Int J Pharm Bio Sci 2013 Jan; 4(1): (P) 357 - 372

Review Article **Medicinal Chemistry**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

SOLID-PHASE SYNTHETIC APPROACH TO THE SYNTHESIS OF AZEPINE HETEROCYCLES OF MEDICINAL INTEREST

NAVJEET KAUR

Department of Chemistry, Banasthali University, Banasthali-304022 (Rajasthan), India

ABSTRACT

Solidphase organic synthesis is a rapidly expanding area of synthetic chemistry which is being widely exploited in the search for new medicinally important compounds by combinatorial techniques. In recent decades, a large number of reports related to solid-phase synthesis of heterocycles have appeared owing to a wide variety of their biological activity. In this review, we report the important role of solid-phase synthesis in the synthesis of azepine ring containing heterocycles.

KEYWORDS : Solid-Phase synthesis, Heterocycles, Azepines, Solvent-free synthesis

NAVJEET KAUR
Department of Chemistry, Banasthali University, Banasthali-304022 (Rajasthan), India

Corresponding author

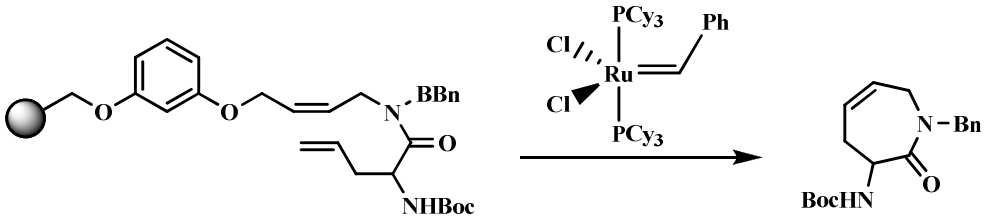
INTRODUCTION

Since Merrifield pioneered solid-phase synthesis in 1963, the subject has evolved radically, thereafter, Merrifield's solid-phase synthetic concept, first developed for biopolymer, has spread in every field where organic synthesis is involved. Since then many laboratories and companies have been focusing on the development of technologies and chemical procedures suitable to solid-phase synthesis . This resulted in the spectacular outburst of combinatorial chemistry, which profoundly changed the approach for new drugs discovery. Combinatorial chemistry has emerged as a powerful methodology for the preparation of libraries of small organic molecules and in accelerating the drug discovery process. Combinatorial chemistry is a technique not only useful in drug discovery processes, but also attractive to all disciplines of chemistry where large numbers of compounds are desirable. Combinatorial chemistry and parallel synthesis have been applied extensively by medicinal chemists as one approach to the discovery and optimization of molecules. While solution-phase parallel synthesis is being used more routinely in the laboratory, solid-phase synthesis continues to be an important approach to synthesize combinatorial libraries, especially for heterocyclic compounds requiring multi-step syntheses. Solid-Phase approach is interesting since the reaction can be driven to completion by using excess reagents, which are subsequently removed by simple filtration. The work-up is therefore easy and can be automated. Azepine heterocycles have a central position in organic chemistry, because of the useful medicinal properties of many members of these compounds. Due to their impressive properties, azepine systems play an important role as potentially active compounds in drug design and synthesis. Azepine heterocycles have been shown to possess wide range of biological activity, including antibacterial, antifungal, antihypertensive, antiasthmatic, CCK antagonist, bronchodilatory, and lipoxygenase inhibition. In addition, these heterocycles serve as intermediates in the preparation of various biologically important compounds.[1-6] Numerous methods have been developed for their synthesis. They often require harsh reaction conditions if the carbon-carbon double bond or triple bond is not sufficiently polarized. Some studies have been published on the solid-phase synthesis of a wide variety of azepines. The preparation of combinatorial libraries of azepine heterocyclic compounds by solid-phase synthesis is of great interest for accelerating pharmaceutical research. There has been an emphasis on the preparation of azepine heterocycles with extensive chemical diversity, which can give rise to structural members with more desirable physical and biological properties. This has permitted dramatic increase in the speed of synthesis through both simplification of work-up, and automation. Additionally, the freedom to use, and wash away, large excesses of reagents permits some reactions that are wholly impractical in solution-phase, in an environmentally benign way by solid phase synthetic approach. The preparation of azepine compounds on the solid phase has become an accepted and powerful drug discovery tool. In this respect, various approaches for the preparation of these privileged structures with drug-like properties have been developed on solid-phase strategies. As a result, an increasing range and number of pharmaceutically useful azepine heterocyclic compounds recently have been prepared using solid-phase methodology. In particular, access to azepine heterocyclic compounds by solid-phase synthesis is urgently required, since small, substituted heterocycles offer a high degree of structural diversity and they are proven to be exceptionally useful in pharmaceutical applications. This article provides an overview of emerging applications of combinatorial approaches in azepine heterocycles synthesis. In this review, we focus

on methods for the synthesis of medicinally important azepine heterocyclic rings on solid support, since it has emerged as an efficient method for the diversificiation of azepines and for the preparation of seven-membered ring system.

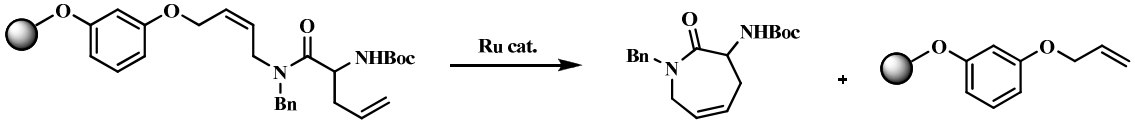
Solid-phase *synthesis of medicinally important azepine heterocycles:*

The use of Grubb's ruthenium catalyst with a solid support was applied by Miller et al[7] in a non-cleaving sense. The synthesis of Friedlinger lactam from cinnamoyl alcohol was accomplished (scheme-1). In fact cleavage by metathesis can provide a means of achieving a traceless linkage.



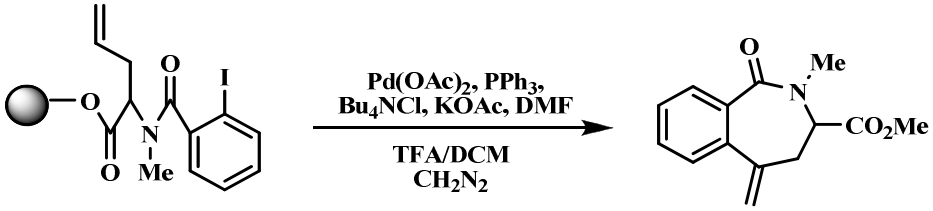
Scheme-1

A novel approach to the synthesis of seven-membered lactams involved a ring-closing metathesis reaction. A ring opening metathesis reaction was reported by Cuny et al.[8] to afford highly substituted cyclopentanes (scheme-2).



