Review

Recent Advances in the Preparation of Heterocycles on Solid Support: A Review of the Literature

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Reviews

Recent Advances in the Preparation of Heterocycles on Solid Support: A Review of the Literature

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1. Introduction

Experience has shown that compounds with biological activity are often derived from heterocyclic structures. It is therefore not surprising that this structural class have received special attention in combinatorial synthesis and that several methods for the preparation of heterocycles have been transferred to the solid phase. Small heterocycles, in particular, are used as rigid, highly functionalized molecular scaffolds and are biologically very interesting. The first example of a compound, coming directly from an optimization library, exhibiting biochemical efficacy and oral bioavailability could recently be described.[1] Due to my current interest in solid-phase chemistry, and especially in the possibilities for the preparation of heterocycles on a solid support, I found it important to review recent papers in the field. The attempts to review the whole combinatorial chemistry field have been published in a number of articles[2−4] and in several books.[5−7] However, an extensive review on the most utilized methods for the efficient preparation of heterocycles on solid support including all major classes of heterocycles prepared through cyclization has not been published. This paper is a result of a review through 238 papers on the synthesis of three-, four-, five-, six-, seven-, and eight-membered rings on solid support. The chapters on the cyclization methods for the preparation of five-, six-, and seven-membered rings have been subdivided into sections on the preparation of monocyclic compounds and fused heterocycles. Moreover, in all chapters the compounds have been grouped depending on the amount of nitrogen atoms in the ring. In the paper, structures representing compound libraries and recently published synthetic schemes for the preparation of more obscure heterocycles are reported. An important goal of the paper is not only to compare recent advances in solid-phase synthesis with previously existing solution-phase methods but also to discuss the transformation of traditional synthesis protocols for use in solid-phase combinatorial chemistry. References to solution-phase syntheses are not reported; they can be found in several book series on heterocyclic chemistry. Publications cited herein are, in addition, mostly from refereed journals and not from patents.

2. Formation of a Three-Membered Ring on Solid Support

A few three-membered rings without any heteroatoms have been synthesized on solid support. For example, cyclopropene derivatives **1** have been prepared by reaction of acetylenes with a rhodium carbenoid bound to a polystyrene resin,[8] and cyclopropanecarboxylates **2**[9] through the coupling of bromoacetic acid with Wang resin followed by pyridium ylide formation and condensation of the ylide with ethylidene malonate derivatives. Also a few three-membered rings with a heteroatom have been published. Aziridines are important heterocycles in organic and medicinal chemistry. These

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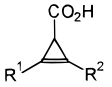

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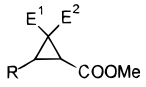

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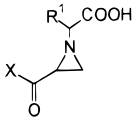

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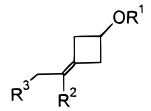
compounds can be prepared by nucleophilic displacement reactions in solution; for example, β-amino-halides and β-amino-sulfates give aziridines on heating or on treatment with alkali. In the work by Filigheddu et al.,[10] several aziridine 2-carboxylates **3** were prepared using a solid-phase version of the Gabriel−Cromwell reaction (Scheme 1). Aziridine oligopeptides were prepared by addition of Wang resin containing amino groups to α-bromoacrylates and α-acrylamides, or by addition of different primary amines to bromoacrylates loaded on the resin. In addition, an epoxidation reaction has been produced on a polymer resin.[11] Surprisingly, no other heterocyclic compounds with one or two heteroatoms have been reported including the formation of oxiranes, thiiranes, oxaziridines, diaziridines, and diazirines, respectively.

3. Synthesis of β-Lactams, β-Sultams, and Other Four-Membered Rings on Solid Support

Both four-membered rings with no heteroatoms and heterocycles with up to two heteroatoms have been prepared on solid support. One example of a four-membered ring synthesis on a polymeric resin was described by Rebek and Gavina[12] when the preparation of a cyclobutene ring was demonstrated. Another example has recently been published by Cheng et al.[13] in the utilization of allylic sulfones in solid-phase synthesis. Polymer-bound allyl sulfones were utilized in geminal cycloalkylations with epichlorohydrin. After cleavage from the resin, a set of cyclobutylidenes **4** were obtained. In solution, several four-membered heterocycles, e.g., β-lactones and β-lactams, have conveniently been prepared from ketenes. On solid support, β-lactams **5** (2-azetidinones) and β-sultams **6** have been synthesized: Ruhland et al.[14] utilized the Staudinger reaction in the synthesis



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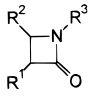

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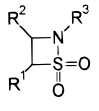

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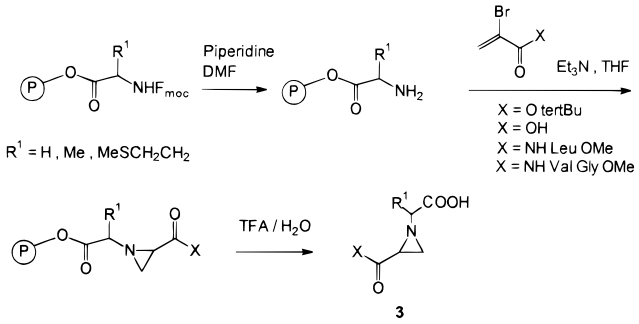
of structurally diverse β-lactams on solid support. Singh and Nuss[15] have recently described the preparation of several other β-lactams via the same reaction. Moreover, in a paper by Bheemashankar and Ganesan,[16] the preparation of a polymer-bound β-lactam is described. Also, the Suzuki and Heck cross-coupling reactions have successfully been applied for the preparation of biaryl- and styryl-substituted β-lactams (4-arylazetidin-2-ones).[17] A convenient approach toward four-membered rings containing two heteroatoms was described by Gordeev et al.[18] in the solid-phase synthesis of β-sultams **6**. Imine intermediates generated from polymer-immobilized amino acids and aldehydes were reacted with (chlorosulfonyl)acetates in the presence of pyridine to afford the solid-phase-tethered β-sultam products (Scheme 2). It is a surprise that no papers have described the synthesis of other four-

Scheme 1



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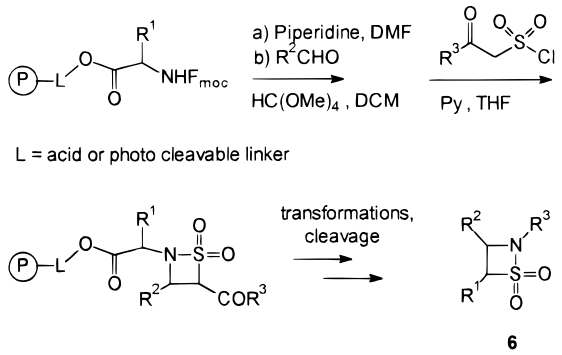
Scheme 2



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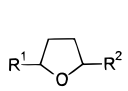
membered rings with heteroatoms in 1,2-positions or 1,3-positions. For example, 1,2-diazetidines and 1,3-diazetidines could probably be synthesized from corresponding azo-compounds and through condensation of isocyanates, respectively, on solid support.

4. Formation of Five-Membered Rings on Solid Support

4.1. Monocyclic Compounds. 4.1.1. Synthesis of Five-Membered Rings Containing One Heteroatom Other Than Nitrogen. In solution, cyclic enol ethers are formed from γ-keto-alcohols, β,γ-unsaturated lactones are prepared from γ-keto-acids, and for the preparation of thiophenes and furans, the most versatile method is the Paal−Knorr synthesis. On solid support, cyclic ethers **7** have been prepared by electrophilic cyclization of tetrahydrofuroisoxazolines.[19−21] Several methods have been discovered for the preparation of γ-lactones **8** on solid support. For example, 3,5-disubsti-



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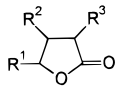

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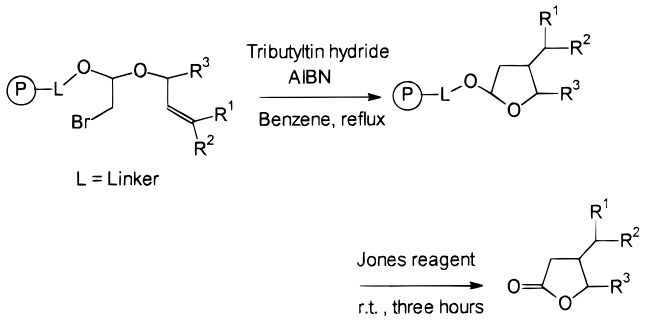
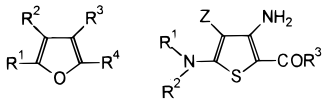
tuted-γ-butyrolactones have been synthesized through a three-step approach from polymer-bound pyrrolidines via N-acylation, C_α-alkylation, and iodolactonization.[22,23] γ-Butyrolactones have also been prepared from epoxides, reaction with sodium azide or thiophenols, and cleavage from the solid support.[24] Hanessian and Xie[25] demonstrated a reaction where a lactonized product was released from the resin. The polymer-bound lactone was obtained from a resin-bound aldehyde that was reduced with sodium borohydride under sonication. Maybe the most interesting approach toward the synthesis of γ-butyrolactones on solid support has recently

Scheme 3

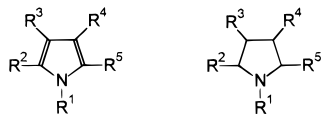


been published by Watanabe et al.[26] (Scheme 3). Polymer-supported β-bromoethylacetals were treated with tributyltinhydride in the presence of a catalytic amount of α,α′-azobisisobutyronitrile. Radical cyclization gives thereafter the carbon−carbon double bond. Finally, the γ-butyrolactones are released by Jones oxidation. Two reports have recently appeared for the solid-phase preparation of furans **9**. Gowravaram and Gallop[27] presented a "traceless" solid-phase synthesis of furans via 1,3-dipolar cycloaddition reactions of isomünchnones. Whitehouse et al.[28] have reported a rhodium(II)-mediated solid-phase 1,3-dipolar cycloaddition for the synthesis of furan scaffolds. Isothiocyanates have been utilized as intermediates for the solid-phase preparation of substituted thiophenes **10**. The method by Stephenson and Zaragoza[29] for the synthesis of thiophenes is the only method that has appeared for the synthesis of this type of compound.



