5-*endo-dig* Cyclisations of homopropargylic sulfonamides: a new route to 2,3-dihydropyrroles and β-iodopyrroles

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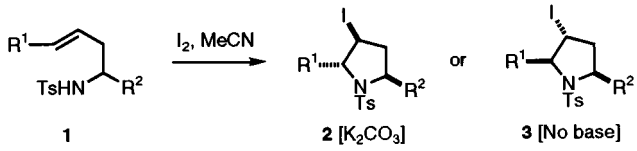
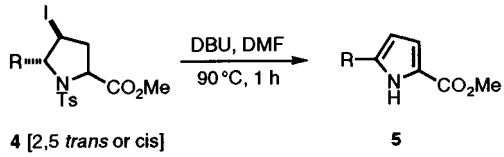
5-*endo-dig* Iodocyclisations of the homopropargylic sulfonamides 12a–c and 13 give excellent yields of the iododihydropyrroles 14a–d and thence the β-iodopyrroles 15a–d, following base-catalysed elimination of sulfinic acid.

We have recently reported that (*E*)-homoallylic tosylamides **1** (R^1, R^2 = alkyl, aryl) undergo highly efficient and stereoselective iodocyclisations to give the 2,5-*trans* iodopyrrolidines **2** in the presence of a base such as K_2CO_3, seemingly *via* a well-defined chair-like transition state conformation. In contrast, in the absence of a base, the corresponding 2,5-*cis* diastereoisomers **3** are obtained exclusively by acid-catalysed isomerization of the initial products **2** (Scheme 1).[1] Although apparently



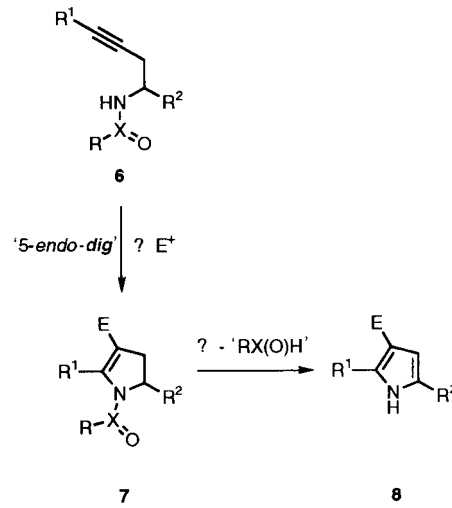
Scheme 1

5-*endo-trig* cyclisations, we do not regard these as exceptions to Baldwin's rules[2] as the process is electrophile- rather than nucleophile-driven; other aspects of our own studies and those of other research groups appear to substantiate this principle.[3] More recently, we have found that the method can be readily extended to include preparations of both 2,5-*trans* and 2,5-*cis* isomers of the substituted prolines **4** and that these undergo a double elimination of both HI and toluene-*p*-sulfinic acid upon warming with DBU in DMF, giving excellent yields of the pyrrole-2-carboxylates **5** (Scheme 2).[4]



Scheme 2

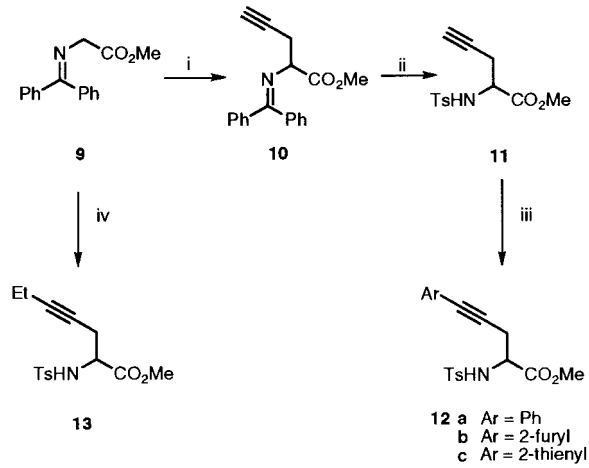
While this is a useful route to such pyrroles and is related to the established Kenner method, we felt that it was something of a backward step to lose this degree of functionality during the elimination, especially the iodine atom which could otherwise provide a handle for further elaboration. It was with this in mind that we wondered if it might be possible to effect similar cyclisations of related *homopropargylic* amine derivatives, inspired by our recent success in an approach to highly substituted furans.[5] The idea of working at this higher oxidation state is outlined in Scheme 3. If a suitably protected propargylic (prop-2-ynylic) amine **6** were to undergo a 5-*endo-dig* cyclisation, the resulting dihydropyrroles **7** might then be amenable to elimination of the protecting group, leading to pyrroles **8**, in which the electrophilic species used to trigger cyclisation is retained and hence would be available for additional reactions. Further, the dihydropyrrole species **7** might well be useful for



