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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7906–7910

A general approach to polysubstituted pyrroles

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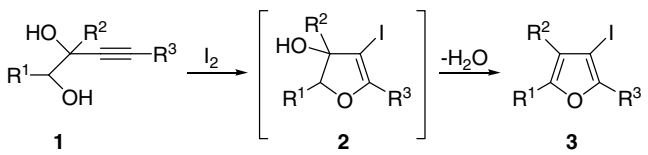
Received 24 July 2007; accepted 21 August 2007
Available online 31 August 2007

Abstract—Exposure of a range of 3-hydroxy-2-sulfonylamino-4-alkynes to excess iodine delivers good yields of a series of iodopyrroles. Unexpectedly, the hydroxyl-dihydropyrroles, which were assumed to be the first-formed intermediates, turn out to be stable entities which have been isolated for the first time.

When used in heterocyclic syntheses, halocyclisations[1] are distinguished by the fact that not only is the heterocycle formed in often excellent yield and, where relevant, with often high levels of stereocontrol, but also that a synthetically useful halogen atom is incorporated. This is illustrated by an approach to β-iodofurans **3**, which we reported some time ago, wherein a series of 3-alkyne-1,2-diols **1** undergo smooth overall 5-*endo*-dig cyclisation to give good to excellent yields of the final products **3**, presumably via the initially formed dihydrofurans **2** (Scheme 1).[2] As all attempts to isolate or even observe the latter intermediates failed, we assume that the initial iodocyclisation is the rate determining step.

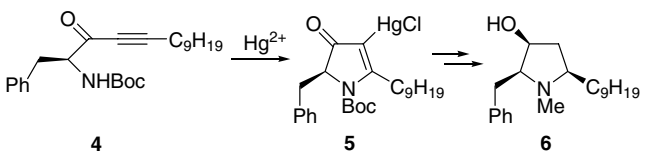
Of course, the iodine atom which is inevitably incorporated now provides the means for final homologations to fully substituted furans by the application of one of a plethora of coupling reactions now available, by halogen–metal exchange or by radical formation. At the time of our first foray into the area of 5-*endo*-dig cyclisations, such reactions were somewhat obscure, but have recently been shown capable of making a significant contribution to heteroaromatic synthesis.[3] We were intrigued by the prospects of extending the chemistry shown in Scheme 1 to examples having various modified amino groups as the nucleophile, with a view to developing new pyrrole syntheses, along perhaps with other azaheterocycles. Certainly, such an idea is not completely without precedent: in a remarkable and seemingly unique contribution, Overhand and Hecht used a mercury(II)-induced 5-*endo*-dig cyclisation of alkynone **4** to obtain heterocycle **5**, the global reduction of which led to the natural product Preussin **6** (Scheme 2).[4]



Scheme 1.

We had previously reported an approach to pyrrole-2-carboxylates **8** by a double elimination of the elements of hydrogen iodide and *p*-toluenesulfinic acid from iodo-pyrrolidines **7**,[5] obtained from the corresponding homoallylic sulfonamides by a 5-*endo*-trig iodocyclisation (Scheme 3).[6] Arguably, this is one of the less useful transformations involving these initial products **7**, as the two potentially useful functional groups are lost.

However, a combination of the successful Preussin synthesis and a desire to access pyrroles more directly led us to examine similar cyclisations of homopropargylic sulfonamides, which proved successful as a relatively general protocol for pyrrole synthesis.[7] This then set the stage for, potentially, the most direct route to β-iodopyrroles, which would be to carry out such 5-*endo*-dig cyclisations on suitable nitrogen analogues



Scheme 2.

