protected peptide

Linker

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Perkin 1 Abstracts: Solid Phase Organic Synthesis are a selection of significant papers published in the recent literature covering the broad area of Solid Phase Organic Synthesis (SPOS). The abstracts cover preparation of single compounds on solid support as well as combinatorial libraries. Advances in new linker design are also covered.

Facile silyl linker strategy for the synthesis of glycopeptides: synthesis of an N-terminal fragment of IL-2 (1-10). Linker

A. Ishii, H. Hojo, A. Kobayashi, K. Nakamura, Y. Nakahara, Y. Ito and Y. Nakahara, Tetrahedron, 2000, 56, 6235.

glycopeptide using an on-resin deallylation and acidic cleavage strategy. Synthesis of the heptapeptide fragment used in the illustrated synthesis from the silyl linker is also reported.

Analysis of solid-phase reactions: product identification and quantification by use of UV-chromophorecontaining dual-linker analytical constructs.

linker 2 (L2)

NO_{2O} (a) SPPS (b) TFA-CH2Cl2 anthracene (8:2)= H,H:D,D(1:1)

isotope label G. M. Williams, R. A. E. Carr, M. S. Congreve, C. Kay, S. C. Mckeown, P. J. Murray, J. J. Scicinski and S. P. Watson, Angew. Chem., Int. Ed., 2000, 39, 3293.

chromophore

MS sensitiser

linker 1 (L1)

The illustrated fibrinogen receptor, which is usually difficult to prepare due to the absence of a diagnostic chromophore, was prepared using the illustrated dual-linker. Each step in the synthesis was monitored by the cleavage of a sample of resin at L1 and the analysis of the analytical fragments from HPLC-MS. Synthesis of the dual-linker in 6 steps from ArgoGel-NH resin is also reported.

Germanium-based linker and its application to pyrazole synthesis.

Linker (a) RNHNH2•HCl Bredereck's BuOH-AcOH reagent (50:1), 100 °C, 1 h and/or THF, 70 °C, 3 h (b) TFA, rt, 16 h, or 1 step from argogel resin Br2, CH2Cl2 rt, 15 min E = H, 4'-Br or 3'-Br

Bredereck's reagent = (CH₃)₃COCH[N(CH₃)₂]₂

31 examples (HPLC-MS purity 68-98%). The hydrazine substituent is shown to influence the regioselectivity of the illustrated condensative ring closure giving 1,5 and/or 1,3-disubstituted pyrazoles. Synthesis of the germyl linker, its coupling to the resin and ipso-degermylation of the linker with various electrophiles is also reported.

A. C. Spivey, C. M. Diaper and H. Adams, J. Org. Chem., 2000, 65, 5253.

Linker Vinyl ether linker.

S. Yoo, Y.-D. Gong, M.-Y. Choi, J. Seo and K. Y. Yi, Tetrahedron Lett., 2000, 41,6415

4 examples (yield 60-70%). Attachment of a variety of moieties to the vinyl ether is also reported (yield 45-72%).

Polystyrylboronic acid: a reusable polymeric support for oligosaccharide synthesis.

Support

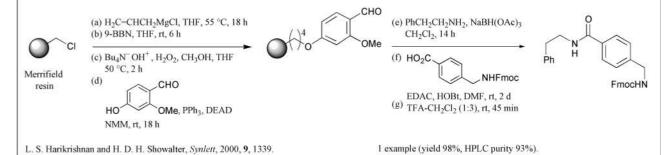
3 examples and 1 other example using a polymer-supported thioglycosyl donor (yields 68-95%).

XP = OBn, OBz or NPht

G. Belogi, T. Zhu and G.-J. Boons, Tetrahedron Lett., 2000, 41, 6965.

Synthesis and use of a dialkoxybenzaldehyde support.

Support



Solid-phase purification methods applied to a solution-phase Mitsunobu reaction.

Scavenger

12 examples (yield 43-100%, ¹H NMR purity 86-97%).