9 **10**

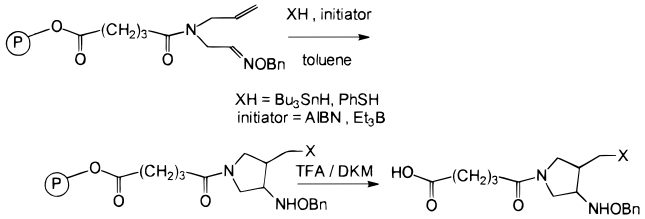
4.1.2. Synthesis of Pyrroles and Pyrrolidines. The Knorr pyrrole synthesis is the most important route to pyrroles **11** in solution. This method involves the condensation of a β-keto-ester with an α-amino-ketone. The versatile Paal−Knorr synthesis is also extensively used for the preparation of pyrroles. Pyrrolidines, on the other hand, may be prepared from tetramethylene dibromides. Pyrrolidines may also be synthesized by the Mannich reaction. On solid support the preparation of five-membered rings with one nitrogen atom,



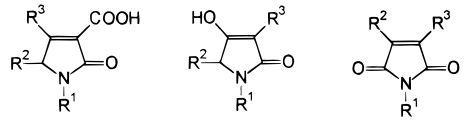
11 **12**

e.g., pyrroles, pyrrolidines, and pyrrolinones, has been reported in several publications. A versatile solid-phase synthesis of pyrrole-3-carboxamides from enaminones and α-alkyl-α-nitro alkenes was presented by Trautwein and Jung.[30] A few years earlier, two methods for the synthesis of pyrroles on solid support through a four-component condensation was presented: Mjalli et al.[31] described a method for the synthesis of tetra- and penta-substituted pyrroles via a 1,3-dipolar cycloaddition of alkynes to

Scheme 4



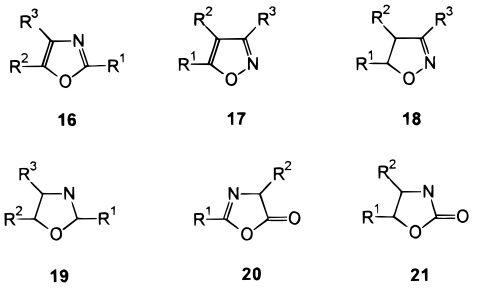
polymer-bound münchnones. Strockner et al.,[32] on the other hand, utilized a Ugi four-component condensation reaction on a resin for the synthesis of pyrroles. For the preparation of highly functionalized pyrrolidines **12**, several papers have recently appeared in different journals. In 1995, Murphy et al.[33] prepared pyrrolidines by a 1,3-dipolar cycloaddition reaction of resin-bound azomethine ylides with olefins or acetylene dipolarophiles. Hollinshead[34] used a similar method for the stereoselective synthesis of pyrrolidines. Pearson and Clark[35] described a solid-phase synthesis of pyrrolidines via 2-azaallyl anion cycloadditions with alkenes. Recently, Miyabe et al.[36] utilized the radical cyclization of oxime ethers on a polymer support. Triethylborane was used as the radical initiator for the production of pyrrolidines via an effective carbon−carbon bond-forming reaction (Scheme 4). Miller et al.[37] described a novel method for the preparation of carboxypyrrolinones **13**. Several malonamides bound to a polymer resin were oxidized to the corresponding ketones



13 **14** **15**

that in turn were cyclized to the corresponding carboxypyrrolinones. Kulkarni and Ganesan[38] have utilized resin-bound N-acylated α-amino acids for the preparation of tetramic acids **14** through cyclative Claisen-type condensation upon treatment with base. Moreover, recently Barn and Morphy[39] described the solid-phase synthesis of cyclic imides **15**. This cyclative cleavage strategy proved to be very efficient as a synthesis protocol for this kind of compounds.

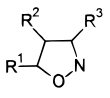
4.1.3. Synthesis of Oxazoles, Isoxazoles, Oxazolines, Isoxazolines, and Related Compounds. α-Halogeno-ketones react with amides to give oxazoles **16** in solution. Oxazoles are also prepared by cyclization of α-acyl amino-ketones. The standard synthesis for isoxazoles **17** involves the reaction of β-dicarbonyl compounds with hydroxylamines. The reaction takes place under mild conditions and is of very wide applicability. Also, acetylenes add nitrile oxides to give isoxazoles. α,β-Unsaturated ketones form isoxazolines **18**, the intermediate being an oxime. 1,2-Difunctional ethanes react with aldehydes and ketones to form oxazolidines **19**. α-Acylamine-carboxylic acids are converted into 5(4*H*)-oxazolinones **20** by acid anhydrides. Finally, 1,2-difunctional ethanes react with carbonyl chloride to give 2-oxazolidinones **21**. On solid support, several reports for the efficient preparation of compounds belonging to this group have been reported. 5-Aryl-oxazoles have recently been synthesized using polystyrene-SO_2CH_2NC and aromatic



16 **17** **18**

19 **20** **21**

aldehydes.[40] Isoxazoles were, in fact, prepared already in 1980, when Yedidia and Leznoff[41] investigated the regioselectivity in cycloaddition reactions on solid support. They discovered that polymer-bound benzyl propiolate and polymer-bound phenyl propiolate reacted with benzonitrileoxide in a 1,3-dipolar addition reaction to give polymer-bound isoxazoles, which after cleavage gave isoxazoles. Marzinzik and Felder[42] reported in 1996 a four-step reaction sequence including a Claisen condensation, an α-alkylation, and a cyclization of a *β*-diketone with monosubstituted hydrazines for the generation of several substituted isoxazoles on solid support. Several isoxazoles and isoxazolines were synthesized by Pei and Moos[43] on solid support through [3 + 2] cycloaddition reactions of alkynes and alkenes with highly reactive nitrile oxides. The 1,3-dipolar cycloaddition of nitrile oxides generated, in the presence of a variety dipolaraphiles, a library of isoxazoles and isoxazolines as reported by Shankar et al.[44] Chang and Mjalli[45] utilized a similar method in the preparation of isoxazolines on solid support: 1,3-dipolar cycloaddition of nitrile oxides provided a useful method for a wide variety of compounds. Three interesting papers appeared in 1998 on the synthesis of oxazolidinones. In a publication by Buchstaller,[46] these compounds could be prepared via a novel cyclization/cleavage reaction (Scheme 5). Resin-bound carbamates were alkylated with glycidyltosylate to the corresponding epoxides. Nucleophilic opening of the epoxides with pyrrolidine and subsequent cyclization yielded the oxazolidinones. Peter ten Holte et al.[47] utilized an activation/cyclo-elimination process for the solid-phase synthesis of 1,3-oxazolidin-2-ones. Kobayashi and Akiyama[48] used a 1,3-dipolar cycloaddition reaction on solid support for the preparation of several 2-isooxazoline derivatives. As a dipolarophile, and as a substituent in these compounds, several oxazolidinone rings were used. Diverse isoxazolidines **22** have, in addition, been prepared via a 1,3-dipolar



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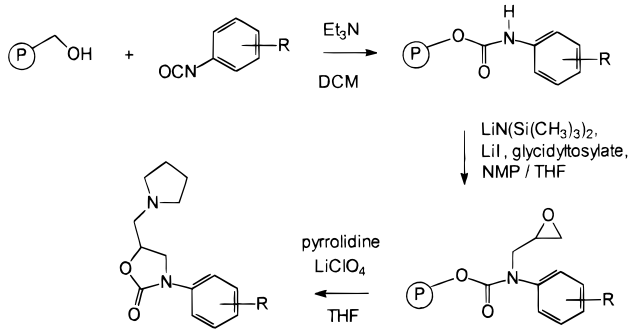
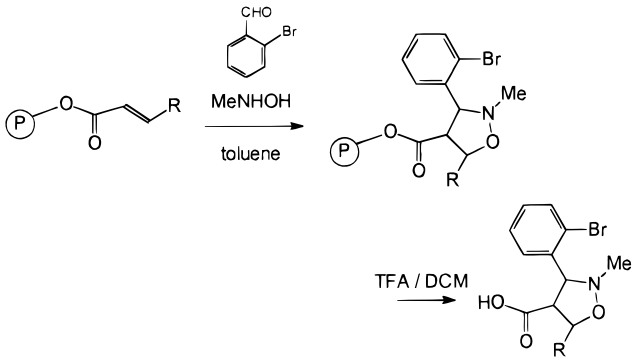
cycloaddition reaction on solid support[49] (Scheme 6). In this paper, hydroxylamines were condensed with aldehydes, and resulting nitrones were trapped with various dipolarophiles. The one-pot three-component cycloaddition yielded isoxazolidines in good yield.

4.1.4. Synthesis of Thiazoles and Thiozolidinones. In solution, α-halogeno-ketones react with thioamides to give thiazoles **23**. Thiazoles may also be prepared by cyclization of α-acylamino-ketones. A convenient method for the

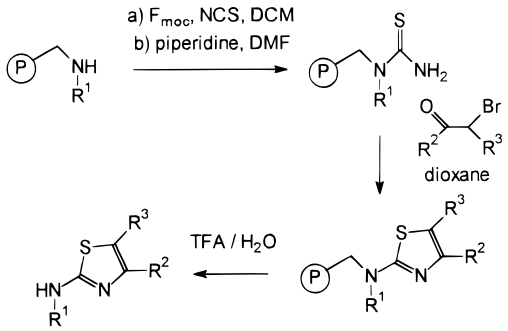
Scheme 5



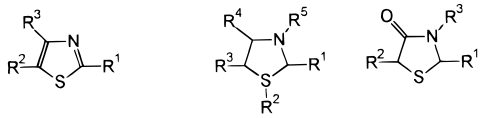
Scheme 6



Scheme 7



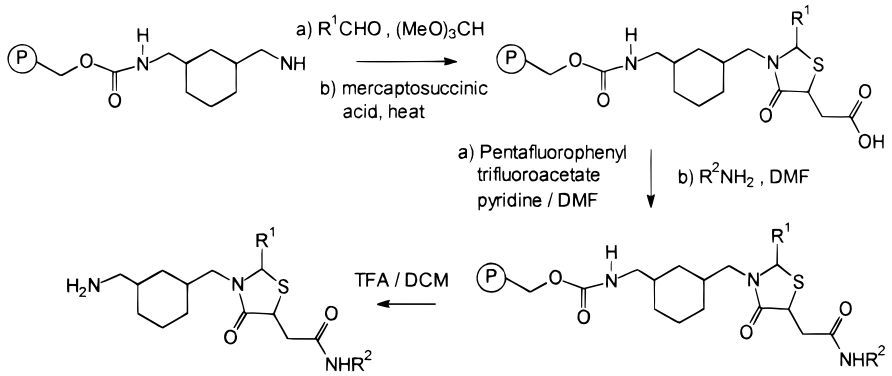
preparation of 2-aminothiazoles is the Hantzsch synthesis, were an α-bromoketone and a thiourea produces the product. On solid support, a few reactions have been reported for the synthesis of thiazoles and related compounds. Kearney et



23 **24** **25**

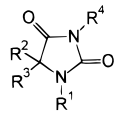
al.[50] prepared recently 2-aminothiazoles from polymer-bound primary amines and α-bromoketones with good yield and high purity (Scheme 7). Zaragoza[51] reported a few years ago a solid-phase method for the synthesis of 2-methylene-2,3-dihydrothiazoles. A resin-bound cyanoacetamide reacted with isothiocyanates. Following alkylation, the products were cleaved via acidolysis. Patek et al.[52] presented a simple and direct route for the solid-phase synthesis of thiazolidine derivatives **24**. This method included the reaction of aldehydes with unprotected (*R*)-cysteine attached to the polymeric support. Transformation into *N*-acyl derivatives followed by

Scheme 8



alkaline hydrolysis produced the desired compounds. Thiazolidinones **25** have also been synthesized on solid support. Holmes et al.[53] demonstrated a one-pot three-component condensation reaction on solid support of amino acids, aldehydes, and mercapto carboxylic acids to generate 4-thiazolidinones and 4-metathiazanones. The same research group also demonstrated an efficient synthesis of three 4-thiazolidinone combinatorial libraries, each containing up to 540 compounds. Munson et al.[54] recently prepared aminothiazolidinones using an acid-labile carbamate linker (Scheme 8). An unprotected symmetrical diamine was incorporated onto a carbonylimidazole activated Wang resin. Following imine formation, cyclization, and amide bond formation, the products were obtained.