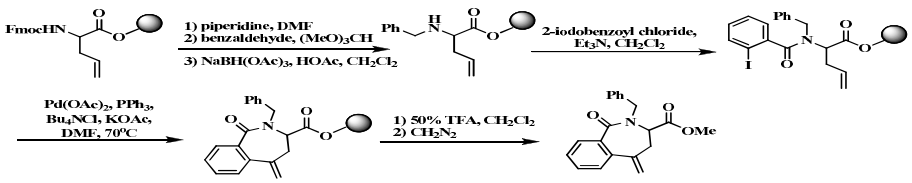
Scheme-2

A macrocyclization on solid-support using the Heck reaction has also been utilized by Akaji and Kiso when a cyclic tetrapeptide derivative was synthesized. Lately, Bolton and Hodges[8] (scheme-3) have prepared substituted benzazepines via intramolecular Heck cyclization on solid-phase.



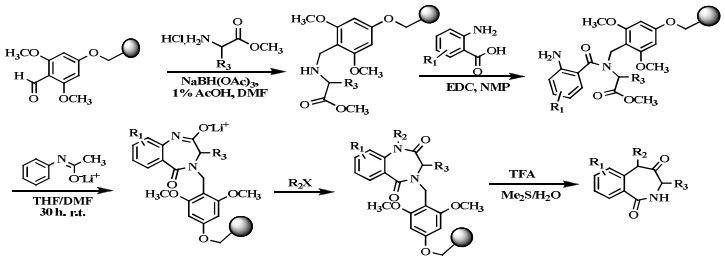
Scheme-3

Bolton and Hodges described the synthesis of benzazepines via intramolecular Heck cyclization (scheme-4). Following deprotection of immobilized allylglycine ester, reductive amination with benzaldehyde cleanly produced the secondary amine. Subsequent acylation with 2-iodobenzoyl chloride and efficient Heck cyclization produced bicyclic lactam following acidic cleavage and esterification.[9]



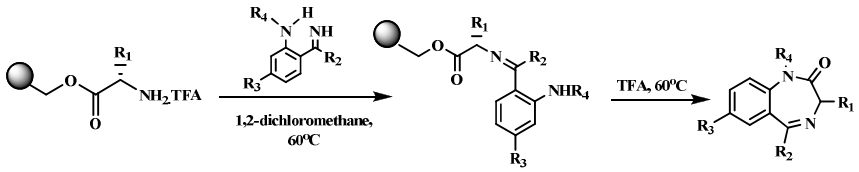
Scheme-4

The synthesis of 1,4-benzodiazepine-2,5-diones is initiated by loading an R-amino ester onto the aldehyde-derivatized support by reductive amination employing $NaBH(OAc)_3$ in DMF with 1% AcOH (scheme-5).[10]



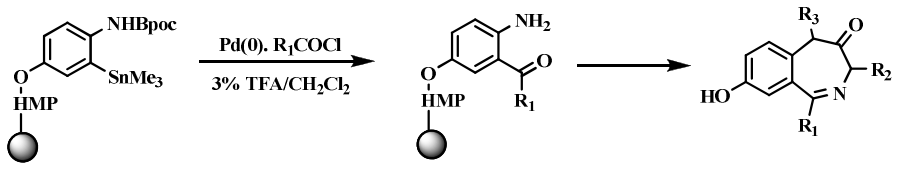
Scheme-5

In one of the early reports of small molecule library synthesis, DeWitt and co-workers[11] described (scheme-6) an alternative strategy by treating each of five amino acid resins with each of eight 2-amino benzophenone imines for the synthesis of 1,4-benzodiazepin-2-ones.



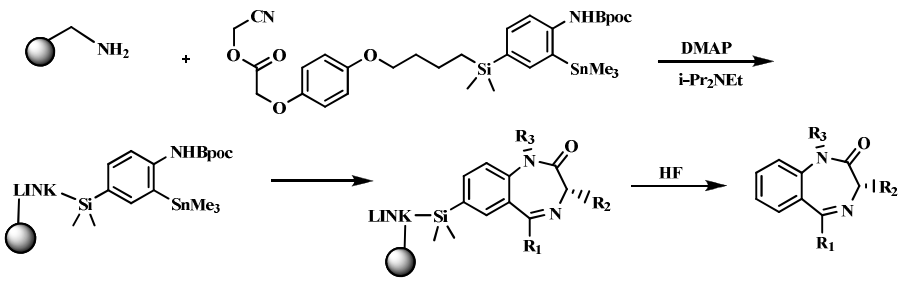
Scheme-6

A [[2-(4-biphenyl)is opropyl]oxy]carbonyl (Bpoc)-protected (aminoaryl)stannane, which is prepared in four steps in solution, is coupled to the solid support through the HMP linker. Stille coupling[12] (scheme-7) can then be carried out with a range of different acid chlorides and the catalyst $Pd_2(dba)/CHCl_3$.



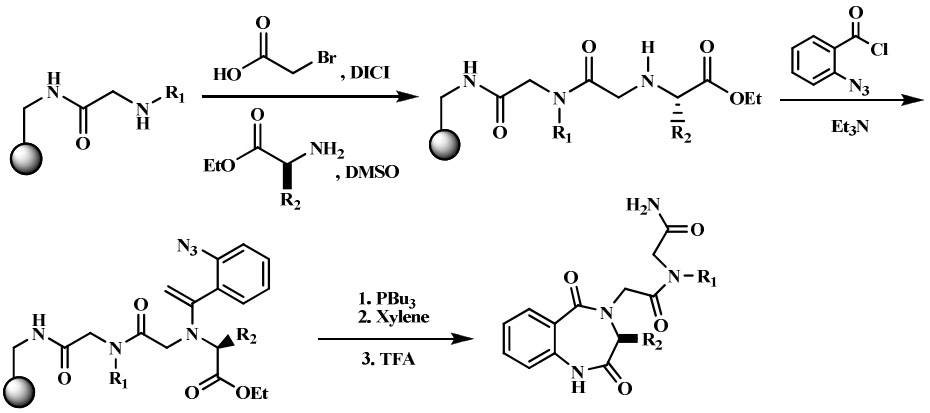
Scheme-7

Plunkett and Ellman[13] have also demonstrated a silyl linkage strategy for the synthesis of benzodiazepine derivatives (scheme-8).



