

# Solid-Phase Synthesis of Seven-Membered Heterocycles with Two Nitrogen Atoms

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**Abstract** Due to the importance of diazepines and diazepanes in medicinal chemistry and chemical biology, their preparation from diverse starting materials has been frequently reported. In this chapter, we summarize all strategies employing the method of solid-phase synthesis. More than seventeen different types of target compounds are accessible. The individual approaches are grouped according to the type of the target scaffold.

**Keywords** Benzodiazepines • Combinatorial chemistry • Diazepanes • Diazepines • Solid-phase synthesis

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## Abbreviations

AA	Amino acid
Boc	<i>t</i> -Butyloxycarbonyl
BAL	Backbone amide linker
BTC	Bis(trichloromethyl) carbonate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIC	<i>N,N'</i> -Diisopropylcarbodiimide
DIEA	<i>N,N</i> -Diisopropylethylamine
DEAD	Diethyl azodicarboxylate
DECP	Diethyl cyanophosphonate
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
EEDQ	<i>N</i> -ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
Fmoc	Fluorenylmethoxycarbonyl
HATU	[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i> ]pyridinium 3-oxid hexafluorophosphate)
HOBt	1-Hydroxybenzotriazole
MBHA	Methylbenzhydramine
NMP	<i>N</i> -Methylpyrrolidone
Nos	Nitrobenzenesulfonyl
TBTU	<i>N,N,N',N'</i> -Tetramethyl- <i>O</i> -(benzotriazol-1-yl)uronium tetrafluoroborate
TBP	Tributylphosphine
TEA	Triethylamine
THF	Tetrahydrofuran

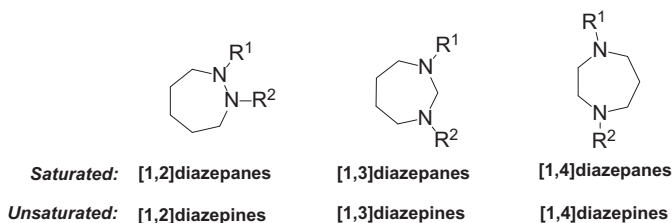
TFA	Trifluoroacetic acid
TFMSA	Trifluoromethanesulfonic acid
TPP	Triphenylphosphine

## 1 Introduction

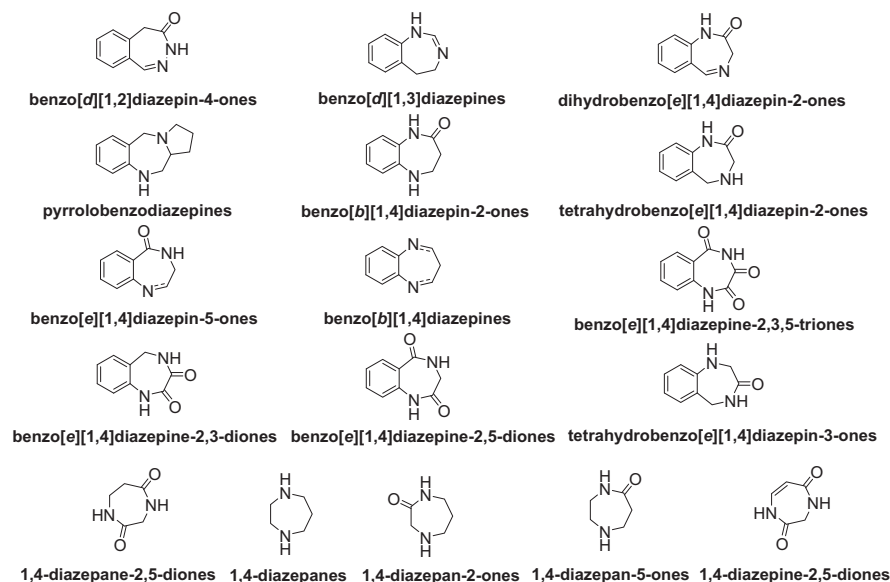
Within the large family of heterocyclic compounds, diazepines and diazepanes are an interesting group of derivatives with specific physical-chemical and biological properties. Depending on the position of the two nitrogen atoms in the seven-membered scaffold, three general classes of compounds are distinguished, namely, 1,2-diazepanes, 1,3-diazepanes, and 1,4-diazepanes, as well as the corresponding unsaturated analogues, the diazepines (Fig. 1).

From a historical perspective, the most frequently studied class in this field of research is the [1,4]diazepines, which are typically condensed with a benzene ring. Although the majority of these compounds reported to date are of synthetic origin, the scaffold is also found in natural products such as diazepinomicin [1] or callysponine [2]. Synthetic benzo[1,4]diazepines have been identified as important molecules in drug discovery, especially as potent central nervous system (CNS) agents with strong anxiolytic, muscle relaxant, and tranquilizing effects due to their specific binding sites within GABA<sub>A</sub> receptors [3]. Although the CNS effect of benzodiazepines is considered most important, there are many other beneficial properties, such as an antiarrhythmic effect [4], antagonism of cholecystokinin receptors [5], inhibition of HIV-1 reverse transcriptase [6], opioid receptor activity [7], anticancer [8] or anti-inflammatory [9] effects, and many others. For these reasons, benzodiazepines are conventionally classified as “privileged scaffolds”.

The gold era of the solid-phase syntheses of heterocycles began in the mid-1990s. Among other methods to prepare heterocyclic scaffolds, a variety of methodologies to prepare diazepane/diazepine derivatives was also developed. Unsurprisingly, the medicinal importance of benzo[1,4]diazepines reported by Sternbach [10] redirected the research focus of solid-phase chemists so that the majority of reported results was related to this group of compounds. Interestingly, the first literature evidence of benzo[1,4]diazepine solid-phase synthesis occurred in 1977 ([www.espatentes.com/pdf/0445831\\_A1.pdf](http://www.espatentes.com/pdf/0445831_A1.pdf)), only twelve years after



**Fig. 1** General structural classification of seven-membered cycles with two nitrogen atoms



**Fig. 2** Individual scaffolds reported using solid-phase synthesis

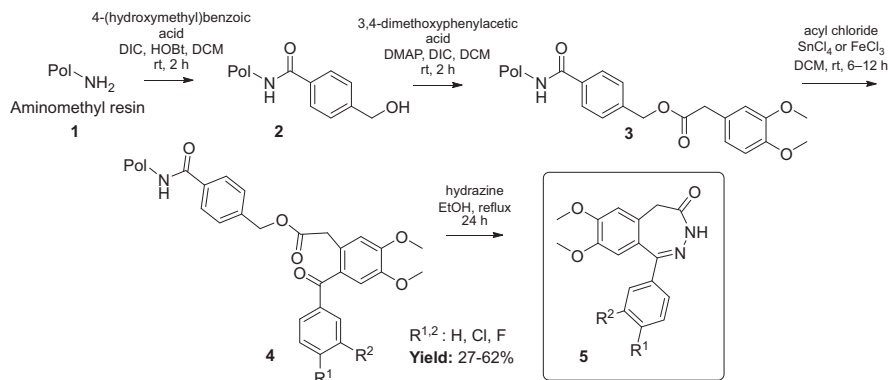
Merrifield's introduction of solid-phase peptide synthesis [11] and almost twenty years before the beginning of the solid-phase heterocyclic era.

In 2006, the preparation of benzodiazepines was reviewed by Kamal [12] and was partially addressed in several other review articles [13, 14]. The following section summarizes all strategies reported to date. Although a significant part of the text is devoted to benzodiazepine chemistry, the methods are extended to the entire group of diazepane/diazepine derivatives. The individual approaches are grouped according to the type of scaffold, as depicted in Fig. 1, and are divided into subsections devoted to more specific scaffolds (Fig. 2).

## 2 1,2-Diazepines

### 2.1 Benzo[d][1,2]diazepin-4-ones

To date, there is a single strategy applicable for the solid-phase synthesis of this scaffold containing compounds reported by Bevacqua et al. [15] This approach is based on using aminomethyl polystyrene resin **1** coupled with 4-(hydroxymethyl) benzoic acid. The resin was acylated with 3,4-dimethoxyphenylacetic acid, followed by the Friedel-Crafts acylation with different benzoyl chlorides to yield resin-bound **4**. The final cleavage with hydrazine afforded the target 1-aryl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones **5** (Scheme 1) as compounds with potentially



**Scheme 1** Solid-phase synthesis of 2,3-benzodiazepin-4-ones

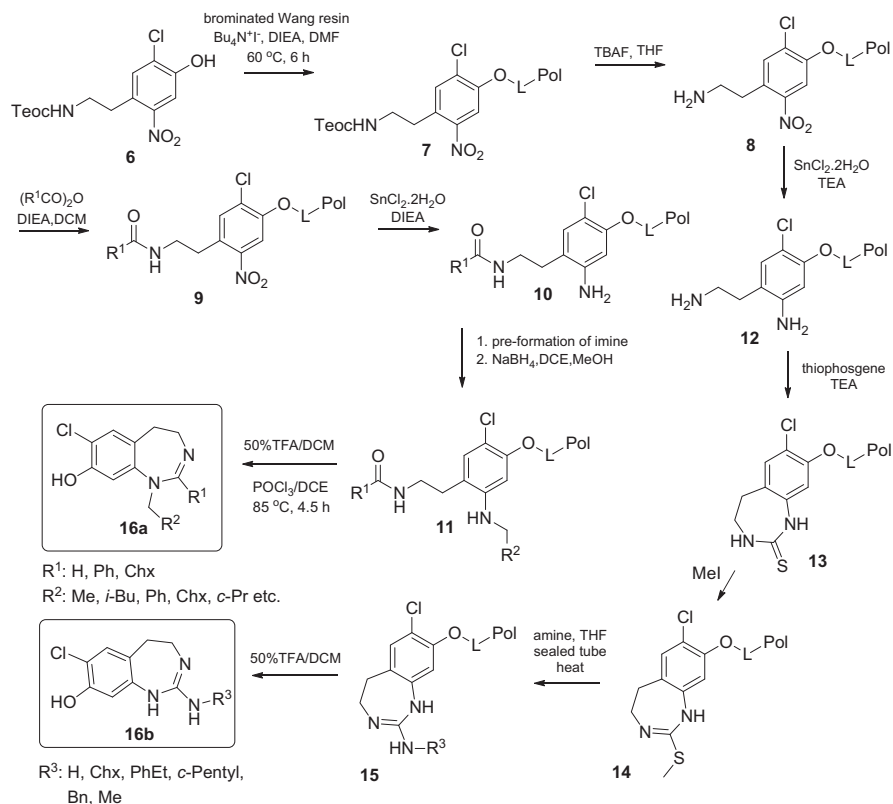
antiepileptic properties. The authors also attempted to synthesize 1-alkyl analogues of products **4**, successfully performing acylation with propionyl chloride. However, the cyclization with hydrazine did not give the desired 1-ethyl-2,3-benzodiazepin-4-ones.

### 3 1,3-Diazepines

#### 3.1 Benzo[d][1,3]diazepines

The preparation of 1,3-benzodiazepines as novel dopamine antagonists was described by Zhu et al. [16]. The phenolic building block **6** was attached to a brominated Wang resin, and after deprotection and acetylation of the amino group, the nitro derivative **9** was reduced to aniline **10** with tin(II)chloride dihydrate. The intermediate **10** was reductively alkylated and cleaved from the resin using trifluoroacetic acid (TFA). Cyclization of the final diazepines **16a** was accomplished in the solution phase using POCl<sub>3</sub> (Scheme 2). Similarly, solid-phase *N*-arylation chemistry using boronic acids and Cu(OAc)<sub>2</sub> was used to generate *N*<sup>1</sup>-arylbenzodiazepines [17]. Alternatively, intermediate **8** was reduced and cyclized with thiophosgene to give the cyclic thiourea **13**. Subsequent methylation, amination, and cleavage led to 2-amino-1,3-benzodiazepines **16b**.

In 2011, Yu et al. [18] reported the solid-phase synthesis of similar compounds based on a different approach. Methylbenzhydrylamine (MBHA) resin **17a** was acylated with diverse Boc-L-amino acids. After the protecting group was removed, resin **18** was acylated with 2-bromophenyl acetic acids, followed by the reduction of diamide **19** with BH<sub>3</sub>-THF. Cyclization with cyanogen bromide gave the monocyclic guanidine **21**. Target benzodiazepine derivatives **22** were obtained by treatment with Pd(OAc)<sub>2</sub>, Cu(OAc)<sub>2</sub>, and Cs<sub>2</sub>CO<sub>3</sub> in dimethylformamide (DMF)

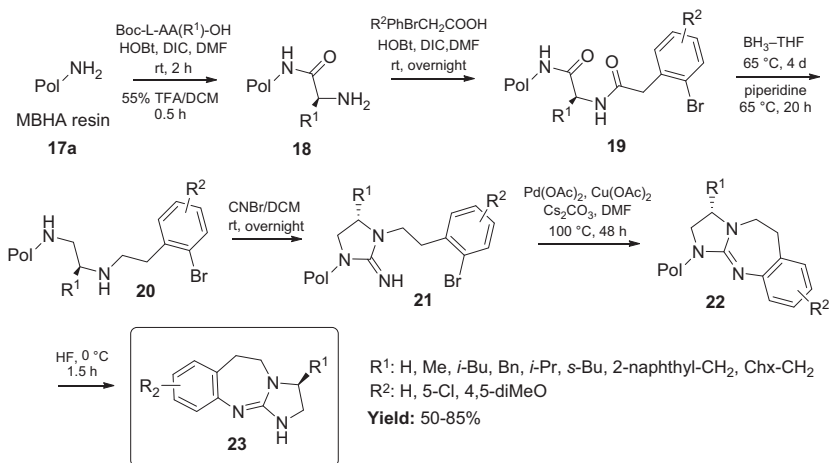


**Scheme 2** Solid-phase synthesis of 1,3-benzodiazepines

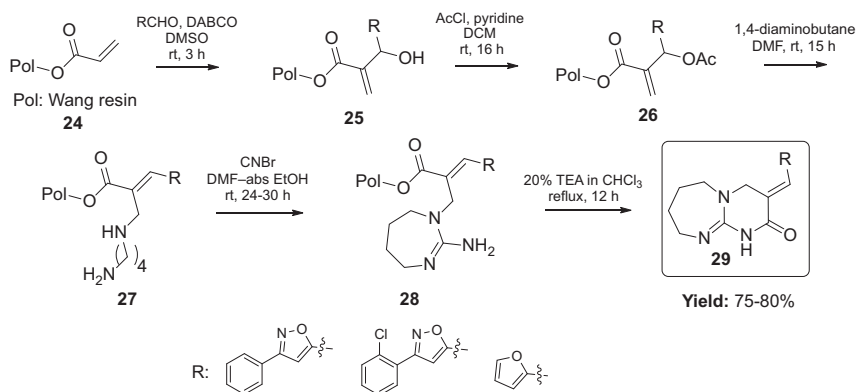
(Scheme 3). The reaction did not require any ligands or additives and was performed under air.