4.1.5. Synthesis of Five-Membered Rings Containing Two or Three Heteroatoms. Hydantoin-based scaffolds have been found to possess significant pharmacological activity as central nervous system agents.[55,56] In solution, hydantoins **26** may be synthesized via a reaction of a carbonyl compound, potassium cyanide, and ammonium



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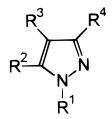
carbonate in dilute alcoholic solution. Another preparation involves the reaction of a pyrrolidone carboxylic acid and potassium thiocyanate combined with desulfurization. The first solid-phase synthesis of hydantoin libraries was reported by Hobbs DeWitt[57,58] in which cyclization was performed on solid support through a C-terminal ester linkage. Aqueous hydrochloric acid was employed to cyclize and cleave the final hydantoins from the support. A few years later, Dressman et al.[59] introduced a method for the synthesis of hydantoins that employed N-terminal amino acid attachment and a base-catalyzed cyclization/cleavage strategy. An 800-compound library was constructed using a diverse set of amino acids and primary amines. At the same time, Hanessian and Yang[60] reported the synthesis of 50 discrete 5-alkoxyhydantoins, and Short et al.[61] reported the solid-phase synthesis of hydantoin 4-imides via the Ugi four-component condensation reaction. The next year, in 1997, Matthews and Rivero[62] reported a solid-phase route for the efficient preparation of 1,3,5-trisubstituted hydantoins. In the approach, a reductive alkylation of a resin-bound α-amino acid with a variety of aldehydes was performed followed by acylation, base-promoted cyclization, and cleavage. Xiao et al.[63] synthesized hydantoins through the reaction of a resin-bound phenyl carbamate with primary or secondary amines, and reaction with a tertiary amine base afforded hydantoins in good yield. A variety of N,N-disubstituted hydantoin libraries have also been constructed using derivatives of amino acids, aromatic aldehydes, and isocyanates.[64] Diisopropylamine was used for the cyclization. Moreover, hydantoins have been prepared starting from resin-bound N-alkylated glycine residues,[65] by treatment of a resin-bound diamino acid containing dipeptide with carbonyl diimidazole or triphosgene,[66] through construction of resin-attached hydrazino acid precursors,[67] and through direct conversion of Fmoc-protected dipeptides to hydantoins.[68] The last mentioned approach uses $MeSiCl_3$ in the presence of Et_3N to cleave Fmoc-protected amines to form isocyanates that cyclize and form the corresponding hydantoins. The standard syntheses for pyrazoles **27** in solution involves the reaction



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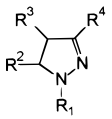

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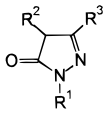
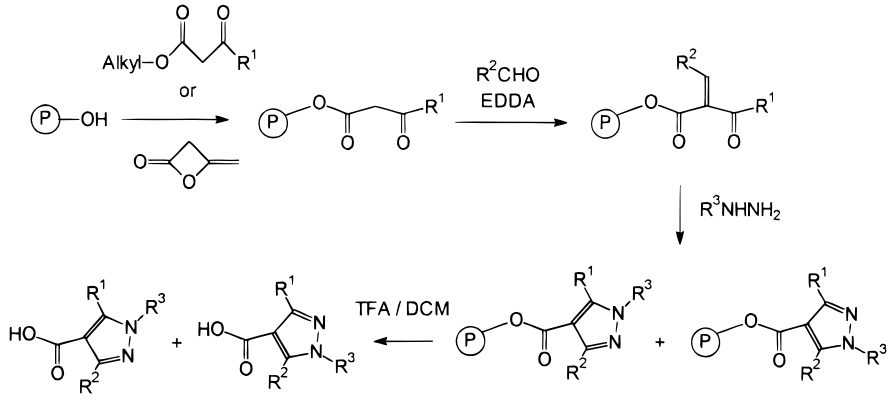


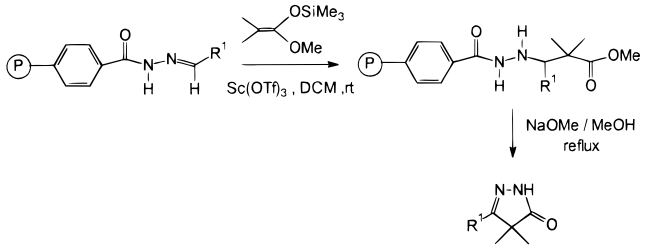
29

of β-dicarbonyl compounds with hydrazines. Pyrazolones are prepared from β-keto-esters and hydrazine by similar reaction conditions. α,β-Unsaturated ketones form pyrazolines **28**. In two recent papers by Watson et al.,[69,70] the solid-phase synthesis of 5-aminopyrazoles and their derivatives was reported. Reaction of hydrazines with solid supported β-ketonitriles afforded 5-aminopyrazoles containing an amino group readily acylated or sulfonylated. Grosche et al.[71] also presented a versatile solid-phase synthesis of trisubstituted pyrazole carboxylic acids by reaction of polymer-bound arylidene- or alkylidene-β-oxo esters with phenylhydrazines (Scheme 9). Lately, Lyngsjo and Nielsen[72] reported the synthesis of 3-amino-2-pyrazolines. Conjugate addition of hydrazines to α,β-unsaturated nitriles followed by cyclization and acylation/sulfonation yielded a 24-member library of 3-amino-2-pyrazolines. A few methods have in addition, been reported for the solid-phase preparation of structurally diverse pyrazolones **29**. Tietze and Steinmetz[73,74] reacted γ-alkylated β-keto-esters with phenylhydrazine, and after cyclization and cleavage several 1-phenyl-pyrazolones were obtained. Kobayashi et al.[75] have recently developed an interesting route

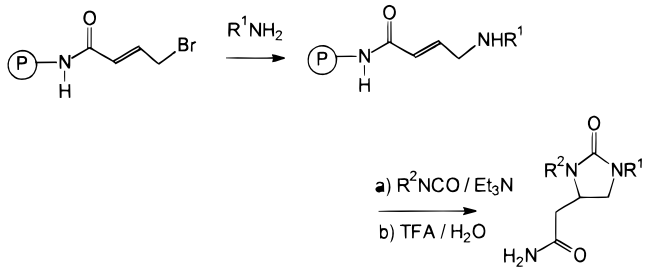
Scheme 9



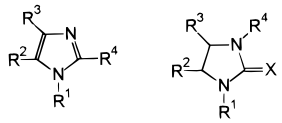
Scheme 10



Scheme 11

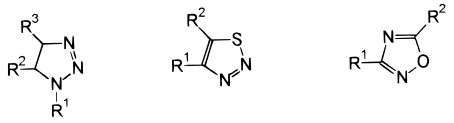


for the preparation of pyrazolone derivatives (Scheme 10). Polymer-supported acylhydrazones were reacted with ketene silyl acetals in the presence of an catalyst to afford the *β*-hydrazino-esters that upon cyclization and cleavage produced the target compounds. α-Halogeno-ketones react with amides in solution to give imidazoles **30**. Also α-amino-



30 **31**

ketones react with imino-esters to give imidazoles. On solid support, tetrasubstituted imidazoles have been synthesized via α-(*N*-acyl-*N*-alkylamino)-*β*-ketoamides on Wang resin by Zhang et al.[76] This was the first example of a Ugi four-component condensation of arylglyoxals, 1° amines, carboxylic acids, and isocyanides. In another paper, Sarshar et al.[77] described the synthesis of highly substituted imidazole libraries using an aldehyde, an amine, and a 1,2-dione in the presence of NH_4OAc. Moreover, a direct resin attachment to the imidazole core was utilized by Bilodeau and Cunningham[78] for the solid-phase synthesis of 12 diverse imidazoles. Nefzi et al.[79] described an efficient method for the solid-phase preparation of 1,3,4-trisubstituted-2-imidazolidones and 1,3,4-trisubstituted-2-imidazolidinethiones **31** from reduced N-acylated dipeptides. (Other heterocyclic compounds, i.e., cyclic ureas and thioureas have also been synthesized from linear peptides on solid support.[80] The reduction of acylated dipeptides followed by treatment with carbonyldiimidazole or thiocarbonyldiimidazole affords the corresponding cyclic urea or thiourea in good yield.) 2-Imidazolidones have also been prepared by tandem aminoacylation/Michael addition as described by Goff et al.[81] (Scheme 11). Reaction of isocyanates with unsaturated amines bound to a solid support can lead to either 2-imidazolidones or 2-imioxazolidinones. In solution, acetylenes react with alkyl- and aryl-azides to give 1,2,3-triazoles **32**. Diazoketones are

