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Tetrahedron Letters 46 (2005) 7069–7072
Tetrahedron Letters

New pyrrole-based amino acids for the synthesis of peptidomimetic constrained scaffolds

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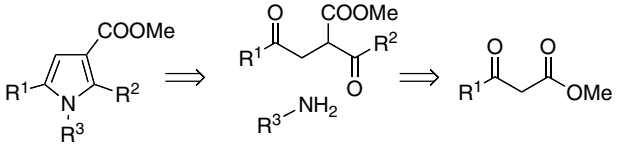
Received 27 June 2005; revised 26 July 2005; accepted 29 July 2005
Available online 26 August 2005

Abstract—A new family of pyrrole-based amino acids have been prepared through the microwave assisted Paal–Knorr reaction of 1–4 ketoesters derived from the corresponding β-ketoester with a functional homologation. The carboxylic group is located in position 3 of the pyrrole, whereas the amino group, protected with the Cbz moiety, is present on the side chain in positions 1 or 2. These compounds were used to prepare constrained oligopeptides.

The development and the synthesis of new amino acids and peptidomimetics have attracted considerable interest with the aim of finding new bioactive molecules based on natural peptide structures.[1] A widespread approach for designing of peptidomimetics is the introduction of conformationally constrained scaffolds, which may help to introduce turns in a short peptide, often a requisite to bioactive structures.[2] In connection with our interest in the synthesis of rare and unnatural amino acids and their application as peptidomimetic structural templates,[3] we considered a pyrrole-based amino acid as a suitable building block for the preparation of drug like scaffolds for combinatorial chemistry. Amino acids containing five member heterocyclic rings are present in several naturally occurring peptides isolated from marine organisms[4] and analogues compounds have been described as peptidomimetics,[5] macromolecular scaffolds[6] or building blocks for high throughput synthesis.[7]

We report here the synthesis of new short peptides containing highly functionalised pyrroles designed to be incorporated into longer strands through their NH_2 and COOH groups. Recently, we described a convenient preparation of pyrroles based on a microwave assisted Paal–Knorr reaction[8] and we started to explore this reaction for the preparation of pyrrole amino acids (Scheme 1).



Scheme 1.

As the carboxylic group was already installed in the heterocycle in position 3 during the synthesis, the possibility of having an amino group on R^1, R^2 or R^3 was explored. In order to introduce a NHCbz moiety in the R^1 substituent, N–Cbz–β-ketoester **2** was prepared from N–CbzPheOMe (**1**) through a Claisen cross condensation with EtOAc.[9] The product was submitted to functional homologation with Et_2Zn/CH_2I_2 followed by addition of benzaldehyde, but exclusively the product of simple homologation (**3**) was obtained, probably for the presence of the acid proton on the NHCbz group (Scheme 2).[10] We tried to use the *N*,*N*-dibenzyl derivative **4**, but its reaction with Et_2Zn/CH_2I_2 and PhCHO gave compound **5** in low yield. Moreover oxidation with PCC gave degradation of the product and other oxidants did not induce any transformation in the starting material.

Disappointed by the result on position 5, the introduction of an amino group in the substituent R_2 was attempted. As observed before, starting from ketoester **6**, the use of an NHCbz amino aldehyde as the electrophile gave exclusively the homologated compound **6a** (Scheme 3). As the undesired reactivity was attributed

Keywords: Paal–Knorr reaction; Cyclocondensation; Microwaves; Peptides.
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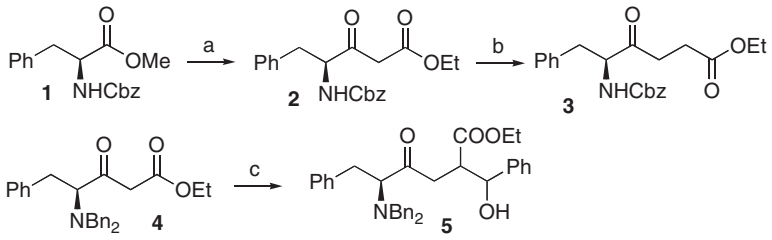
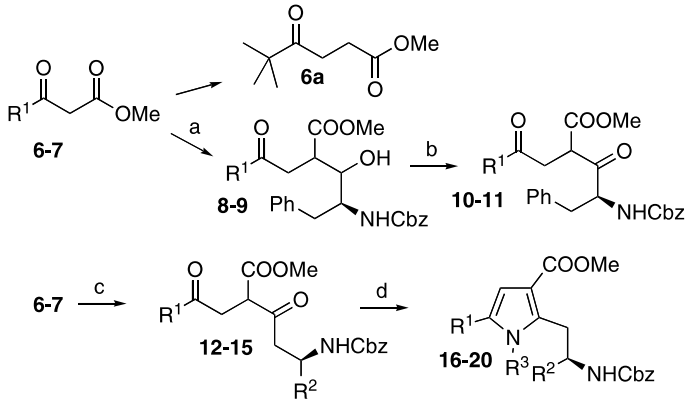
doi:10.1016/j.tetlet.2005.07.155