### 3.2 [1,3]Diazepines

The only reported solid-phase strategy to prepare 1,3-diazepine derivatives is based on the Baylis-Hillman reaction [19]. Wang resin **24** acylated with acryloyl chloride was subjected to reaction with aldehydes in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO). Baylis-Hillman adducts **25** were then converted to acetates **26** using acetyl chloride in pyridine. Subsequently, a Michael addition with 1,4-diaminobutane resulted in allyl amine derivatives **27**. After cyclization of the diazepine scaffold with cyanogen bromide, the cyclative cleavage induced with triethylamine (TEA) was performed to release the final products **29** from the resin (Scheme 4). NMR studies revealed the exclusive formation of E-isomers.



**Scheme 3** Solid-phase synthesis of 1,3-benzodiazepines via a Pd-catalyzed intramolecular coupling reaction

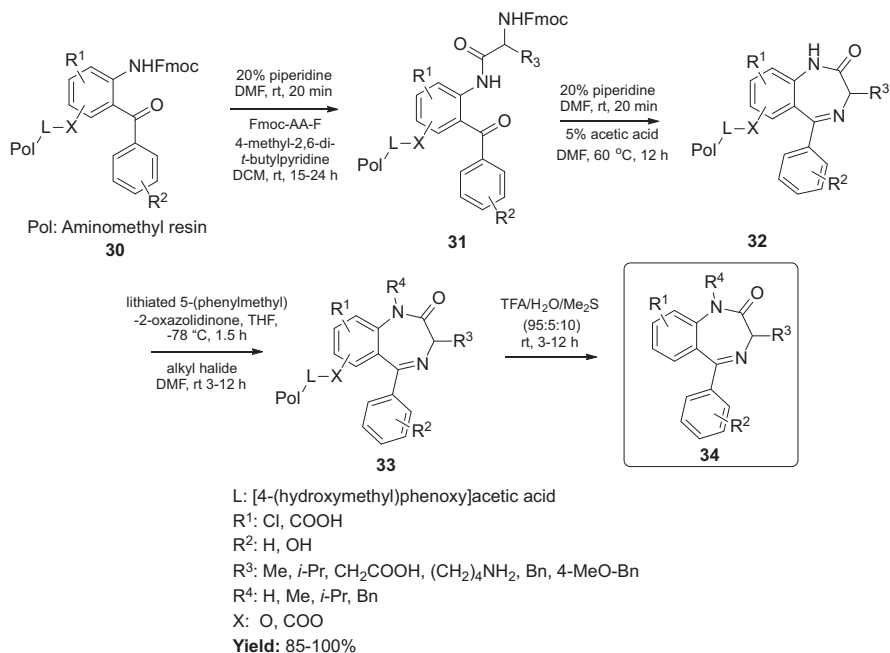


**Scheme 4** Solid-phase synthesis of 1,3-diazepines based on the Baylis-Hillman reaction

## 4 1,4-Diazepines

### 4.1 Dihydro-benzo[e][1,4]diazepin-2-ones

As previously mentioned, 1,4-benzodiazepines are the most frequently reported diazepines in solid-phase synthesis. The first contributions appeared in the early 1990s and were devoted to the preparation of 1,3-dihydro-2*H*-benzo[e][1,4]diazepin-2-ones, which are related to the structure of CNS benzodiazepine modulators. The pioneer in this field was Jonathan Ellman, who reported a solid-phase synthesis starting from 2-aminobenzophenones **30** attached to a polystyrene solid support through either a hydroxy or carboxylic acid functionality employing the

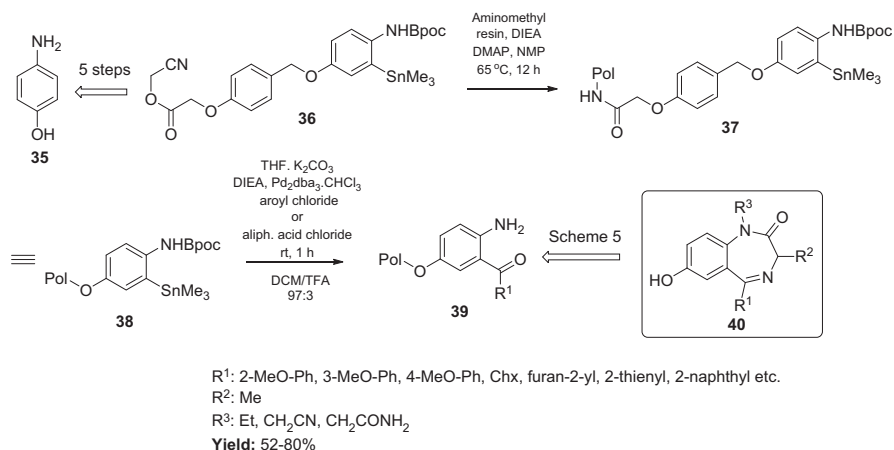


**Scheme 5** Synthesis of 1,4-benzodiazepines by Ellman

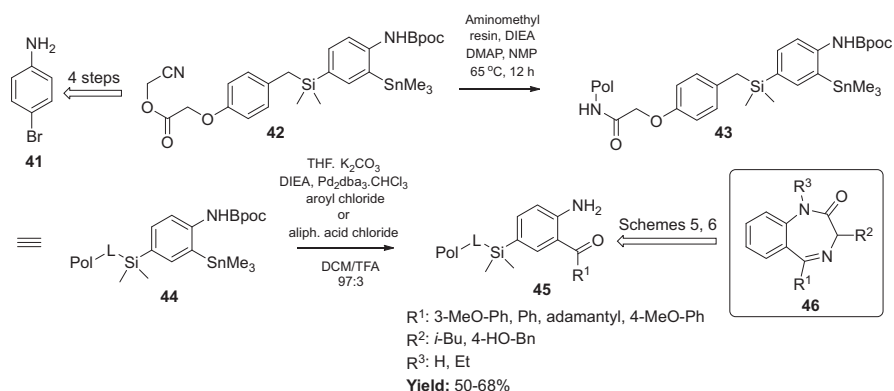
acid-cleavable linker [4-(hydroxymethyl)phenoxy]acetic acid [20]. After removal of the Fmoc-protecting group and acylation with Fmoc-amino acids, the ring closure to **32** was performed by heating the unprotected resin in diluted acetic acid. The fourth diversity position R<sup>4</sup> was created using alkyl halides, followed by the cleavage of final compounds **34** from the resin in very high yields (Scheme 5). Two years later, Ellman employed his strategy for the combinatorial synthesis of 192 structurally diverse benzodiazepines using Geysen's pin apparatus [21].

Despite the great diversity in the structure of the final compounds **34**, the disadvantage of this method from a combinatorial perspective is the limited availability of the starting compounds, 2-aminoaryl ketones, which must be pre-synthesized in the solution phase. To improve his initial method, Ellman developed a strategy applicable to the preparation of these building blocks directly on the solid phase [22]. The key intermediate **36** was synthesized from *p*-aminophenol **35** in five steps and was attached to an aminomethyl polystyrene resin (Scheme 6). The resin **37** was then subjected to Stille coupling with aryl- or alkyl chlorides. To minimize protodestannylation and premature carbamate deprotection, potassium carbonate and diisopropylethylamine (DIEA) were used as acid scavengers. The modification of intermediate **39** was continued according to the previously reported protocols (see Scheme 5). The developed strategy provides rapid access to a large number of diverse 2-aminoaryl ketone derivatives **39** from commercially available acid chlorides.



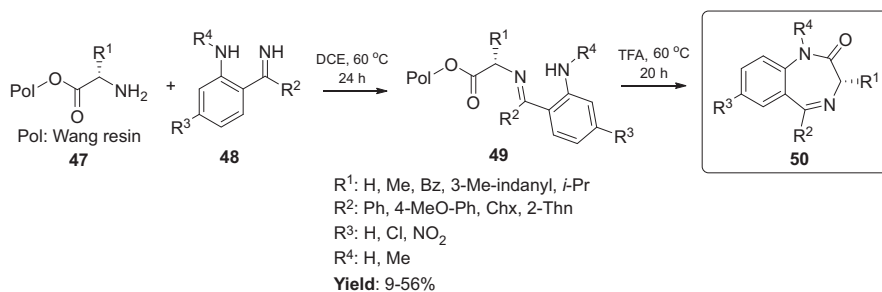


**Scheme 6** Preparation of 1,4-benzodiazepines via the solid-phase synthesis of aminoketone building blocks



**Scheme 7** Traceless synthesis of 1,4-benzodiazepines

Ellman further reported the preparation of 1,4-benzodiazepines in a traceless manner [23]. The incentive for the development of this alternative approach was that after cleavage from the solid support at the end of a synthesis sequence, the functional group resulting from the linker body (e.g., a hydroxy group, see Scheme 6) can have a negligible, positive or negative effect on the biological or chemical activity of the target molecule, depending on where it is situated. Therefore, silicon-based linker **42** was synthesized from 4-bromoaniline **41** in four steps (Scheme 7). After attaching the linker to the aminomethyl resin and completing the reaction sequence according to Schemes 5 and 6, the final compounds **46** were cleaved with either HF or TFA, leaving behind no trace or “memory” of the solid-phase synthesis. Later, silicon was replaced with germanium, resulting in an easy electrophilic



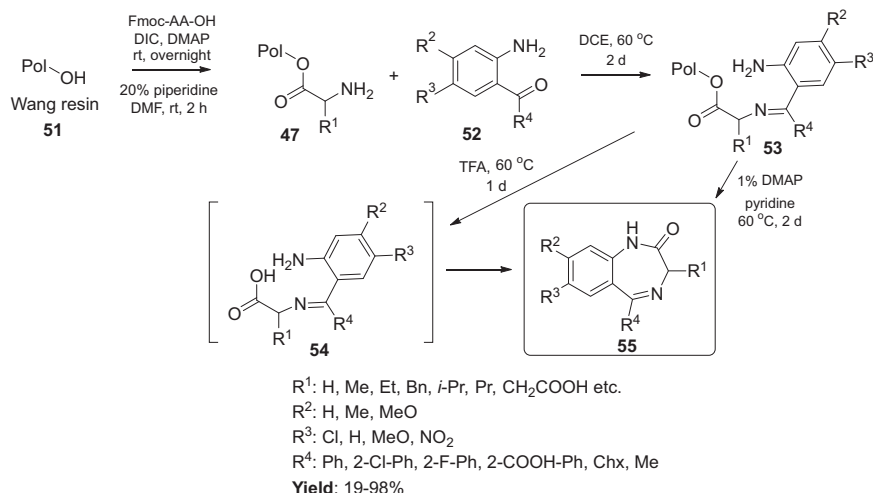
**Scheme 8** DeWitt's method for the solid-phase synthesis of 1,4-benzodiazepines

demetalation, which significantly increased the tolerance level of the sequence toward diverse functional groups [24].

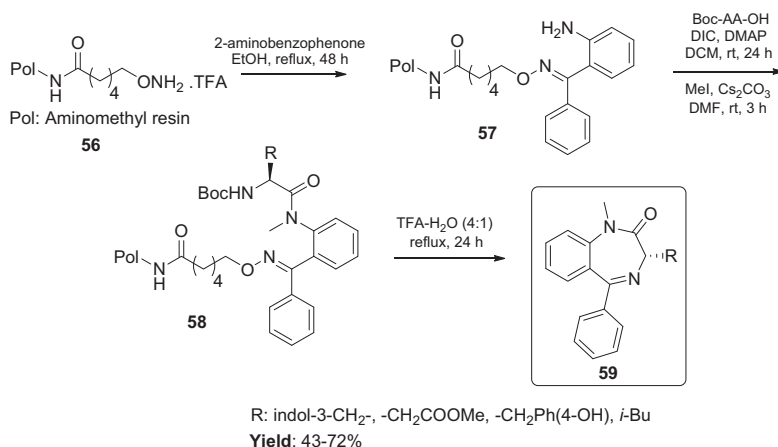
In 1993, DeWitt reported a three-step traceless synthesis of 1,4-benzodiazepines from polymer-supported amino acids **47** and 2-amino benzophenone imines **48** [25, 26]. To obtain the final compounds, resin **49** was treated with neat TFA at an elevated temperature, which caused the consecutive cleavage and cyclization to **50** (Scheme 8). Forty benzodiazepines were synthesized using this method and were isolated with a crude purity above 90%. A few years later, DeWitt's method was successfully utilized to introduce a novel polymer support derived from an ion exchange resin [27]. Furthermore, in 2007, Sams followed DeWitt's protocol employing a "catch and release" strategy [28]. To avoid the purification requirement of the crude imine building blocks **48**, a catch with polymer-supported amino acids **47** was applied, followed by washing the unreacted side products from the resin using *N*-methylpyrrolidone (NMP). To obtain the final benzodiazepines **50** in high purity, Sams modified the cleavage protocol and replaced TFA with acetic acid. In this way, the products were released from the resin only by the cyclative cleavage, thus avoiding the potential contamination of the final compounds with cleaved linear intermediates **49**.

Ellman's and DeWitt's approaches were combined by Lattmann in a project aimed at preparing 1,4-benzodiazepines for the cholecystokinin (CCK) radioligand binding assay [29]. The Wang resin **51** was acylated with various Fmoc-amino acids that upon reaction with aminoketones gave the imine resin **53**. The acid-mediated cleavage resulted in the final products **55** (Scheme 9). Alternatively, a cyclative cleavage method was applied using pyridine and 4-*N,N*-dimethylaminopyridine (DMAP) to trigger the reaction. The synthesis of 168 benzodiazepines was achieved from eleven ketones and fourteen amino acids in a combinatorial fashion employing Synphase crowns.

