Pergamon

Tetrahedron Letters 43 (2002) 4431–4434

TETRAHEDRON LETTERS

Solid-phase synthesis of new peptide–arene hybrids from *N*-TCP amino acids

Marta Planas, Esther Cros, Ricard-Aleix Rodríguez, Rafael Ferre and Eduard Bardají*

Department of Chemistry, University of Girona, 17071 Girona, Spain

Received 8 April 2002; revised 24 April 2002; accepted 30 April 2002

Abstract—New linear and macrocyclic arene–peptide hybrids may be synthesized from *N*-tetrachlorophthaloyl protected amino acids through mild phthalimide opening by 1,3-diaminopropane.

The synthesis of new macrocyclic compounds has become a topic of growing interest due to the wide range of properties associated to this large family of compounds, like the formation of supramolecular structures.[1,2] Cyclic peptides and cyclic arene–peptide hybrids belong to such type of compounds.[3] Here we report on the application of *N*-tetrachlorophthaloyl (TCP) protected amino acids as building blocks for the synthesis of new linear and cyclic peptide–arene compounds.

N-TCP protected amino acids have been described as building blocks for solid-phase synthesis of *C*-terminal peptide amides.[4] TCP group exhibits stability toward harshly acidic conditions and proved to be unaffected by piperidine treatments, being compatible with Fmoc deprotection conditions. TCP group removal is carried under ethylene diamine:DMF or hydrazine:DMF treatments. However, we observed that when *N*-TCP protected amino acids were treated with 1,3-diaminopropane at room temperature for 1–5 min only *N*,*N*′-disubstituted tetrachlorophthalamides were obtained (Fig. 1). This result prompted us to study the synthesis of new peptide–arene hybrids from *N*-TCP protected amino acids.

The solid-phase synthesis of linear arene–peptide hybrids (Table 1, entries 1–3 and 5) from *N*-TCP protected amino acids was performed onto an Fmoc-PAL-PEG-PS resin (0.16 mmol/g, 1 equiv.). After Fmoc removal, the corresponding *N*-TCP protected amino acid (3 equiv.) was coupled with HBTU:DIEA (3:3) or DIPCDI:HOAt (3:3) in DMF, 4 h at 25°C. Upon completion of coupling, ninhydrin test was nega-

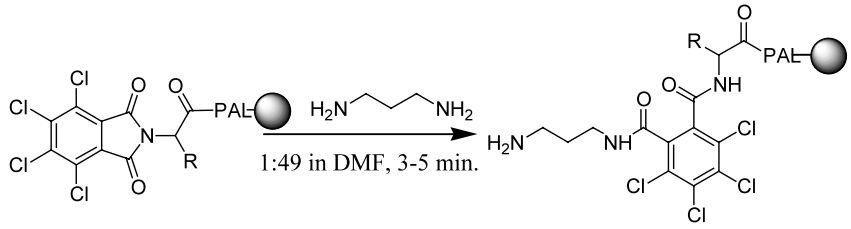


Figure 1. Formation of *N*,*N*′-disubstituted phthalamides from *N*-TCP protected amino acids.

Abbreviations: *t*Bu, *tert*-butyl; DIPEA, *N*,*N*-diisopropylethylamine; DIPCDI, *N*,*N*′-diisopropylcarbodiimide; DMF, *N*,*N*-dimethylformamide; ESI MS, electrospray ionization mass spectrometry; Fmoc, 9-fluorenylmethoxycarbonyl; HBTU, *N*-1*H*-(benzotriazol-1-yl) (dimethylamino)methylene-*N*-methylmethanaminium hexafluorophosphate-*N*-oxide; HOAt, 7-aza-1-hydroxy-benzotriazole; HPLC, high-performance liquid chromatography; IRAA, 'internal reference' amino acid; PAC, *p*-alkoxybenzyl alcohol handle; PAL, 5-(4-aminomethyl-3,5-dimethoxy-phenoxy)-valeric acid handle (Peptide Amide Linker); PEG-PS, poly(ethylene glycol)-polystyrene (graft resin support); TCP, tetrachlorophthaloyl; TFA, trifluoroacetic acid; Amino acid symbols denote the L-configuration unless noted otherwise.

