then cooled to room temperature and quenched using saturated aqueous $K_2CO_3$. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over $K_2CO_3$, filtered through a plug of silica gel and the filtrates and washings evaporated to give the isoindole **10b** as a yellow oil (77 mg, yield: 81%).
*ii*) (*E*)-*N*-[2-(4-Chlorostyryl)benzyl]-4-methylbenzenesulfonamide **9b** (106 mg, 0.267 mmol, 1.0 equiv) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 40 °C for 48 h, then cooled to room temperature and quenched with saturated aqueous $K_2CO_3$. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over $K_2CO_3$, filtered through a plug of silica gel and the filtrates and washings evaporated to give the isoindole **10b** as a yellow oil (74 mg, yield: 70%).
The two samples showed identical spectroscopic and analytical data. IR (film): 3277, 3062, 3028, 2923, 2855, 1598, 1448, 1274, 815, 750, 658 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.75–7.52 (m, 4 H, 2 × Ts CH and 2 × Ar CH), 7.35–6.88 (m, 8 H, 2 × Ts CH and 6 × Ar CH), 5.31 (d, 1 H, *J* = 15.4 Hz, $CH_aH_bN$), 4.59 (d, 1 H, *J* = 15.4 Hz, $CH_aH_bN$), 4.11 (t, 1 H, *J* = 6.2 Hz, CHN), 2.98 (app. br s, 2 H, CH2), 2.28 (s, 3 H, Ts CH3). $^{13}C$ NMR (400 MHz, $CDCl_3$) δ = 143.2 (C), 139.8 (C), 137.0 (C), 132.6 (C), 132.4 (C), 132.2 (C), 129.6 (ArCH), 129.5 (2 × TsCH), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 127.4 (ArCH), 127.2 (ArCH), 127.1 (2 × TsCH), 126.5 (ArCH), 125.9 (ArCH), 54.7 (CHN), 44.0 ($CH_2N$), 32.3 ($CH_2$), 21.6 ($TsCH_3$). HRMS (APCI): *m*/*z* calcd. for $C_{22}H_{21}ClNO_2S$ $[M + H]^+$ = 398.0982 ($Cl^{35}$); found 398.0983 ($Cl^{35}$).

(8) AlHadi, A.; Knight, D. W. unpublished observations.