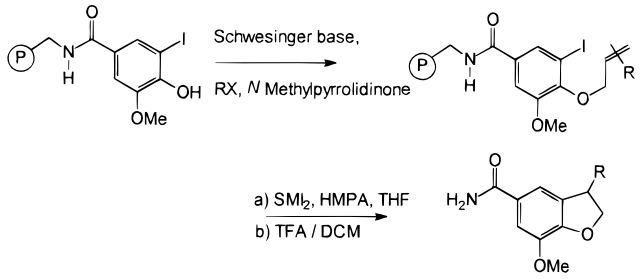


32 **33** **34**

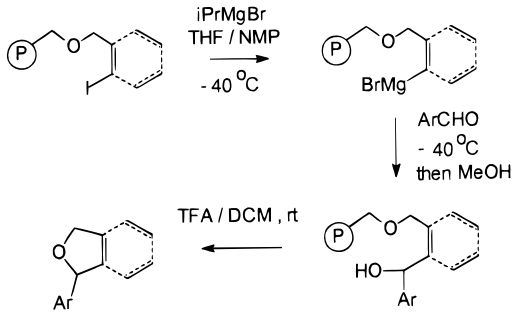
converted by amines into 1,2,3-triazoles, and for example, *o*-phenylene diamine is readily converted into benzo derivatives of 1,2,3-triazole. Moreover, diazoketones are converted by hydrogen sulfide into 1,2,3-thiadiazoles **33**. On solid support a few reactions leading to these types of compounds have been reported. Zaragoza and Petersen[82] discovered that a resin-bound 3-oxobutyramide could efficiently be condensed with primary aliphatic amines. The resulting 3-amino-2-butenoic acid amides could be cyclized and treated with tosyl azide in the presence of a tertiary amine. Acidolytic cleavage yielded 1,2,3-triazoles. 1,2,3-Thiadiazoles can be prepared through a recent method by Hu et al.[83] Diverse ketones are prepared in solution and captured to the solid support via sulfonylhydrazone formation. Reaction with thionyl chloride in DCE gives the products in good yield. Amidoximes react with acid chlorides to give 1,2,4-oxadiazoles **34** in solution. Recently a method for the efficient preparation of 1,2,4-oxadiazoles on solid support has been developed. In a paper by Hebert et al.,[84] aliphatic and aromatic nitriles linked to a solid support were converted to amide oximes and cyclized to oxadiazoles using N-protected amino acid anhydrides.

4.2. Fused Polycyclic Compounds. 4.2.1. Synthesis of Benzofurans. The synthesis of benzofurans in solution can involve lactone formation with *o*-hydroxyphenylacetic acid.

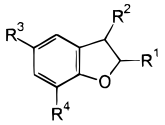
Scheme 12



Scheme 13



Elimination of a hydrogen halide from a *o*-hydroxy-(*β*-haloethyl- or ethylene-)benzene is also a common route to benzofurans. Moreover, benzofuran derivatives may be a result from the action of alkali on *o*-hydroxy-*β*-halostyrenes. On solid support, benzofuran derivatives **35** have been



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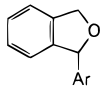
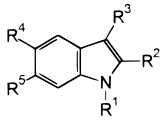


36

synthesized via SmI_2-mediated arylradical cyclization[85,86] (Scheme 12). Previously, Routledge et al.[87] reported a study on tributyltinhydride-mediated radical cyclization for the generation of benzofuran and furan rings. However, the method by Du and Armstrong[85] proved to be more efficient, rapid, and also more easy to carry out at room temperature. The research team of Balasubramanian has recently focused on the utilization of a dithiane-protected benzoin photolabile safety catch linker. In one of their latest papers,[88] they report a polymer-bound benzofuran. In a paper by Berteina and Mesmaeker,[89] a tandem radical cyclization of aryl iodides bound to polystyrene produced benzofurans. The palladium-mediated cyclization has been utilized in two recent papers for the preparation of 2-substituted benzofurans[90] and benzofuran acetamides.[91] Chang and Maryanoff[90] reported also the synthesis of several indoles. Recently, a paper appeared on the preparation of 1-substituted 1,3-dihydroisobenzofurans **36**[92] via an iodine−magnesium exchange reaction (Scheme 13). In the report, the resin-bound iodides were transferred to resin-bound aryl- and alkenyl-magnesium compounds followed by reaction with aldehydes and cyclization/cleavage.

4.2.2. Synthesis of Indoles, Indolines, and Benzoxazoles. The Fisher indole synthesis is the most important preparative method for indoles **37** in solution. The Borsche synthesis of tetrahydrocarbazoles is a special case of the Fisher indole synthesis in which cyclohexanone phenylhydrazones are used as starting material. Cyclization of α-halogeno-ketones give



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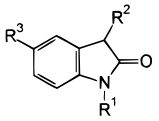
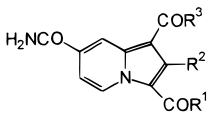


38

indoles when reacted with anilines or aromatic amines (Bischler indole synthesis). In the Brunner synthesis, phenylhydrazides give oxindoles **38**. On solid support, the Fisher indole synthesis was adapted to the solid phase by Hutchins and Chapman.[93] Since the indole cyclization required acid catalysis, the HMB (hydroxymethylbenzoic acid) linker was chosen for the preparation of 2-arylindoles. Cheng and Chapman[94] also described a method for the solid-phase synthesis of spiro indolines using the Fisher indole reaction. Several products could be isolated in good yields and high purity. The synthesis of indoles through the versatile Heck reaction has been reported in several papers. Yun and Mohan[95] described the intramolecular Heck reaction of polymer-bound aryl halides and the preparation of several indole analogues. A library consisting of indoles has also been reported by Collini and Ellingboe,[96] Fagnola et al.,[97] Zhang et al.,[98] Wang and Huang,[99] and recently by Smith et al.[100] Also 2-oxindole derivatives via the intramolecular Heck reaction have been reported.[101] Other methods for the preparation of indoles and indole analogues include the preparation of 1-hydroxy-6-indolecarboxylic acids.[102] The compounds were obtained by treatment of Wang resin-bound 4-fluoro-3-nitrobenzoic acid with 1,3-dicarbonyl compounds, followed by reduction and cleavage. A multicomponent solid-phase Tsuge reaction for the preparation of maleimide-fused indolizinium carboxylates, through sequential cycloaddition of maleimides and nitrile oxides to resin-bound pyridium methylides and cleavage, was presented by Bicknell et al.[103] A 2-substituted indole has been obtained by the elaboration of a polymer-bound phosphonium salt and subsequent cleavage.[104] The Diels−Alder reaction has also been successfully utilized in the preparation of hydroisoindole derivatives,[105] and recently, a modification of the method has been used in the preparation of indolizines **39**[106] utilizing a formal [3 + 2] dipolar cycloaddition of a resin-bound pyridinium



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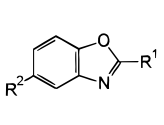

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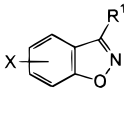

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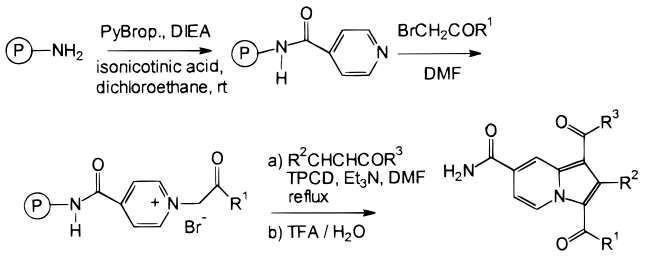
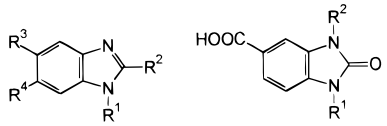
salt followed by oxidation (Scheme 14). Resin-bound indoles have also been modified by the Mannich reaction.[107] In this report, several 3-substituted indoles were prepared. Surprisingly few papers have reported the solid-phase synthesis of benzoxazoles **40**, although these compounds have been shown to have remarkable biological activity. The first solid-phase synthesis of benzoxazoles was described by Wang and Hauske[108] via a Mitsunobu reaction. Several 2-amidophenols attached to a resin were converted to benzoxazoles by

Scheme 14



treatment with triphenylphosphine and diethylazodicarboxylate. Recently, Stephensen[102] reported a method where resin-bound 4-fluoro-3-nitrobenzoic acid amides reacted with acetonitriles and formed an intermediate which upon reduction yielded ben[c]isoxazoles **41**. Moreover, the Kaiser oxime resin was utilized in a paper by Lepore and Wiley[109] for the synthesis of a few 3-aminobenzisoxazoles.

4.2.3. Synthesis of Benzimidazoles and Benzimidazolones. In solution, benzimidazoles **42** can be prepared by cyclization of *o*-amino-anilides under mild conditions. Benzimidazolones **43**, on the other hand, are prepared by the reaction of carbonic acid derivatives with the corresponding



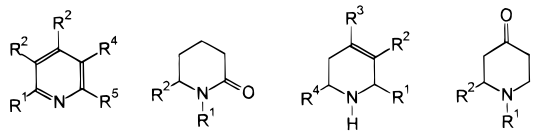
42 **43**

o-substituted anilines. On solid support the first efficient method for the preparation of benzimidazoles was presented by Phillips and Wei.[110] A polymer-bound *o*-fluoronitroaromatic compound was reacted with an amine. Reduction of the *o*-nitroaniline derivative, followed by cyclization and cleavage, gave a library of benzimidazoles in 70−95% crude yield. Recently, the preparation of several benzimidazole libraries has been reported using almost the same approach: Tumelty et al.[111] synthesized 1-phenyl-2-aminomethyl-benzimidazoles and 1-phenyl-2-thiomethyl-benzimidazoles, and Mayer et al.[112] utilized the method for the automated solid-phase preparation of a set of benzimidazoles. Moreover, the solid-phase preparation of 1-alkenyl-2-alkylthio-5-carbamoyl benzimidazoles[113] and other benzimidazole libraries[114−116] has recently been published. The approach toward the preparation of benzimidazolones on solid support resembles that of Phillips and Wei.[110] In a recent paper,[117] a library of 13 discrete benzimidazolones was presented. Recently, benzimidazolones have also been prepared successfully in liquid phase.[118]

