Pergamon

Tetrahedron Letters 42 (2001) 3061–3063

TETRAHEDRON LETTERS

A new efficient approach to N-linked glycopeptoids[†,‡]

Klaus Burger,* Christoph Böttcher, Gabor Radics and Lothar Hennig

Department of Organic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany

Received 6 February 2001; accepted 26 February 2001

Abstract—A preparatively simple synthesis of N-linked glycopeptoids from glycosylamine and imino diacetic acid using hexafluoroacetone as protecting and activating agent is described.

Major drawbacks of peptide drugs are their rapid degradation by proteases, their low lipophilicity and the lack of transport systems to direct peptides into cells. Therefore, cell membranes generally resist passage of most peptides. Consequently, peptides are rapidly excreted. The high conformational flexibility of peptides creates another problem: bioactive peptides often bind to different receptor sites causing undesired side effects.[2,3] Different strategies to solve these problems have been developed, including the design of peptidomimetics,[4,5] i.e. by incorporation of α-alkyl[6,7] and α-trifluoromethyl amino acids[8] into strategic positions on the peptide chain, the synthesis of glycopeptides[9,10] and of 'non-peptide peptidomimetics' utilizing multifunctional heterocycles[2] and carbohydrates[11] as scaffolds can be carried out.

The design of peptoids[12] added a new dimension to peptide modification.[13] Peptoids are *N*-substituted oligoglycines with alkylated N^{α}-atoms, having no stereogenic centers.[14] Other characteristics are high conformational flexibility, high structural diversity and improved proteolytic stability. It is noteworthy that the peptoid approach is amenable to solid-phase synthesis.[15]

Roy et al. were the first to combine the advantages of the peptoid and the glycopeptide approach. They synthesized a series of N-linked[16] and O-linked glycopeptoids[17] and used them as building blocks for the construction of HIV-1 protease inhibitors[18] and of T_N-antigen glycopeptidomimetic clusters.[19] Recently Kessler et al. reported on a stereoselective synthesis of *C*-glycosylated peptoid building blocks.[20] Herein we want to describe a new, preparatively simple, access to N-linked glycopeptoids using hexafluoroacetone as protecting and activating agent.

The first example of this new class of 'non-natural biooligomers', an asparagine linked *N*-acetylglucosaminide pentapeptoid, has been synthesized by R. Roy et al.[16a] via a sequence of consecutive substitution and acylation steps, an elegant adaptation of the submonomer approach described by Zuckermann et al.[15]

On application of hexafluoroacetone as protecting and activating agent[21] the *N*-glycosylated tripeptoid can be obtained in five steps with an overall yield of 12–23%, starting from the imino diacetic acid **1**. First, **1** is transformed into a lactone **2** on reaction with hexafluoroacetone. This process includes simultaneous functionalization of the imino and of one of the carboxy groups. The second carboxy group remains unaffected. The lactone moiety formed represents an activated ester. In a second step the exocyclic carboxy group is transformed into an acid chloride on treatment with phosphorus pentachloride to give a double activated dicarboxylic acid derivative **3**. Subsequently, a sequence of two regioselective acylation reactions can be performed. On treatment with various nucleophiles like glycosylamines in the presence of a base, e.g. *N*-ethyl morpholine, the more reactive acid chloride reacts selectively to give the *N*-glycosylated, carboxy activated glycine derivative **4**, which in a consecutive step can be used for acylation of amino acid esters and amides (Scheme 1).

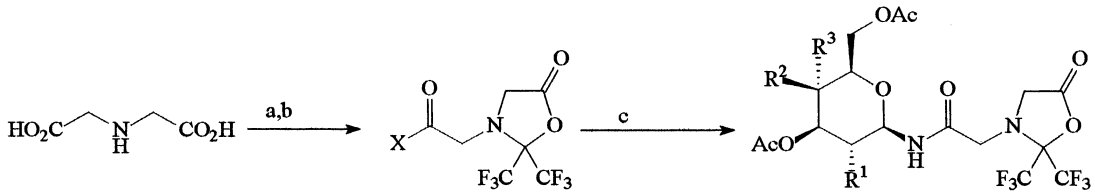
Keywords: imino diacetic acid; hexafluoroacetone; glycosylamines; glycopeptoids.

* Corresponding author. Fax: (49) 341 9736599; e-mail: burger@organik.chemie.uni-leipzig.de

† Hexafluoroacetone as protecting and activating agent in glycopeptide and glycopeptoid chemistry, Part 2. For Part 1, see Ref. 1.

‡ Dedicated to Professor Dr. L. Moroder on the occasion of his 60th birthday.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00351-3



1 **2 X=OH** **3 X=Cl** **4**

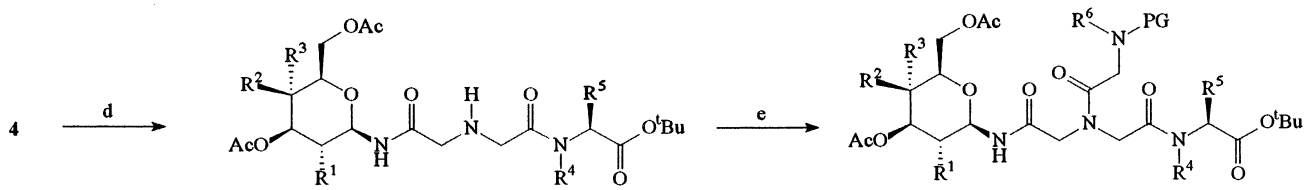
a R^1=OAc, R^2=H, R^3=OAc, 82%

b R^1=NHAc, R^2=H, R^3=OAc, 71%

c R^1=OAc, R^2=OAc, R^3=H, 78%

d R^1=OAc, R^2=H, R^3=β-D-Ac_4-Glc, 80%

Scheme 1. *Reagents and conditions*: (a) 2HFA, DMSO, 86%; (b) PCl_5, 80%; (c) glycosyl–NH_2, NEM, CH_2Cl_2, 0°C.