* Corresponding author. Tel.: +34 972 418959; fax: +34 972 418150; e-mail: eduard.bardaji@udg.es

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00836-5

tive.[5] Ring-opening of the *N*-TCP protecting group was mediated by 1,3-diamino-propane:DMF (1:49), during 5 min at rt. Sequential coupling and opening cycles were performed. After cleavage with TFA–H_2O (19:1) the expected linear hybrids were obtained, and were analyzed by HPLC and characterized by ESI MS (Table 1).

The synthesis of cyclic arene–peptide hybrids (entries 4 and 6, Table 1) proceed with the preparation of the corresponding linear sequences according to the methodology described above, but starting with anchoring of *N*-TCP-Glu-OAl. Cyclic compounds were obtained after *N*-TCP ring-opening with 1,3-diaminopropane followed by allyl ester deprotection[6] with $Pd(PPh_3)_4$ (5 equiv.) in $CHCl_3$/HOAc/NMM (37:2:1), 3 h at 25°C and on-resin cyclization was mediated by PyAOP/HOAt/DIEA (5:5:10) in NMP.[7] Final cleavage of the anchoring linkage with TFA/H_2O (19:1) provided the macrocyclic arene–peptide hybrids as the unique compounds, which were analyzed by HPLC and characterized by ESI MS (Table 1, Scheme 1).

We observed that the order in which *N*-TCP ring-opening and allyl group removal was performed was crucial for the success of the synthesis. Allyl group was cleaved following the standard procedure that included washings with sodium *N*,*N*-diethyldithiocarbamate.[8] During the synthesis of c(DAP-TCP-Ala-DAP-TCP-Gln), if the allyl group was removed in presence of the *N*-TCP group the expected cyclic compound ($[M+H]^+$ 879.6) was formed together with another compound (1:1 ratio) that was isolated and analyzed by ESI MS ($[M+H]^+$ 955.9). The observed mass accounted for the proposed macrocyclic structure **1**, and its formation is plausibly explained by a nucleophilic attack of the *N*,*N*-diethyldithiocarbamate to the carbonyl group of the *N*-TCP-Ala- moiety as shown (Scheme 2).

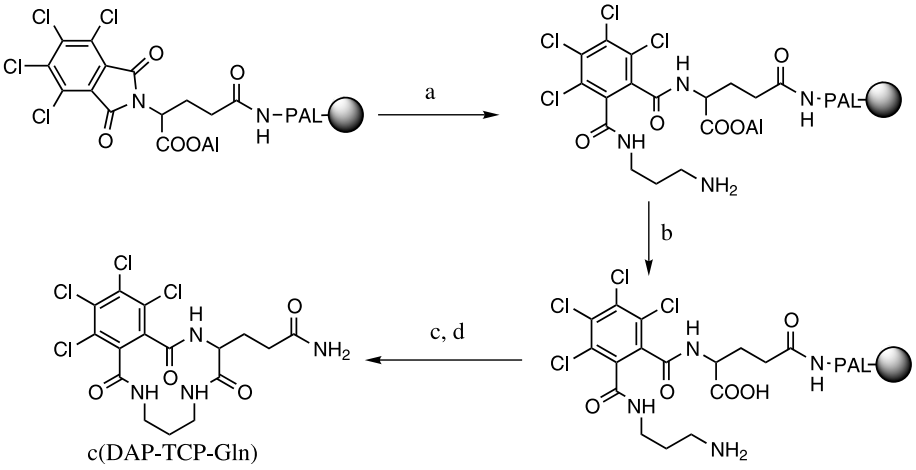
The use of haloaromatic building blocks has been proved useful as tags for binary encoding combinatorial libraries.[9]

The presence of chlorine atoms in the structure of the described linear and cyclic hybrids confers characteristic ESI MS patterns, as shown in Fig. 2, for compounds containing one or two TCP moieties. This property makes *N*-TCP amino acids and its derivatives potential interesting building blocks for encoding strategies.

