Pd-Catalysed Synthesis of 5-Substituted Proline Derivatives from Acetylene-Containing Amino Acids

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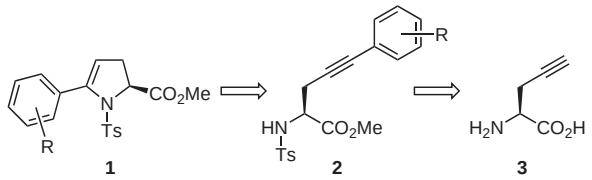
Abstract: 2,5-Disubstituted pyrrolines have been synthesised via Pd-catalysed 5-*endo-dig* cyclisations of substituted acetylene-containing amino acids. It has also been shown that these pyrrolines can be efficiently transformed into the corresponding saturated proline derivatives.

Key words: Pd-catalysis, amino acids, acetylenes, cyclisations, proline derivatives

Substituted prolines in general have gained considerable interest in recent years, which is reflected by the number of stereoselective syntheses of such prolines that have been reported in the literature.[1] These unnatural substituted proline derivatives can be considered as conformationally constrained amino acids and, in fact, have already been applied in biologically active peptides and peptidomimetics.[2] Some of these proline derivatives have also been recognized as a privileged element in medicinal chemistry of which *cis*-5-phenylproline is the most prominent example.[3]

The main existing synthetic approaches towards *cis*-5-phenylproline and other 5-substituted proline derivatives rely either on the convenient ring opening of pyroglumates by organometallic reagents and subsequent ring closure[4] or on the stereoselective addition of organocuprate reagents to pyroglumate-derived *N*-acyliminium ions.[5] On the other hand, these molecules have recently also been prepared in the group of Knight via iodine-mediated 5-*endo-dig* cyclisations of several homopropargylic sulfonamides.[6]

We envisaged that the 2,5-disubstituted pyrrolines **1** might be valuable precursors to access novel 5-substituted proline derivatives via stereoselective reduction of the enamide moiety (Scheme 1).



Scheme 1

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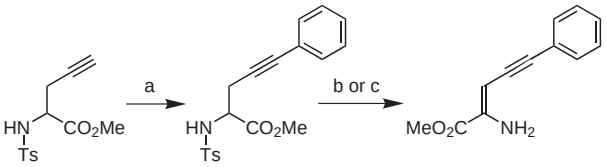
Building on methodology that has recently been developed in our group,[7,8] we anticipated that these pyrrolines **1** might be readily synthesised from the corresponding protected precursors **2** via a Pd-catalysed 5-*endo-dig* cyclisation. Compounds **2**, in turn, should be easily accessible from enantiopure 2-amino-4-pentynoic acid **3**[9] whose relatively inert side chain offers the possibility to introduce a range of aromatic[10] and aliphatic[11] groups via Pd-catalysis.[12]

In order to probe the feasibility of pyrroline formation via a Pd-catalysed cyclisation, precursor **5** was synthesised from the racemic 2-amino-4-pentynoic ester **4** via a Sonogashira-type coupling with iodobenzene affording **5** in 84% yield (Scheme 2).

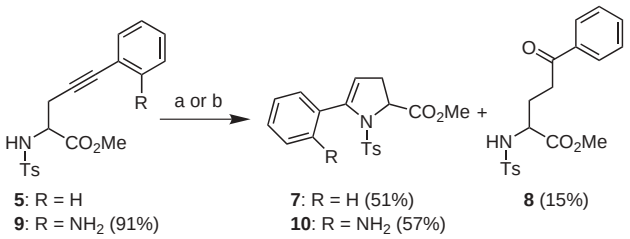


Scheme 2 *Reagents and conditions*: (a) Iodobenzene, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, Et_2O, r.t., 2 h; (b) $Pd(PPh_3)_4$, K_2CO_3, DMF, 80 °C, 18 h; (c) K_2CO_3, DMF, 80 °C.

