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Combinatorial Chemistry on Solid Supports

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Combinatorial Chemistry on Solid Supports

Volume Editor: Stefan Bräse

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278
Topics in Current Chemistry

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Preface

The modern billion-dollar drug-discovery process strongly relies on both high-throughput synthesis and screening methods. Whereas the latter is based on molecular biological methods, the efficient and reliable generation of compound collections often makes use of combinatorial chemistry. Discovered in the 1980s, this methodology was explored extensively in the 1990s by groups in academia and in industry. Without any doubt, combinatorial chemistry changed the whole drug-discovery process and found many applications in crop science and the material sciences.

However, since its implementation, solution- and solid-phase techniques have been competing with each other, and although many companies started their combinatorial chemistry program with solid-phase techniques, solution-phase combinatorial methods have taken over and now account for approximately 25% of all combinatorial efforts.

The syntheses of complex, non-polymeric structures, discovered in the 1960s by the late Bruce Merrifield, was largely ignored in the context of solid supports, mainly due to the fact that appropriate synthesis techniques were not available.

Since solid-phase chemical methodology strongly differs from traditional solution-phase chemistry, two chapters deal with this topic. The Bräse group (Jung, Wiehn, Bräse) gives an overview of multifunctional linkers, which can be used for the generation of diversity-oriented collections, simply by cleavage from resins.

Still in its infancy, solid-phase reactions employ "simple" amide chemistry in most cases due to their high-yielding, reliable protocols. Ljungdahl, Bromfield, and Kann address solid-phase organometallic chemistry, which is now one of the great challenges in reliable solid-phase organic synthesis.

The next four chapters address the construction of designed and native complex structures, such as polyamines (Hahn and Schepers), natural products (Mentel and Breinbauer) and peptides, with a focus on identification of bioactive hormone structures (Haack and Beck-Sickinger). Furthermore, the automated synthesis of carbohydrates is addressed in detail by Castagner and Seeberger.

Finally, Winssinger, Pianowski, Debaen give an overview of array techniques that are suitable for solid-phase chemistry.

In this volume, state-of-the-art solid-phase synthesis is presented from different angles. Ranging from methodology development to application in the synthesis of complex native and designed structures, a complete overview is presented.

We are confident that addressing the fascinating interface between chemistry and biology is only possible by innovative methods in both disciplines. Combinatorial chemistry is surely one of these.

The editor thanks the editorial staff of *Topics in Current Chemistry*, in particular Mrs. Kollmar-Thoni and Dr. Marion Hertel for their professional support.

Karlsruhe, April 2007 Stefan Bräse

Contents of Volume 254

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Contents

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Multifunctional Linkers for Combinatorial Solid Phase Synthesis

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Abstract This review covers recent results in the area of multifunctional linkers for solid phase synthesis during the period 2000–2006.

Keywords Diversity-oriented synthesis · Linkers · Solid phase synthesis

Abbreviations

AA	amino acid
Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitril
AM	aminomethyl
AMB	α-methyl benzyl
BAL	backbone amide linker
9-BBN	9-borabicyclo[3.3.1]nonane
BHA	benzhydrylamine
BME	β-mercapto ethanol
Bn	benzyl
Boc	*t*-butyloxycarbonyl
BOP	benzotriazole-1-(yloxy) tris-(dimethylamino) phosphonium hexafluorophosphate
BPO	benzoylperoxide
BSA	bovine serum albumin
BTC	*bis*-trichloromethyl carbonate
CAN	cerium ammonium nitrate
Cbz	carbobenzyloxy
CDI	carbonyl diimidazole
CSA	camphor sulfonic acid
DBU	diaza(1,3)bicyclo[5.4.0]undecane
DCC	dicyclohexyl carbodiimide
DCH	1,3-dichloro-5,5-dimethylhydantoin
DDQ	dichlorodicyanobenzoquinone
DEAD	diethylazodicarboxylate

DEAM	diethanolaminomethyl
DEPEC	diethyl phosphorocyanidate
DIBAL	diisobutylaluminumhydride
DIC	diisopropyl carbodiimide
DIEA	diisopropylethylamine
DMAP	diemthylaminopyridine
DMF	dimethylformamide
DMPU	*N,N'*-dimethylpropylene urea
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DNA	desoxyribonucleic acid
DOS	diversity-oriented synthesis
dppe	1,3-bis(diphenylphosphino)ethane
dppf	1,3-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DSC	*N,N*-disuccinimidyl carbonate
DVB	divinylbenzene
EDCI	*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimid
Fmoc	9-fluorenylmethyloxycarbonyl
FMP	4-formyl-3-(methoxyphenoxy)methyl-PS
Gly	glycin
HASC	heteroatom-substituted carbonyl linker
HAL	hypersensitive acid-labile
HFIP	hexafluoroisopropanol
HMDS	hexamethyldisiloxane
HMPA	hexamethylphosphoramide
HMPB	4-hydroxymethyl-3-methoxyphenoxy-butyric acid
HOAt	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenzotriazol
LDA	lithiumdiisopropylamide
MAMP	Merrifield α-methoxyphenyl
MBHA	methylbenzhydrylamine
*m*CPBA	*m*-chlorperbenzoic acid
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMM	*N*-methyl morpholine
NMP	*N*-methyl pyrrolidone
NPCF	4-nitrophenylchloroformate
NpSSMpact	2-methoxy-5-[2-((2-nitrophenyl)dithio]-1-oxopropyl)phenylacetic acid
Nu	nucleophile
PAC	peptide acid linker
PAM	phenylacetamidomethyl
PEG	polyethylene glycol
PEGA	polyethylene glycolpoly-(*N,N*-dimethyl-acrylamide)
PFS	perfluoroalkylsulfonyl
PPF	1,1'-bis(diphenylphosphino)ferrocene
PPTS	*p*-pyridinumtoluene sulfonic acid
PNA	peptide nucleic acid
PS	polystyrene
PTMSEL	(2-phenyl-2-trimethylsilyl)ethyl
Py	pyridine