Table 1. Characterization of the linear and macrocyclic sequences synthesized

Entry	Peptide sequence[a]	R_t (min)[b]	Purity[c]	Yield[d]	ESI MS (m/z)
1	H-Phe-DAP-TCP-Gly-Val-NH_2	14.3	84	80	$[M+H]^+$ 661.1
2	TCP-Phe-DAP-TCP-Leu-NH_2	23.6	85	78	$[M+H]^+$ 883.7
3	H-DAP-TCP-Gln-OH	13.2	95	88	$[M+H]^+$ 487.3
4	c(DAP-TCP-Gln)	14.6	99	91	$[M+H]^+$ 468.7
5	H-DAP-TCP-Ala-DAP-TCP-Gln-OH	17.0	92	86	$[M+H]^+$ 897.9
6	c(DAP-TCP-Ala-DAP-TCP-Gln)	17.2	89	79	$[M+H]^+$ 879.6

[a] Side-chain anchoring of TCP-Glu-OAl yields after deprotection and cleavage the corresponding Gln acid termination for entries 3 and 5.
[b] HPLC retention time (linear gradient from 0.1% aqueous TFA to 0.1% TFA/CH_3CN for 23 min; l=220 nm).
[c] Percent determined by HPLC from crude product of synthesis.
[d] Isolated yields. (DAP=-NH-CH_2-CH_2-CH_2-NH-), (TCP=-CO-C_6Cl_4-CO-).



Scheme 1. Solid-phase synthesis of c(DAP-TCP-Gln) (entry 4, Table 1). *Reagents and conditions*: (a) 1,3-diaminopropane/DMF (1:49), 5 min; (b) $Pd(PPh_3)_4$ (5 equiv.), $CHCl_3$/HOAc/NMM (37:2:1), 3 h at rt; (c) PyAOP/HOAt/DIEA (5:5:10) in NMP, 6 h; (d) TFA/H_2O (19:1), 2 h.

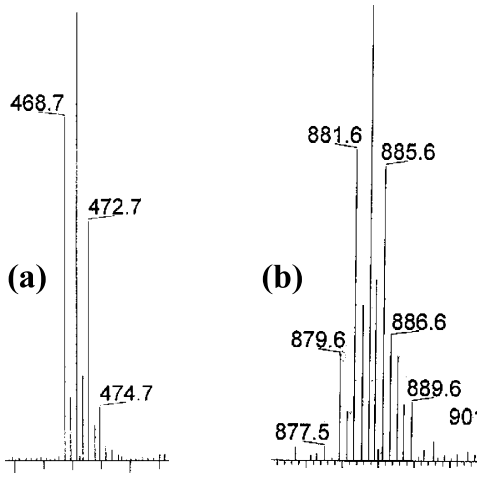


Figure 2. ESI MS of (a) c(DAP-TCP-Gln) and (b) c(DAP-TCP-Ala-DAP-TCP-Gln).

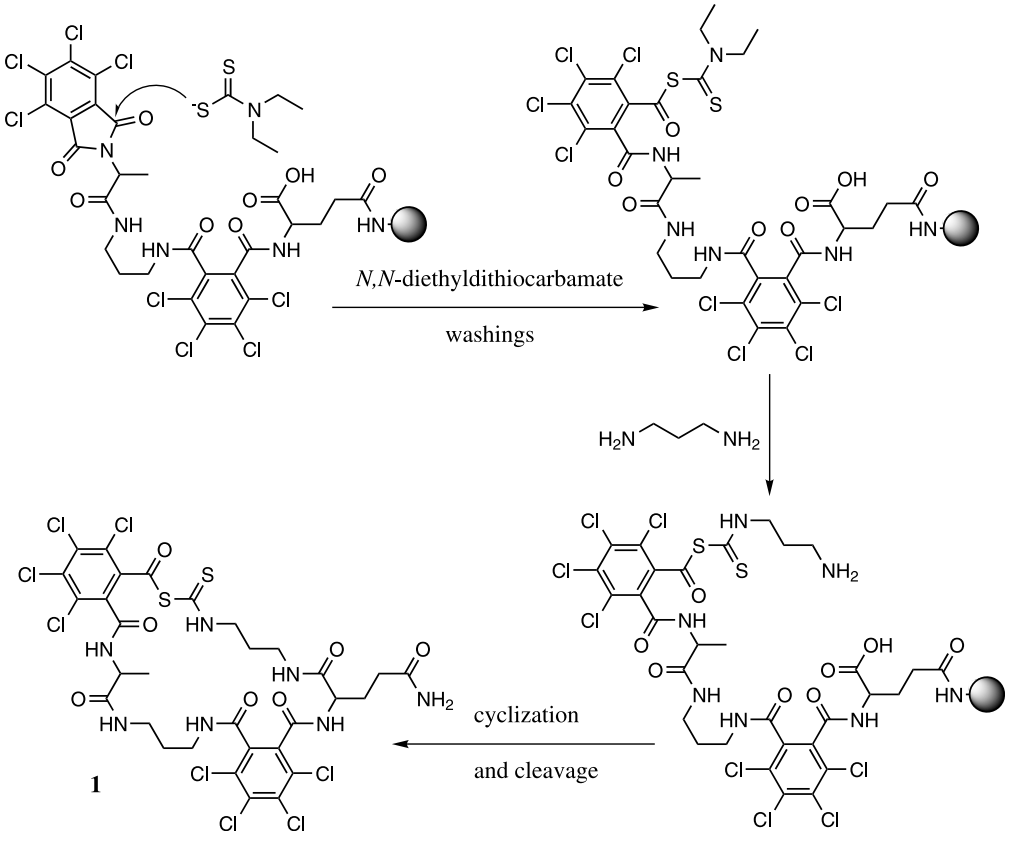
In summary, we have described an efficient procedure for the synthesis of a new family of linear and macrocyclic peptide–arene hybrids from *N*-TCP protected amino acids.