Interestingly, subsequent subjection of **5** to previously reported cyclisation conditions[8] did not lead to the anticipated formation of the phenyl-substituted pyrroline. Instead, a complex mixture of products was obtained, from which elimination product **6**, being the major product, could be isolated as a single geometrical isomer in 19% yield.[13] This is probably the result of base-mediated elimination of *p*-toluenesulfinic acid,[14] followed by isomerisation of the imine double bond to the thermodynamically more stable enamine position. The double bond of **6** was assigned the sterically least hindered (*Z*)-geometry after conducting ^{1}H NMR NOE experiments. In line with this reasoning, the same conversion could even be accomplished in a cleaner fashion by heating **5** in DMF in the presence of K_2CO_3, without the Pd-catalyst present (70% based on recovered starting material).

Having observed these results, we turned our attention to earlier reported conditions[7,15] and exposed cyclisation precursor **5** to $PdCl_2(MeCN)_2$ in refluxing acetonitrile (Scheme 3). These conditions led to the rapid formation of

pyrroline **7** as the sole product in 51% yield after column chromatography. In addition, subjection of **5** to the same catalyst at room temperature also led to the formation of cyclised product **7**, albeit the reaction was significantly slower.



5: R = H
9: R = NH_2 (91%)

7: R = H (51%)
10: R = NH_2 (57%)

8 (15%)

Scheme 3 *Reagents and conditions*: (a) $PdCl_2(MeCN)_2$, MeCN, reflux, 2 h; (b) $PdCl_2(MeCN)_2$, MeCN, r.t.

In the latter case, as the result of a competitive reaction, ketone **8** was formed as a side product in 15% yield. This result is markedly different from our earlier reported results, in which a similar Boc-protected compound did not show any cyclisation.[7] Furthermore, subjection of the substituted aniline **9**, obtained in 91% yield starting from 2-amino-4-pentynoic acid derivative **4**, to the aforementioned catalyst in refluxing acetonitrile also led to the rapid formation of cyclic enamide **10** in 57% yield. Surprisingly, exposure of **9** to the same conditions at room temperature gave rise to the formation of **10** in 51% yield after prolonged reaction times of over several days, but, in that case, formation of the corresponding ketone was not observed.

In order to gain insight in the scope and limitations of the cyclisations, we prepared a variety of cyclisation precursors via Sonogashira coupling between 2-amino-4-pentynoic acid derivative **4** and several (substituted) aryl iodides. The substituted acetylenes **11**–**18** were thus obtained in good yields and subjected to the cyclisation conditions at reflux (Table 1).

Subjection of precursor **11**, substituted with an electron-donating methoxy group, led to the formation of the corresponding cyclic enamide in 49% yield (entry 1). Likewise, the *p*-methyl substituted precursor **12** underwent cyclisation to give pyrroline **20** in 50% yield (entry 2). In contrast to these results, not shown in Table 1, the cyclisation of the precursor derived from 2-amino-4-pentynoic ester **4** and *p*-nitrophenyl iodide did not lead to the corresponding cyclised product, indicating that the cyclisation is sensitive to electronic effects. In addition, the enantiopure 2-pyridyl substituted acetylene **16** did not undergo a cyclisation but lead to substantial recovery of the starting material. Likewise, the 3-pyridyl substituted acetylene **17** did not undergo cyclisation (entry 6). Presumably, in both cases, this behaviour could be attributed to the electron deficient nature of the pyridyl moiety. The naphthyl substituted acetylene **14** as well as **15** – containing a pharmaceutically relevant fluorophenyl substituent – both underwent cyclisation affording pyrrolines **22** and **23** in 44 and 51% yield, respectively (entries 4 and 5). Interestingly, the sterically more hindered precursor **13** cyclised relatively cleanly, leading to the cyclic enamide **21** in an acceptable yield of 68% (entry 3).