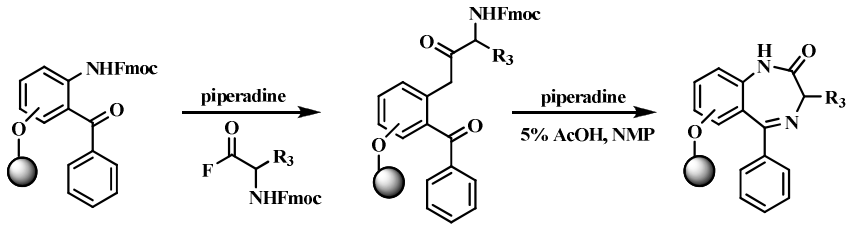
Scheme-8

A synthetic route to the 1,4-benzodiazepin-2,5-dione class was also reported by Zuckermann and co-workers[14] (scheme-9) at Chiron. In this study the 1,4-benzodiazepin-2,5-dione was synthesized from the *N*-terminus of a support-bound peptoid intermediate.



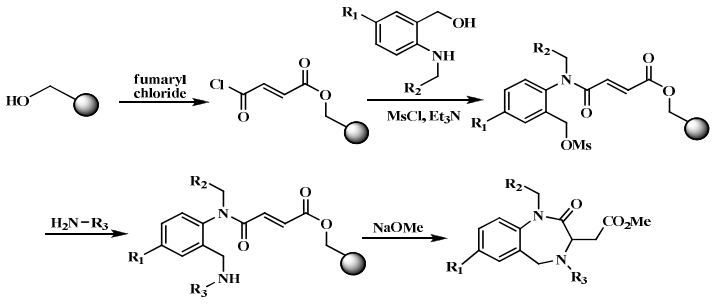
Scheme-9

Synthesis of the benzodiazepine derivative on solid support proceeds by removal of the Fmoc protecting group by treatment with piperidine in DMF followed by coupling an R-*N*-Fmoc amino acid fluoride to the resulting unprotected 2-aminobenzophenone (scheme-10).[15]



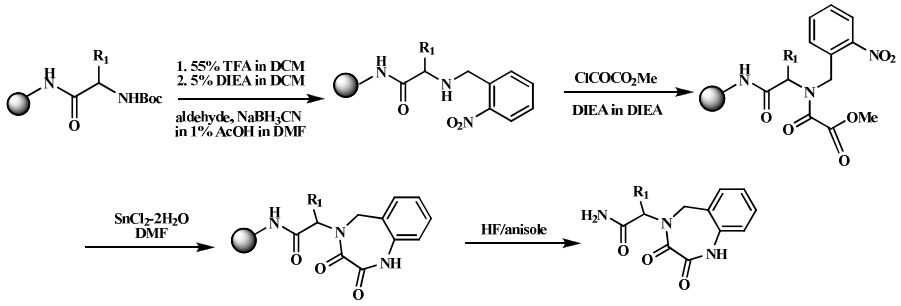
Scheme-10

Bhalay et al.[16] synthesized tetrahydro-1,4-benzodiazepin-2-ones on the solid-phase Wang resin in a single cyclization/cleavage step via a 7-*exo-trig* cyclization (scheme-11).



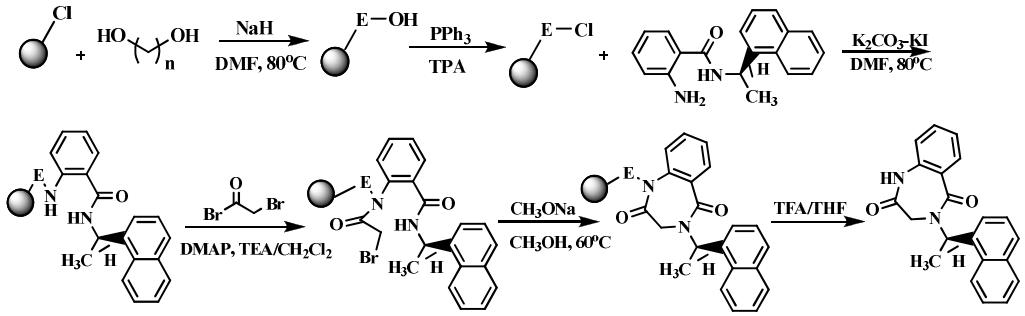
Scheme-11

The reductive alkylation of resin-bound primary amine with different substituted *o*-nitrobenzaldehydes generated a secondary amine, which was treated further with methyl chlorooxoacetate. The nitro group was reduced with tin(II) chloride. During the overnight reduction, an in situ intramolecular cyclization occurred to provide, following HF cleavage, the desired 4,5-dihydro-1*H*-1,4-benzodiazepin-2,3-dione (scheme-12).[17]



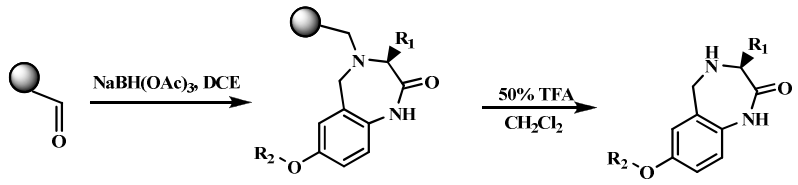
Scheme-12

Polymer bound 4-*N*-naphthylethyl-1,4-benzodiazepine-2,5-dione with the naphthyl group as the probe was synthesized according with scheme-13 given below.[18]



Scheme-13

The resulting 1,4-benzodiazepine-2-one scaffold was loaded onto the 4-formyl-3,5-dimethoxyphenoxy (PL-FDMP) resin by reductive amination (scheme-14) in high yield (>95%), even when only 1.5 equiv of the scaffold was used.[19]

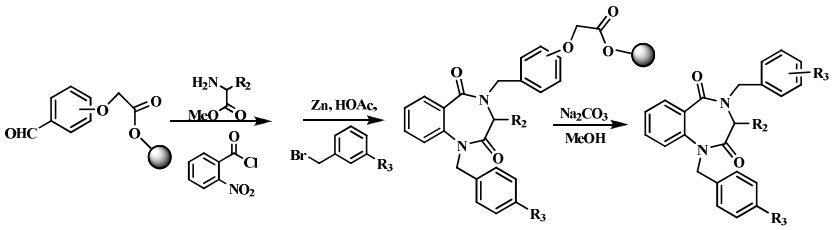


Scheme-14

Heating the Wang resin-bound anthranilic ester at 150°C with a primary amine in a microwave apparatus effected a tandem N-alkylation-intramolecular cyclization that proceeded with concomitant cleavage of the 1,4-disubstituted-1,4-benzodiazepine-2,5-dione product from the resin (scheme-15).[20]