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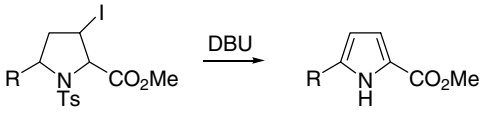
doi:10.1016/j.tetlet.2007.08.097



7 8

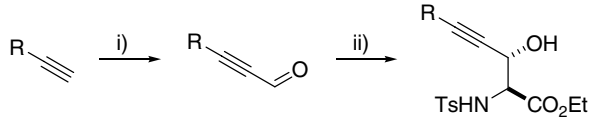
Scheme 3.

of 3-alkyne-1,2-diols **1**, used in our furan synthesis (Scheme 1). Herein, we report in preliminary form on the successful outcomes of various versions of this idea, which have led to the definition of a new, broadly applicable pyrrole synthesis, as well as to an unexpected surprise—the isolation of the intermediate hydroxy-dihydropyrroles as stable entities.

Our first efforts were centred on the development of a rapid route to 3-hydroxy-2-sulfonylamino-4-alkynoates **11**, which we anticipated could be precursors of substituted pyrrole-2-carboxylates (cf. Scheme 1). These, we found, could be prepared routinely in reasonable overall yields from 1-alkynes **9** by sequential formylation using the excellent protocol developed and explained by Journet et al.[8] and condensation of the resulting conjugated ynals **10** with the tin(II) enolate derived from methyl *N*-tosyl glycinate using the method developed by Kazmaier (Scheme 4).[9] Unexpectedly, the *anti*-diastereoisomers **11** turned out to be the major products.[10]

We were very pleased to discover that exposure of a representative series of such sulfonamides **11** to a typical set of iodocyclisation conditions [3 equiv I_2, 3 equiv K_2CO_3, MeCN, 20 °C] resulted in a controlled loss of the starting material and the emergence of a single product. Upon quenching the excess iodine using sodium sulfite followed by a simple aqueous work-up, we were amazed to find that the isolated products were in fact hydroxy-dihydropyrroles **12** (Table 1, entries 1–6). While clearly not pyrroles, these products were recognised by characteristic resonances in their ^{1}H NMR spectra, along with other supportive spectroscopic and analytical data.[11] Although not requiring any significant purification, all these compounds proved stable to silica gel column chromatography.

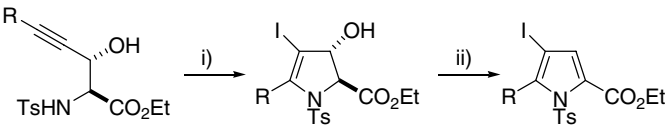
Isolation of the major diastereoisomers **12** (typically from a ca. 9:1 mixture of *anti*/*syn*-isomers[10]), while not set up for E_2 elimination, was unexpected, especially in view of the failure to even observe the related intermediates **2**, examples of which have been reported previously,[12] in the furan synthesis (Scheme 1). This was, of course, exacerbated by the driving force of aromaticity



9 10 11

Scheme 4. Reagents and conditions: (i) BuLi, −78 °C, THF, then DMF and reverse quench with NH_4Cl (aq) [Ref. 8]; (ii) $TsHNCH_2CO_2Et$, **2**·LDA, THF, −78 °C, **2**·$SnCl_2$, then 1 equiv **10** [Ref. 9].

Table 1. Iodocyclisations of sulfonamides **11**



11 12 13

Entry	R	% yield **12**	% yield **13**
1	Ph	93	83
2	Bu	93	65
3	$BzO(CH_2)_3$	96	66
4	$TBSO(CH_2)_3$	91	73
5	$TBSO(CH_2)_4$	92	65
6	Cyclohex-2-en-1-ylethyl	86	74
7	^{t}Bu	51[a]	—[d]
8	Ph	—[b]	98
9	Isopropenyl	—[c]	56
10	Bu	—	84[e]

Reagents and conditions: (i) 3 equiv iodine, 3 equiv K_2CO_3, MeCN, 20 °C, 2–16 h; (ii) 1.1 equiv MsCl, 2.2 equiv Et_3N, CH_2Cl_2, 20 °C, 16 h.

[a] The iodocyclisation was carried out in 1:1 MeCN–H_2O at 20 °C for 72 h.

[b] The crude product (78 mg) was left in chloroform solution for 24 h, by which time it was completely converted into the iodopyrrole.