Polymer-supported triphenylphosphine and its oxide can be easily removed by filtration from the reaction medium. Excess DNAD can form a complex with polymer-supported triphenylphosphine that can also be removed by filtration. Grubbs' catalyst is used to remove DNADH₂ from the reaction medium *via* ring-opening metathetic polymerisation followed by filtration.

A. G. M. Barrett, R. S. Roberts and J. Schroder, Org. Lett., 2000, 19, 2999.

Reusable polymer-supported cobalt phosphine complex: use in catalytic oxidation and acid anhydride synthesis.

Catalyst

OH
$$R^{1} \longrightarrow R^{2}$$

$$PPh_{2}-Co-PPh_{3} \quad (1-2 \text{ mol}\%)$$

$$Cl$$

$$Bu'OOH-H_{2}O \quad (7:3), CH_{2}Cl_{2}, \Delta, 4 \text{ h}$$

$$R^{1} \longrightarrow R$$

6 examples of the oxidation of benzylic and 2° alcohols (yields 68-92%). Preparation of 5 acid anhydrides using the illustrated Co catalyst (yields 70-87%) and preparation of the catalyst from a polystyrene resin is also reported.

N. E. Leadbeater and K. A. Scott, J. Org. Chem., 2000, 65, 4770.

Antifungals based on 4-substituted imidazoles.

A. K. Saha, L. Liu, R. L. Simoneaux, M. J. Kukla, P. Marichal and F. Odds, Bioorg. Med. Chem. Lett., 2000, 10, 2175.

Biological activity and synthesis of >100-member library is reported (no yields or purity given).

chloride resin

2-Aminoquinazolin-4(3H)-ones

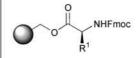


Merrifield resin

R.-Y. Yang and A. Kaplan, Tetrahedron Lett., 2000, 41, 7005.

10 examples (yields 53-88%, HPLC purity 84-100%).

2-Aminoimidazolinones



(a) piperidine-DMF (1:4), rt, 1 h (b) ArNCS, THF, rt, 15 h

(c) Mukaiyama's reagent, Et₃N

R²NH₂, THF, rt, 1 d or R²R³NH, THF, rt, 1 d

X Y N N $X = R^2 \text{ or Ar}$ $Y = NHAr \text{ or } NR^2R^3$

amino acid loaded Wang resin

CH₂Cl₂ or CH₃CN, 45 °C 3.5 h

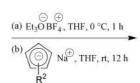
D. H. Drewry and C. Ghiron, Tetrahedron Lett., 2000, 41, 6989.

11 examples (yields 34-94%, HPLC purity >90%).

Heterosteroids



1 step from amino methyl polystyrene resin







$$R_3$$
 R_3
 OH
 $X = NR^4 \text{ or } O$

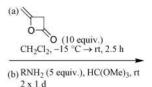
B.-C. Hong, Z.-Y. Chen and W.-H Chen, Org. Lett., 2000, 2, 2647.

Preparation of a 110-member library (sample yields 32-42%, HPLC purity >95%) is reported.

Nenitzescu indole synthesis.



1 step from ArgoPore Rink NH-Fmoc resin



O R NH

$$H_2N$$
 R^3 R^2 R^2

D. M. Ketcha, L. J. Wilson and D. E. Portlock, Tetrahedron Lett., 2000, 41, 6253.

14 examples (yields 21-95%, HPLC purity 14, 64-100%).

N-(ω-Hydroxyalkyl)pyridinium salts via the Zincke reaction.



3 steps from Wang or NovaSyn TGA resin

$$R_2$$
 N
 R_1

M. Eda, M. J. Kurth and M. H. Nantz, J. Org. Chem., 2000, 65, 5131.

16 examples (yields 0, 43-89%, HPLC purity 93-99%).