In 2010, the immobilization of aminoketone building blocks on the alkoxyamine linker **56** was reported [30]. In contrast to Lattmann's procedure, the starting polymer-supported amino acids were replaced with resin **57** (Scheme 10). The authors reported optimized procedures for *N*-alkylation and managed to increase the enantiomeric excess of the final products **59** to 99%



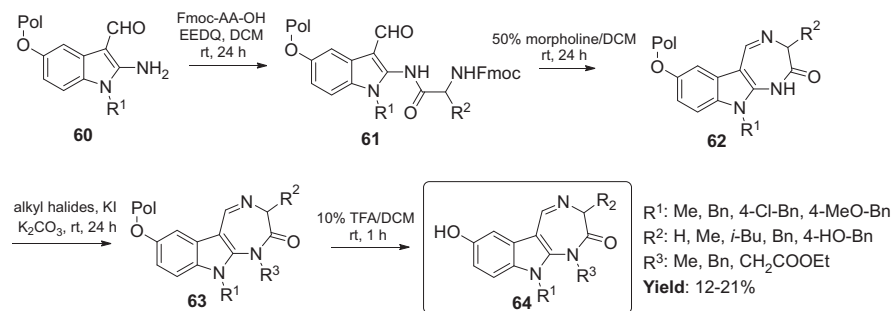
**Scheme 9** Combined Ellman and DeWitt approaches reported by Lattmann



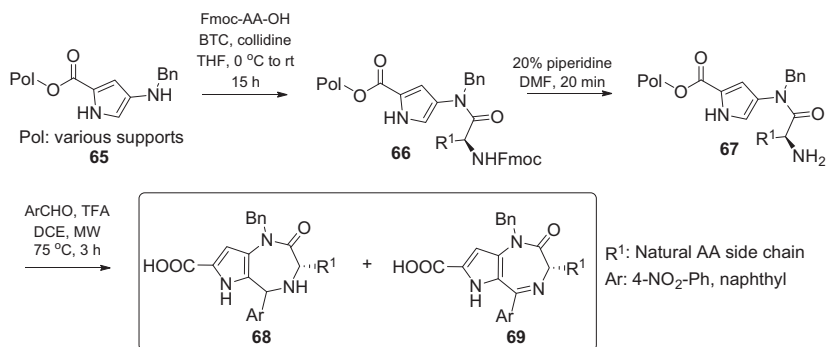
**Scheme 10** Solid-phase synthesis of 1,4-benzodiazepines employing an alkoxyamine linker

using (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) instead of DMAP in the acylation step.

The preparation of heterocyclic analogues of 1,4-benzodiazepines with a condensed indole instead of a benzene ring was reported by Lee [31]. The key intermediate **60** was synthesized from a polystyrene chlorotrityl resin and 2-chloro-3-formyl-5-hydroxyindole in four steps. After acylation with Fmoc-amino acids to give resin **61**, the Fmoc-cleavage was followed by spontaneous cyclization to yield the tricyclic products **62** (Scheme 11). Interestingly, the commonly used procedure employing a piperidine/DMF cocktail afforded the desired



**Scheme 11** Solid-phase synthesis of indole-diazepine-fused heterocycles



**Scheme 12** Solid-phase synthesis of pyrrole-diazepine-fused heterocycles

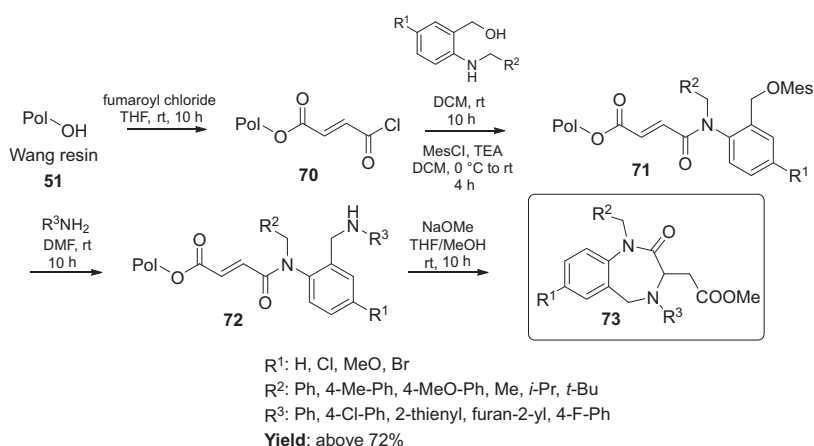
products in very low yield. Therefore, the cleavage of the Fmoc-protecting group was performed with 50% morpholine/DCM. Prior to the cleavage, the *N*<sup>1</sup>-alkylation was accomplished using alkyl halides.

In the field of research concerning dihydrobenzo[*e*][1,4]diazepin-2-one heterocyclic analogues, an interesting strategy for the preparation of compounds with a differential modulation of urotensin II receptor-mediated vasoconstriction was recently introduced by Lubell [32, 33]. As the key intermediate, resin-bound **65** was synthesized from immobilized 4-hydroxyproline. After acylation with Fmoc-amino acids and after Fmoc-protecting group cleavage, the final scaffold was obtained via the Pictet-Spengler cyclization using microwave heating with aldehydes (Scheme 12). The cyclization afforded a mixture of compounds **68** and **69** in variable ratios. The method was tested for different polymer supports (a Wang resin, a Merrifield resin, and a soluble TAP methylbiphenyl support), and the highest efficacy was reported for the Wang resin with average overall yields of 32%.

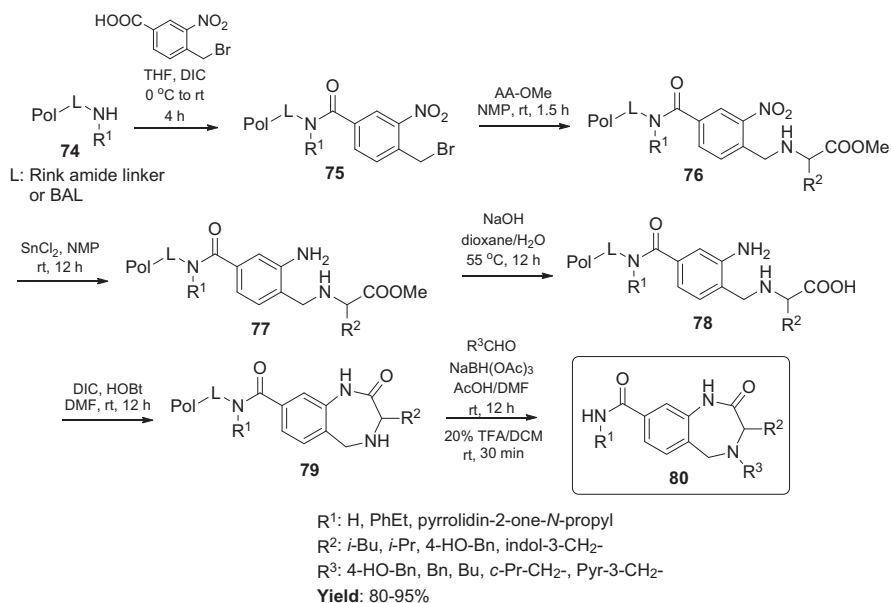
## 4.2 Tetrahydrobenzo[e][1,4]diazepin-2-ones

In addition to 1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-ones, considerable attention was also given to the solid-phase syntheses of their tetrahydro-analogues. The first contribution in this field was reported in 1997 by Bhalay et al. [34]. This approach was based on the acylation of Wang resin **51** with fumaroyl chloride, followed by the reaction of resin **70** with alcohols pre-synthesized from methyl anthranilates in two steps. After mesylation and reaction with various amines to give the polymer-supported intermediates **72**, the final compounds were obtained via cleavage and concomitant cyclization triggered by sodium methanolate (Scheme 13). This method was used to prepare 120 benzodiazepinones **73** by the combinatorial synthesis of twenty-four intermediates **71** and five amines  $R^3NH_2$ .

A different strategy was reported by Lou et al. [35]. Starting with the Rink amide resin or the reductively aminated BAL resin **74**, the reaction sequence continued by acylation with 4-(bromomethyl)-3-nitrobenzoic acid. Nucleophilic substitution with various amino acid methyl esters was performed followed by reduction of the nitro compounds **76** with  $SnCl_2$  and saponification of methyl esters **77**; then, the seven-membered ring was cyclized using the HOBt method (Scheme 14). Note that the direct cyclization of methyl ester **77** was not achieved, even under harsh reaction conditions. Prior to the acid-mediated cleavage from the resin, the third diversity position was introduced employing  $N^4$ -reductive alkylation with aldehydes. This method was also applicable to cyclic amino acid esters, such as proline methyl ester, to give structurally constrained tricyclic compounds. The same approach was later utilized by Ede to synthesize the benzodiazepines **80** on Synphase lanterns [36]. However, in contrast to Lou's procedure, the  $N^4$ -alkylation was performed with alkyl halides in the stage of linear intermediates **77**. Furthermore, the hydrophilicity of the polyamide support required an optimization of the



**Scheme 13** Synthesis of 1,4-benzodiazepines by Bhalay et al.

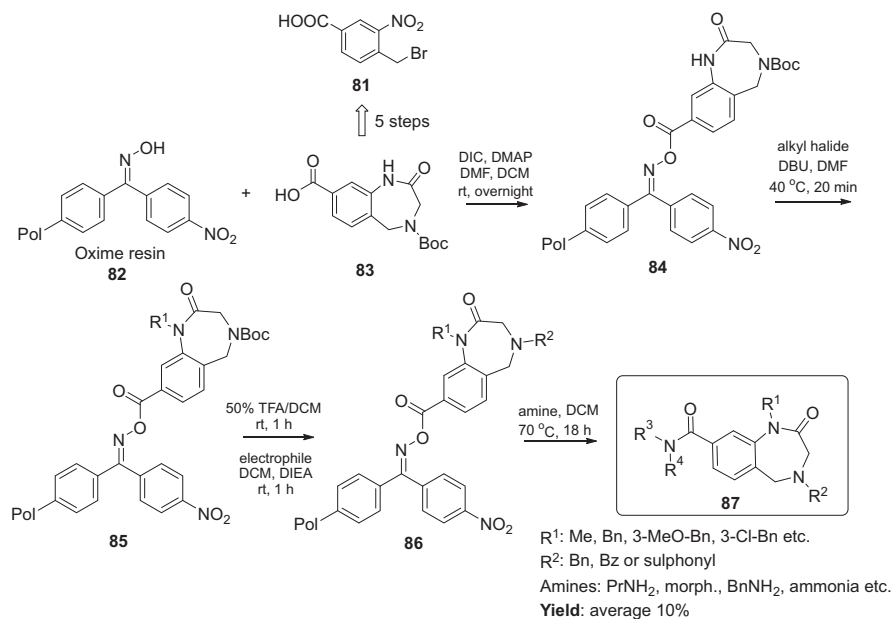


**Scheme 14** Preparation of benzodiazepines by Lou et al.

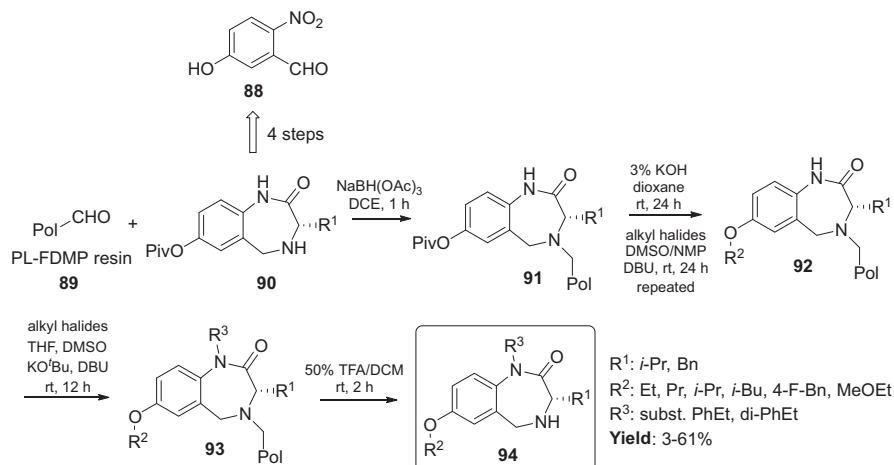
reduction step, revealing that the use of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}/\text{NH}_4\text{OAc}$  in a mixture of water and ethanol was the preferred method.

In 2003, Hone published an alternative method based on the combination of solution-phase/solid-phase chemistry [37]. First, the benzodiazepine *N*<sup>1</sup>-Boc-8-carboxylic acid **83** was synthesized in the solution phase according to Lou's procedure and was subsequently attached to the oxime resin **82**. *N*<sup>4</sup>-alkylation with alkyl halides was followed by the cleavage of the Boc-protecting group and *N*<sup>1</sup>-alkylation with various electrophiles. The aminolysis of resin **86** led to the release of the products from the resin, and the corresponding carboxamides **87** were obtained (Scheme 15). The authors claimed the use of this method for the preparation of a chemical library containing more than 1,300 compounds.