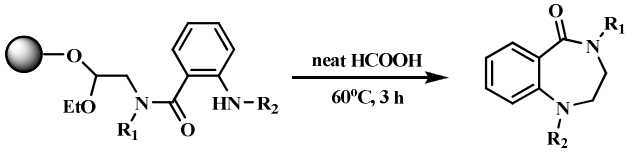
Scheme-15

PEG5000 monomethyl ether is used as the support to construct a library of 1,4-benzodiazepin-2,5-diones (scheme-16). As the target 1,4-benzodiazepin-2,5-dione requires an *N*4-aryl substituent, was deliberately used the PEG-bound benzaldehydes to couple with the esters of α-amino acids.[21]



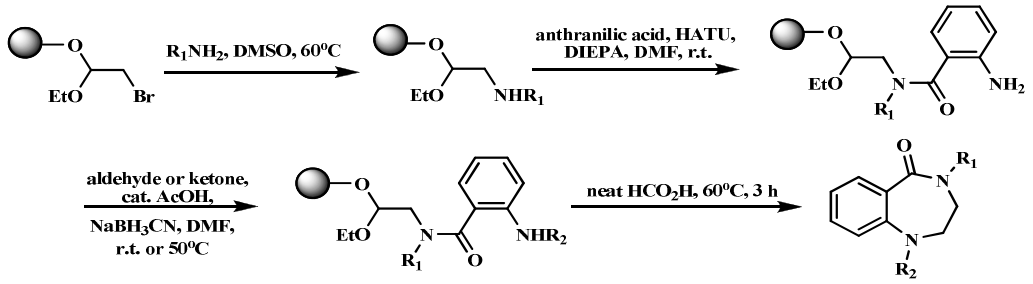
Scheme-16

A novel and efficient strategy has been developed to synthesize privileged tetrahydro-1,4-benzodiazepines with excellent yields and purities; this synthetic pathway (scheme-17) was established by the revitalization of the Leuckart-Wallach (LW) reaction via solid-phase synthesis.[22]



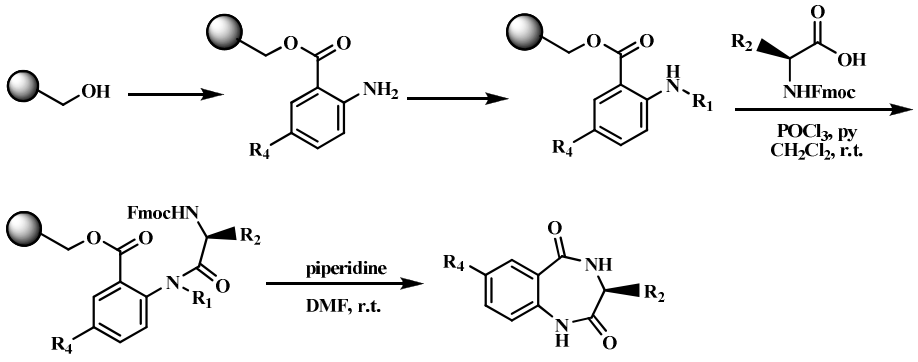
Scheme-17

The simple amination of the bromoacetal resin was done with primary amines in dimethyl sulfoxide (DMSO), the resulting secondary amine was coupled with anthranilic acid or chloro-anthranilic acid. The reductive amination of an aldehyde or ketone in dimethylformamide (DMF) yielded the compound (scheme-18).[23]



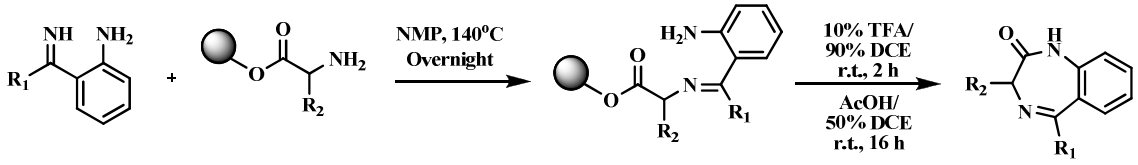
Scheme-18

The N-benzylation of the resin under the reported conditions gave the N-benzylated anthranilate resin, which on further reaction with N-Fmoc-protected phenylalanine in the presence of $POCl_3$ and pyridine in CH_2Cl_2 at room temperature afforded the amino acid coupled anthranilic acid resin. Deprotection of the resin in 20% piperidine-DMF at room temperature directly furnished the 1,4-benzodiazepin-2,5-dione derivative (scheme-19).[24]



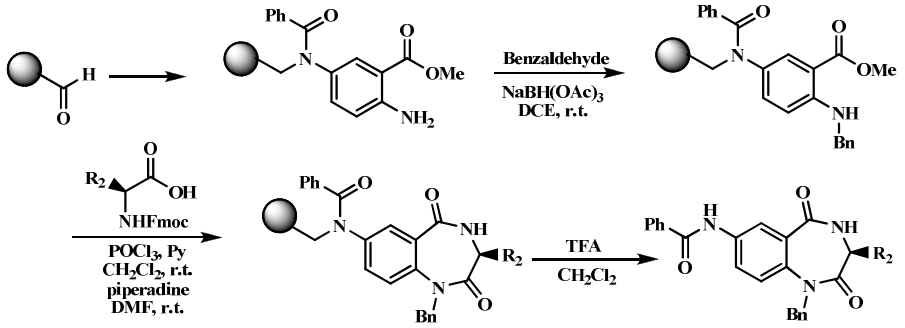
Scheme-19

Line S. Laustsen et al.[25] has developed an efficient solid-phase method for the parallel synthesis of 1,3-dihydro-1,4-benzodiazepine-2-one derivatives. A key step in this procedure (scheme-20) involves catching crude 2-aminobenzoimine products on an amino acid Wang resin.



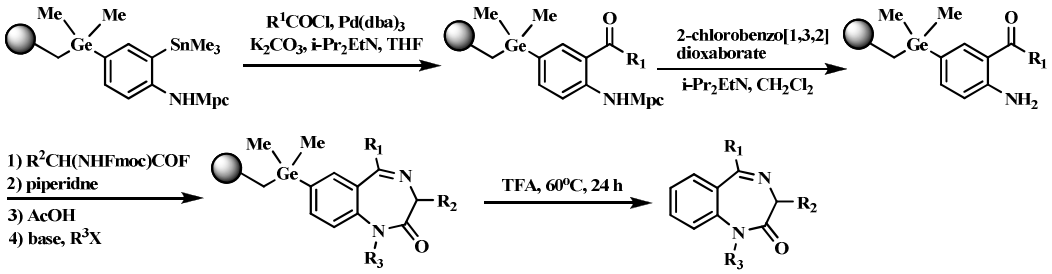
Scheme-20

The novel protocol (scheme-21) was established for the resin-bound anthranilic acid derivatves for the prepration of the 1,4-benzodiazepin-2,5-dione derivatives with amino-related benzamido functionality at the 7-position from the resin intermaediate.[25]