[c] Iodocyclisation was carried out using IBr (3 equiv) and $NaHCO_3$ (3 equiv) in dichloromethane at 20 °C for 2 h, which gave a 3:1 mixture of hydroxy-dihydropyrrole and pyrrole-2-carboxylates. Immediate dehydration [MsCl, py, CH_2Cl_2, 0 °C, 1 h] gave 56% yield of the iodopyrrole.

[d] Dehydration using PPTS in hot toluene for 16 h gave only ca. 10–15% yields of the deiodopyrrole.

[e] Iodocyclisation using 3 equiv each of IBr and $NaHCO_3$ in MeCN for 16 h gave only the iodopyrrole.

creation which would accrue upon dehydration to iodopyrrole-2-carboxylates **13**. To the best of our knowledge, only one set of examples of this structural type has been reported, from related studies in which substrates **11** were cyclised using copper(I) catalysts.[13]

To return to the central cyclisation (Table 1), this appears to be of a reasonably broad scope. Both simple aryl and alkyl substituents are tolerated (entries 1 and 2), and there was no interference from the protected hydroxyl groups in the hydroxypropyl derivatives (entries 3 and 4; potential 5-*exo*- or 6-*endo*-dig) or in the hydroxylbutyl analogue (entry 5; potential 6-*exo*-dig). A relatively remote alkene group (entry 6) also remained unmolested. However, problems did arise when trying to form the rather crowded *t*-butyl derivative (entry 7) when somewhat different cyclisation conditions had to be used; even then, the yield was much lower than was typical, presumably due to extreme steric hindrance.

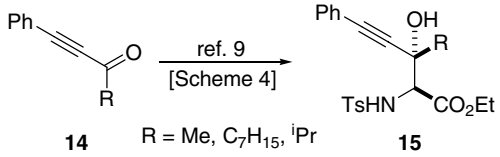
As might be expected, the very stability of hydroxyl-dihydropyrroles **12** did pose some problems in completing the projected syntheses of iodopyrrole-2-carboxylates **13**. While the latter could be obtained using a number of well established procedures, both acidic and basic, in our hands a workable but perhaps not optimal procedure was the elimination of the derived mesylates, formed in situ without isolation. In this way, around 70% isolated yields of iodopyrrole-2-carboxylates **13**

could be routinely obtained (Table 1; entries 1–6). In the case of the highly hindered *t*-butyl derivative (entry 7), a pyrrole was only formed upon heating with pyridinium *p*-toluenesulfonate (PPTS) in toluene which proved to be a low yield of deiodinated material, again reflecting both the extreme steric hindrance and the reversibility of the iodocyclisation. In an isolated example with the 5-phenyl example (entry 8), essentially quantitative, presumably acid-catalysed, dehydration was observed for an NMR sample left in $CDCl_3$ overnight. However, despite a number of attempts, this method was never satisfactorily scaled up. In the case of the rather sensitive 2-propenyl derivative (entry 9), cyclisation was carried out using a combination of iodine monobromide and the weaker base, sodium hydrogen carbonate, to give a mixture of products, convertible to the final iodopyrrole again using the mesyl chloride method. This same method when applied to the butyl-substituted precursor [**11**; R = Bu] delivered the corresponding iodopyrrole-2-carboxylate [**13**; R = Bu] directly in very good yield (Entry 10). In other examples, the use of similar reagents and conditions gave mixtures of the two products.

The viability of this type of cyclisation was also tested on more highly substituted precursors with the aim of obtaining fully substituted pyrroles. We were also intrigued to learn if such a sequence would result in a more facile dehydration of the tertiary alcohol present. The first few examples were prepared using our previously developed methodology but starting with alkynones **14**; perhaps surprisingly, the tin(II) enolate of methyl *N*-tosyl glycinate was added with the same sense of stereoselectivity to again give very largely the *anti*-isomers **15** (Scheme 5).[10]