Scheme 2. Reagents and conditions: (a) EtOAc, LDA, −78 °C; (b) Et_2Zn, CH_2I_2, DCM; (c) Et_2Zn, CH_2I_2, DCM, PhCHO.



Comp.	R^1; R^2 ; R^3	Yield	Comp.	R^1; R^2 ; R^3	Yield
6, 8, 10	R^1= *t*-Bu	**8**: 65%	**16**	R^1= *t*-Bu; R^2= H; R^3= CH_2Ph	67%
		10: 78%			
7, 9, 11	R^1= Et	**9**: 52%	**17**	R^1= *t*-Bu; R^2= H;	75%
		11: 75%		R^3= CH_2CHMe_2	
12	R^1= *t*-Bu; R^2= H	66%	**18**	R^1= *t*-Bu; R^2= CH_2Ph;	72%
				R^3= CH_2Ph	
13	R^1= *t*-Bu	71%	**19**	R^1= Et; R^2= H; R^3= CH_2Ph	66%
	R^2= CH_2Ph;				
14	R^1= Et; R^2= H	60%	**20**	R^1= Et; R^2= H;	69%
				R^3= CH_2CHMe_2	
15	R^1= Et; R_2= CH_2Ph	56%			

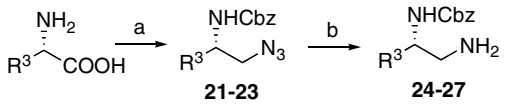
Scheme 3. Reagents and conditions: (a) Et_2Zn, CH_2I_2, DCM, N–Cbz–Phe–CHO/Et_2Zn; (b) PCC, DCM, SiO_2; (c) Et_2Zn, CH_2I_2, DCM, R^2–CH(NHCbz)CH_2CHO, Et_2Zn followed by PCC, DCM, SiO_2; (d) R^3–NH_2, AcOH, MW, 130 °C, 5–12 m, 200 psi.

to the presence of an acidic NH, we tried to remove it from the aldehyde by treatment with Et_2Zn. Thus, when the α-amino aldehyde was mixed with 1.2 equiv of diethylzinc and this mixture was added to the flask containing the intermediate generated from **6**–**7**, diethyl zinc and CH_2I_2, products **8**–**9** were obtained in acceptable yields. Oxidation with PCC gave ketones **10**–**11** that were isolated pure after a passage on a short pad of silica gel. Unfortunately, these compounds did not give the expected pyrroles following the classical Paal–Knorr reaction conditions (MW, AcOH, 150 °C, 5 min). Attempts to increase the temperature and the time of irradiation, as changes in the nature of solvent, did not afford the ring closing. In order to find a structure suitable for cyclisation, compounds **12**–**15** were prepared using different β-NHCbz-substituted aldehydes as the electrophile in the functional homologation. Even in this case, the aldehyde must be treated with Et_2Zn to remove the acid NH proton.

When products **12**–**15**, with a CH_2 between the NHCbz and the centre interested in the cyclisation, were submitted to MW assisted Paal–Knorr reaction in the presence of primary amines, pyrroles **16**–**20** were obtained in good yields (Scheme 3).[11]

The introduction of the amine in the substituent in position 1 was finally attempted using the Cbz protected diamines **24**–**27** prepared from natural amino acids as reported in Scheme 4.

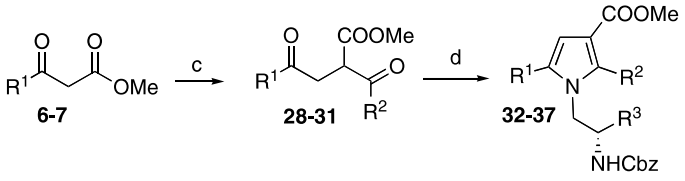
Whereas compound **24** (formally derived from Gly) is commercially available, the amino acids Phe, Ala and Leu were reduced with $LiAlH_4$ in THF and the crude



R^3 = H: **24**
R^3 = $PhCH_2$-: **21** (72%); **25** (80%)
R^3 = CH_3-: **22** (73%); **26** (81%)
R^3 = Me_2CHCH_2-: **23** (67%); **27** (78%)