Acknowledgements

This work was supported by grants UdG98-404 and UdG99-094.

References

1. (a) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988–1011; (b) Ranganathan, D.; Haridas, V.; Gilardi, R.; Karle, I. L. *J. Am. Chem. Soc.* **1998**, *120*, 10793–10800.
2. (a) Mrybakakimova, E. V. *Rev. Inorg. Chem.* **2001**, *21*, 207–298; (b) Costamagna, J.; Ferraudi, G.; Matsuhiro, B.; Camposvallette, M.; Canales, J.; Villagran, M.; Vargas, J.; Aguirre, M. J. *Coord. Chem. Rev.* **2000**, *196*, 125–164; (c) Pina, F.; Bernardo, M. A.; Garcia-España, E. *Eur. J. Inorg. Chem.* **2000**, 2143–2157; (d) Ruizhitzky, E.; Casal, B.; Aranda, P.; Galvan, J. C. *Rev. Inorg. Chem.* **2001**, *21*, 125–159; (e) Alfonso, I.; Rebolledo, F.; Gotor, V. *Chem. Eur. J.* **2000**, *6*, 3331–3338; (f) Konig, B.; Pelka, M.; Klein, M.; Dix, I.; Jones, P. G.; Lex, J. *J. Incl. Phenom. Macrocycl. Chem.* **2000**, *37*, 39–57.
3. (a) Ranganathan, D.; Haridas, V.; Karle, I. L. *J. Am. Chem. Soc.* **1998**, *120*, 2695–2702; (b) Kubik, S.; Goddard, R. *J. Org. Chem.* **1999**, *64*, 9475–9486; (c) Kubik, S. *J. Am. Chem. Soc.* **1999**, *121*, 5846–5855; (d) Ranganathan, D.; Thomas, A.; Haridas, V.; Kurur, S.; Madhusudanan, K. P.; Roy, R.; Kunwar, A. C.; Sarma, A. V. S.; Vairamani, M.; Sarma, K. D. *J. Org. Chem.* **1999**, *64*, 3620–3629.
4. (a) Cros, E.; Planas, M.; Bardají, E. *Synthesis* **2001**, 1313–1320; (b) Cros, E.; Planas, M.; Mejías, X.; Bardají, E. *Tetrahedron Lett.* **2001**, *42*, 6105–6107.
5. Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595–598.
6. Jensen, K. J.; Alsina, J.; Songster, M. F.; Vágner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441–5452.



Scheme 2. Insertion of a dithiocarbamate moiety onto a *N*-TCP protected fragment.

7. (a) Kates, S. A.; Solé, N. A.; Johnson, C. R.; Hudson, D.; Barany, G.; Albericio, F. *Tetrahedron Lett*. **1993**, *34*, 1549–1552; (b) Planas, M.; Bardají, E.; Barany, G. *Tetrahedron Lett*. **2000**, *41*, 4097–4100.
8. As described in Ref. 7, after $Pd(PPh_3)_4$ treatment, the peptide–resins are washed with THF (3×2 min), DMF (3×2 min), CH_2Cl_2 (3×2 min), DIPEA/CH_2Cl_2 (1:19, 3×2 min), CH_2Cl_2 (3×2 min), sodium *N*,*N*-diethyldithiocarbamate (0.03 M in DMF, 3×15 min), DMF (5×2 min), CH_2Cl_2 (3×2 min), and DMF (3×1 min).
9. Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev*. **2000**, *100*, 2091–2157.