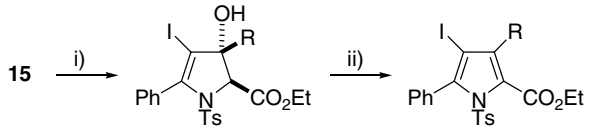
All these substrates underwent smooth iodocyclisation, although the outcome was again dependent upon the conditions: using potassium carbonate as the base allowed for the isolation of the intermediate hydroxy-dihydropyrroles **16** in good yields (Table 2). In contrast, the use of sodium hydrogen carbonate led to extensive dehydration, even under relatively mild conditions. Once again, dehydration was carried out as a separate step, by mesylation, and gave the final iodopyrroles **17** in ca. 80% purified yields. Hence, even though all these examples contained a tertiary alcohol, dehydration, presumably via an E1cB mechanism, was just as demanding as in previous, less substituted, examples.

So far, all examples have contained an α-carboxylate group, mainly for synthetic expedience in terms of precursor synthesis. To check whether the other types of substrates were amenable to these cyclisations, and to also demonstrate the viability of an alternative precursor synthesis, we used the two symmetrical alkenes **18** as starting materials (Scheme 6). Amino-hydroxylation[14] gave good yields of the partly-protected amino-alcohols **19**, which were then oxidised to the corresponding amino-ketone derivatives **20**.[15] Direct addition of a lithio-acetylide then gave the necessary precursors **21** as stereoisomeric mixtures.



Scheme 5.

Table 2. Iodocyclisation of precursors **15** with tertiary OH groups

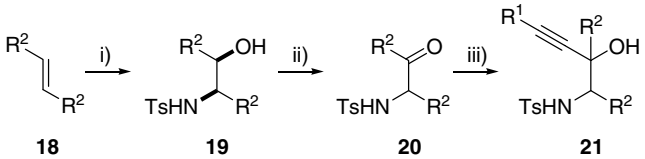


Entry	R	% yield **16**	% yield **17**
1	Me	95[a]	67
2	C_7H_{15}	71[b]	79
3	^{i}Pr	—[c]	82[c]

Reagents and conditions: (i) 3 equiv iodine, 3 equiv K_2CO_3, see notes, 20 °C, 2–16 h; (ii) 1.1 equiv MsCl, 2.2 equiv Et_3N, CH_2Cl_2, 20 °C, 16 h.
[a] The solvent was MeCN.
[b] The solvent was CH_2Cl_2.
[c] Iodocyclisation using 3 equiv IBr and 4 equiv $NaHCO_3$ in CH_2Cl_2 at −10 °C for 2 h to give a 4:3 ratio of dihydropyrrole and pyrrole. Dehydration using MsCl, py in CH_2Cl_2 at reflux for 16 h gave the overall 82% yield.

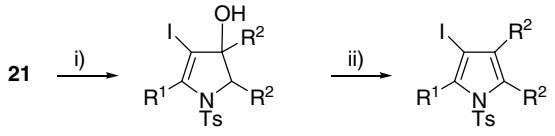
That the carboxylate group had little influence on the foregoing examples was established when it was found that such precursors underwent equally smooth cyclisation to give the isolable hydroxy-dihydropyrroles **22** and thence the fully substituted iodopyrroles **23** (Table 3). The slightly lower yields of intermediate **22** reflect the fact that some premature dehydration occurred, such that these were isolated admixed with ca. 5–15% of iodopyrroles **23**. Clearly, less symmetrical examples will be readily accessed by starting with alternatives to the amino-alcohols or -ketones **19** or **20**.[15]

A series of 'pseudo'-symmetrical examples **27** were also prepared in a final demonstration of the utility of this methodology (Table 4). Thus, reaction between an *N*-tosyl α-amino-ester **24** and an excess of a lithiated 1-alkyne led to good yields of the double addition products **25**, which behaved well in the central cyclisation reaction to give excellent yields of the hydroxy-dihydropyrroles **26**. In the valine-derived examples (entries 3 and 4), significant dehydration to the pyrroles **27** was



Scheme 6. Reagents and conditions: (i) 3 equiv chloramine-T, $(DHQD)_2$-PHAL (cat.), $K_2OsO_2(OH)_2$ (cat.), ^{t}BuOH–H_2O (1:1), 16 h, 20 °C [75–85%]; (ii) 3.8 equiv PCC, 4 Å mol. sieves, CH_2Cl_2, 16 h, 20 °C [85–90%]; (iii) 2.5 equiv 1-alkyne, add 2.5 equiv BuLi, −30 °C, THF, 1 h, then add 1 equiv **20**, 16 h, 20 °C [80–85%].