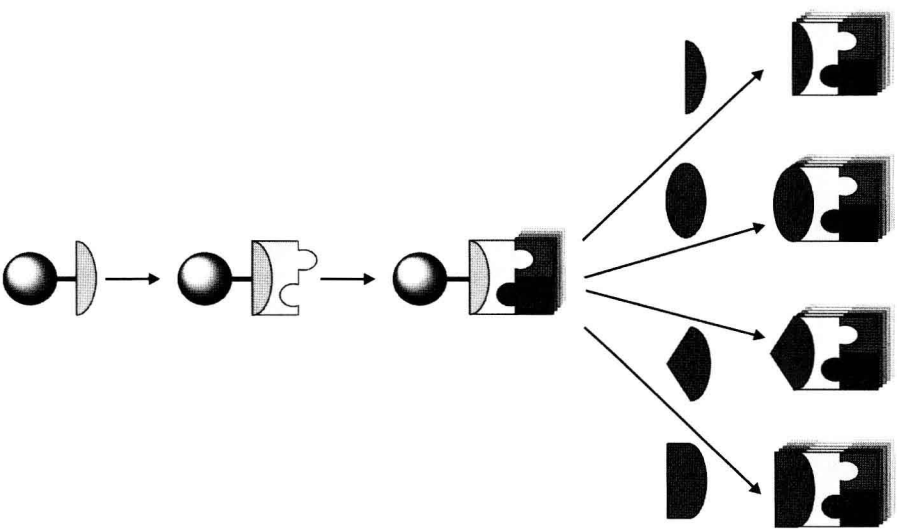
PyBrOP	bromo-tris-pyrrolidino phosphoniumhexafluorophosphate
RAM	Rink amide
RCM	ring-closing metathesis
RRTR	resin-to-resin transfer reaction
SAC	silyl acid
SASRIN	super acid sensitive resin
SCAL	safety catch acid labile
SEC	2-alkylsulfonylethyl carbamate
SPPS	solid phase peptide synthesis
TBAF	tetrabutylammoniumfluoride
TBDPS	*t*-butyldiphenylsilyl
TBTU	*O*-(benzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
TEA	triethylamine
THF	tetrahydrofuran
Tf	trifluormethylsulfonyl
TFA	trifluoro acetic acid
TFAA	trifluoro acetic acid anhydride
THP	tetrahydropyran
TMEDA	tetramethylethylenediamine
TMG	2-*t*-butyl-1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Trt	trityl
XAL	xanthenylamide linker
XAN	9-xanthenyl linker
XPHOS	2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-biphenyl

1 Introduction

The advent of combinatorial chemistry being implemented in the modern drug discovery process in the 1990s [1] has reinitiated the use of solid phase synthesis originally developed by the late Bruce Merrifield [2]. While in the early stages of solid phase synthesis, first peptides and later nucleic acids were favorably synthesized using this technique due to the ease of automation [3], small molecular entities obeying the Lipinski rules have been prepared in the last decades with the notable exception by Frechet and others [4, 5]. In particular, the invention of the split-and-mix-technique by Furka [6] and later the technological platforms derived from this, e.g. the IRORI techniques [7], triggered the design and preparation of large compound libraries with more than 2 000 000 compounds [8]. Diversity-oriented synthesis (DOS), originally proposed by S. L. Schreiber [9, 10], is today used by many laboratories both in academia and industry. In particular solid phase synthesis has served as a technology platform and allows the rapid assembly of building blocks to generate quite complex structures in few synthetic steps. A crucial point in the design of compound libraries is the careful choice of the appropriate

linker attaching the molecule to the solid support [11, 12]. Linkers do not only serve as the point of attachment, they also control the chemistry being allowed during the assembly stage and importantly are directing the functional group being generated upon cleavage. While peptide synthesis requires more or less the detachment of carboxylic acids and amides, diversity-oriented synthesis strongly relies on the cleavage of various functional groups in order to avoid constraints. Thus, a high number of various linkers have been prepared and discussed in a number of reviews.

Linkers allowing the cleavage of one certain functional group have been named mono-functional linkers [13]. However, an attachment being cleavable to generate more than one functional group is named a multifunctional linker [14–16] (Scheme 1).



Scheme 1 Solid phase synthesis and multifunctional cleavage

We will define *multifunctional linkers as attachments which allow the generation of more than one functional group upon cleavage from a solid support either with or without implementation of building blocks.*

Linkers which allow cleavage of reactive functional groups that in turn can be reacted with added building blocks in a one-pot method are also called multifunctional.

In this review we will discuss the multifunctional linkers in terms of assembly on solid supports, stability towards reaction conditions, and finally the issue of introduction of multifunctionality.