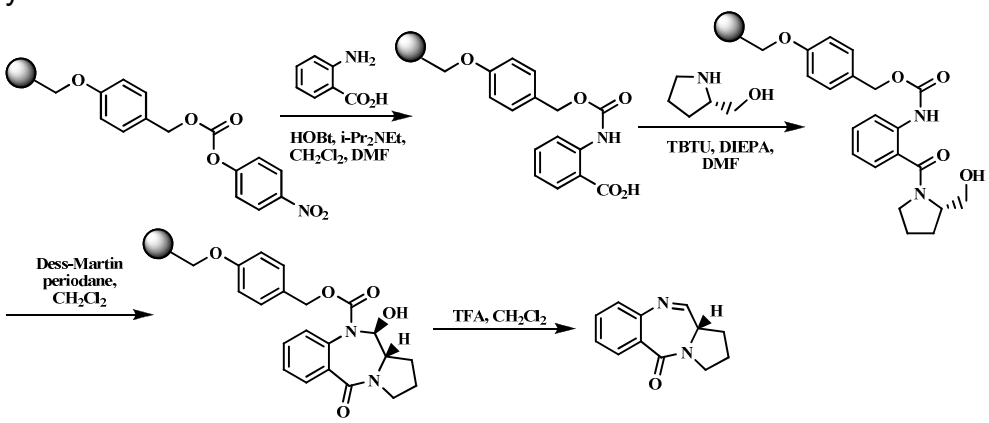
Scheme-21

Immobilised aryl halides have been coupled with aryl and alkenylstannanes to a large extent. Stannanes attached to a solid support have been used less frequently for Stille reactions, but they have been used in Ellman's benzodiazepine synthesis. Starting from the stannane, palladium catalysed Stille coupling with acid chlorides furnished ketones. The latter were deprotected to give anilines. The benzodiazepine moiety was elaborated in a four step sequence (scheme-22). Final cleavage from solid support gave hydrocarbons via traceless cleavage of arylbromides.[26]



Scheme-22

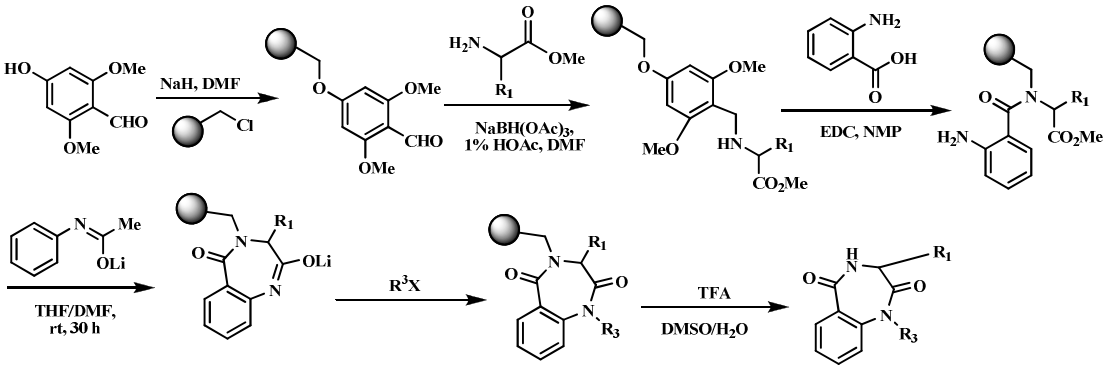
Berry et al.[27] coupled anthranilic acid to the p-nitrophenyl carbonate Wang resin (scheme-23). After this, pyrrolidinemethanol was added to the immobilized A-ring. The closure of the B-ring was achieved by an oxidation to give the benzodiazepine. Cleavage from the solid support gave the product in good yield.



Scheme-23

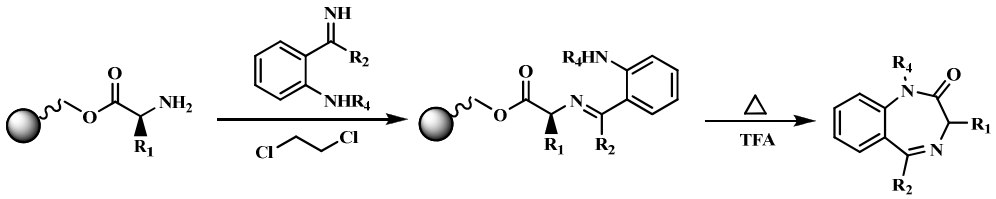
Boojamra et al.[28] used a different synthetic strategy to 1,4-benzodiazepin-2,5-diones (scheme-24). Merrifield resin was derivatized with the sodium salt of the phenol. The amino ester was loaded on

this then formed BAL linker by reductive amination. Acylation of the resulting secondary amine with unprotected anthranilic acids provides the support-bound tertiary amide. After cyclization the 1,4-benzodiazepine-2,5-diones were cleaved off the solid support.



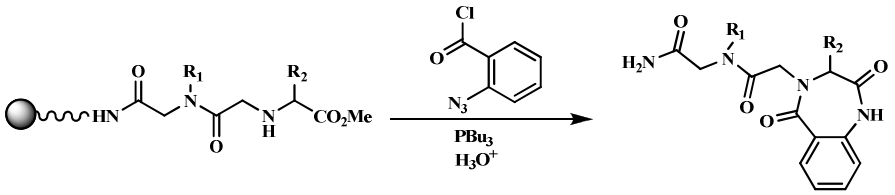
Scheme-24

Amino acids were tethered to the solid-phase and were treated with 2-aminobenzophenones. Subsequent treatment with heat and acid then induced cyclisation to provide the target compounds (scheme-25). A similar type of strategy has been applied to the synthesis of hydantoins .[29]



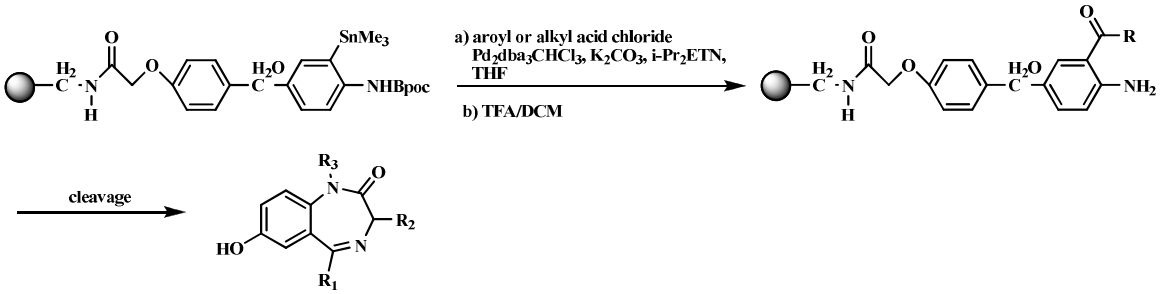
Scheme-25

Zuckermann and Goff[14] have shown that the NSG backbone can be transformed into benzodiazepinediones and isoquinolones (scheme-26). The critical step in the synthesis of the benzodiazpinediones is the intramolecular Wittig-type reaction of the iminophosphorane produced by azide reduction by tributylphosphine.