4.2.4. Synthesis of Other Types of Fused Five-Membered Heterocycles. Several methods for the synthesis of other fused five-membered heterocycles have recently been published. These are not categorized into their own group and are discussed briefly in this chapter. One of these reactions describes the formation of azabicyclo[4.3.0]nonen-8-one amino acid derivatives via intramolecular Pauson−Khand cyclization.[119] This approach provides a rapid and stereocontrolled method for the synthesis of highly functionalized fused bicyclo amino acid derivatives. In two papers by Kurth et al.,[120,121] diverse isoxazoles, isoxazolines, and polyisoxazolines have been synthesized. The two-reaction iterative protocol proved to be a good strategy for the preparation of polyfunctional oligomers of this type. Moreover, an indazole was prepared on solid support to be used for reaction monitoring experiments,[122] and in a recent paper, the convenient solid-phase synthesis of proline analogues via a three-component 1,3-dipolar cycloaddition was reported.[123] Sequential Hantzsch condensation and cyclative cleavage reactions have been used for the preparation of pyrrolo[3,4-*b*]pyridines and related pyridine-fused heterocycles.[124] Recently, several bicyclic and polycyclic structures featuring the formation of a five-membered ring have been reported. This includes, for example, the synthesis of trisubstituted bicyclic guanidines,[125] 3-aminoimidazo[1,2-*a*]azines,[126] bicyclic pyrrolidines,[127] tricyclo octanes,[128] and 2,5,6,7-tetra-substituted 1*H*-pyrrolo [1,2-*c*]imidazoles.[129] A variety of fused five-membered rings have also been synthesized on the resin, although the final products have not been cleaved. These reactions describe the efficient utilization of polymers for the introduction of rings onto different templates. In an early paper describing the use of polymer supports in organic synthesis, Leznoff et al.[130,131] described the preparation of monoacetals. This monoblocking approach of symmetrical diketones could efficiently be used for the introduction of the Grignard reaction with solid supported templates.[132] In a paper by Schore and Najdi,[133] Pausond−Khand cycloadditions were performed on a resin. A new five-membered ring was introduced in the reaction between polymer-bound pentynes with norbornadiene. Look et al.[134] monitored a thiazolidinone ring formation using ^{13}C NMR, and ozone was shown to be a versatile reagent for the solid-phase synthesis in a report by Sylvain et al.[135] An interesting five-membered ring, an ozonide, was subsequently treated with various reagents. Recently, during this year, several other interesting reactions have been reported on solid support leading to the formation of a five-membered ring. As an example, the preparation of polymer-bound 1*H*-benzotriazoles on solid support[136,137] can be mentioned.

5. Formation of Six-Membered Rings on Solid Support

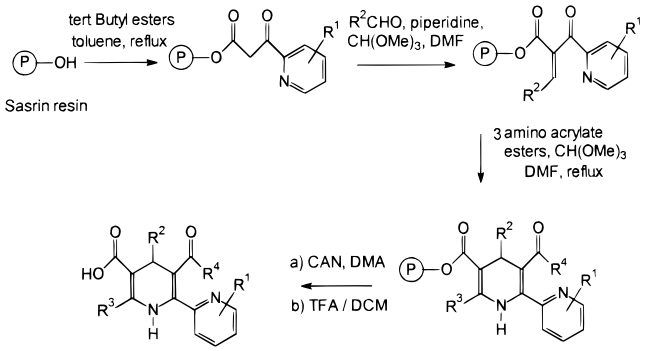
5.1. Monocyclic Compounds. 5.1.1. Synthesis of Six-Membered Heterocycles with One Nitrogen Atom in the Ring. In this chapter the solid-phase synthesis of pyridines **44** and structurally related compounds, e.g., lactams **45**, piperidines **46**, and piperidinones **47**, will be discussed. A very convenient method for the preparation of pyridines in solution is the Hantzsch pyridine synthesis involving the



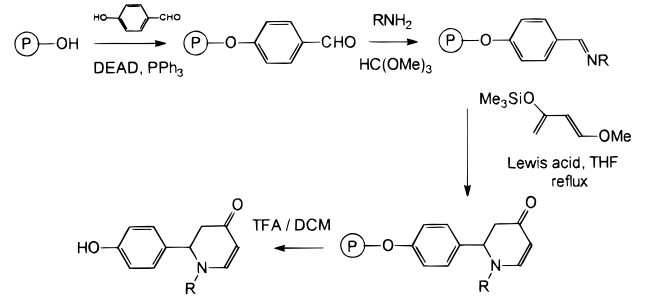
44 **45** **46** **47**

condensation of two molecules of a β-keto ester with an aldehyde and ammonia. Tadesse et al.[138] transferred the synthesis onto solid support and prepared highly functionalized bipyridines based on a sequential Knoevenagel and Hantzsch condensation (Scheme 15). Gordeev et al.[139] reacted N-immobilized enamino esters with 2-arylidene-β-keto esters

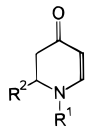
Scheme 15



Scheme 16



and aldehydes to afford, upon cleavage, 1,4-dihydro-pyridine derivatives. 2,4,6-Trisubstituted pyridines have, in addition, been synthesized through a Claisen-Schmidt/Michael reaction on Wang resin and cyclization.[140] An efficient method for the preparation of 2,3-dihydro-4-pyridones **48** on solid support through a Lewis-acid-catalyzed tandem Mannich−



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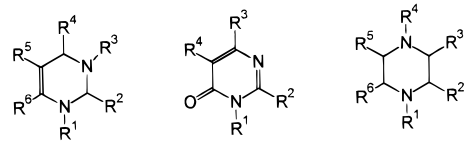
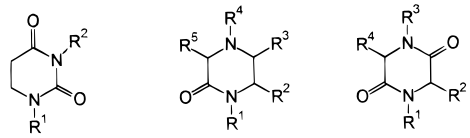
Michael reaction of Danishefsky's diene with polymer-bound aldimines has been reported by Wang and Wilson[141] (Scheme 16). Recently, Zhang et al.[142] reported a ytterbium(III) trifluoro methanesulfonate-catalyzed aza Diels−Alder/cleavage reaction for the preparation of piperidine derivatives. Piperidin-4-ones have been prepared in a heterocyclization reaction between divinyl ketones with amines.[143] Also, several five- and six-membered ring lactams have been synthesized recently. Short and Mjalli[144] reported the synthesis of lactams via the condensation of ω-ketoacids, isocyanides, and amines. In another paper, Short et al.[145] prepared several lactams through the Ugi four-component condensation. A recent review of the synthesis of lactams and pyridines on solid support has been published in *Accounts of Chemical Research*.[146]

5.1.2. Synthesis of Six-Membered Rings with Two Heteroatoms. Papers in this chapter are divided into two major classes: those reporting the solid-phase synthesis of heterocycles with two nitrogen atoms, and those reporting the synthesis of compounds with one sulfur and one nitrogen atom in the ring. The compounds having two nitrogen atoms are mostly reporting the synthesis of pyrimidines **49**, pyrimidinones **50**, and piperazines **51**. A few compounds do not belong to either of these groups, and they are discussed separately at the end of the chapter.



49 **50** **51**

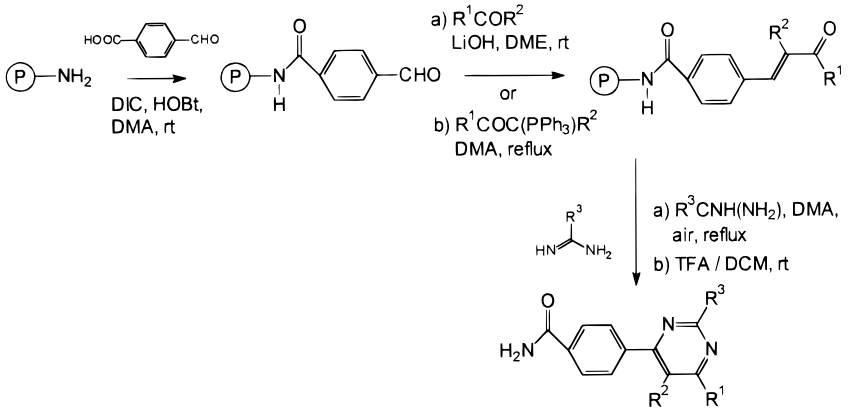
In an early paper by Gavina et al.,[147] the preparation of a cyclic diimine on solid support was discussed. Not until recently had other heterocycles with two nitrogens in the ring been reported. For the synthesis of pyrimidines, a few approaches have been published. Wipf and Cunningham[148] utilized the solid-phase Biginelli condensations of β-keto-esters, aldehydes, and ureas for the synthesis of dihydropyrimidines. A few years later, a new and efficient route toward diverse pyrimidines was introduced by Obrecht et al.:[149] The polymer-bound thiouronium salt reacted in a cyclocondensation reaction with acetylenic ketones. Oxidation and cleavage produced the products in high yield. Lately, Marzinzik and Felder[150] synthesized pyrimidines from polymer-bound α,β-unsaturated ketones, obtained via a Wittig and a Claisen−Schmidt reaction (Scheme 17). Dihydropyrimidinones and pyrimidinones have also been synthesized on solid support. In a paper by Nizi et al.,[151] 2,6-disubstituted-4(3*H*)-pyrimidones, and in a paper by Hamper et al.,[152] dihydropyrimidone carboxylate esters were obtained. The method for preparation included a Knoevenagel condensation followed by condensation with amidines. Cleavage with TFA afforded the carboxyl acids that through decarboxylation gave the final products. A series of 1,3-disubstituted-5,6-dihydropyrimidine-2,4-diones **52** have, in addition, been synthesized



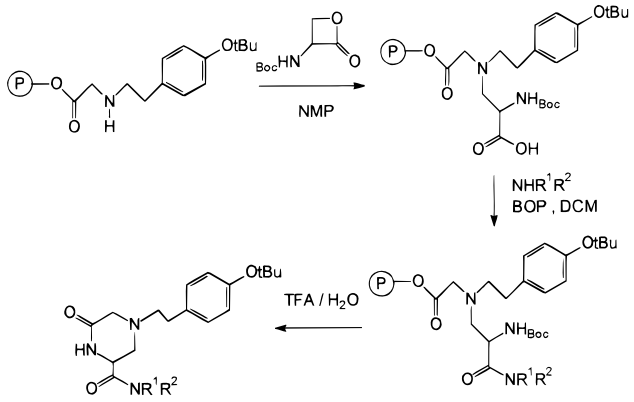
52 **53** **54**

using a cyclization−cleavage strategy from readily available amines and isocyanates.[153] Several papers have reported the solid-phase synthesis of piperazines **51** and piperazine analogues including compounds with one keto group (piperazinones **53**) and with two keto groups (diketopiperazines **54**). A recent paper was published describing the synthesis of 1,2-disubstituted piperazines[154] from resin-bound reduced N-acylated amino acids. Piperazinones have been synthesized by intramolecular Michael addition by Goff and Zuckermann.[155] These compounds have also been obtained through N-alkylation of Wang resin-bound *N*-(4-*tert*-butyloxy-phenethyl)-glycine with the Vederas lactone[156] (Scheme 18). After conversion to resin-bound tertiary amides, cleavage, deprotection, and cyclization, several diverse piperazinones were obtained. Di- and trisubstituted 2-oxopiperazines have been synthesized by Goff[157] by the tandem S_N2 Michael addition of amines to unsaturated peptoids on solid support. Three papers have described the preparation of diketopiperazines: Szardenings and Burkoth[158] presented a solid-phase approach toward several diketopiperazine derivatives, Gordon and