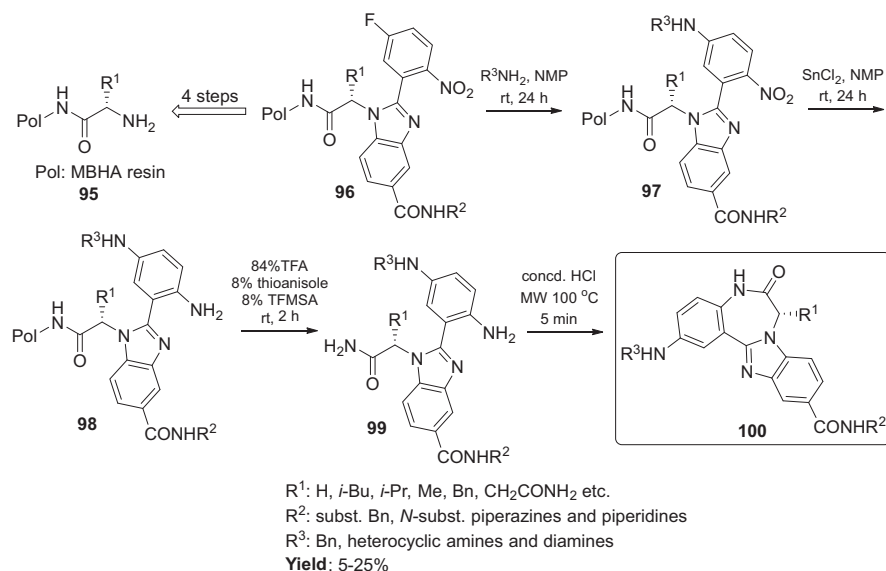
Kim reported the synthesis of  $\beta$ -turn mimetics based on the immobilization of the benzodiazepine building block and its subsequent modification on the solid phase [38]. The benzodiazepine derivative **90** was pre-synthesized in the solution phase in four steps from 2-nitro-5-hydroxybenzaldehyde **88**. After the attachment of **90** to the 4-formyl-3,5-dimethoxyphenoxy (PL-FDMP) resin **89** by reductive amination, the pivaloyl intermediate **91** was unmasked and alkylated with alkyl halides employing  $\text{LiO}^t\text{Bu}$  as a base (Scheme 16). The final compounds **93** were released from the resin using TFA, and the crude products were passed through strong anion exchange (SAX) resins to remove TFA. Later, the method was used for the combinatorial synthesis and biological evaluation of the peptide-binding GPCR-targeted library of 162 discrete compounds [39].



**Scheme 15** Combined synthesis of benzodiazepines by Hone et al.



**Scheme 16** Synthesis of 7-alkoxy-4-arylalkyl-1,3,4,5-tetrahydro-benzo[*e*][1,4]-diazepin-2-one by Kim et al.



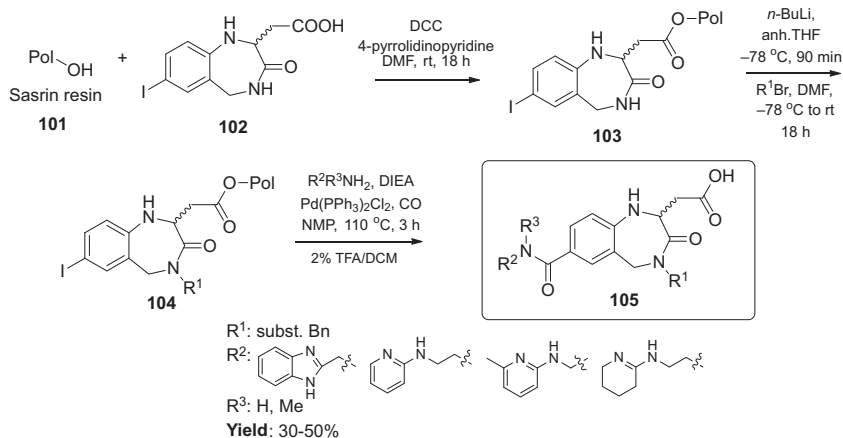
**Scheme 17** Benzo[*e*][1,4]diazepin-2-ones fused with benzimidazole scaffolds

The latest contribution devoted to the solid-phase synthesis of tetrahydrobenzo[*e*][1,4]diazepin-2-ones was made by Olsson in 2009 [40]. In a project aimed at novel non-peptidergic MrgX1 and MrgX2 receptor agonists, the preparation of tetracyclic derivatives **100** containing the benzodiazepinone scaffold was developed. Starting from amino acids immobilized on a MBHA resin, polymer-supported benzimidazole intermediates **96** were synthesized in four steps. After replacement of the fluorine substituent with amines followed by the reduction of the nitro group, the linear intermediates **99** were cleaved from resin **98**, and the benzodiazepinones **100** were achieved by short microwave heating in concentrated HCl (Scheme 17). The authors also developed a solution-phase protocol, but the solid-phase alternative was considered superior because the former process required the time-consuming purification of reaction intermediates, which led to significantly reduced yields. The solid-phase strategy was utilized to prepare a chemical library of 500 compounds and to synthesize selected hits in gram quantities.

### 4.3 Tetrahydrobenzo[*e*][1,4]diazepin-3-ones

The immobilization and solid-phase modification of the 1,4-benzodiazepine-3-one scaffold was reported by Ali with a focus on selective  $N^4$ -alkylation [41]. Carboxylic derivative **102** was attached to super acid-sensitive resin (Sasrin) **101** to avoid





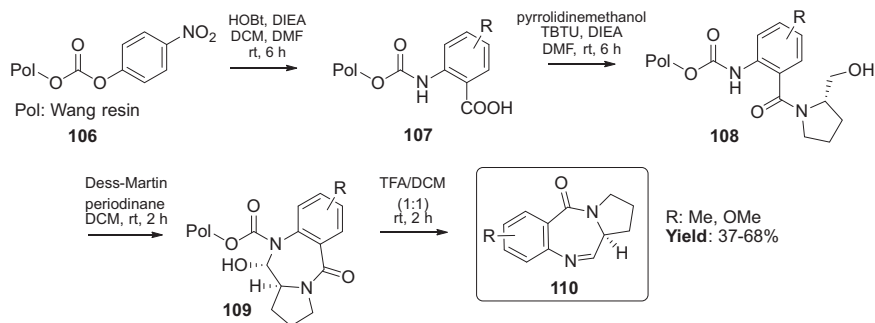
**Scheme 18** Regioselective solid-phase  $N^4$ -alkylation reported by Ali et al.

benzodiazepine scaffold decomposition due to exposure to strong acids. After selective  $N^4$ -benzylation with diverse benzyl bromides, the resin **102** was subjected to Heck coupling, and the final compounds **105** were released from the resin using 1–2% TFA (Scheme 18).

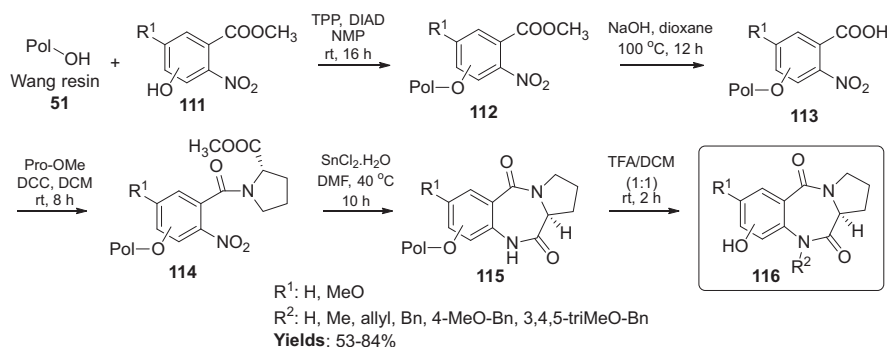
#### 4.4 Pyrrolobenzodiazepines

Pyrrolobenzodiazepines are antibiotic antitumor agents produced by various *Streptomyces* species. These agents bind selectively in the minor groove of DNA via a covalent aminal bond between the  $C^{11}$  position of the scaffold and the nucleophilic  $C^2$  amino group of a guanine base, resulting in the observed biological activity [42]. For this reason, pyrrolobenzodiazepines were targeted by medicinal chemists, and numerous contributions devoted to their solid-phase synthesis were reported. The first study was published in 2000 by Thurston, targeting 5-oxo derivatives. The first step involved coupling anthranilic acids to the *p*-nitrophenyl carbonate Wang resin **106** (Scheme 19). The intermediate **107** was coupled with pyrrolidinemethanol to give resin **108**. Following the Dess-Martin oxidation of the hydroxy group, the resin **109** was subjected to cleavage with TFA, and final compounds **110** were isolated [43].

One year later, Kamal reported a method applicable for the preparation of the corresponding 5,11-diones **116** [44]. Instead of anthranilic acids, methyl esters of 2-nitrobenzoic acids were attached to Wang resin **51** via an ether group. After saponification of ester **112**, the polymer-supported carboxylic acids **113** were used for the acylation of L-proline methyl ester (Scheme 20). Reduction of the nitro derivatives **114** led to the formation of the desired scaffold. Prior to acid-mediated



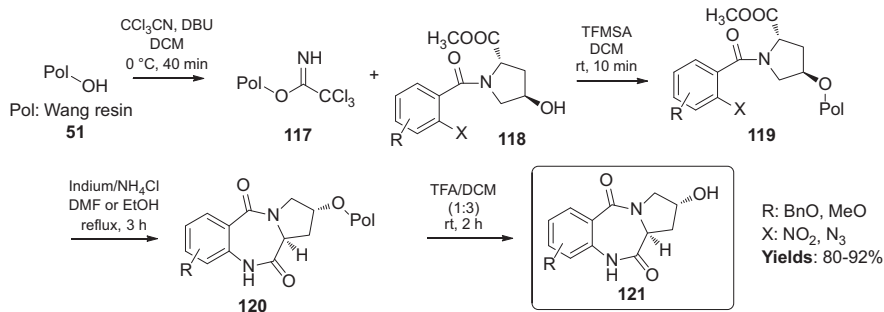
**Scheme 19** Preparation of pyrrolobenzodiazepine-5-ones by Thurston



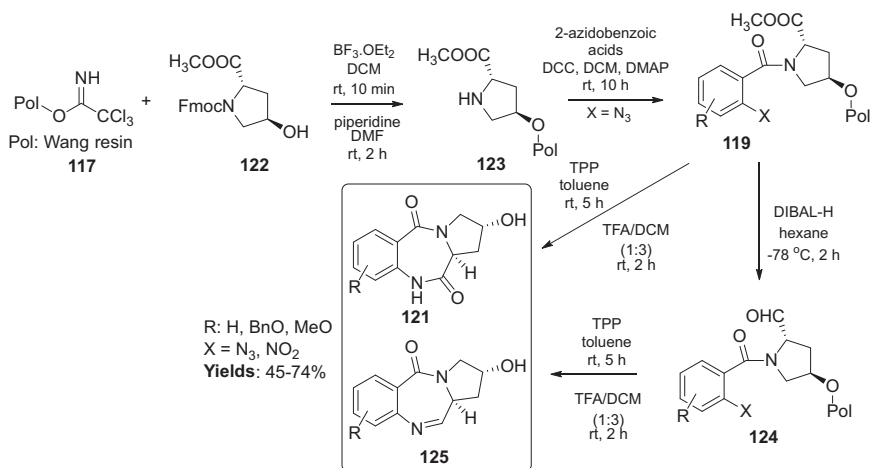
**Scheme 20** Preparation of pyrrolobenzodiazepine-5,11-diones by Kamal

cleavage, the second diversity position was created via  $N^{10}$ -alkylation with alkyl halides.

Simultaneously, Kamal published an alternative approach consisting of immobilizing the building block **118** via the hydroxy group employing the trichloroacetimidate method (Scheme 21) [45]. Further, reduction with tin(II)chloride dihydrate was replaced with In/NH<sub>4</sub>Cl. Despite the advantages of tin reduction, there are examples in the literature wherein substantial quantities of tin by-products remain bound within the resin matrix and are liberated upon acidic cleavage of the desired product [46]. Furthermore, most of the biologically screened cell lines have been shown to be intolerant to tin at these levels. To remove the excess indium, resin **120** was rinsed with water, ethanol, DMF, and DCM. Note that the indium method was also applicable for azido analogues (Scheme 21, X = N<sub>3</sub>). In 2009, Santos reported the reductive cyclization of resin **119** with Ni<sub>2</sub>B. After microwave irradiation, the products **121** were obtained in good yields, ranging from 64 to 81%, requiring low reaction times [47].

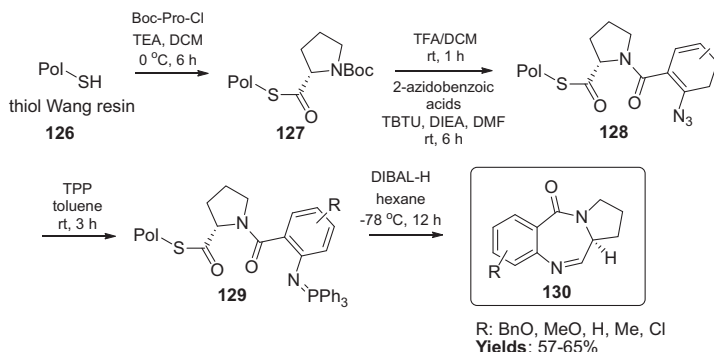


**Scheme 21** Preparation of pyrrolobenzodiazepine-5,11-diones via the immobilization of the benzoylproline intermediate

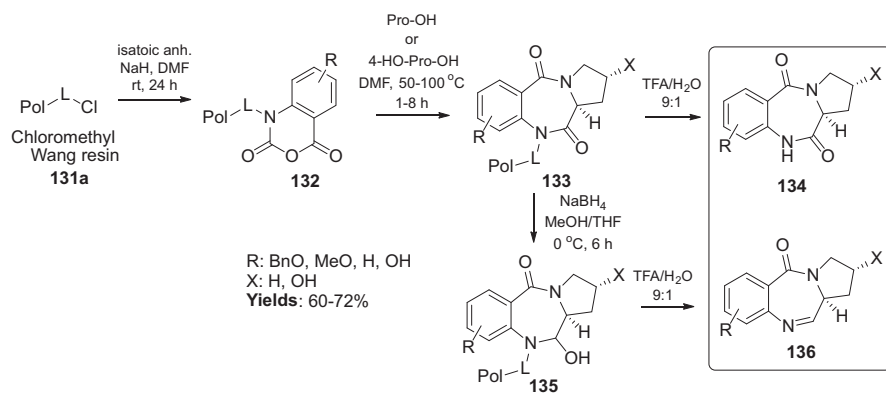


**Scheme 22** Preparation of pyrrolobenzodiazepine-5,11-diones and pyrrolobenzodiazepine-5-ones via reduction with TPP

To avoid the necessary solution-phase pre-synthesis of intermediates **118** (Scheme 21), the reaction sequence was further modified employing 4-hydroxy-Fmoc-Pro methyl ester as the building block [48]. After immobilizing 4-hydroxy-Fmoc-Pro methyl ester on the modified Wang resin **117** and after cleavage of the Fmoc-protecting group, resin **123** was acylated with 2-azidobenzoic acid. Reduction with triphenylphosphine (TPP) followed by TFA cleavage afforded the pyrrolobenzodiazepine-5,11-diones **121**. Alternatively, reduction of methyl ester **119** with diisobutylaluminum hydride (DIBAL-H) led to the corresponding aldehydes **124**, which furnished pyrrolobenzodiazepine-5-ones **125** (Scheme 22) upon reduction with TPP. Later, reduction with TPP was successfully replaced with  $\text{Al/NiCl}_2 \cdot 6\text{H}_2\text{O}$  and  $\text{Al/NH}_4\text{Cl}$  [49]. As reported, reduction with  $\text{Al/NiCl}_2$  was faster than that with  $\text{Al/NH}_4\text{Cl}$ , proceeding at room temperature and affording higher yields. Additionally, the reduction method was successfully applied to the corresponding nitro analogues **119** ( $\text{X} = \text{NO}_2$ ). In 2006, Kamal introduced an