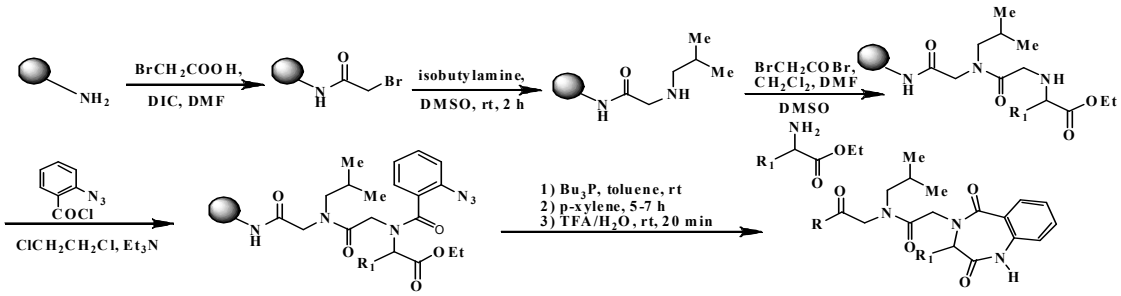
Scheme-26

Ellman and co-workers have discovered an excellent method for the preparation of 1,4-benzodiazepine derivatives on solid-support and using the Stille coupling (scheme-27). He could produce structurally diverse derivatives. Recently, the group has utilized the Stille coupling in the preparation of new traceless linkers to be used in solid-phase synthesis.[30]



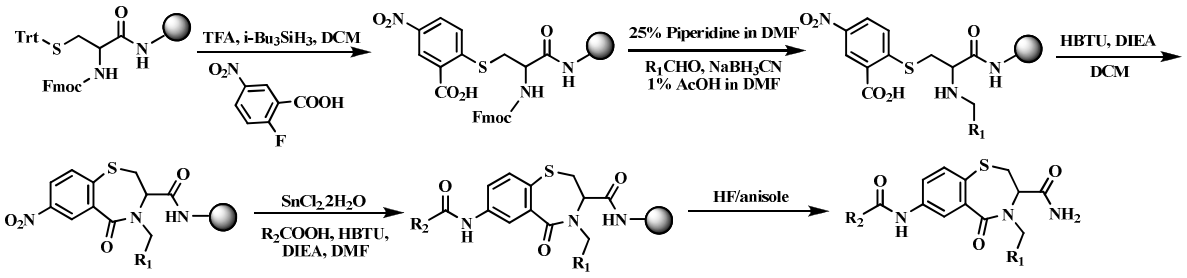
Scheme-27

The Aza-Wittig reaction was used for the cyclization in the synthetic pathway of Goff and Zuckermann (scheme-28).[14] In the first step, they connected the Rink amide resin with the bromoacetic acid. Then, the bromide was displaced by isobutylamine. Bromoacetylation and displacement with amino acid esters affected the intermediates, which were directly acylated with o-azidobenzoyl chloride. Cleavage of the solid support yielded the 1,4-benzodiazepin-2,5-iones.



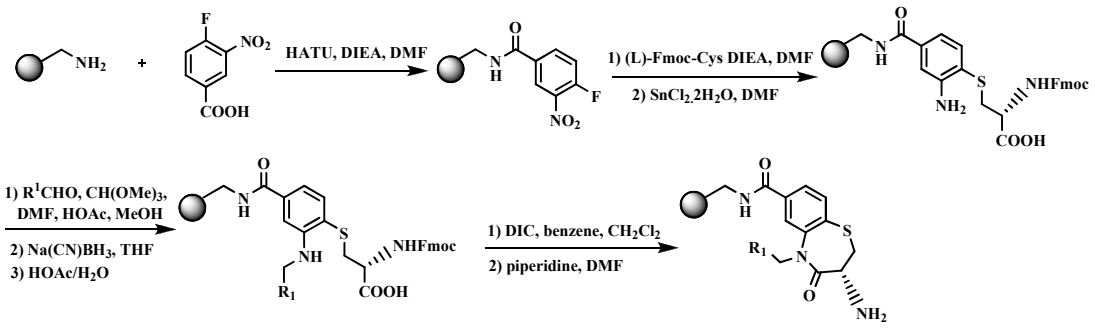
Scheme-28

Pathway to benzothiazepines was described by Nefzi et al.[31], N-a-Fmoc-S-trityl-l-cysteine was coupled to p-methylbenzhydrylamine resin, the trityl group was cleaved and the benzoic acid was connected. The protected amine was deprotected and reductively alkylated. Cyclization resulted in the benzothiazepine skeleton. The nitro group was reduced and coupled to the carboxylic acid followed by an intra molecular cyclization, is described (scheme-29).



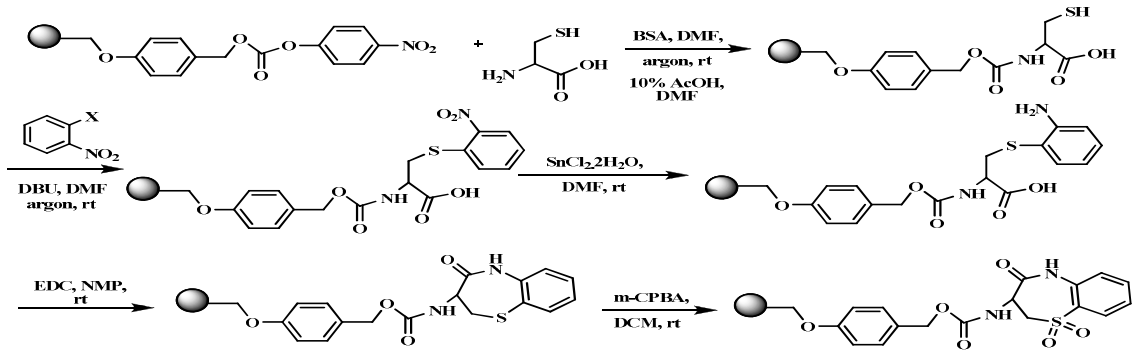
Scheme-29

Schwarz et al.[32] described a synthetic pathway to benzothiazepines (scheme-30). They started with a nucleophilic aromatic substitution of the benzoic acid after immobilization. The nitro group was reduced by tin(II)chloride. Reductive alkylation of gave the secondary anilines. Intramolecular cyclization formed the 3,5-disubstituted 2,3-dihydro-1,5-benzothiaepin-4(5H)-ones.



