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Rapid access to *cis* 3-substituted prolines

Nadia Pellegrini, Martine Schmitt* and Jean-Jacques Bourguignon

Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081 CNRS/ULP, Université Louis Pasteur, Faculté de Pharmacie, 74 Route du Rhin, 67401 Illkirch Cedex, France

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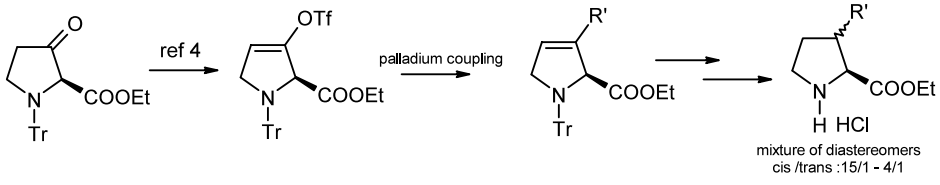
Abstract—The *O*-triflate of 2-cyano-3-oxopyrrolidine was obtained and used in a palladium coupling reaction. The resulting Δ^2-pyrrolidine derivatives allowed diastereocontrol at C2 and C3 after catalytic hydrogenation and led to chiral 3-substituted prolines as conformationally constrained amino acids.

The introduction of a proline ring into bioactive peptides restricts their conformational flexibility. This approach helps to study specific conformational requirements for small peptidic ligands for binding.[1,2] Recent efforts in our laboratory focused on new strategies towards proline derivatives as conformationally constrained amino acids.[3] More recently 2-cyano-3-oxo pyrrolidine was used in a Wittig reaction for the preparation of glutamate and arginine semi-rigid compounds.[3] In this work, the 3-OTf of 2-cyano-3-oxo pyrrolidine was used as an efficient intermediate for typical Pd coupling reactions.

More recently, an enantioselective approach to 3-substituted prolines has been reported by Kamenecka et al. by palladium-mediated coupling using the corresponding enol triflate obtained after oxidation of the available 3-(*R*)-hydroxy-2-(*S*)-proline ethyl ester (Scheme 1).[4] However, the enol intermediate presented a double bond between C3 and C4 and catalytic hydrogenation of corresponding products resulting from coupling reactions provided final products with only good to modest diastereoselectivity.[4]

Because of the presence in the O-Tf **2** of the more electron-withdrawing group (cyano group) combined with N-Boc protection when compared to carboxylate,[4] the prototropic rearrangement led to a quantitative migration of the double bond between C2 and C3. By catalytic hydrogenation, the pure *cis* isomer could be obtained as a racemate mixture.

Boc-protected 3-oxo-2-cyanopyrrolidine **1** was obtained in good yield by the procedure described previously (Scheme 2).[3] The triflate **2** was prepared using a conventional procedure (triflic anhydride, triethylamine and a catalytic amount of DMAP).[5] This enol triflate was submitted to various palladium coupling reactions as indicated in Table 1.[6] Catalytic hydrogenation of dihydropyrroles **3** afforded 2,3-*cis* substituted derivatives **4**.[7] After deprotection of Boc protecting group and *N*-benzoylation, the cyano group could be converted into an amide by TMSCl and H_2O,[8] or into an ester as previously described.[3] These compounds constitute semi-rigid derivatives of phenylalanine (**5a**, R = Ph) or tyrosine (**5c**, R = *p*-MeOPh).



Scheme 1.

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* Corresponding author. Tel.: +33 390 24 42 31; fax: +33 390 24 43; e-mail: 10schmitt@pharma.u-strasbg.fr

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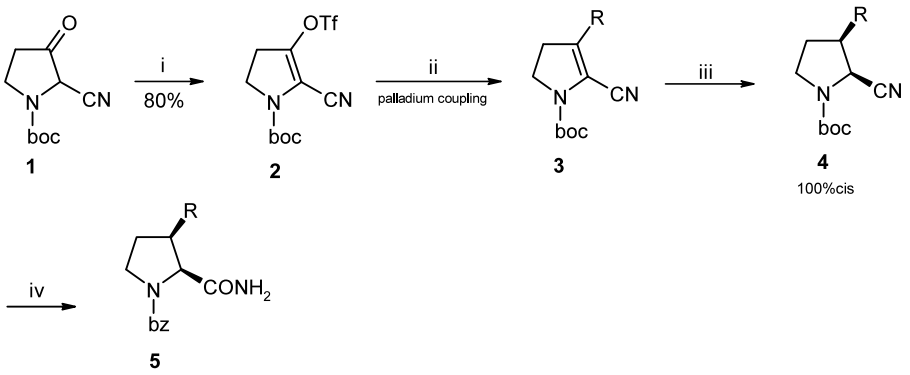

Scheme 2. *Reagents and conditions*: (i) Tf_2O, TEA, DMAP, CH_2Cl_2; (ii) a. $PdCl_2$(dppf), K_2CO_3, toluene/MeOH (9/1), rt, b. $PdCl_2$, PPh_3, CuI, TEA, CH_3CN, rt; (iii) H_2, Pd/C, EtOH; (iv) 1. HCl/EtOAc, 2. PhCOCl, TEA, DCM, 3. TMSCl, H_2O.