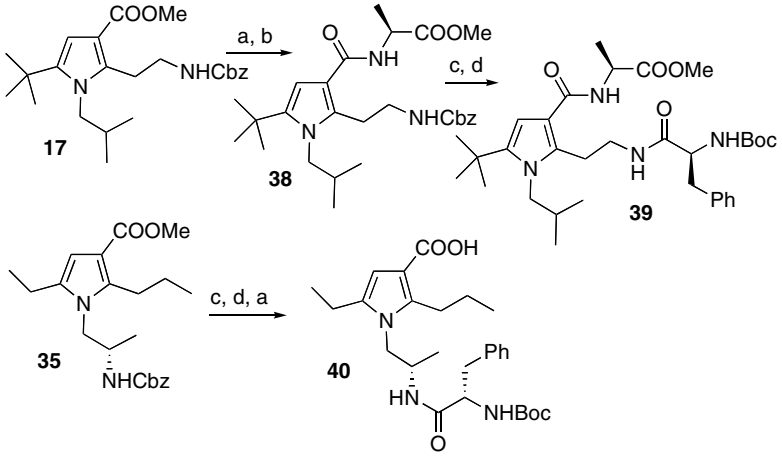
Scheme 4. Preparation of monoprotected diamines derived from Phe, Ala and Leu.

amino alcohols protected with CbzCl in THF/Na_2CO_3. The OH was treated with MsCl/Et_3N in the presence of NaN_3 to give the azides **21**–**23** in good yields.[12] Reduction with PPh_3/HCl/H_2O in THF gave amines **25**–**27** in very good yields. Cyclisation of **24**–**27** with diketones **28**–**31** was carried out under microwave irradiation providing compounds **32**–**37** in good yields (Scheme 5). The transformation of the so obtained pyrrole-containing amino acids into a peptidic backbone was carried out starting from compounds **17** and **35**. Thus, hydrolysis of the methyl ester of **17** was carried out with LiOH in THF/H_2O and the acid coupled with H–Ala–OMe (DMTMM,[13] THF, NMM, 80%) to give **38**. The Cbz was removed by MW assisted transfer hydrogenolysis[14] and the amine coupled with Boc–Phe–OH to give **39** in 88% overall yield.[15] From **35**, removing of the Cbz followed by coupling with BocPheOH and ester hydrolysis provided the acid **40** (72% yield from **35**) that could be coupled with other amino acids or peptides in solution or solid phase synthesis (See Scheme 6).



Comp.	R^1; R^2 ; R^3	Yield	Comp.	R^1; R^2 ; R^3	Yield
28	R^1= *t*-Bu R^2= Ph;	69%	**33**	R^1= t-Bu; R^2= -C_3H_7; R^3= H	75%
29	R^1= *t*-Bu; R^2= -C_3H_7	61%	**34**	R^1= t-Bu; R^2= -C_3H_7; R^3= -CH_2Ph	72%
30	R^1= Et; R_2= Ph	76%	**35**	R^1= Et; R^2= -C_3H_7; R^3= Me	65%
31	R^1= Et; R_2-C_3H_7	77%	**36**	R^1= Et; R^2= Ph; R^3= CH_2CHMe_2	60%
32	R^1= t-Bu; R^2= Ph; R^3= H	67%	**37**	R^1= Et; R^2= -C_3H_7; R^3= CH_2CHMe_2	71%

Scheme 5. Reagents and conditions: (a) (i) $LiAlH_4$, THF, reflux, 12 h, (ii) CbzCl, THF, Na_2CO_3, (iii) MsCl, NaN_3, TBAI, toluene, 80 °C, 6 h; (b) PPh_3, THF, followed by HCl 1 M; (c) (i) Et_2Zn, CH_2I_2, DCM, R^2CHO, rt, 2 h, (ii) PCC, DCM, rt, 12 h; (d) **24**–**27**, AcOH, MW, 130 °C, 5–12 m, 200 psi.



Scheme 6. Reagents and conditions: (a) LiOH, THF/H_2O, rt 24 h; (b) HAlaOH, DMTMM, NMM, THF, rt 12 h; (c) $HCOONH_4$, *i*-PrOH, MW, 120 °C, 6 min; (d) BocPheOH, DMTMM, NMM, THF, rt 12 h.

Scaffolds **39** and **40** show a high level of diversity with variations in positions 1, 2 and 5 around the pyrrole related to the original synthetic scheme. One additional level of diversification at positions 1, 2 and 3 is possible using traditional combinatorial peptide chemistry. Moreover, this system can be used to achieve rigidity inside a peptide strand or to mimic a potentially active turn.