Crystallisation of this product afforded good quality crystals that were subjected to an X-ray crystal structure analysis, unambiguously confirming its structure (Figure 1).[16] We also wished to verify that no (partial) racemisation had taken place in the cyclisation process, to ensure that this sequence is suitable for the synthesis of enantiopure proline derivatives. Thus, the enantiomerically pure cyclisation precursor **18** was subjected to the Pd-catalyst in refluxing acetonitrile. This provided the pyrroline **24** as the sole product in 48% yield without detectable loss of enantiopurity according to chiral HPLC analysis.[17]

To explore the synthetic opportunities of the resulting pyrrolines, we set out to investigate the reduction of the enantiopure pyrroline **24** to the corresponding saturated proline derivative.

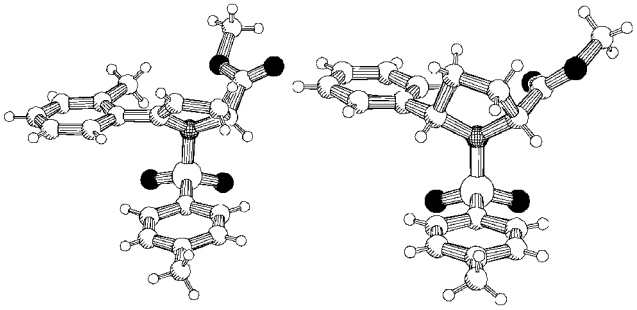
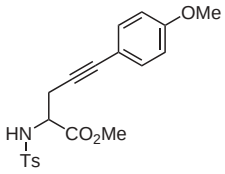
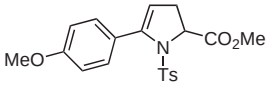
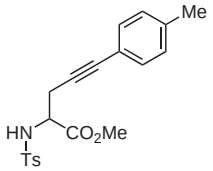
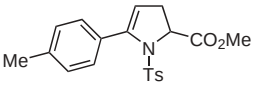
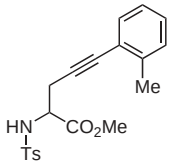
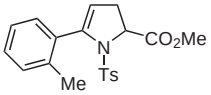
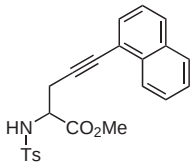
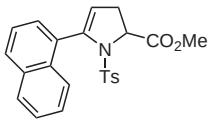
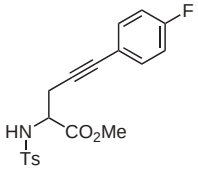
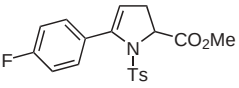
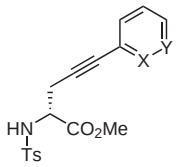
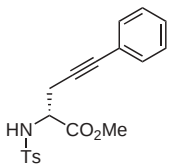
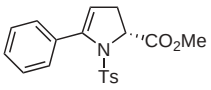


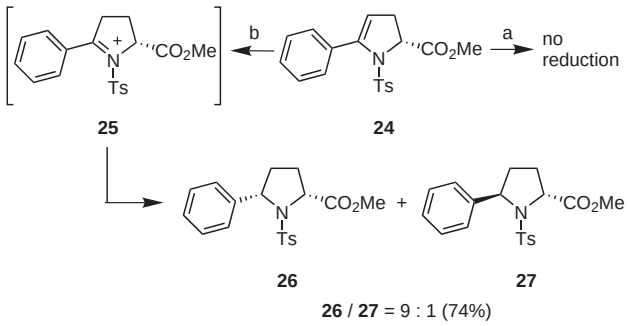
Figure 1 PLATON[18] drawing of the X-ray crystal structures of pyrrolines **21** (left) and **26** (right).