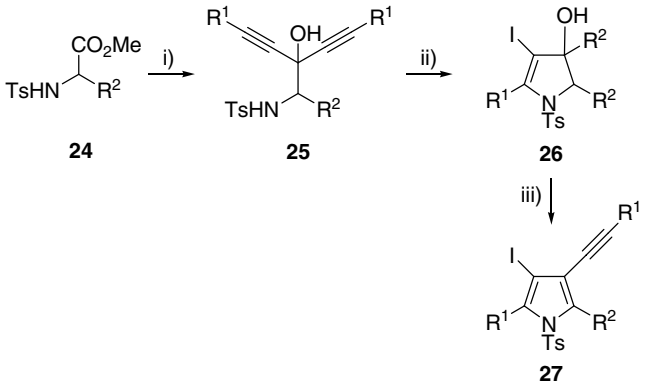
Table 3. Cyclisation of precursors **21** lacking a carboxylate group



Entry	R^1	R^1	% yield **22**	% yield **23**
1	Bu	Ph	80	88
2	Ph	Ph	73	93
3	Bu	Me	71	91

Reagents and conditions: (i) 3 equiv iodine, 3 equiv K_2CO_3, CH_2Cl_2, 20 °C, 16 h; (ii) 1.1 equiv MsCl, 2.2 equiv Et_3N, CH_2Cl_2, 20 °C, 16 h.

Table 4. Cyclisation of bis-alkynyl precursors **25**

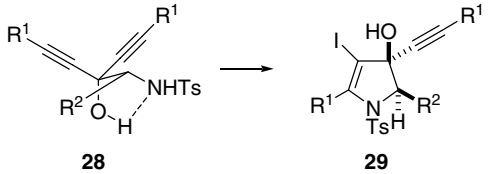


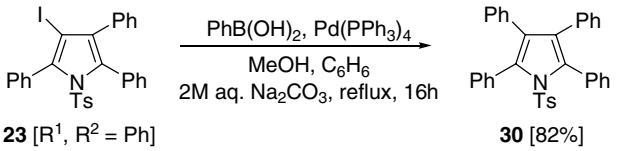
Entry	R^1	R^1	% yield **26**	% yield **27**
1	Bu	Me	90	65
2	Ph	Me	87	91
3	Bu	^{i}Pr	—[a]	67
4	Ph	^{i}Pr	—[a]	69

Reagents and conditions: (i) 3.5 equiv R^1CCLi, THF, −78 °C to 0 °C [~90%]; (ii), (iii) as Table 3, (i) and (ii).

[a] As a mixture with the corresponding iodopyrrole.

observed. As in many of the foregoing examples, this final dehydration step was satisfactory, if not exactly spectacularly efficient. The intermediate dihydropyrroles **26** were isolated very largely as single diastereoisomers. Although not proven, we speculate that the more favourable conformation for the cyclisation step may be that shown as formula **28**, which benefits both from an equatorial-like position of the substituent R^2, as well as intramolecular hydrogen bonding between the hydroxyl and sulfonamide groups. This implies that the resulting stereoisomers **29** would be the major products, making their isolation all the more remarkable by reason of the *anti* relationship between the α-protons and the hydroxyl groups.





Scheme 7.