In summary, we have explored the possibility to use the Paal–Knorr reaction to prepare pyrrole-based amino acids and developed a convenient route to new highly functionalised scaffolds for parallel synthesis. The synthesis of new cyclic peptides incorporating these pyrrole-based building blocks and the structural studies are currently under investigation.

Acknowledgment

This work was financially supported by Nikem-Research srl (Milan).

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11. *(Benzyloxycarbonylaminoethyl)-1-benzyl-5-tert-butyl-3-carboxymethyl-pyrrole* **16** *General procedure*. Diethyl zinc (30 mL of a 1.0 M solution in hexane, 30 mmol) was dissolved into dry dichloromethane (60 mL) under nitrogen and the mixture cooled to 0 °C. Diiodo methane (2,4 mL, 30 mmol) was slowly added and the mixture stirred for 10 min. After the formation of a white precipitate, 4,4-dimethyl 3-oxopentanoate (1.3 mL, 7.3 mmol) was added and the reaction was stirred for 30 min. A solution of 3-Cbz-aminopropanal (1.51 g, 7.3 mmol) in DCM (8 mL) containing diethyl zinc (8 ml of a 1.0 M solution in hexane, 8 mmol) was slowly added and the mixture stirred at 0 °C for 1 h. Silica gel (20.0 g) was added and the mixture stirred at room temperature for additional 30 min. The mixture was filtered under vacuum and the solvent evaporated. The crude (2.16 g) was dissolved in dry dichloromethane, PCC (3.3 g, 15.3 mmol) was added and the mixture stirred at room temperature until TLC analysis (eluent hexane/AcOEt 1:1) showed disappearance of the starting material. Eventually, additional PCC could be added. The mixture was passed through a short path of silica gel and eluted with dichloromethane. The solvent was collected and evaporated under vacuum to give product **12** (1.65 g, 66% yield). An analytical sample was purified by column chromatography on silica gel (eluent hexane/AcOEt 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 9H, *t*-Bu), 3.00–3.10 (m, 4H, $2CH_2CO$), 3.36 (t-like, 2H, $COCH_2$), 3.55 (s, 3H, COOMe), 3.99 (m, 2H, CH_2N), 4.34 (m, 1H, CH), 5.10 (s, 2H, Cbz), 6.00 (s, 1H, NH), 7.28 (m, 5H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 32.4, 33.5, 38.5, 44.9, 49.0, 51.0, 56.8, 126.5, 128.0, 129.3, 138.5, 165.8, 171.2, 202.5, 211.7. MS (ES/MS), 378 (M^++1). Product **12** (1 g, 2,63 mmol) was dissolved into acetic acid (3 mL) into a 50 mL round-bottom flask equipped with a stir bar and a reflux condenser. Benzyl amine (1.84 g, 17.2 mmol) was added and the flask inserted into the cavity of a Discover Microwave System apparatus (from CEM) and heated at 150 W for 12 min (internal temperature 170 °C). The mixture was diluted with AcOEt and the solvent washed several times with a saturated solution of $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. The ^{1}H NMR spectrum of the crude showed the presence of compound **16** together with benzylamine acetate. The required pyrrole was purified by flash chromatography (eluent hexane/AcOEt 8:1, $R_f = 0.37$) that gave product **16** as a solid, mp 90–91 °C. (0.79 g, 67% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 9H, *t*-Bu), 3.13 (t, $J = 7$ Hz, 2H, CH_2-pyrrole), 3.60 (s, 3H, COOMe), 4.30 (t, $J = 8$ Hz, 2H, CH_2NHCbz) 4.86 (s, 2H, CH_2–N), 5.16 (s, 2H, OCH_2Ph), 6.11 (br s, 1H, NH), 6.32 (d, 1H, H-4), 7.30 (m, 10H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 15.3, 29.5, 31.2, 31.9, 33.4, 40.7, 44.6, 52.7, 70.9, 103.4, 111.8, 126.3, 127.4, 127.6, 128.6, 128.7, 131.6, 133.6, 134.6, 137.4, 138.7, 155.7, 165.4. ES/MS 449 (M^++1). Anal. Calcd for $C_{27}H_{32}N_2O_4$: C, 72.30; H, 7.19; N, 6.25. Found C, 72.20; H, 7.12; N, 6.29.
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15. ^{1}H NMR (300 MHz) spectra of **39** and **40** showed the presence of a single diastereoisomer, proving that no racemisation (at least < 5%) occurred during the synthesis.