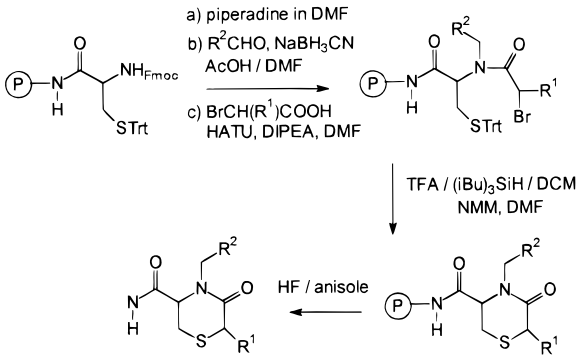
Scheme 17



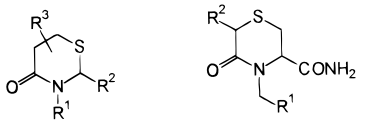
Scheme 18



Scheme 19



Steele[159] synthesized a combinatorial library of 1000 compounds having the piperazinedione structure, and Li and Peng[160] introduced an efficient method for the preparation of trisubstituted (*Z*)-3-alkylidene-2,5-piperazinediones. In all these preparations a cyclization/cleavage strategy was utilized as the final step. Two papers described the preparation of six-membered heterocycles containing a sulfur atom in the ring. Holmes et al.[161] developed a method for the polymer-supported preparation of 4-metathiazanones **55**. In the same

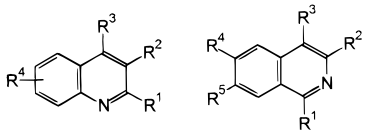


55 **56**

paper, the group introduced a method for the synthesis of 4-thiazolidinones. Both compounds were derived from amino acids. Nefzi et al.[162] have recently described the preparation of 2,4,5-trisubstituted thiomorpholin-3-ones **56** (Scheme 19). The reductive alkylation of a resin-bound protected cysteine followed by amide formation and intramolecular thioether formation gave these compounds in good yield.

5.1.3. Synthesis of Other Six-Membered Rings. A few papers have described the preparation of six-membered rings not belonging to any group mentioned above. These include the efficient synthesis of monosaccharide derivatives on solid phase,[163] a six-membered cyclic keto-ether,[164] several substituted phenols,[165] dihydropyrans[166] and a few six-membered ring structures containing three nitrogens (1,2,4-triazine-3,6-diones[167]). Also some reports on the formation of a six-membered ring on a polymer without cleavage could be found. In a paper by Deans and Rotello,[168] a triazine-functionalized polymer was prepared. Moreover, Ren et al.,[169] and Leznoff and Greenberg[170] reported a six-membered cyclic acetal.

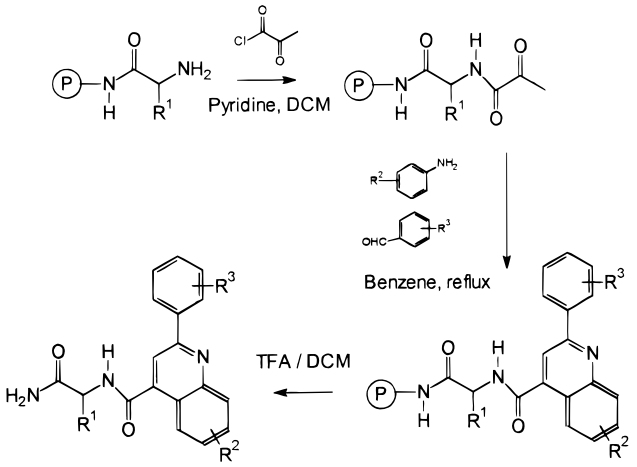
5.2. Fused Polycyclic Compounds. 5.2.1. Synthesis of Quinolines, Isoquinolines, and Other Fused Heterocycles Containing One Nitrogen Atom. In solution, quinolines **57** and isoquinolines **58** can be prepared using several methods: The Friedlaender synthesis and the Pfitzinger synthesis involve an aldol reaction to form quinolines from *o*-aminobenzaldehydes and ketones and from ketones and isatinic acid,



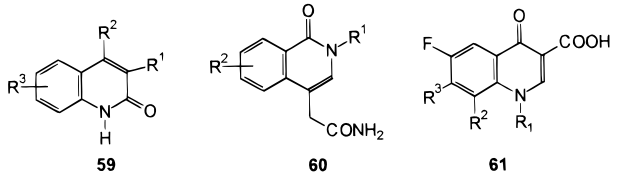
57 **58**

respectively. Michael addition of a primary aromatic amine to an α,*β*-unsaturated aldehyde or ketone followed by cyclization and oxidation of the dihydroquinolines yields quinolines. In addition, the Doebner reaction has been utilized in the synthesis of 2-arylquinoline-4-carboxylic acid derivatives. A ring closure of disubstituted benzenes, e.g., homophthalaldehydes, gives isoquinolines and isoquinoline 2-oxides by reaction with NH_3 and NH_2OH, respectively. Bischler−Napieralski synthesis of 3,4-dihydroisoquinolines are formed from acylated 2-phenyethylamines. Other methods for the preparation of isoquinolines are through the utilization of the Pictet−Gams method, and the Pomeranz−Fritsch syn-

Scheme 20



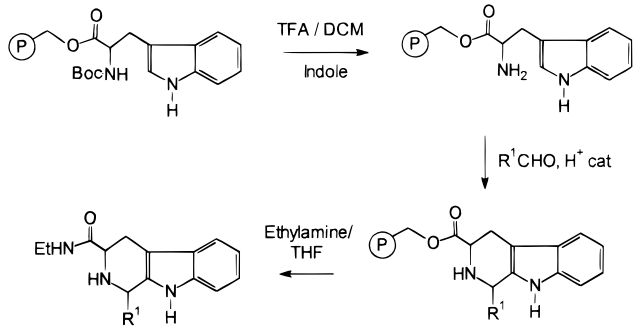
thesis. On solid support the Doebner quinoline synthesis has been adopted to solid phase[171] (Scheme 20). Acylation of an resin-bound amino acid with pyruvyl chloride followed by reaction with a Schiff's base or an aldehyde and aniline gave, after TFA cleavage, 2-arylquinoline-4-carboxylic acid amides. Tetrahydroquinolines have also been prepared by a three-component condensation involving aromatic amines, aldehydes, alkenes, and TFA as a catalyst[172] or $Yb(OTf)_3$ as a catalyst.[173] The same group has also prepared tetrahydroquinolines via a three-component condensation of aldehydes, anilines, and electron-rich olefins catalyzed by TFA.[174] Ruhland and Kunzer[175] have prepared 2,6-disubstituted quinolines in seven steps involving three commercially available compounds: ω-functionalized fatty acids, arylmethyl ketones, and primary amines. Lorsbach et al.[176] have described the solid-phase synthesis of isoquinolines through a Reissert-based "traceless" solid-phase route. The synthesis of tetrahydro-isoquinolines has been described in three papers: Meutermans and Alewood[177] have adopted the Bischler−Napieralski approach onto solid phase, an eight-step reaction sequence for the synthesis of 1,2,6-trisubstituted-1,2,3,4-tetrahydroisoquinolines has been described by Rolfing et al.,[178] and Hutchins and Chapman[179] utilized substituted *m*-tyramines, histamines, and various aromatic, aliphatic, and heterocyclic aldehydes in the synthesis of 1,2,3,4-tetrasubstituted tetrahydroisoquinolines. The preparation of several quinolinones **59** has been described recently. C-Acylation of cyanoacetic acid loaded on Wang resin was cleaved and cyclized upon heating leading to 4-hydroxyquinolin-2(1*H*)-ones.[180] The synthesis of 4-amino-3,4-



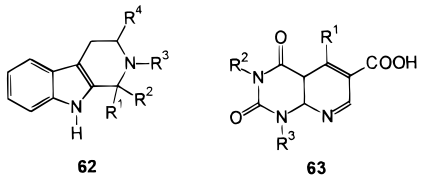
59 **60** **61**

dihydro-2(1*H*)-quinolinones has been accomplished through the rearrangement of β-lactam intermediates on solid support.[181] Goff and Zuckermann[182] have utilized the intramolecular Heck reaction in the preparation of highly substituted peptoid 1(2*H*)-isoquinolinones **60**. Moreover, the synthesis of structurally related bicyclic alkenes has been described

Scheme 21



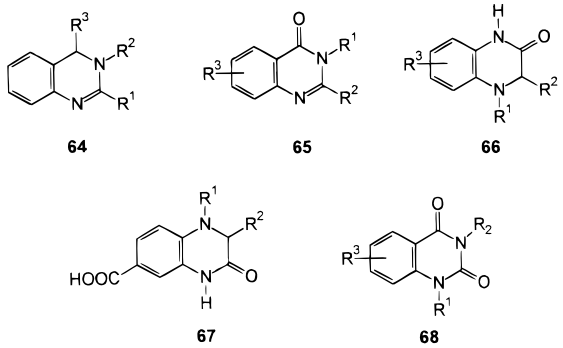
by Cuny et al.[183] Two papers have also appeared recently, describing the preparation of quinolones **61**. Hobbs DeWitt et al.[184,185] used the DIVERSOMER technology[58] for the synthesis of this class of antibacterial agents. In solution, tetrahydro-β-carbolines **62** are synthesized by an internal



62 **63**

Mannich reaction. The access to this class of compounds can also be realized through the Pictet−Spegler cyclization, and four recent papers have described the adaption of the method in a solid-phase protocol. 1,2,3,4-tetrahydro-β-carbolines were synthesized on four different polymers: on Merrifield resin[186] (Scheme 21), on Wang resin,[187] on a Kaiser-oxime resin,[188] and on a TentaGel-S-NH_2 resin with a serine-based linker.[189] Moreover, Gordeev et al.[190] reported the solid-phase synthesis of pyrido[2,3-*d*]pyrimidines **63**. O-Immobilized keto-ester reacted with aldehydes, and subsequent reaction with 6-aminouracils, oxidized by CAN, gave the products.