**Scheme 23** Preparation of pyrrolobenzodiazepine-5-ones by reductive cleavage

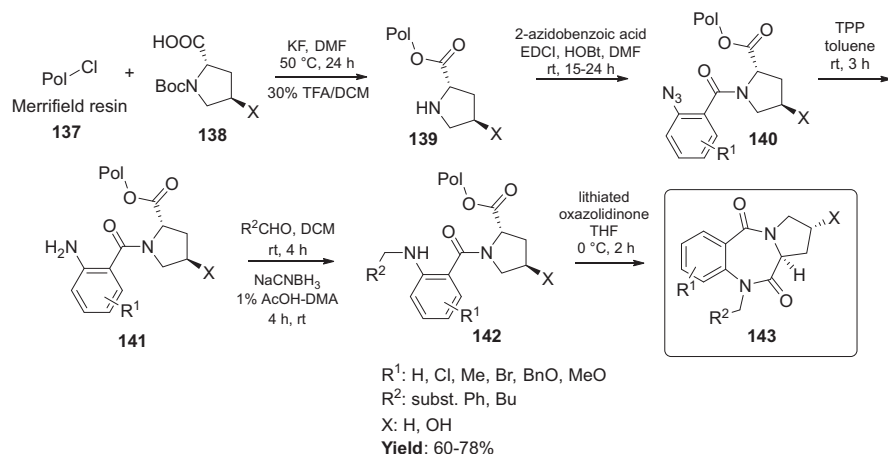


**Scheme 24** Preparation of pyrrolobenzodiazepines from polymer-supported isatoic anhydrides

alternative reduction of azido intermediates with boron trifluoride diethyletherate and ethanethiol [50]. The same author reported direct conversion of intermediates **119** to products **121** employing an azido-reductive cyclization approach using AlCl<sub>3</sub> in combination with NaI [51].

When thiol Wang resin **126** was used in combination with Boc-Pro-Cl, the proline intermediate was attached to the resin as the thioester **127** [52]. After cleavage of the Boc-protecting group followed by acylation with 2-azidobenzoic acids, the corresponding iminophosphoranes **129** were obtained using TPP. Treatment of resin **129** with DIBAL-H resulted in the reductive cleavage to release the final compounds **130** from the resin, which could be reused for the preparation of intermediate **127** (Scheme 23).

In addition to anthranilic and 2-nitrobenzoic acids, immobilized isatoic anhydrides **132** were also used to construct the pyrrolobenzodiazepine scaffolds **134**. *N*-alkylation of isatoic anhydrides with chloromethyl Wang resin **131a** was followed by reaction with proline, which directly furnished the polymer-supported pyrrolobenzodiazepine-5,11-diones **133** (Scheme 24). Later, the same strategy



**Scheme 25** Preparation of pyrrolobenzodiazepine-5,11-diones via cyclative cleavage with lithiated 5-phenyl-2-oxazolidinone

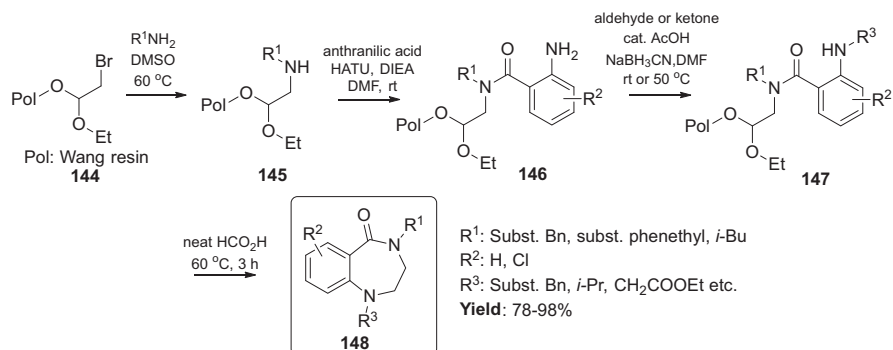
was applied for the preparation of analogical benzodiazepinones bearing thiophene instead of a benzene ring, with the corresponding thieno-oxazine-2,4(1*H*)-dione as the key building block [53]. Furthermore, to access pyrrolobenzodiazepine-5-ones, resin **133** was subjected to reduction with  $\text{NaBH}_4$  or  $\text{LiBH}_4$ , followed by the acid-mediated dehydration and cleavage from resin **135** to give derivatives **136**. The isatoic anhydride method was later applied by Waldmann for a solution-phase synthesis of the selected pyrrolobenzodiazepine-5,11-dione, which was immobilized on a chlorotriptyl resin and modified to mimic the lipidated C-terminus of the H-Ras protein [54].

The largest chemical library of 210 pyrrolobenzodiazepinediones was reported in 2007 to study antitubercular activity of target compounds [55]. Employing Merrifield resin **137** and Boc-Pro-OH or 4-hydroxy-Boc-Pro-OH **138**, the intermediates **139** were synthesized in a similar manner to the previously described protocols. Reductive alkylation of anilines **141** was followed by treatment of the resin with lithiated 5-phenyl-2-oxazolidinone to afford the desired products **143** (Scheme 25). Although a variety of different bases, such as  $\text{K}_2\text{CO}_3$ ,  $\text{KO}^t\text{Bu}$ , or  $\text{NaOMe}$ , also triggered the cyclative cleavage, the oxazolidine method gave the best results.

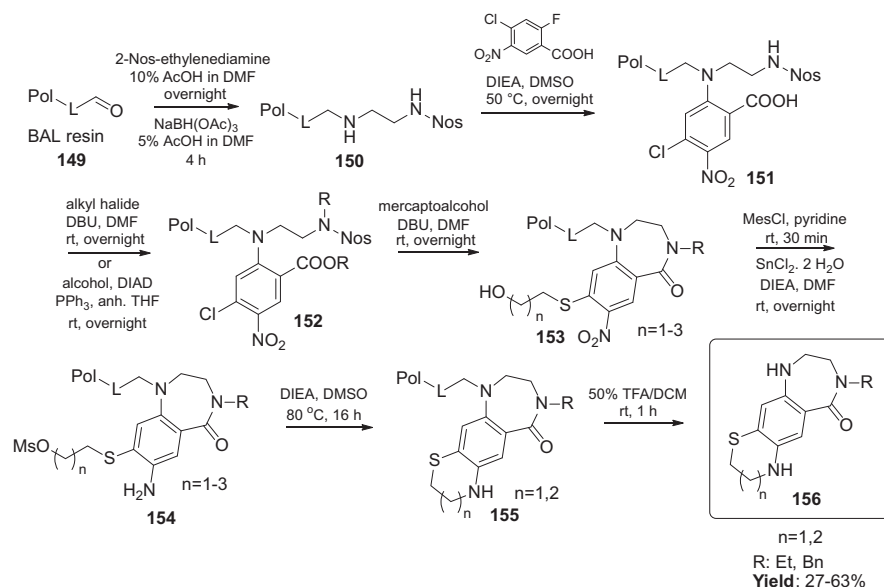
Similar approaches to those described above were used for the solid-phase synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine dimers [56] or pyrrolobenzodiazepine-chalcone conjugates [57].

## 4.5 Benzo[*e*][1,4]diazepin-5-ones

The solid-phase synthesis of benzo[*e*][1,4]diazepin-5-ones was first reported by Park in 2007 [58]. Starting from bromoacetal resin **144**, primary amines were



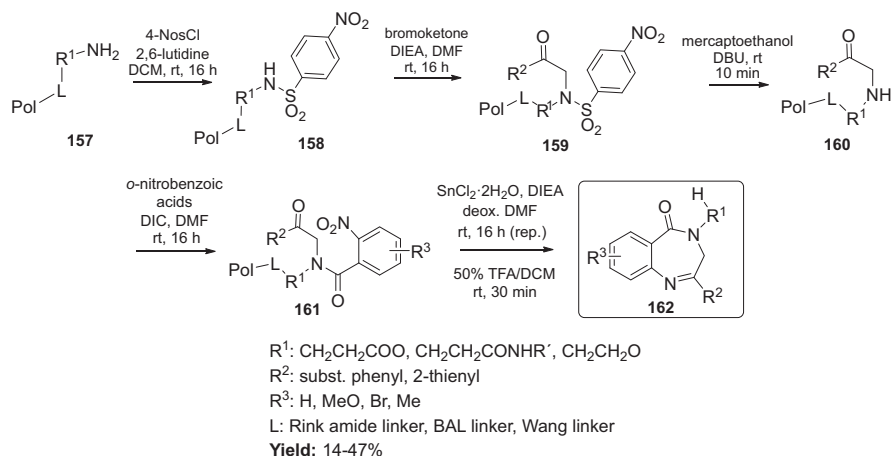
**Scheme 26** Preparation of benzo[*e*][1,4]diazepin-5-ones using the Leuckart-Wallach reaction



**Scheme 27** Preparation of benzo[*e*][1,4]diazepin-5-ones using polymer-supported ethylenediamine

immobilized and acylated with anthranilic acids. After reductive alkylation of resin **146**, the target benzodiazepines **147** were formed by the Leuckart-Wallach reaction (Scheme 26). The robustness and practicality of the synthetic pathway were validated by the successful construction of a 96-member pilot library with excellent overall yields and purities.

In 2012, an alternative method was reported starting from Nos-protected ethylenediamine immobilized by the reductive amination of BAL resin **149** [59]. Intermediate **150** was arylated with 2-fluoro-4-chloro-5-nitrobenzoic acid, followed by the alkylation of resin **151**, which led to parallel esterification of the

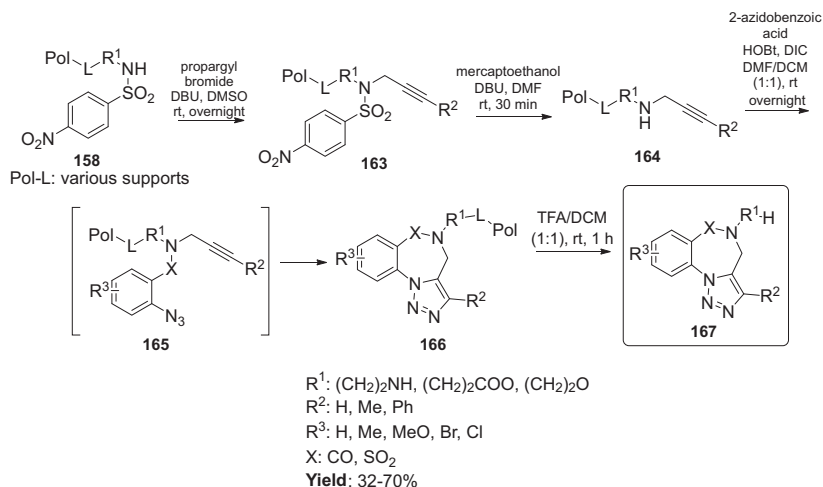


**Scheme 28** Preparation of benzo[*e*][1,4]diazepin-5-ones from bromoketones and 2-nitrobenzoic acids

carboxylic group and isolation of resin-bound **152**. A reaction with mercaptoalcohols released the Nos-protecting group, which caused the spontaneous ring closure of benzodiazepine **153** (Scheme 27). Subsequently, the fused heterocycles **156** were prepared via mesylation and reduction of the nitro derivative **153**. The final cyclization of polymer-supported intermediates **154** was successful only for six- and seven-membered rings, whereas the corresponding thiazocines ( $n = 3$ ) were not detected.

In the same year, the preparation of 3,4-unsaturated benzo[*e*][1,4]diazepin-5-ones **162** was reported [60]. Various polymer-supported amines **157** were reacted with 4-nitrobenzenesulfonyl chloride (4-Nos-Cl) and subjected to alkylation with bromoketones. Cleavage of the 4-Nos derivatives **159** enabled acylation of the resulting aminoketones **160** with 2-nitrobenzoic acids. Note that the acylation step resulted in partial cleavage of the phenacyl group. After reduction of the nitro derivative **161**, the seven-membered scaffold was spontaneously formed on the resin, and the final acid-mediated cleavage afforded the target benzodiazepines **162** (Scheme 28). The use of 2-nitrobenzenesulfonyl chlorides (2-Nos-Cl)s resulted in intermediate **159** with the nitro group in the *o*-position, and then, reduction and cyclization afforded the corresponding benzothiadiazepine 1,1-dioxide derivatives [61]. Furthermore, employing 2-Nos-Cl)s and benzothiadiazepine 1,1-dioxides was recently obtained from polymer-supported  $\alpha$ -amino acids using alcohols as the building blocks for the Fukuyama-Mitsunobu  $N^2$ -alkylation [62].

The previously mentioned method was further modified to prepare triazolobenzodiazepinones and triazolobenzothiadiazepine 1,1-dioxides [63]. Starting from the intermediates **158**, the alkylation with propargyl bromides was performed. Cleavage of the Nos group followed by the acylation of resin **164** with 2-azidobenzoic acids led to a spontaneous, catalyst-free Huisgen 1,3-dipolar reaction that yielded triazole derivatives **166** (Scheme 29,  $\text{X} = \text{CO}$ ). When



**Scheme 29** Solid-phase synthesis of benzotriazolo[1,4]diazepin-6(5H)-ones and their sulfonyl analogues

2-azidobenzoic acids were replaced with 2-azidobenzenesulfonyl chloride, the corresponding thiadiazepine-1,1-dioxides were obtained ( $\text{X} = \text{SO}_2$ ). A similar reaction was described to prepare *N*-unsubstituted triazolobenzodiazepinones with basic alumina as the solid support. However,  $\text{Cu}(\text{phen})(\text{PPh}_3)\text{Br}$  was required as the catalyst to trigger triazole formation [64].