Pyrazoles and isoxazoles.

$$O_{S_{N}} \stackrel{O_{2}}{\longrightarrow} R^{1}$$

1 step from an aryl sulfonamide safety-catch resin

(b)H₂NY•HCl (6-10 equiv.) H₂SO₄-MeOH, 50 °C, 19 h

(c) Me₃SiCHN₂ (10 equiv.) THF-hexanes, (1:1), 2 x 2 h

(d) R⁴NHR⁵ (1.5 equiv.) THF, 50 °C, 19 h

+ isomer

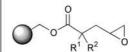
 $Y = NHR^3$ or OH

 $X = NR^3$ or O

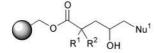
A library of 1,3,5-trisubstituted pyrazoles is prepared (number of examples, yields and purity are not given). Preparation of 1,4,5- & 1,3,4-trisubstituted pyrazoles and related isoxazoles, *via* a similar route, is also reported.

D.-M. Shen, M. Shu and K. T. Chapman, Org. Lett., 2000, 2, 2789.

γ-Methyl-substituted-γ-butyrolactones via a cyclisation-cleavage strategy.



nucleophile -



(a) chemical modification (b) TFA-CH₂Cl₂ (3:7), 4 h R^1

Merrifield resin

 $Nu^1 = I \text{ or } N_3$

Nu² = amido, amino or triazole

N. Gouault, J.-F. Cupif, A. Sauleau and M. David, *Tetrahedron Lett.*, 2000, 41, 7293.

22 examples (yields 13-71 %).

N-Substituted hydroxamic acids.



2 steps from Wang resin (a) O R¹ R² (10 equiv.) HOAc-(CH₂Cl)₂-TMOF, rt, 16-18 h (b)BH₃•py (15 equiv.)

dichloroacetic acid (22 equiv.), CH2Cl2

 $O_{H} \stackrel{R^{2}}{\longrightarrow} R^{1}$

R³ X (10 equiv.) DIPEA, 4-DMAP, CH₂Cl₂

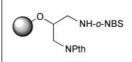
HO N R

D. E. Robinson and M. W. Holladay, Org. Lett., 2000, 2, 2777.

rt, 16-18 h

9 examples (yields 15- >95%).

1,3-Diamino ketones



1 step from Ellman's THP linker

(a) N₂H₄•nH₂O, THF-DMF (3:1) rt, 16 h

(b) R¹CO₂H, DIC, HOBt, DMF or R¹SO₂Cl, DIPEA, (CH₂Cl)₂

rt, o/n

O NH-o-NBS

(c) β-mercaptoethanol, DBU, NMP rt, 1 d

(d) R²CO₂H, DIC, HOBt, DMF, rt

> (e) TFA-H₂O (6:1), rt, 15 min (f) H₂CrO₄, CH₃COCH₃

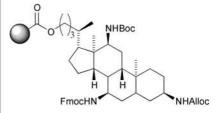
 $0 \longrightarrow N \\ H \\ NXR^1$

 $X = CO \text{ or } SO_2$

C. Subramanyam and S.-P. Chang, Tetrahedron Lett., 2000, 41, 7145.

5 examples (yields 25-60%, sample HPLC purity >90%).

A triamine derivative of cholic acid.



1 step from acid chloride polystyrene resin

(a) TFA, CH2Cl2

(b) Boc-Phe, DIC, HOBt, CH2Cl2

(c) dicyclohexamine, DMF (1:1)

(d) Boc-Gly, DIC, HOBt, CH₂Cl₂

(e) Bu₃SnH, Pd(PPh₃)₄, AcOH

(f) Boc-Ala, DIC, HOBt, CH₂Cl₂

(f) Boc-Ala, DIC, HOBt, Cl (g) TFA, CH₂Cl₂

(h) NaOMe, MeOH

HO 3 HN Ph Ph NH2

1 example (yield 56%). Solution-phase synthesis of the orthogonally protected cholic acid derivative and the triamine derivative is also reported.

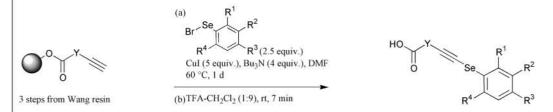
X.-T. Zhou, A. Rehman, C. Li and P. B. Savage, Org. Lett., 2000, 19, 3015.

Phenoxypropanolamines.

W. M. Bryan, W. F. Huffman and P. K. Bhatnagar, Tetrahedron Lett., 2000, 41, 6997

Preparation of a 5800-member library is reported (sample purity >70%).