5.2.2. Synthesis of Fused Bicyclic-Compounds with Two Nitrogen Atoms in the Ring. Compounds belonging to this group consist mainly of the following types of molecules: quinazolines **64**, quinazolinones **65**, quinoxalinones **66**, benzopiperazinones **67**, and quinazolinediones **68**. At the end of this section a few other types of compounds are listed, not previously mentioned. Polymer-supported cinnamyl

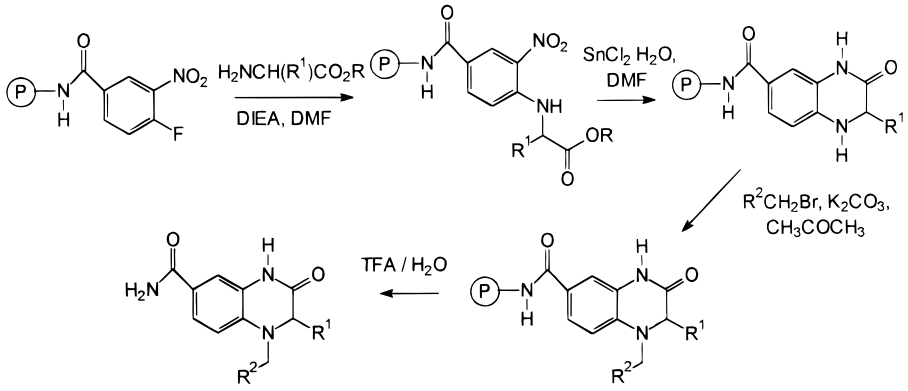


64 **65** **66**

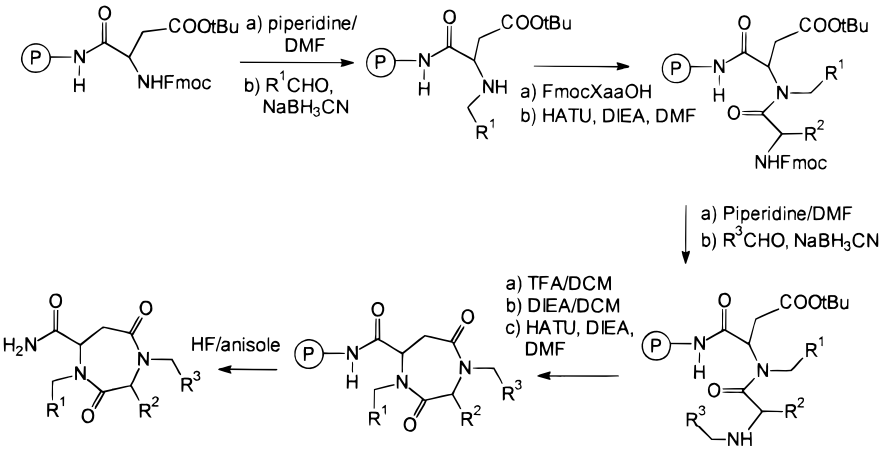
67 **68**

iminophosphorane has been treated with an aryl isocyanate followed by reaction with a secondary amine. 1,2-Addition followed by an intramolecular Michael addition gives 3,4-dihydro-quinazolines.[191] Mayer et al.[192] have described the

Scheme 22



Scheme 23

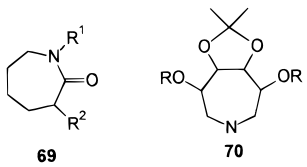


synthesis of several 4(3*H*)-quinazolinones under acidic conditions from resin-bound anthranilamide precursors and aldehydes. Lee et al.[193] have synthesized 3,4-disubstituted-7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones on solid support through aromatic substitution, reduction, and subsequent intramolecular cyclization (Scheme 22). Diverse quinoxalinones are obtained through selective alkylation and cleavage from the support. Benzopiperazinones have been prepared by Morales et al.[194] This approach follows the same route as that used by Lee et al.[193] Several reports describing the efficient synthesis of quinazolinedione derivatives have been published: In a paper by Smith et al.,[195] the anthranilic acids are linked to a chloroformate resin and amines are coupled to the free carboxylic acid. Thermal cyclization leads to the formation of 1,3-disubstituted-quinazoline-2,4-diones. Gouilleux et al.[196] described a similar approach, although utilizing a carbamate linker for the synthesis of 3-substituted quinazoline-2,4-diones. Buckman and Mohan[197] utilized a slightly modified method for the synthesis of 1,3-dialkyl-quinazoline-2,4-diones. In addition, also Gordeev et al.[198] and Shao et al.[199] have synthesized several discrete quinazoline-2,4-diones on solid support. Several other heterocycles containing 2-nitrogens have been synthesized on solid support. These include the preparation of substituted cinnolines,[200] tetrahydro-β-carboline-2,3-bislactams,[201] 1-acyl-3-oxopiperazine analogues,[202] and indolyl diketopiperazine alkaloids based on a cyclization/cleavage strategy.[203]

5.2.3. Synthesis of Other Fused Six-Membered Heterocycles. A few six-membered rings have also been prepared on solid support including compounds with no nitrogen atoms in the ring,[204,205] and three reports could be found where the final product containing the ring was not cleaved from the support.[206−208]

6. Formation of Seven-Membered Rings on Solid Support

6.1. Monocyclic Compounds. 6.1.1. Synthesis of Lactams and Azepane Scaffolds. Seven-membered rings containing one heteroatom play an important role in the development of new drugs. Medium ring lactams display a biological activity and are important synthetic intermediates. In solution, a general method for the preparation of these compounds include the Beckmann or the Schmidt rearrangement. On solid support several approaches toward the synthesis of lactams **69** have been reported. These include the work by Huang and Kalivretenos,[209] Maarseeven et al.,[210] and Piscopio et al.[211,212] Moreover, Gauzy et al.[213] synthesized

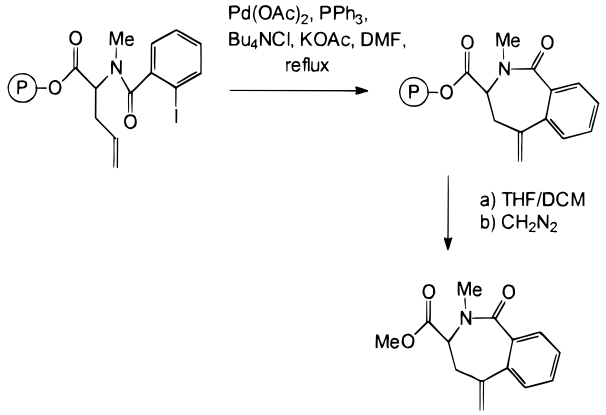


69 **70**

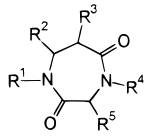
recently several enantiopure C_2-symmetric azepanes **70** as scaffolds for the synthesis of peptidomimetics.

6.1.2. Synthesis of Perhydro-1,4-diazepine 2,5-Diones. In the literature, two representative examples could be found on the preparation of perhydro-1,4-diazepine-2,5-diones **71**

Scheme 24



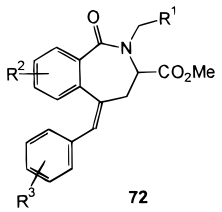
on solid support: In a paper by Nefzi et al.,[214] the solid-phase synthesis of 1,3,4,7-tetrasubstituted perhydro-1,4-diazepine-2,5-diones was reported (Scheme 23). *p*-Methyl-



71

benzhydrylamine resin-bound aspartic acid and an aldehyde were reacted to obtain the corresponding enamine which was Fmoc-protected. Following dipeptide formation, removal of the Fmoc group, a reductive alkylation, and finally amide formation, 40 distinct diazepines could be obtained. In another paper by Krchnak and Weichsel,[215] the polymer-supported synthesis of another set of perhydro-1,4-diazepine-2,5-diones was described. Secondary diamines and Fmoc-protected amino alcohols were attached to chlorotrityl resin. Following acylation, alkylation, reaction with bromoacetic acid, bromide displacement by primary amines, and removal of the allyl ester function, the seven-membered ring could be obtained upon mild activation of the carboxyl group. Cleavage from the support was achieved by TFA.

6.2. Fused Polycyclic Compounds. 6.2.1. Synthesis of Benzazepines. When two aldehyde groups separated by four carbon atoms are treated with a primary amine, an azepine ring may be formed in solution. The formation of this biologically important ring often involves the reaction between groups which are attached to different rings, and thus the azepine ring is fused to two others in the product. On solid support, a convenient method has been introduced for the selective synthesis of benzazepines. In the paper by Bolton and Hodges,[216] a small library of substituted benzazepines **72** was prepared via intramolecular Heck cyclization (Scheme 24). The same approach has also been adapted for the synthesis of several other heterocycles on solid support.



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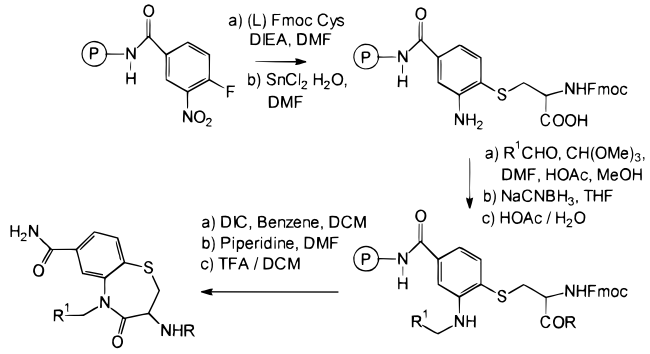
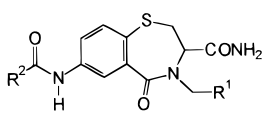
Scheme 25



6.2.2. Synthesis of Benzothiazepin-5-ones and Diben-[*b,f*]oxazepinones. Benzothiazepines have shown biological activity with interesting properties in several studies. Moreover, a number of 1,4-benzothiazepines have displayed anticancer properties. In a recent paper by Nefzi et al.,[217] the solid-phase synthesis of 1,4-benzothiazepin-5-one derivatives **73** was presented. The resin-bound protected cystein was reacted with 2-fluoro-5-nitro-benzoic acids followed by



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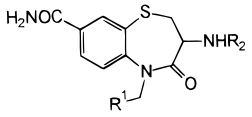

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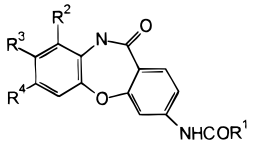