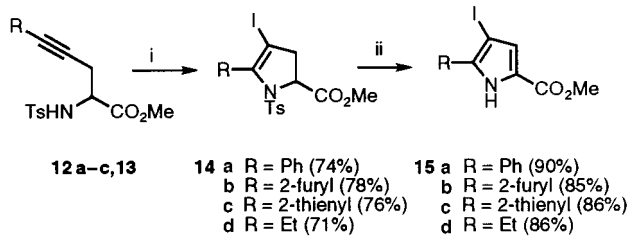
Scheme 3

further elaboration; however, at the outset, we had no idea whether these would be stable compounds. We were encouraged by the fact that, perhaps at first sight surprisingly and in direct contrast to the 5-*endo-trig* mode, 5-*endo-dig* cyclisations are favoured under Baldwin's rules.[2] Herein, we report on a first successful implementation of the approach shown in Scheme 3.

The success of the pyrrolidine and pyrrole syntheses (Schemes 1 and 2) naturally led us to choose as a first option the toluene-*p*-sulfonyl (tosyl) group to mask the amine nitrogen; the routes used to obtain representative substrates are shown in Scheme 4. The benzophenone imine of methyl glycinate **9**[6] was

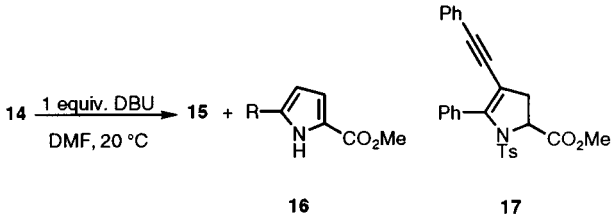


Scheme 4 *Reagents and conditions*: i, propargyl bromide, K_2CO_3, Bu_4NI, MeCN, reflux, 7 h; ii, 2 M aq. HCl, Et_2O, 20 °C, *ca.* 1 h, then TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 20 °C, 15 h; iii, ArI, CuI (cat.), $Pd(PPh_3)_4$ (cat.), Et_2NH, 20 °C, *ca.* 3 h (TLC monitoring); iv, as i, using 1-bromopent-2-yne



12a–c,13 **14** a R = Ph (74%) b R = 2-furyl (78%) c R = 2-thienyl (76%) d R = Et (71%) **15** a R = Ph (90%) b R = 2-furyl (85%) c R = 2-thienyl (86%) d R = Et (86%)

Scheme 5 *Reagents and conditions*: i, I_2, K_2CO_3 (3 equiv. each), dry MeCN, 0–20 °C, 14 h; ii, DBU (2.1 equiv.), DMF, 20 °C, 14 h



16 **17**

Scheme 6

alkylated[7] with propargyl bromide and the *N*-protecting group of the resulting propargyl glycine **10** exchanged for a tosyl group. Sonogashira coupling[8] of the sulfonamide **11** so obtained with representative iodides provided excellent yields of the cyclisation substrates **12**. An alkyl derivative **13** was obtained using 1-bromopent-2-yne as the alkylating agent, followed by protecting group exchange.‡ An alternative strategy involving couplings between aryl iodides and the imine **10** was unsuccessful. We were delighted to find that exposure of the sulfonamides **12** and **13** to 3 equiv. of I_2 and K_2CO_3 in dry MeCN at ambient temperature resulted in slow but clean cyclisation to give excellent isolated yields of the iododihydropyrroles **14** (Scheme 5).[9] The aryl derivatives **14a–c** turned out to be stable crystalline solids with sharp melting points, whereas the alkyl derivative **14d** was a somewhat sensitive oil which nevertheless could be fully characterized.‡ Further, by stirring these dihydropyrroles **14** with DBU in DMF at ambient temperature, excellent yields of the corresponding iodopyrroles **15** were obtained by elimination of toluene-*p*-sulfinic acid (Scheme 5).‡ It was important to use 2 equiv. of the base; if only 1 equiv. was used, then approximately 50% of the product was the deiodopyrrole **16**, along with the expected product **15** (Scheme 6). We assume that the released sulfinic acid is responsible for this deiodination, perhaps by attack at iodine by sulfur, leading to the sulfonyl iodide, a process greatly reduced by the presence of an additional equivalent of base. Proton-catalysed cycloreversion, with loss of iodine, cyclisation and elimination is another possibility.