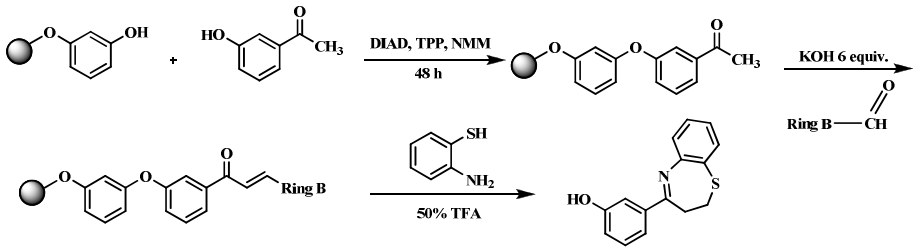
Scheme-30

Cysteine was reacted with the nitrophenyl carbonate derivative of Wang resin by first using bis-(trimethylsilyl)-acetamide (BSA) to dissolve the amino acid. The thiol was then reacted with a variety of halo-nitrobenzene derivatives. Cysteine could be cleanly reduced with tributyl phosphine and further reacted with the halo-nitrobenzene derivative. Reduction of the nitro group with tin-dichloride dihydrate and cyclization with EDC afforded the benzothiazepine derivative (scheme-31). Further diversity could be obtained by oxidation of the sulfide to the sulfone with *m*-CPBA.[33]



Scheme-31

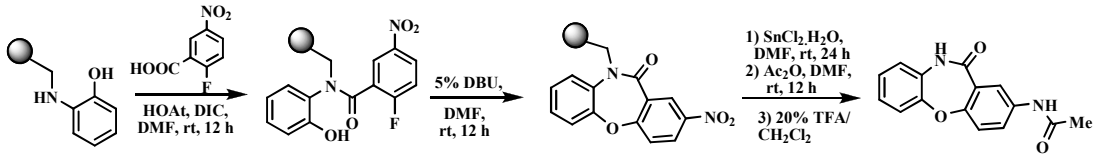
Solid-phase synthesis of 2,3-dihydrobenzothiazepines has been carried out through [4+3] annulation of α,β-unsaturated ketones with aminothiophenol, using Wang resin as solid support (scheme-32). Moreover, the substitution of hydroxy group at C-3 in ring A led to increased activity when compared to unsubstituted- and OH substituted benzothiazepines.[34]



Scheme-32

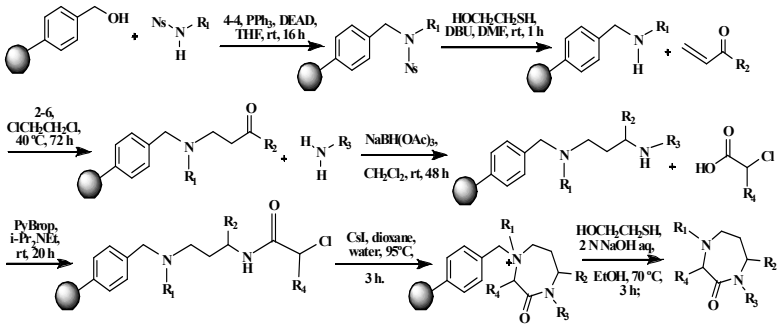
Ouyang et al.[35] reported a synthetic strategy toward the benzoxazepine ring (scheme-33). The resin was prepared by the reductive amination of o-aminophenol on AMEBA polystyrene resin. This resin

was further modified to afford the immobilized substrate, which was ready for the assembly of the desired derivative. Cleavage of the solid support gave the benzoxazepine in quantitative yield.



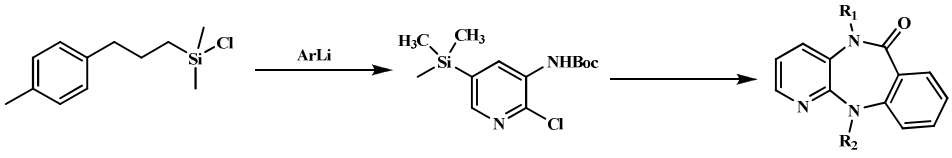
Scheme-33

The synthesis began with Mitsunobu reaction on 4-hydroxymethyl polystyrene with *N*-monosubstituted 2-nitrobenzenesulfonamides. Next, *N,N*-disubstituted-2-nitrobenzenesulfonamides provided the secondary amines by deprotection of the 2-nitrobenzenesulfonyl group. Next, by Michael addition, were transformed into amino ketones, which were then converted to the corresponding diamines by reductive amination. Diamines were transformed into the key intermediates by acylation with haloacetic acids. Intramolecular cyclization and the quaternarization of the resin-bound tertiary nitrogen were carried out in the presence of CsI in dioxane-H_2O at 95ºC. The products were treated with thiols under conditions reported in the literature to provide the desired compound in high purity (scheme-34).[36]



Scheme-34

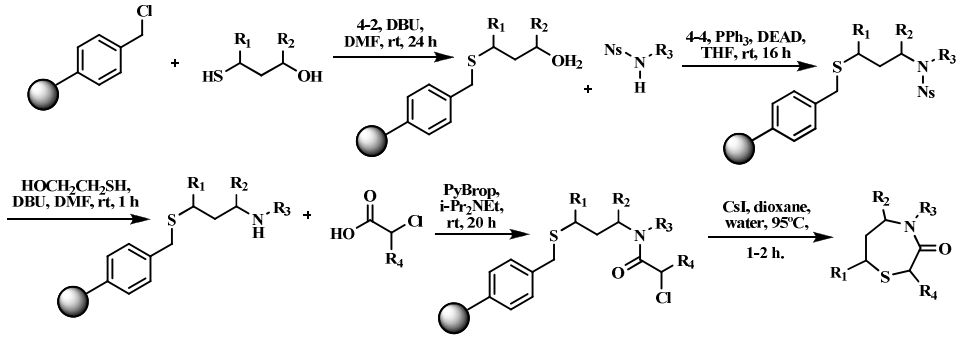
Ellman et al.[37] also described a trialkylsilyl chloride linker for the direct loading of aromatic compounds. Darling et al. described a similar resin prepared by the hydrosilylation of residual vinyl groups in a divinylbenzene copolymer (scheme-35).