First, compound **24** was subjected to straightforward hydrogenation conditions using Pd on carbon under a hydrogen atmosphere. These conditions, however, did not lead to the reduction of the enamide moiety, but instead gave partial decomposition probably as a result of hydrogenolysis at the benzylic position. The reluctance of enamide **24** to undergo a catalytic hydrogenation might be explained by the crystal structure of pyrroline **21** (Figure 1). This structure clearly shows the shielding of the enamide double bond by the *p*-toluenesulfonamide moiety from the bottom side and the methyl ester from the top side, which may severely hamper the approach of the double bond to the catalyst surface. Next, we turned our attention to previously reported conditions,[8] involving the reduction of enamide **24** via the intermediate *N*-sulfonyliminium ion **25**.[19] This was achieved using a mixture of triethylsilane (5 equiv), trifluoroacetic acid (5 equiv) and trifluoroacetic anhydride (5 equiv) in CH_2Cl_2. The initially formed tertiary iminium ion was trapped by the hydride donor to give proline derivatives **26** and **27** as a 9:1 mixture of diastereoisomers in a combined yield of 74% (Scheme 4).

Table 1 Pd-Catalysed Cyclisations of Functionalised Cyclisation Precursors

Entry	Precursor	Product	Yield (%)[a]
1	 **11** (79%)	 **19**	49
2	 **12** (82%)	 **20**	50
3	 **13** (81%)	 **21**	68
4	 **14** (81%)	 **22**	44
5	 **15** (78%)	 **23**	51
6	 **16** (75%; X = N, Y = CH) **17** (86%; X = CH, Y = N)	No cyclisation	
7	 **18** (79%)	 **24** $[\alpha]_D$ +82.9	48

[a] Isolated yield after column chromatography.



Scheme 4 *Reagents and conditions*: (a) H_2, Pd/C, EtOAc, r.t.; (b) Et_3SiH, TFA, TFAA, CH_2Cl_2, 0 °C to r.t., 1.5 h.

Luckily, proline derivative **26** could be obtained in a pure form by repeated column chromatography and crystallisation, after which its structure was unambiguously identified by means of X-ray crystal structure analysis (Figure 1).[16] This result clearly established the *cis*-proline derivative **26** to be the major isomer.[20] The use of triphenylsilane as a more bulky hydride source under the same conditions did not lead to an improvement of the diastereoisomeric ratio, in fact the proline derivatives **26** and **27** were then obtained as a 7.5:1 mixture of isomers in a somewhat lower combined yield of 67%.

In conclusion, we have shown that the synthesis of 2,5-disubstituted pyrrolines can be achieved via 5-*endo-dig* Pd-catalysed cyclisation of acetylene-containing amino acids in reasonable yields. It has also been demonstrated that this pathway in case of enantiopure starting materials proceeds without detectable racemisation and thus can be applied to the synthesis of enantiomerically pure proline derivatives. In addition, we have demonstrated the feasibility of converting the obtained pyrrolines in an efficient manner into the corresponding saturated 5-aryl substituted proline derivatives.

Acknowledgement

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(16) Crystallographic data of structures **21** and **26** have both been deposited at the Cambridge Crystallographic Data Centre and have been allocated the deposition numbers CCDC 212273 and CCDC 212274, respectively.

(17) To determine the enantiopurity of compound **24**, racemic **24** was synthesised and separated on a Chiralcel OD column (eluant: *i*-PrOH/hexane = 1:9). Using this assay, the ee of pyrroline **24** was determined to be >99%.