It was shown some time ago that β-iodopyrroles in general are suited to Suzuki coupling reactions and, hence, probably to many other related homologations.[16] In this respect, the tosyl group and, where relevant, the 2-carboxylate groups, will play a useful role in reducing the electron density of these otherwise electron-rich heterocycles and, hence, aid such reactions by encouraging the initial oxidation addition of Pd(0) to the C–I bond. Other N-protecting groups were not tested, as the tosyl function proved highly suitable throughout the precursor syntheses and the central cyclisations. Significantly and in contrast to many other types of sulfonamides, such tosyl groups are readily removed from pyrrole derivatives in general by reason of the latter's relatively low pK_a values (ca. 17.5). However, the functionality is not sufficiently delicate that it is lost in a standard Suzuki coupling: homologation of iodopyrrole [**23**; $R^1 = R^2 = Ph$] using phenylboronic acid and sodium carbonate as base gave an unoptimised 82% yield of the tetraphenylpyrrole **30** (Scheme 7).

In conclusion, we would suggest that the present schemes represent generally useful and relatively efficient routes to a large range of pyrroles. The unexpected isolation of the various hydroxy-dihydropyrroles, also in generally good yields, adds a further dimension to this methodology, which we are at present exploring.

Acknowledgements

We are very grateful to the Erasmus scheme, to the government of Thailand and to the EPSRC for the financial support.

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11. A typical procedure is as follows: (2S*R*,3*RS*)-Ethyl 5-butyl-3-hydroxy-4-iodo-1-(4-toluenesulfonyl) 2,3-dihydropyrrole-2-carboxylate 12; entry 2, Table 1: To a vigorously stirred mixture of (2*SR*,3*SR*)-ethyl 2-(4-toluenesulfonylamino)-3-hydroxynon-4-ynoate **11** (0.50 g, 1.36 mmol)[10] and finely ground anhydrous potassium carbonate (0.55 g, 4.1 mmol) in dry acetonitrile (12 ml) cooled in an ice-water bath was slowly added a solution of iodine (1.04 g, 4.1 mmol) in dry acetonitrile (20 ml). The resulting purple suspension was stirred without further cooling for 16 h, then quenched by the addition of saturated aqueous sodium thiosulfate, until the iodine colouration disappeared. The organic layer was separated and the aqueous layer extracted with dichloromethane (3×15 ml). The combined organic solutions were washed with brine (20 ml), then dried ($MgSO_4$), filtered through a plug of silica gel and evaporated to leave essentially a pure hydroxy-dihydropyrrole **12**, entry 2, as a yellow oil (0.625 g, 93%) which showed ν_{max} (film) 3490, 1735, 1628, 1597, 1457, 1354, 1166, 1090, 1028, 912, 666 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.86 (3H, t, $J = 7.2$ Hz, 4′-Me), 1.06 (3H, t, $J = 7.1$ Hz, OCH_2Me), 1.27 (2H, hextet, $J = 7.2$ Hz, 3′-CH_2), 1.41 (2H, quintet, $J = 7.2$ Hz, 2′-CH_2), 2.33 (3H, s, ArMe), 2.56–2.66 (2H, m, 1′-CH_2), 3.45–3.55 (1H, br s, OH), 3.89 (2H, q, $J = 7.1$ Hz, OCH_2), 4.02–4.08 (1H, app. br s, 2-H), 4.29–4.34 (1H, app. br s, 3-H), 7.26 (2H, d, $J = 8.3$ Hz, $2 \times$ ArH), 7.68 (2H, d, $J = 8.3$ Hz, $2 \times$ ArH); δ_C ($CDCl_3$, 100 MHz) 14.2 (Me), 14.4 (Me), 22.1 (ArMe), 22.6 (CH_2), 29.9 (CH_2), 30.1 (CH_2), 62.8 (OCH_2), 70.1 (CH), 79.5 (4-C–I), 80.6 (CH), 128.1 ($2 \times$ ArCH), 130.4 ($2 \times$ ArCH), 134.5 (ArC), 144.2 (ArC), 170.2 (C=O); *m*/*z* (ES) 494 ($M+H^+$, 45%), 476 ($M+H^+-H_2O$, 100). [Found: $M+H^+$, 494.0499. $C_{18}H_{25}INO_5S$ requires M, 494.0498].
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