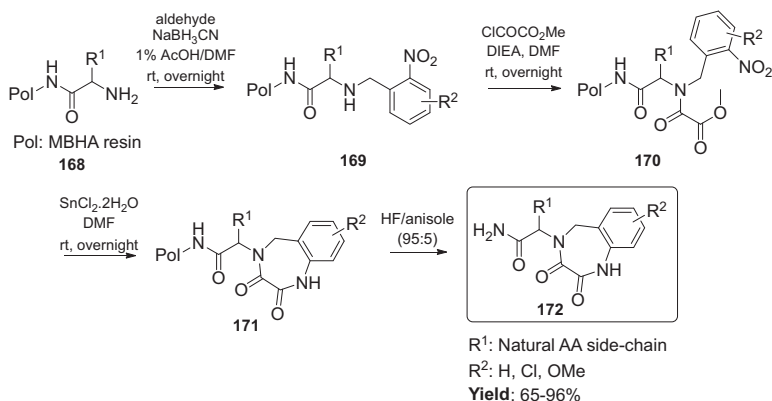
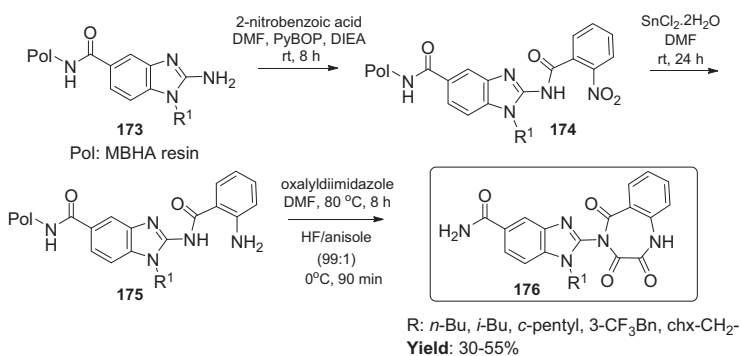
#### 4.6 Benzo[*e*][1,4]diazepine-2,3-diones

Starting from a MBHA resin with immobilized amino acids **168**, benzo[*e*][1,4]diazepine-2,3-diones **172** were synthesized in four steps [65]. First, reductive alkylation with benzaldehydes was performed. The immobilized secondary amines **169** were then treated with methyl chlorooxoacetate to provide the corresponding resin-bound methyl aminooxoacetate **170**. After reduction of the nitro group, benzodiazepine derivatives **171** were spontaneously formed on the resin (Scheme 30). This method was successfully used for the preparation of a chemical library consisting of 200 compounds with yields ranging from 65 to 96%.

#### 4.7 Benzo[*e*][1,4]diazepine-2,3,5-triones

In 2015, Nefzi reported the preparation of benzo[*e*][1,4]diazepine-2,3,5-triones tethered with a benzimidazole moiety [66]. Similar to the construction of the

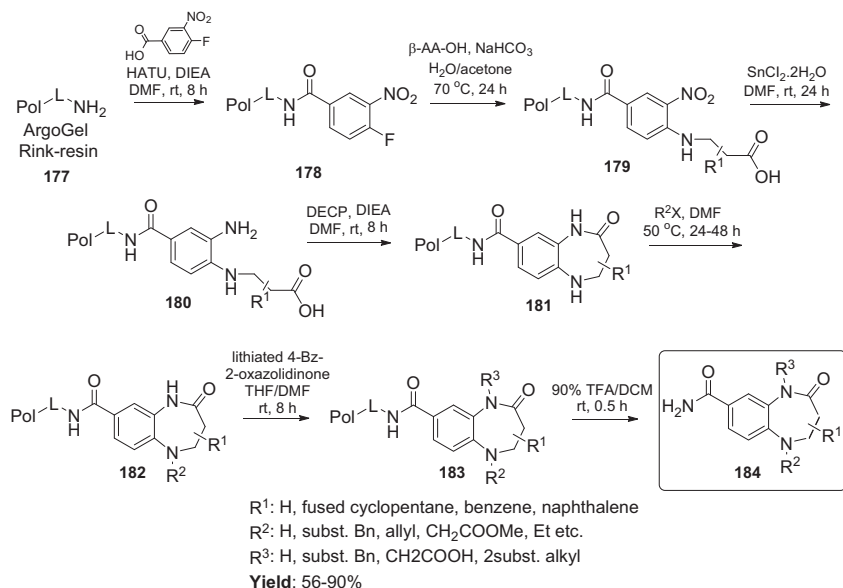


**Scheme 30** Solid-phase synthesis of benzo[*e*][1,4]diazepine-2,3-diones**Scheme 31** Solid-phase synthesis of benzo[*e*][1,4]diazepine-2,3,5-triones

benzodiazepinone-2,3-dione scaffold (see Sect. 4.6), an oxalic acid derivative was used to access the seven-membered ring. To prepare linear intermediates **175**, the 2-aminobenzimidazole resin **173** was acylated with 2-nitrobenzoic acid, followed by the reduction of the nitro group. Treatment with oxalyl diimidazole furnished the final bisheterocycles **176** that were cleaved from the resin using HF (Scheme 31). Alternatively, intermediate **175** was reacted with 1,1-carbonyldiimidazole to generate the isocyanate derivative, which underwent intramolecular cyclization to furnish the resin-bound quinazoline-2,4-diones.

#### 4.8 Benzo[*b*][1,4]diazepin-2-ones

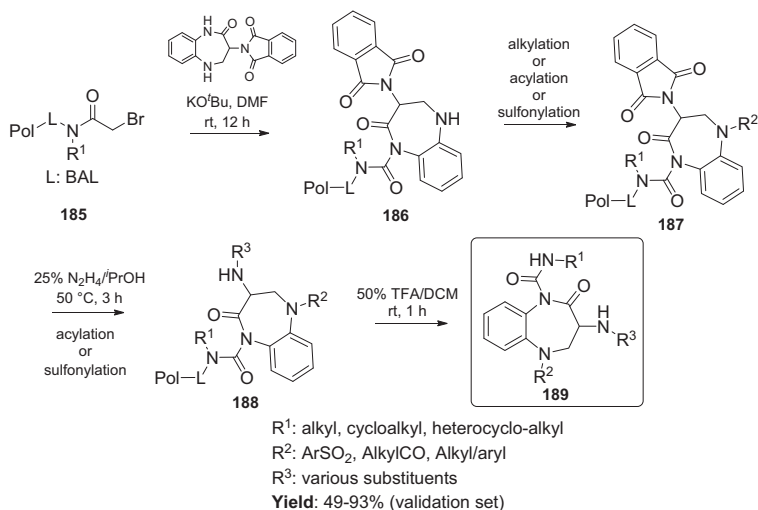
The first solid-phase synthesis of benzo[*b*][1,4]diazepin-2-ones was reported by Schwarz [67]. ArgoGel-Rink-resin **177** was acylated with 4-fluoro-3-nitro-benzoic



**Scheme 32** Solid-phase synthesis of benzo[*b*][1,4]diazepin-2-ones by Schwarz

acid, and resin **178** was subjected to nucleophilic substitution with  $\beta$ -amino acids. After the reduction of the nitro group, the benzodiazepine scaffold was obtained by the cyclization of intermediate **180** using diethyl cyanophosphonate (DECP). The resin was subsequently  $N^1/N^4$  dialkylated to give the final resin-bound product **183** (Scheme 32). The alkyl halides for  $N^4$  encompassed over forty benzyl bromides, allyl bromides, and bromoacetic acid esters, as well as methyl and ethyl iodide. However, other alkyl iodides, along with benzyl chlorides and  $\alpha$ -bromoacetophenones, did not exhibit satisfactory results. The  $N^1$ -alkylation was accomplished using alkyl halides with lithiated 4-benzyl-2-oxazolidinone as a base. From the spectroscopic data of the final products, no evidence was found for C- and/or O-alkylation. In 1999, the same approach was reported by Lee, with an application of the Rink amide resin and  $\beta$ -amino acid methyl esters [68]. Note that the authors did not manage to cyclize the benzodiazepine scaffold via the intramolecular aminolysis of the ester functionality; therefore, the subsequent hydrolysis and HOBt cyclization had to be performed. However, the on-resin cyclization with ethyl ester was successfully performed by heating in TFA when soluble PEG resin was used as the polymer support [69].

In 2000, Herpin reported the preparation of a large chemical library (10,000 compounds) based on the immobilization of the (benzo[*b*][1,4]diazepin-3-yl) isoindoline-1,3-dione building block via its  $N^1$  position [70]. Alkylation of the  $N^4$  position was followed by the cleavage of the phthalimide **187** and acylation of the primary amino group to give the final trisubstituted products **189** (Scheme 33).



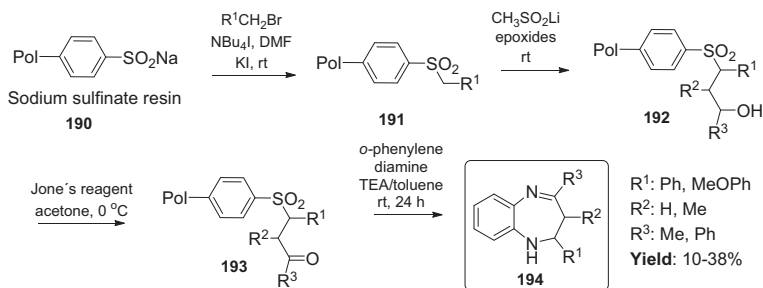
**Scheme 33** Immobilization and on-resin modification of benzo[*b*][1,4]diazepin-2-one scaffold by Herpin et al.

Finally, the preparation of benzo[*b*][1,4]diazepin-2-ones was reported by Kidway from *o*-phenylenediamines and  $\alpha,\beta$ -unsaturated carboxylic acids employing acidic alumina as the solid support [71].

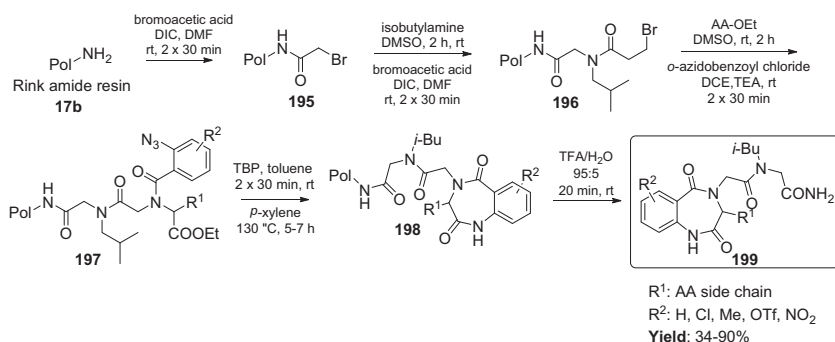
#### 4.9 Benzo[b][1,4]diazepines

The use of polystyrene/1% divinylbenzene sodium sulfinate **190** enabled the preparation of different heterocycles, including 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines [72]. Alkylation followed by the reaction of resin **191** with epoxides led to secondary alcohols **192**, which upon oxidation with Jones reagent, gave the key intermediates **193**. The reaction of these intermediates with *o*-phenylenediamine in toluene in the presence of TEA yielded the product **194** in 10–38% overall yield (Scheme 34). Although the reaction using KOH/ethanol, KOH/DMA, or KOH/DMF instead of TEA/toluene proceeded more rapidly, it gave poorer yields. Four compounds were prepared in this manner.

Recently, the reaction of *o*-phenylenediamine and  $\alpha$ -oxo ketene dithioacetals with basic alumina as the solid support to prepare benzo[*b*][1,4]diazepines was reported by Bhagat [73].



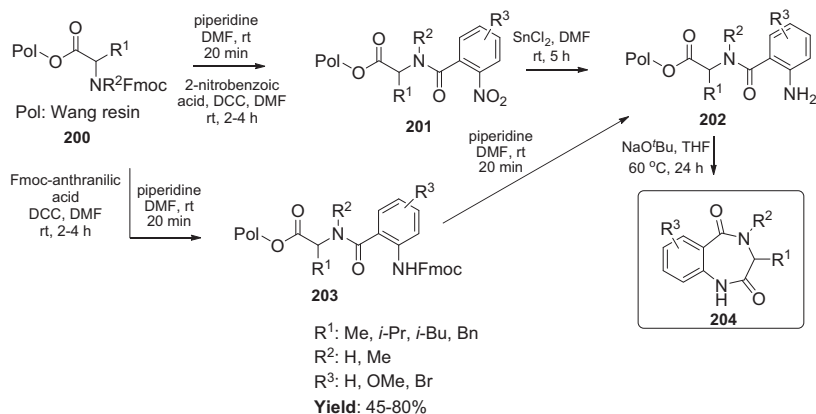
**Scheme 34** Use of a sodium sulfonate resin for the preparation of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines



**Scheme 35** The first solid-phase synthesis of benzo[*e*][1,4]diazepine-2,5-diones

#### 4.10 Benzo[*e*][1,4]diazepine-2,5-diones

Along with the 1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-ones discussed in Sect. 4.1, benzo[*e*][1,4]diazepine-2,5-diones have been the most frequently reported [1,4]diazepines in solid-phase synthesis. The first paper from this field of research was published in 1995 by Goff et al. [74] Starting with the Rink amide resin **17b** acylated with bromoacetic acid **195**, the intermediate **196** was obtained via immobilization of isobutylamine. Repeating the acylation step with bromoacetic acid followed by reacting with amino acid esters afforded a resin that was acylated with 2-azidobenzoyl chlorides. Treatment of resin-bound **197** with tributylphosphine (TBP) gave the iminophosphorane, which was heated to yield the benzodiazepine intermediate **198** that is cleavable by TFA (Scheme 35). This method was successfully tested for a wide range of amino acids with only minor limitations, which are the use of *L*-asparagine *tert*-butyl ester and trityl-protected *L*-histidine methyl ester and sterically hindered *L*-valine methyl ester. In 2008, Goff's strategy was further modified by Subra for the online synthesis of a pseudopeptide library incorporating benzodiazepinone as a mimic with a subsequent biological evaluation of the chemical library on melanocortin-1 (MC1) receptors [75]. Instead of