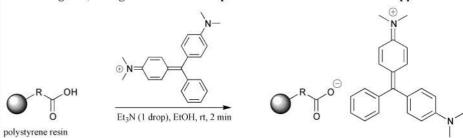
Copper-catalysed coupling of chalcogenyl halides with alkynes: synthesis of selenium-containing retinoids.



F. Gendre and P. Diaz, Tetrahedron Lett., 2000, 41, 5193.

16 examples (yields 0, 5-45%, HPLC purity 45-93%).

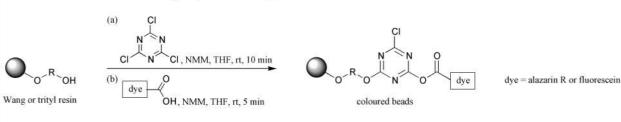
Malachite green, a reagent to monitor the presence of free COOH on solid-supports.



M. E. Attardi, G. Porcu and M. Taddei, Tetrahedron Lett., 2000, 41, 7391.

9 examples of the illustrated transformation are described. Carboxylic acids form salts with malachite green resulting in green polymer-beads.

A visual test for detection of OH groups on solid-supports.



M. E. Attardi, A. Falchi and M. Taddei, Tetrahedron Lett., 2000, 41, 7395.

6 examples of the illustrated transformation are reported. 1° and 2° amines and thiols also give a positive test. A CO₂H group is incompatible.

Fluorescein labeling of base-sensitive oligonucleotides.

J.-C. Bologna, J.-L. Imbach and F. Morvan, Tetrahedron Lett., 2000, 41, 7317.

resin not specified

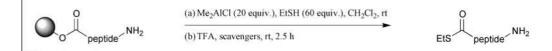
Number of examples are not given (yields 70-85%). Fluorescence properties of carboxyfluorescein-conjugated prooligonucleotides are also reported.

Discovery of selective metal-binding peptoids using ¹⁹F encoded combinatorial libraries.

M. C. Pirrung and K. Park, Bioorg. Med. Chem. Lett., 2000, 10, 2115.

Preparation of a 90-membered library is reported (no yields or purity given). The illustrated polymer-supported library is subjected to metal-binding studies followed by decoding using $^{19}\mathrm{F}$ NMR.

Fmoc-compatible solid-phase synthesis of peptide C-terminal thioesters.

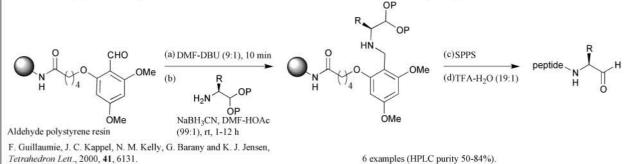


D. Swinnen and D. Hilvert, Org. Lett., 2000, 2, 2439.

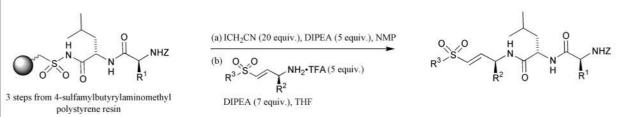
Wang or Pam resin

5 examples (yields 24-63%). Solution-phase amino thioester synthesis is also reported.

C-Terminal peptide aldehydes from acetals anchored to a backbone amide linker (BAL) handle.



Peptide vinyl sulfone and peptide epoxyketone proteasome inhibitors.



H. S. Overkleeft, P. R. Bos, B. G. Hekking, E. J. Gordon, H. L. Ploegh and B. M. Kessler, *Tetrahedron Lett.*, 2000, **41**, 6005.

6 examples (yields 20-31%). Preparation of an epoxyketone derivative, via a similar route, is also reported (yield 5 %).

C-Terminal glycopeptides from polymer-supported glycosyl azides via a modified Staudinger reaction.

J. P. Malkinson, R. A. Falconer and I. Toth, J. Org. Chem., 2000, 65, 5249.

2 examples (yields 70-81%, HPLC purity 69-72%).