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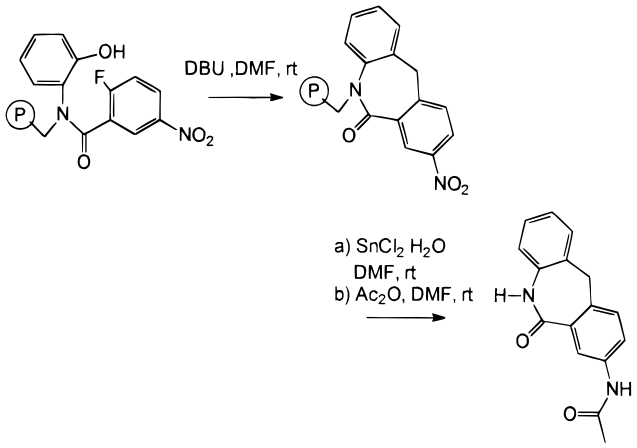
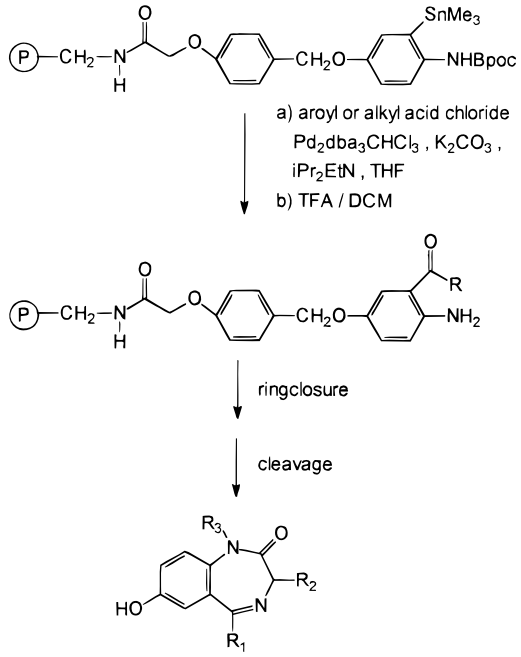
reductive alkylation and an intramolecular cyclization. Twelve individual benzothiazepines were synthesized. In another paper, recently published, Schwarz et al.[218] described a convenient solid-phase route affording 3,5-disubstituted 1,5-benzothiazepin-4(5*H*)-ones **74** (Scheme 25). With this four-step synthesis, 26 different compounds could be obtained. It is known that amino and carboxyl groups separated by five carbons and one sulfur react under the influence of DCC to form a fused thiazocinone ring. With this in mind, it is maybe possible to prepare 1,4-thiazocin-5-ones or related compounds on solid support. Several synthetic strategies toward the dibenz[*b*,*f*]oxazepin-11(10*H*)-one framework have been reported in solution. In the paper by Ouyang et al.,[219] the nucleophilic aromatic substitution (S_NAr) of a halogen atom with the phenolic oxygen in 2-X-5-nitrobenzamides of *o*-aminophenols was utilized on solid support in the preparation of a diverse array of compounds with a seven-membered ring **75** (Scheme 26). Due to the efficient assembly, it can be expected that also 1,2,3-triazolo[4,5-*b*][1,5]-benzoxazepin-10-ones could be synthesized on solid support. The base-induced reaction in solution phase of suitably placed halogen and alcohol or phenol functions as reported in the literature should easily be transferable onto solid phase.

6.2.3. Synthesis of Benzodiazepin-2-ones. For the preparation of 1,4-diazepin-2-ones **76** in solution, several routes

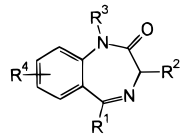
Scheme 26



Scheme 27



have been developed. For example, a haloacylamine group adjacent to a ketone function is a commonly used precursor of this ring; ammonium carbonate or hexamethylene-tetramine provides the second nitrogen atom. Another route



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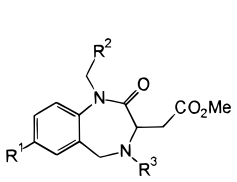
involves the reaction between an aliphatic carboxyl and an aromatic amino group in an appropriate structure that may be brought about either by hot PPA or spontaneously during hydrogenation of a nitro group. Also an amine and a ring-nitrogen in different rings react with a difunctional reagent such as bromoacetyl chloride in TEA to give a doubly fused diazepinone. A similar ring is formed in a reaction between an arylamine and an *N*-bromoethyl lactam carrying a displaceable ethoxy group. On solid support, however, the mostly used method for the preparation of benzodiazepines is that originally developed by Ellman et al.[220−225] His work represents one of the first examples of the application of combinatorial organic synthesis to nonpolymeric organic synthesis. The benzodiazepines are synthesized on a solid support by the connection of three building blocks, each of different types. Another synthesis method by Ellman et al.,[226] in which the 2-aminoaryl ketones are assembled on the solid phase by Stille coupling of protected 2-aminoarylstannanes and acid chlorides, is more flexible than the previous solid-phase benzodiazepine synthesis (Scheme 27). This route provides elegant access to hundreds of different 2-aminoaryl ketones, since over 500 acid chlorides are commercially available. Another benzodiazepine synthesis has been reported by Chenera et al.[227] in which the benzophenones are assembled on the solid phase by halogen−metal exchange and reaction with benzyl chloride. In addition, Bhalay et al.[228] suggested a general method for the construction of tetrahydro-1,4-benzodiazepine-2-ones **77** on solid support utilizing



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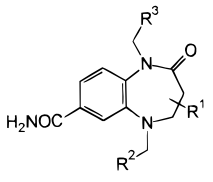
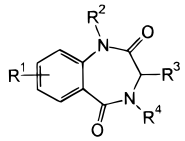


78

a cleavage-conjugate addition protocol as the key step. In the literature, there are only few examples of an efficient synthesis of 1,5-benzodiazepine-2-ones **78**: In the paper by Schwarz et al.,[229] a total of 18 compounds were reported. Resin-bound 4-fluoro-3-nitrobenzoic acid was reacted with different β-amino acids, followed by nitro group reduction and formation of the seven-membered ring. A subsequent alkylation at *N*(1) and *N*(5) was performed. In another paper, by Lee et al.,[230] the preparation of several 3,4,5-substituted 8-carboxamido-1,5-benzodiazepin-2-ones was described.

6.2.4. Synthesis of 1,4-Benzodiazepin-2,5-diones. The 1,4-benzodiazepine-2,5-diones **79** have been reported as anticonvulsants, mimetics of the RGD tripeptide, and synthetic precursors to benzodiazepine receptor antagonists. The benzodiazepine skeleton is a constituent of many bioavailable



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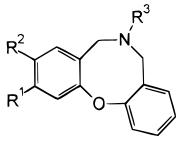
therapeutic agents, and this medicinally important type of compound has been reviewed in several papers. Following the solid-phase synthesis of benzodiazepines reported by Camps et al.,[231] Hobbs DeWitt et al.[57] developed a method for the synthesis of benzodiazepines based on the Fmoc strategy. Diversity of the target compounds was, however, limited by the availability of the 2-aminobenzophenones. In a benzodiazepinedione synthesis from Ellman et al.,[232,233] the anthranilic acids could be used as obtained commercially, since the reaction conditions did not require any protective groups. α-Amino acid esters were linked to dimethoxybenzaldehyde-functionalized Merrifield resin by reductive alky-

lation. Another 1,4-benzodiazepine-2,5-dione synthesis originates from the laboratory of Geoff and Zuckermann,[234] who used the benzodiazepinedione unit to introduce a higher degree of diversity and rigidity in their peptoids. In a paper by Mayer et al.,[235] 1,4-benzodiazepine-2,5-diones were synthesized by a simple procedure utilizing polymer-supported amino acids and *o*-nitrobenzoic acids or protected anthranilic acids (Scheme 28). Cyclization of the aminoamide intermediate with concomitant release from the support produced the title compounds in high yields and good purity. Moreover, pyrrolo-1,4-benzodiazepine-2,5-diones have also been synthesized by aza-Wittig ring closure by Baldwin et al.[236]

7. Formation of Eight-Membered Rings on Solid Support

In solution, several methods have been reported for the efficient preparation of an eight-membered ring. For example, benzo[*b*][1,4]diazocino[7,6-*f*]indoles are formed by heating an *o*-diketone with *o*-phenylenediamine in the presence of an acid, a 1-benzoxocin-ring can be obtained by a Wittig-type cyclization, and an azocin-2-one may be prepared by a base-induced intramolecular reaction of suitably placed ester and amino groups. On solid support, however, only a few eight-membered compounds **80** have been synthesized: In two recent papers by Ouyang and Kiselyov, the syntheses



80

of dibenzo[*b*,*g*]1,5-oxazocines[237] and dibenz[*b*,*f*]oxazocines[238] were reported. The approach toward the preparation of these compounds was based on the intramolecular nucleophilic aromatic substitution of fluorine from the derivatives of 2-fluoro-5-nitrobenzaldehyde with the OH function of immobilized phenols. Since several tricyclic aza-heterocyclic systems and other heterocycles containing the eight-membered ring are of current interest for medicinal purposes, it is expected that several papers on the synthesis of these types of compounds will soon be published.

8. Conclusions

As a conclusion, heterocycles can be prepared efficiently through cyclization on the solid phase, even in the case of very complex structures, allowing the discovery of novel compounds with interesting and varying activity. The development of solid-phase synthesis toward new heterocycles is becoming more demanding, as being demonstrated via recent observations reviewed in this current work. Although many new approaches for the preparation of several types of heterocycles have recently been introduced, there are still several molecules, including compounds with biological activity, for which only solution-phase approaches exist. It is, however, expected that these syntheses will soon be transformed onto the solid-phase, thereby making possible an effective screening of libraries with unexpected biological activity.

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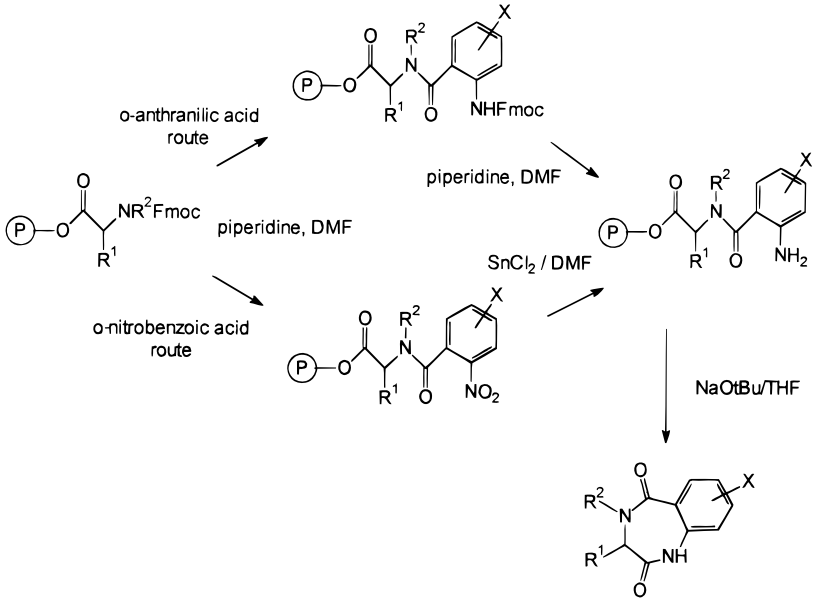
Scheme 28



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