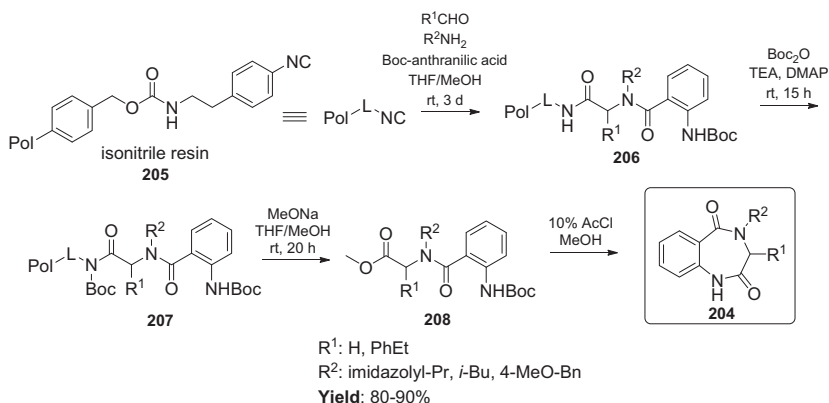


**Scheme 36** Solid-phase synthesis of benzo[*e*][1,4]diazepine-2,5-diones by Mayer

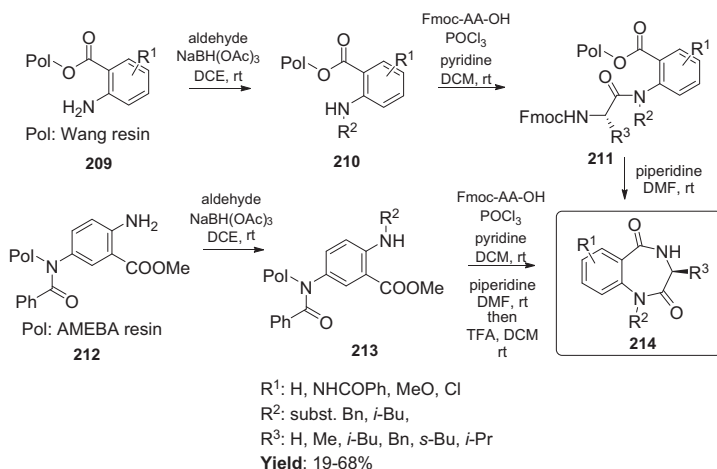
2-azidobenzoyl chlorides, 2-nitrobenzoyl chlorides were used, and resin-bound benzodiazepines were obtained after the reduction of the nitro group [76].

One year after Goff's finding, a simple method was reported by Mayer [77]. Fmoc-amino acid-derivatized Wang resin **200** was subjected to cleavage of the Fmoc-protecting group, and the resulting resin was acylated with 2-nitrobenzoic acids, followed by the reduction of the nitro group (Scheme 36). Alternatively, the intermediates **202** were obtained via the acylation with Fmoc-anthranilic acids and deprotection of resin **203** with piperidine. This methodology was later utilized by Waldmann for direct on-bead monitoring of the solid-phase synthesis of benzodiazepines **204** using soft laser desorption time-of-flight mass spectrometry (SLD-TOF MS) without prior cleavage from the resin using a photocleavable linker [78]. A number of cyclization conditions to prepare products **204** was evaluated by Mayer, and optimal results were obtained by heating the resin **202** in tetrahydrofuran sodium-*t*-butoxide. The cyclative release feature of this approach resulted in a significant enhancement of the purity of the final compounds. In 2003, Mayer's method was applied by Migihashi to prepare a chemical library of 400 benzodiazepines employing an ACT-496 automatic synthesizer and IRORI radio-frequency-encoded split-mix synthesis technology [79]. Later, Fmoc-anthranilic acids were replaced with Boc-anthranilic acids, and a library of benzodiazepines was synthesized on a Wang resin [80] or on a Kaiser oxime resin [81]. Compared with Mayer's approach, the final cleavage with TFA/DCM resulted in a significantly easier work-up of the crude products based on simple evaporation of the cleavage cocktail.

An interesting methodology to synthesize benzodiazepines **204** using solid-phase synthesis from anthranilic acids is based on a multicomponent Ugi reaction. Hulme was the first to report this strategy using a safety-catch linker [82]. The isonitrile resin **205** was prepared from a Wang resin in four steps and subjected to a one-pot reaction with aldehydes, amines, and Boc-anthranilic acid to give the resin-bound intermediate **206**. Boc derivatization promoted facile cleavage from the resin **207** with methoxide, giving the corresponding methyl esters **208**. Finally, cleavage



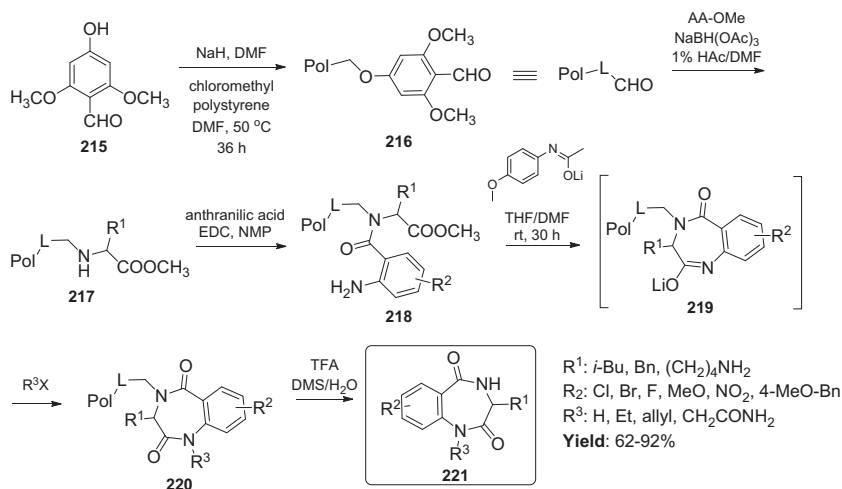
**Scheme 37** Ugi reaction and an isonitrile resin for the preparation of benzo[*e*][1,4]diazepine-2,5-diones



**Scheme 38** Solid-phase synthesis of benzo[*e*][1,4]diazepine-2,5-diones from immobilized anthranilates

of the Boc-protecting group from anthranilate **208** was followed by cyclization, yielding benzodiazepines **204** (Scheme 37). Later, the application of the Ugi reaction to obtain benzodiazepines on a solid phase from Fmoc-anthranilic acids [83] or *N*-substituted anthranilic acids [84] was also reported.

A reversed immobilization scenario was reported by Jeon et al. [85]. Instead of amino acids, anthranilic acids were attached to a Wang resin. Two approaches were developed: (a) immobilization via an anthranilic acid carboxylate (resin **209**) and (b) immobilization via an additional functional group of the aromatic moiety (resin **212**). In the first case, polymer-supported anthranilic acids were reductively alkylated to **210**, and upon the acylation with Fmoc-amino acids, the cleavage of

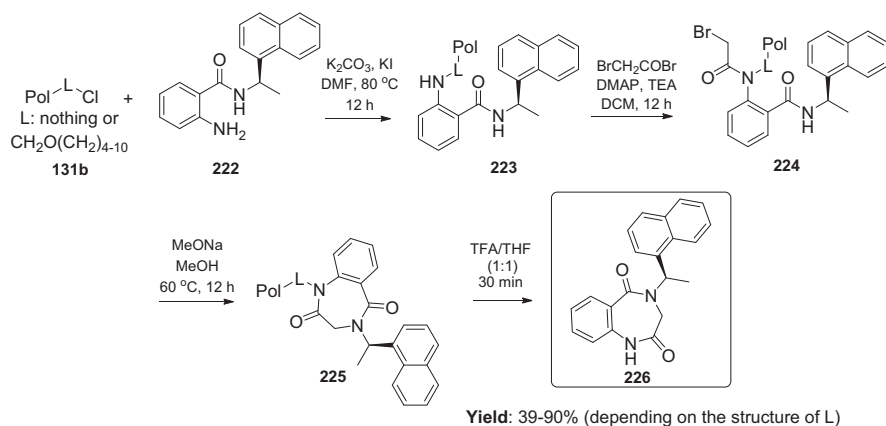


**Scheme 39** Solid-phase synthesis of benzo[*e*][1,4]diazepine-2,5-diones by Ellman et al.

the Fmoc-protecting group led to cyclative cleavage, releasing the final compounds **214** from the resin **211**. In the latter case, the resin-bound anthranilic acid methyl ester **212** was reductively alkylated, and the intermediate **213** was coupled with Fmoc-amino acids. Cleavage of the Fmoc-protecting group led to on-resin cyclization of the benzodiazepine product, which was cleaved from the resin using TFA (Scheme 38). Prior to the cleavage, the intermediates were eventually *N*<sup>4</sup>-derivatized with alkyl halides.

A different strategy was described by Ellman [86]. Starting from a chloromethyl resin equipped with benzaldehyde linker **216**, various amino acid methyl esters were immobilized via the N-terminus using reductive alkylation (Scheme 39). The acylation of intermediate **217** with anthranilic acids required considerable optimization. For example, even highly activated reagents, such as HATU, gave poor conversion. Carbodiimides were the only coupling agents found to efficiently cause this transformation. Furthermore, good yields of acylated material were obtained only when the carbodiimides were employed in conjunction with the hydrochloride salt of a tertiary amine. *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC) was shown to be the most convenient activating agent due to the presence of the tertiary amine hydrochloride in the carbodiimide structure. The reaction of intermediate **218** with the lithium salt of *p*-methoxyacetanilide followed by the addition of an appropriate alkylating agent provided a fully derivatized, resin-bound benzodiazepine **220**. A similar approach was later used to synthesize 7-acylamino benzo[*e*][1,4]diazepine-2,5-diones [87]. In 2008, Ellman's method was applied for the preparation and screening of a benzodiazepine library to identify novel melanocortin receptor agonists with nanomolar potencies [88].

In 2003, Rivero reported the solid-phase synthesis of benzo[*e*][1,4]diazepine-2,5-diones by the intramolecular cyclization of bromoacetyl intermediate **224**



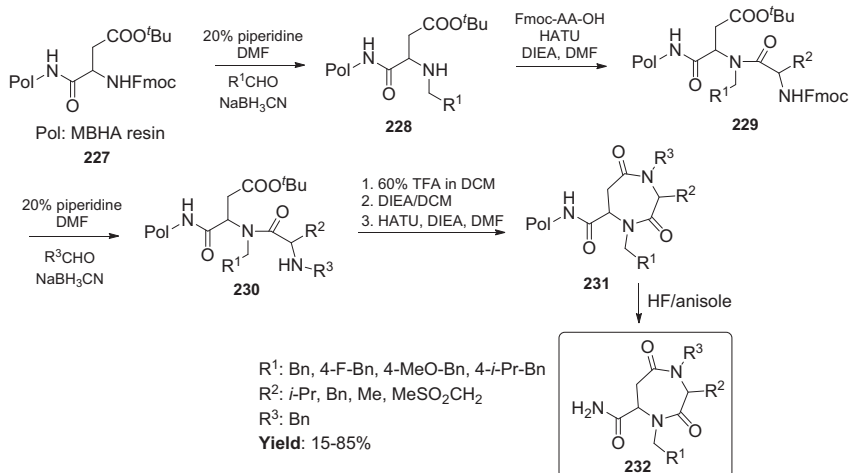
**Scheme 40** Solid-phase synthesis of benzo[*e*][1,4]diazepine-2,5-diones by bromoacetyl resin cyclization

[89]. The resin **223** was prepared from anthranilamide building block **222** immobilized on a chloromethyl resin followed by acylation with bromoacetic acid. The ring formation was performed using four different methods: cesium or sodium carbonate in DMF, sodium methoxide in refluxing methanol, and tetramethylguanidine in NMP (Scheme 40). In contrast to low soluble carbonates, sodium methoxide, which is soluble in methanol, considerably increased the yields of ring formation. However, concurrent hydrolysis of benzamide resin **224** was also observed (30%).

#### 4.11 1,4-Diazepane-2,5-diones

Synthetic strategies for the solid-phase synthesis of diazepane-1,4-diones are similar to those reported for analogous benzodiazepines. Polymer-supported amino acids are typically used as the starting material. One of the first studies in this field was published in the late 1990s by Houghten [90, 91]. Starting from immobilized aspartic acid **227**, the amino group was reductively alkylated, followed by the acylation of intermediate **228** with Fmoc-amino acids (Scheme 41). No racemization was observed when the corresponding imine was reduced immediately upon formation. The subsequent cleavage of the Fmoc-protecting group was followed by reductive alkylation and furnished resin-bound linear intermediate **230**; upon cleavage of the Boc-group, **230** was subjected to cyclization with HATU. Good yields were obtained with Phe and Met(O), whereas low yields were obtained with hindered amino acids, such as Val. Dimerization of the unreacted *N*-substituted aspartic acid (i.e., compound **228** without the *t*-Bu) yielding the 1,5-diazocane scaffold was also observed (5–15%). In 2011, Messegueur reported the synthesis



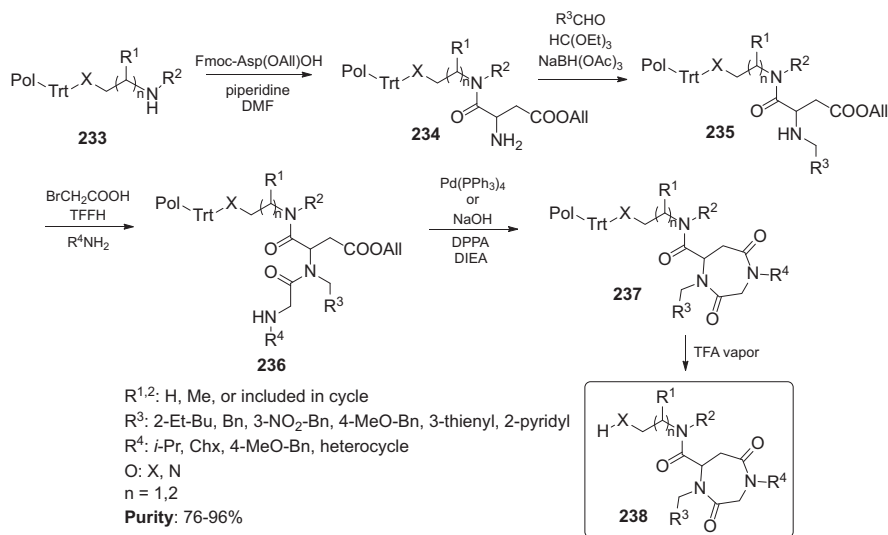


**Scheme 41** Solid-phase synthesis of 1,4-diazepane-2,5-diones by Houghten et al.

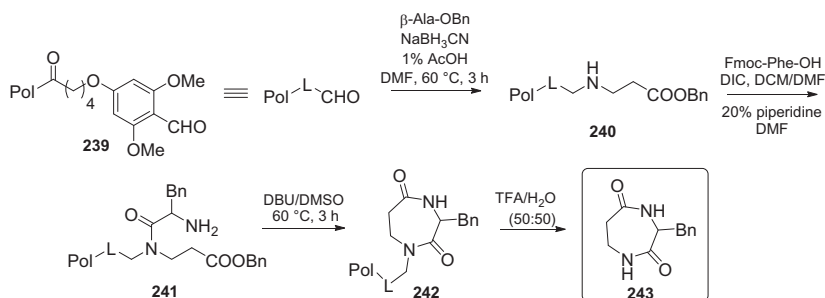
of intermediates **229** (with allyl instead of Fmoc or Boc) from resin-bound amines by reaction with allyl maleate, followed by an aza-Michael reaction [92]. In this case, the diazepine scaffold was obtained after hydrolysis of allyl ester and on-resin cyclization with benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP).