Table 1.

R	Cpd **3** (%)	Cpd **4** (%)	Cpd **5** (%)
C_6H_5	**3a** (78)	**4a** (80)	**5a** (71)
3-MeO-C_6H_4	**3b** (62)	**4b** (87)	**5b** (63)
4-MeO-C_6H_4	**3c** (60)	**4c** (75)	**5c** (65)
≡—CH_2OH	**3d** (50)	–	–
≡—CH_2NHBoc	**3e** (81)	**4e** (67)	–

Yields are not optimized.

Taking into account the easy transformation of the cyano group into carboxylate[3] or carboxamide,[8] this approach using 2-cyano-3-OTriflate pyrrolidine is useful for building new proline derivatives. Moreover it may be also applied to building new bicyclic nitrogen-containing alkaloids with a *cis* junction.

References

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4. Kamenecka, T. M.; Park, Y. J.; Lin, L. S.; Lanza, T.; Hagmann, W. K. *Tetrahedron Lett.* **2001**, *42*, 8571–8573.
5. Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599–1602.
6. Typical procedure: (a) To a solution of 0.3 mmol of **3** and 0.45 mmol of boronic acid in toluene/methanol (10/1, v/v, 8 ml) was added 0.06 g (0.45 mmol) of K_2CO_3 and 12 mg (5 mol%) of $PdCl_2$(dppf). The reaction mixture was stirred at 85°C for 9 h, cooled, concentrated and purified by silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) of **3b**: 1.57 (s, 9H, Boc), 3.15 (t, 2H, CH_2), 3.85 (s, 3H, OMe), 3.91 (t, 2H, CH_2N), 6.45–6.5 (m, 1H, Har.), 6.9–6.95 (m, 1H, Har.), 7.1–7.3 (m, 2H, Har.).
(b) To a solution of 0.3 mmol of **3** and 0.45 mmol of alkyne in acetonitrile (8 ml) was added 16 mg (0.06 mmol) of PPh_3, 6 mg (0.03 mmol) of CuI, 0.06 ml (0.45 mmol) of TEA and 6 mg (0.03 mmol) of $PdCl_2$. The reaction mixture was stirred at room temperature for 9 h, concentrated and purified by silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) of **3e**: 1.55 (s, 9H, Boc), 2.80, (t, 2H, CH_2), 3.90 (t, 2H, CH_2N), 4.20 (d, 2H, CH_2-NHBoc), 4.8–7.0 (s, 1H, NH).
7. All compounds **4** are characterized by an AB system (H2 and H3) in their ^{1}H NMR spectrum.
For example, compound **4c**: ^{1}H NMR A part of AB system (300 MHz, $CDCl_3$): 4.70 (d, 0.6H, H2), 4.84 (d, 0.4H, H2). (300 MHz, d_6-DMSO): 4.10 (d, 1H, H2).
As expected for tertiary amides, two different isomers could be identified in the 300 MHz NMR spectrum ($CDCl_3$) of **4c**: The C2–H methine appeared at 4.70 (60%) and 4.84 ppm (40%) as a part of an AB system, whereas only one isomer was identified in d_6-DMSO solution. This observation confirmed the presence of two isomers, but only one 2,3-*cis* diastereoisomer.
8. Basu, M. K. Luo, F. T. *Tetrahedron Lett.* **1998**, *39*, 3005–3006. Typical procedure: 2 equiv. of TMSCl is added to 1 equiv. of nitrile at 0°C and followed by the drop wise addition of 2 equiv. of water and allowed to warm up to 25°C in 2 h. The reaction mixture is neutralized with saturated bicarbonate solution at 0–5°C and extracted with dichloromethane, dried over $MgSO_4$, concentrated and purified by silica gel chromatography. ^{1}H NMR (200 MHz, $CDCl_3$) of **5c**: 1.9–2.1 (m, 2H, CH_2), 2.2–2.4 (m, 1H, H1), 3.6–3.8 (m, 2H, CH_2N), 3.8 (s, 3H, OMe), 4.7 (d, 1H, H2), 5.6 (s, 1H, NH_2), 6.7 (s, 1H, NH_2), 6.9 (d, 2H, Har.), 7.1–7.6 (m, 7H, Har.).