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(20) Typical experimental procedures and data were as follows. **Formation of Enyne 6:** To a solution of **5** (418 mg, 1.17 mmol) in DMF (20 mL), K_2CO_3 (808 mg, 5.85 mmol) and $Pd(PPh_3)_4$ (71 mg, 0.06 mmol) were added and the reaction mixture was stirred at 80 °C. Upon completion (TLC), the reaction mixture was poured into sat. aq. $NaHCO_3$ (40 mL) and the aqueous layer was extracted with Et_2O (30 ml, 3×). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude

product was purified by chromatography (EtOAc/heptane = 1:9) to afford **6** (45 mg, 0.22 mmol, 19%) as a yellow solid. R_f = 0.23 (EtOAc/heptane = 1:9). IR(neat): 3448, 3354, 1705, 1614, 1591, 1487, 1441 cm^{-1}. Mp 49.4 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44 (m, 2 H), 7.31 (m, 3 H), 5.59 (s, 1 H), 4.57 (br s, 2 H), 3.82 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 141.2, 131.1, 128.3, 128.1, 123.4, 100.3, 86.6, 85.7, 52.8. HRMS (EI) calcd for $C_{12}H_{11}NO_2$: 201.0790. Found: 201.0792.

Formation of Pyrroline 24: To a solution of **18** (396 mg, 1.11 mmol) in MeCN (12 mL), $PdCl_2(MeCN)_2$ (29 mg, 0.11 mmol) was added and the reaction mixture was refluxed. Upon completion (TLC), the reaction mixture was concentrated in vacuo and the crude product was purified by chromatography (EtOAc/heptane = 1:3) to afford **24** (192 mg, 0.54 mmol, 48%) as a white solid. R_f = 0.36 (EtOAc/heptane = 1:2); $[\alpha]_D$ +82.9 (*c* 1.0, CH_2Cl_2). Mp 88.3 °C. IR(neat): 2947, 1736, 1595, 1493, 1444 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (m, 4 H), 7.29 (m, 5 H), 5.35 (dd, *J* = 2.1, 3.6 Hz, 1 H), 4.91 (dd, *J* = 2.1, 9.3 Hz, 1 H), 3.81 (s, 3 H), 2.56 (ddd, *J* = 2.4, 3.6, 17.1 Hz, 1 H), 2.42 (s, 3 H), 2.31 (ddd, *J* = 2.1, 9.6, 17.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 144.9, 144.2, 134.2, 132.6, 129.6, 129.0, 128.0, 128.0, 127.9, 115.3, 63.5, 53.0, 32.7, 21.7. HRMS (EI) calcd for $C_{19}H_{19}NO_4S$: 357.1035. Found: 357.1032.

Formation of Proline Derivative 26: To a solution of **24** (120 mg, 0.34 mmol) in CH_2Cl_2 (6 mL), Et_3SiH (0.27 mL, 1.70 mmol), TFAA (0.24 mL, 1.70 mmol) and TFA (0.13 mL, 1.70 mmol) were added at 0 °C. The reaction mixture was allowed to reach r.t. and stirred until the reaction had reached completion (TLC). The reaction mixture was concentrated in vacuo and purified by chromatography (EtOAc/heptane = 1:4) to afford a diastereomeric mixture of **26** and the *trans*-isomer **27** (**26**/**27** = 9:1, 90 mg, 0.25 mmol, 74%). Purification of this mixture by chromatography (EtOAc/heptane = 1:5) followed by crystallisation from Et_2O gave diastereomerically pure **26** as a white solid. R_f = 0.60 (EtOAc/heptane = 1:1); $[\alpha]_D$ –68.9 (*c* 0.5, CH_2Cl_2). Mp 130.3 °C. IR(neat): 1745, 1597, 1495, 1344 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.4 Hz, 2 H), 7.40 (m, 2 H), 7.18 (m, 5 H), 4.77 (t, *J* = 6.6 Hz, 1 H), 4.57 (t, *J* = 6.3 Hz, 1 H), 3.79 (s, 3 H), 2.36 (s, 3 H), 2.04 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 143.3, 141.1, 135.4, 129.2, 128.1, 127.7, 127.2, 127.0, 65.1, 62.2, 52.7, 36.1, 29.7, 21.8. HRMS (EI) calcd for $C_{19}H_{21}NO_4S$: 359.1191. Found: 359.1183.