5 **6**

a R_4=Bn, R_5=H, 50%

b R_4=Me, R_5=H, 45%

c R_4=H, R_5=^{i}Bu, 69%

d R_4=R_5=CH_2-CH_2-CH_2, 67%

a PG=Ac, R_6=Me, 60%

b PG=TFA, R_6=Bn, 55%

c PG=Bzl, R_6=H, 62%

d PG=TFA, R_6=^{i}Bu, 43%

Scheme 2. *Reagents and conditions*: (d) H-Xaa-O^{t}Bu*HCl, NEM, ^{i}PrOH/EtOAc; (e) PG-Yaa-OH, PyBOP, DIEA, DMF.

In the case of hexafluoroacetone protected amino acids the formation of the peptide bond is always coupled with a spontaneous deprotection of the amino group (**4**→**5**). Therefore, the construction of the peptoid chain can be continued in the N-terminal position without the need of a deprotection step to give the *N*-glycosylated tripeptoids **6** (Scheme 2). Compounds **5** and **6** show complex ^{1}H NMR spectra due to the presence of mixtures of rotamers. The structures of the new compounds are unequivocally confirmed by NMR and mass spectrometry.

In summary, a new strategy for selective functionalization of multifunctional compounds,[21] using hexafluoroacetone as protecting and activating agent, was applied for the synthesis of *N*-glycosylated peptoids and peptides. The readily available *N*-glycosylated peptoid and peptide fragments are valuable building blocks for glycoconjugate synthesis.[22]

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (Bu 277/21-1) and the Fonds der Chemischen Industrie for financial support.

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22. Selected data for **4a**: mp 56–58°C; $[\alpha]_D^{24}$ +21 (*c* 1.25, $CHCl_3$); IR (KBr): 1849, 1754, 1712, 1523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.02–2.07 (4s, each 3H, OAc), 3.66, 3.73 (2d, 2H, $J=16.7$ Hz, CH_2), 3.76 (s, 2H, CH_2), 3.83 (ddd, $J=2.2$, 4.4, 10.1 Hz, 5-CH), 4.11 (dd, 1H, $J=2.2$, 12.6 Hz, 6-CH_2), 4.28 (dd, 1H, $J=4.4$, 12.6 Hz, 6-CH_2), 4.93 (dd, 1H, $J=9.6$, 9.6 Hz, 2-CH), 5.07 (dd, 1H, $J=9.3$, 10.1 Hz, 4-CH), 5.22 (dd, 1H, $J=9.3$, 9.3 Hz, 1-CH), 5.32 (dd, 1H, $J=9.6$, 9.6 Hz, 3-CH), 7.07 (d, 1H, $J=9.3$ Hz, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.7, 20.8, 21.0, 49.9, 51.7, 62.3, 68.8, 71.2, 73.2, 74.4, 78.7, 90.4 (sept, $J=33$ Hz), 122.6 (q, $J=292$ Hz), 166.6, 168.1, 170.3, 170.6, 171.3, 171.5; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −75.36 (q, 3F, $J=7$ Hz), −75.48 (q, 3F, $J=7$ Hz); MS (FAB, 3-NBA): *m*/*z* 610.9 (M^++H). For **5a**: mp 63–65°C; $[\alpha]_D^{24}$ +2 (*c* 1.05, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, 300 K): rotamers ratio 1/1.5, δ 1.42, 1.46 (2s, 9H, $C(CH_3)_3$) 1.87–2.19 (several s, 12H, OAc), 3.31–3.62 (m, 4H, 2×CH_2^{Nasn}), 3.76–3.82 (m, 5-CH, CH_2^{Nphe}, minor rot.), 3.96, 4.01 (2d, $J=17.2$ Hz, CH_2^{Nphe}, major rot.), 4.06–4.11 (m, 1H, 6-CH_2), 4.25–4.31 (m, 1H, 6-CH_2), 4.53 (s, CH_2Ph, major rot.), 4.62, 4.68 (2d, $J=14.8$ Hz, CH_2Ph, minor rot.), 4.93–5.11 (m, 2H, 4-CH, 2-CH), 5.23–5.32 (m, 2H, 1-CH, 3-CH), 7.17–7.40 (m, 5H, H_{ar}), 8.06 (d, $J=9.8$ Hz, NH, major rot.), 8.10 (d, $J=9.9$ Hz, NH minor rot.); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ 20.5–20.8, 27.9, 28.1, 48.0, 48.4, 50.3, 50.4, 50.9, 52.6, 61.7, 68.2, 70.7, 70.8, 72.9, 73.7, 77.8, 82.0, 82.9, 126.7, 127.8, 128.1, 128.6, 128.8, 129.2, 135.4, 136.1, 167.7–172.2; MS (FAB, 3-NBA): *m*/*z* 688.4 (M^++Na). For **6a**: mp 98–100°C; $[\alpha]_D^{20}$ −18 (*c* 1.80, CH_2Cl_2); MS (FAB, 3-NBA): *m*/*z* 779.4 (M^++H; 9.5), 666.3(21), 610.3(12), 558.2(4.7), 432.2(10), 235.2(12), 114.1(100); HRMS (ESI): calcd for $C_{36}H_{50}N_4O_{15}Na$ (M^++Na) 801.3170; found: 801.3166.