Simultaneous with the report by Houghten, Krchňák reported an alternative strategy employing Fmoc-Asp(OAll)OH as the acylating species to obtain intermediates **234** from polymer-supported amino alcohols or symmetrical diamines **233** [93]. After reductive alkylation, the  $R^4$  diversity position was introduced via the reaction of resin **235** with bromoacetic acid followed by nucleophilic displacement with primary amines. To remove the protecting group, the allyl ester **236** was treated with  $\text{Pd}(\text{PPh}_3)_4$  or sodium hydroxide, and the cyclization to benzodiazepines **237** was achieved by mild activation of the carboxylate with diphenylphosphoryl azide (Scheme 42). Using this method, a chemical library was synthesized employing the split/mix technique with 8 secondary diamines and amino alcohols, 17 aldehydes, and 20 primary amines, providing 2,720 compounds.

The preparation of 1,4-diazepane-2,5-diones based on a combination of  $\alpha$ - and  $\beta$ -amino acids was reported by Amblard [94]. The benzaldehyde resin **239** was reductively aminated with  $\beta$ -alanine benzyl ester, followed by acylation with Fmoc-Phe-OH. After cleavage of the Fmoc-protective group, the resin-bound intermediate **241** was subjected to base-induced cyclization (Scheme 43). The procedure was successfully transferred to a secondary amine, forming derivatized (SAF) Synphase<sup>TM</sup> crowns. A reversed immobilization strategy was recently reported for the preparation of 1,4-diazepane-2,5-diones **243** fused with a cyclohexane scaffold [95]. The  $\alpha$ -amino acids were initially immobilized on a Wang resin via a carboxylate group, and the desired scaffold was formed by cyclative cleavage upon acylation with  $\beta$ -amino acids.



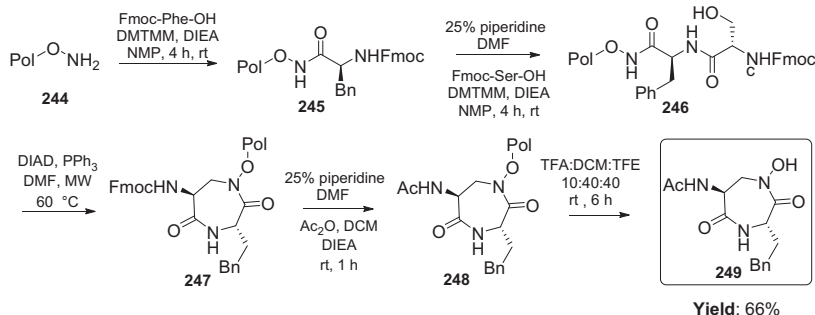
**Scheme 42** Solid-phase synthesis of 1,4-diazepane-2,5-diones by Krchňák



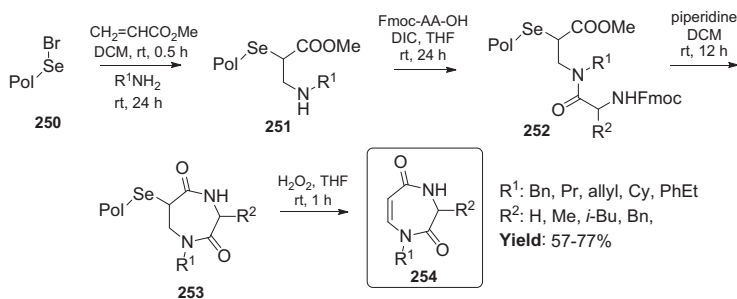
**Scheme 43** Solid-phase synthesis of 1,4-diazepane-2,5-diones from  $\alpha$ - and  $\beta$ -amino acids

Similarly, it was found that using aspartic acid  $\beta$ -benzyl ester in Fmoc-based solid-phase peptide synthesis not only risks the formation of the aspartimide peptide but also results in its further transformation into a 1,4-diazepane-2,5-dione-peptide derivative [96].

Ring closure of the dipeptide via an intramolecular Mitsunobu alkylation was reported employing hydroxylamine linked to a PS-DVB 2-chlorotrityl resin **244** [97]. Acylation with Fmoc-Phe-OH was followed by the formation of resin-bound dipeptide **246**, and the Mitsunobu reaction yielded the polymer-supported diazepine **247** (Scheme 44). Cyclization was performed with DMF as a solvent in the presence of DIAD and PPh<sub>3</sub> in a sealed tube under microwave irradiation. Three cycles were required to complete the reaction. The reaction pathway was also verified for Fmoc-Glu(OAll)OH as the starting amino acid.



**Scheme 44** Solid-phase synthesis of 1,4-diazepane-2,5-diones via the Mitsunobu alkylation



**Scheme 45** Solid-phase synthesis of 1,4-diazepine-2,5-diones with a selenyl bromide resin

#### 4.12 1,4-Diazepine-2,5-diones

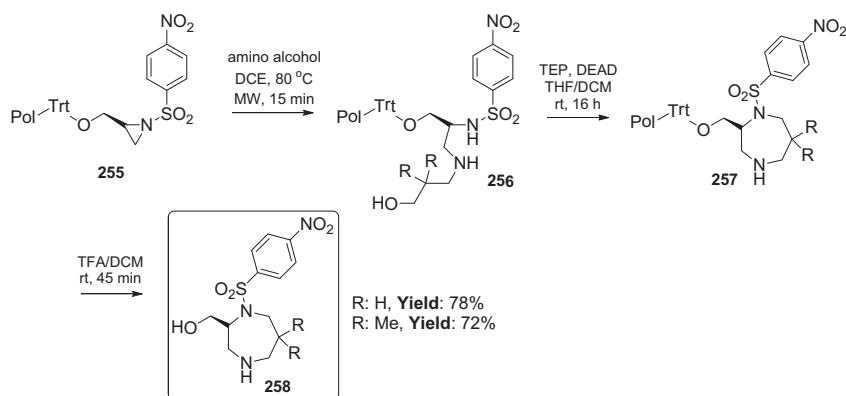
The solid-phase synthesis of unsaturated analogues **254** of the abovementioned 1,4-diazepane-2,5-diones was reported by Huang who employed resin-bound 3-amino-2-seleno ester **251** [98]. Polystyrene-supported selenyl bromide **250** was successively reacted with methyl acrylate and primary amine in one pot to yield the desired resins. C<sup>2</sup>-immobilized  $\beta$ -alanine methyl ester **251** was acylated with Fmoc-amino acids, and after deprotection occurred, spontaneous cyclization gave the resin-bound 1,4-diazepane-2,5-diones **253**. Oxidation and *syn*-elimination led to the cleavage of resin **253** and afforded the final 1,4-diazepines **254** (Scheme 45). When propargylamine was used as the R<sup>1</sup>NH<sub>2</sub> building block, the same methodology was applied to synthesize 1,4-diazepine-indole/benzofuran bisheterocycles [99]. Similarly, the use of mono-Boc-*o*-phenylenediamine afforded fused diazepino[1,2-*a*] benzimidazoles [100].

### 4.13 1,4-Diazepanes

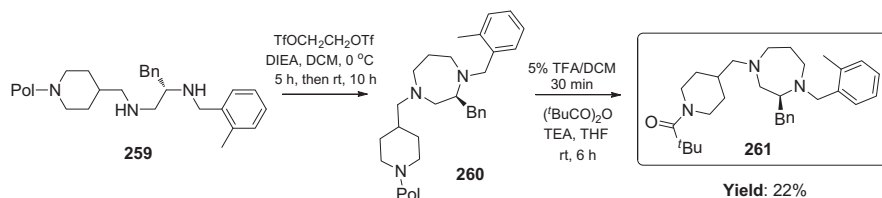
The intramolecular Fukuyama-Mitsunobu alkylation was applied for the preparation of 1,4-diazepanes **258** [101, 102]. The aziridine resin **255** was treated with different aminopropanols, and the resin-bound intermediates **256** were cyclized with triethylphosphine (TEP) and diethyl azodicarboxylate (DEAD) (Scheme 46).

The 1,4-diazepane scaffold was also obtained by the cyclization of polymer-supported diamines **259** prepared from aminomethylpiperidine and a trityl resin in six steps [103]. After the cyclization was performed with propane-1,3-ditriflate, the diazepane **260** was cleaved from the resin and converted to the *N*-pivaloyl product **261** (Scheme 47).

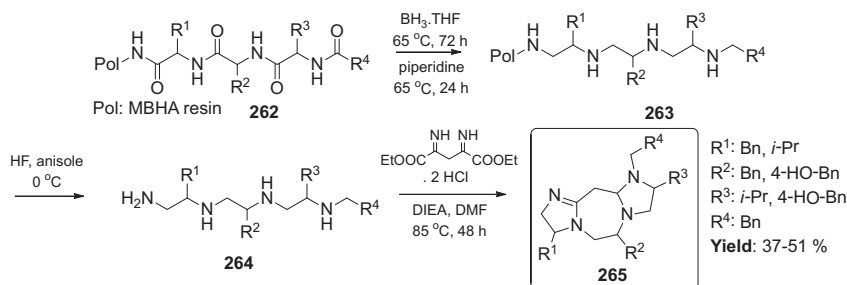
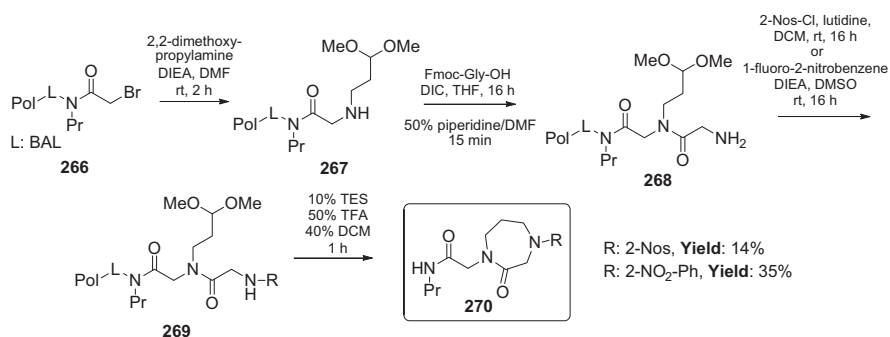
An interesting strategy for the preparation of diimidazodiazepines via solid-phase synthesis was recently reported by Nefzi [104]. The resin-bound tripeptidic intermediate **262** was reduced to the polyamine **263**. After **263** was cleaved from the polymer support, the cyclization with diethyl malonoimide dihydrochloride afforded diimidazodiazepine compounds **265** (Scheme 48).



**Scheme 46** Solid-phase synthesis of 1,4-diazepanes via the Mitsunobu alkylation



**Scheme 47** Solid-phase synthesis of 1,4-diazepanes via cyclization with propane-1,3-ditriflate

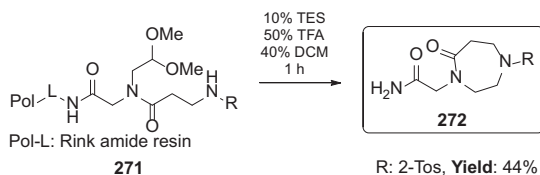
**Scheme 48** Synthesis of diimidazodiazepines via solid-phase synthesis**Scheme 49** Synthesis of 1,4-diazepan-2-ones

#### 4.14 1,4-Diazepan-2-ones

Starting from polystyrene resin equipped with a BAL linker, propylamine was immobilized via reductive alkylation followed by acylation with bromoacetic acid. The intermediate **266** was reacted with 2,2-dimethoxypropylamine (Scheme 49). Acylation with glycine afforded the resin **268**, which upon modification of the amino group, was subjected to cleavage with TFA in the presence of triethylsilane (TES). The diazepanones **270** were obtained in limited yield [105]. When the use of TES was omitted, the cleavage yielded the corresponding unsaturated diazepines [106].

#### 4.15 1,4-Diazepan-5-ones

A similar approach to that used in the previous case was applied for the preparation of diazepanones with different positioning of the carbonyl group [105]. The intermediate **271** was synthesized according to Scheme 49 from the Rink amide resin,



**Scheme 50** Synthesis of 1,4-diazepan-5-ones

2,2-dimethoxyethylamine and Fmoc- $\gamma$ -aminobutyric acid. The cleavage afforded 1,4-diazepan-5-one **272** (Scheme 50) or the corresponding 1,4-diazepin-5-ones in the absence of the reducing agent [106].

## 4.16 Conclusion

The use of solid-phase synthesis for the preparation of pharmacologically promising heterocycles is a challenging field that offers an almost unlimited source of chemical reactions to produce novel, interesting molecules. Although diazepanes and diazepines represent a small group in the large family of heterocycles, the number of different methodologies summarized in this chapter clearly demonstrates the robustness and applicability of solid support chemistry in the area of seven-membered scaffolds. This field has not been fully exploited, and further strategies will be presented to extend the current knowledge.

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