Both iodinated species **14** and **15** have potential for further elaboration, especially using one of the many transition metal-catalysed coupling procedures currently available. β-Iodopyrroles have recently been shown to undergo both Stille[10] and Sonogashira couplings.[11] In the present work we have established that the iododihydropyrroles **14** are compatible with palladium catalysts. Thus, a rapid Sonogashira coupling between dihydropyrrole **14a** and phenylacetylene [CuI (0.2 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), Et_2NH, 20 °C, 2 h] delivered an 82% isolated yield of the enyne **17**, suggesting that they will prove to be useful synthetic intermediates. These aspects and further studies of the scope and limitations of this chemistry are currently being pursued.

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Notes and References

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‡ All compounds reported herein gave satisfactory microanalytical and spectroscopic data.

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9 *Typical experimental procedure* for **14b**: The tosylamide **12b** (70 mg, 0.20 mmol) was stirred in dry MeCN (1 ml) containing anhydrous K_2CO_3 (84 mg, 0.61 mmol) and cooled in an ice bath. I_2 (153 mg, 0.61 mmol) in MeCN (0.6 ml) was added dropwise and the resulting suspension stirred overnight without the addition of further coolant. Saturated aq. sodium thiosulfate was then added until the excess I_2 was decolourized and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 ml) and the combined organic solutions dried ($MgSO_4$) and evaporated. Column chromatography of the residue (6 : 1 hexane–EtOAc) gave **14b** (74 mg, 78%) as a pale yellow solid, mp 88–92 °C, ν_{max}/cm^{-1} 2953, 1742, 1597, 1437, 1361, 1212, 1170, 1089, 1017; $\delta_H(CDCl_3$; 400 MHz) 2.45 (3H, s, Ar-CH_3), 2.59 (1H, dd, *J* 17.1 and 9.7, 3-H_a), 2.85 (1H, dd, *J* 17.1 and 2.4, 3-H_b), 3.82 (3H, s, OCH_3), 4.83 (1H, dd, *J* 9.7 and 2.4, 2-H), 6.50 (1H, dd, *J* 3.4 and 1.8, 4′-H), 6.89 (1H, d, *J* 3.4, 3′-H), 7.31 (2H, d, *J* 8.2, 2 × Ar-H), 7.47 (1H, app. br s, 5′-H), 7.60 (2H, d, *J* 8.2, 2 × Ar-H); $\delta_C(CDCl_3$; 100 MHz) 21.6 (Ar-CH_3), 43.5 (3-CH_2), 53.1 (OCH_3), 62.2 (2-CH), 77.6 (4-C), 111.0 (4′-CH), 113.9 (3′-CH), 127.8 (2 × Ar-CH), 129.6 (2 × Ar-CH), 133.5 (C), 135.8 (C), 143.1 (5′-CH), 144.6 (C), 144.8 (C) and 170.6 (CO); *m/z* (EI) 473 (M^+, 27%), 318 (17), 191 (88), 159 (51), 132 (56), 104 (55), 91 (100) [Found: C, 42.8; H, 3.4; N, 3.1. $C_{17}H_{16}INO_5S$ requires C, 43.1; H, 3.4; N, 3.0%]. For elimination of toluene-*p*-sulfinic acid: To a stirred solution of the **14** (1 mmol) in dry DMF (5 ml) at ambient temperature, DBU (0.3 ml, 2.1 mmol) was added dropwise and the elimination followed by TLC. Upon completion (*ca.* 12 h), 2 M HCl (5 ml) was added and the resulting mixture extracted with hexane (4 × 20 ml). The combined extracts were dried ($MgSO_4$) and concentrated, then passed through a short silica plug; evaporation of the filtrate left the pure iodopyrrole **15**. *Selected data* for **15b**: pale yellow solid, mp 120–124 °C; ν_{max}/cm^{-1} 3282, 2951, 1697, 1508, 1437, 1395, 1317, 1262, 1203; $\delta_H(CDCl_3$; 400 MHz) 3.88 (3H, s, OCH_3), 6.53 (1H, dd, *J* 3.5 and 1.6, 4′-H), 7.07 (1H, d, *J* 2.7, 3-H), 7.21 (1H, d, *J* 3.5, 3′-H), 7.47 (1H, d, *J* 1.6, 5′-H), 9.45 (1H, br s, NH); $\delta_C(CDCl_3$; 100 MHz) 5.19 (OCH_3), 65.2 (4-C), 107.8, 111.8, 124.5 (all Ar-CH), 129.0, 136.0, 140.5 (all Ar-C), 142.0 (Ar-CH), 162.5 (CO); *m/z* (EI) 317 (M^+, 79%), 285 (59), 130 (70), 76 (79), 57 (100) [Found: M^+, 316.9551. $C_{10}H_8INO_3$ requires *M*, 316.9551].
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