Scheme-35

The synthesis began with the nucleophilic displacement of benzyl chloride on Merrifield resin with the sulfanylethanols. Under the Mitsunobu conditions with *N*-monosubstituted 2-nitrobenzenesulfonamides, the polymer-supported alcohols were converted to the *N*,*N*-disubstituted 2-nitrobenzenesulfonamides, which provided the secondary amines by the deprotection of the 2-nitrobenzenesulfonyl group. Then the amines were transformed into the key intermediates by

acylation with chloroacetic acids. The intramolecular cyclization and the debenzylation of the sulfonium salts were carried out in the presence of CsI, providing the product in high purity (scheme-36).[36]



Scheme-36

CONCLUSION

The combinatorial synthesis of azepine heterocyclic organic molecules plays a significant role in the area of drug discovery. Solid-phase azepine heterocycle synthesis has been established as an important tool for preparative chemistry with a broad range of applications in modern organic synthesis. In very few reaction steps, libraries of molecularly diverse compounds can be synthesized by taking advantage of the efficient removal of excess or unconsumed reagents by extraction and filtration as simple workup operations, in high purity without time-consuming purification steps.

REFERENCES

1. Kamble R. R. and Sudha B. S., Synthesis and Pharmacological evaluation of 1,5-benzothiazepine derivatives, *Phosphorus, Sulfur and Silicon*, 183, 1691 (2008).
2. Vijaychand A., Manjula S. N., Bharath E. N. and Divya B., Medicinal and biological significance of quinazoline: a highly important scaffold for drug discovery: A review, International Journal of Pharma and Bio Sciences, 2, 780 (2011).
3. Sathe B. S., Jaychandran E., Jagtap V. A. and Sreenivasa G. M., Anti-mycobacterial activity of some synthesized 2[21-phenyl-41-benzidinyl-51-oxo-imidazoline-1yl-amino]-6 fluoro-7-substituted (1,3) benzothiazoles, International Journal of Pharma and Bio Sciences, 1, 139 (2010).
4. Raval J. P., Desai J. T., Desai C. K. and Desai K. R., A comparative study of microwave assisted and conventional synthesis of 2,3-dihydro-2-aryl-4-oxo2H-chromen-3-yl-1,3-thiazol-2-ylamino-1,5-benzothiazepines and its antimicrobial activity, *Arkivoc*, (xiii), 233 (2008).
5. Pathak V. N., Joshi R. and Gupta N., Synthesis, spectral studies and antimicrobial activity of 7-chloro-2-alkyl/aryl-4-alkyl/aryl-3arylidene-3H-1,5-benzodiazepines, *Ind. J. Chem.*, 46B, 1191 (2007).
6. Puodziunaite B. D, Janciene R. and Kosychova L., On the synthetic way to novel peri-annelated imidazo[1,5]benzodiazepines as the potent non-nucleoside reverse transcriptase inhibitor, *Arkivoc*, 1(iv), 512 (2008).
7. Piscopio A. D., Miller J. F. and Koch K., A second generation solid phase approach to Freidinger lactams: application of Fukuyama's amine synthesis and cyclative release via ring closing metathesis, Tetrahedron Lett., 39, 2667-2670 (1998).

8. Van M. J. H., Den H. J. A. J, Engelen V., Finner E., Visser G. and Kruse C. G., ChemInform Abstract: Solid Phase Ring-Closing Metathesis: Cyclization/Cleavage Approach Towards a Seven-Membered Cycloolefin, Tetrahedron Lett., 37, 8249 (1996).
9. Bolton G. L. and Hodges J. C., Solid-phase synthesis of substituted benzazepines via intramolecular Heck cyclization, J. Comb. Chem. 1, 130 (1999).
10. Landi J. J. and Ramig K., ChemInform Abstract: Regioselective Preparation of 4-Formyl-3,5-dimethoxyphenol, an Intermediate in the Synthesis of the PAL Solid-Phase Peptide Synthesis Handle, Syn. Commun. 21, 167 (1991).
11. DeWitt S. H., Kiely J. S., Stankovic C. J., Schroeder M. C., Cody D. M. R. and Pavia M. R., Annual Reports in Combinatorial Chemistry and Molecular Diversity, Proc. Natl. Acad. Sci. U.S.A. 90, 6909 (1993).
12. Plunkett M. J. and Ellman J. A., Stille Coupling in the Solid-Phase Synthesis of Structurally Diverse 1,4-Benzodiazepine Derivatives, J. Am. Chem. Soc. 117, 3306 (1995).
13. Plunkett M. J. and Ellman J. A., Silicon-Based Linkage Strategy for Traceless Solid-Phase Synthesis, J. Org. Chem. 60, 6006 (1995).
14. Goff D. A. and Zuckermann R. N., Solid-Phase Synthesis of Highly Substituted Peptoid 1(2H)-Isoquinolinones, J. Org. Chem. 60, 5748 (1995).
15. Lorin A. T. and Jonathan A. E., Synthesis and Applications of Small Molecule Libraries, Chem. Rev. 96, 555 (1996).
16. Bhalay G., Blaney P., Palmer V. H. and Baxter A. D., Solid-phase synthesis of diverse tetrahydro-1,4-benzodiazepin-2-ones, Tetrahedron Lett. 38, 8375 (1997).
17. Adel N., Nhi A. O. and Richard A. H., Parallel synthesis of 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-diones, Tetrahedron Lett. 42, 5141 (2001).
18. Ignacio A. R., Margarita P., Socorro H., Domingo M., Georgina P. L. and Daniel C., Intrinsic sensing fluorescent probe for the solid phase synthesis of 1,4-benzodiazepine-2,5-dione, ARKIVOC, (xi) 27 (2003).
19. Isak I., Thomas R. W., Young-Dae G., Jaell K. and Yong-Chul K., Solid-phase synthesis of tetrahydro-1,4-benzodiazepine-2-one derivatives as a beta-turn peptidomimetic library, J. Comb. Chem. 6, 207 (2004).
20. Dolle R. E., MacLeod C., Martinez-Teipel B., Barker W., Seida P. R. and Herbertz T., Solid/Solution-Phase Annulation Reagents: Single-Step Synthesis of Cyclic Amine Derivatives, Angew. Chem .Int. Ed. Engl. 44, 5830 (2005).
21. Ming-Fu C., Hui-Ming Y., Bor-Wen K., Yu C., Ming-Yi C., Tong-Ing H., Yeun-Min T. and Jim-Min F., Practical synthesis of potential endothelin receptor antagonists of 1,4-benzodiazepine-2,5-dione derivatives bearing substituents at the *C*3-, *N*1- and *N*4-positions, Org. Biomol. Chem. 4, 510 (2006).
22. Sung-Chan L. and Seung B. P., Novel application of Leuckart-Wallach reaction for synthesis of tetrahydro-1,4-benzodiazepin-5-ones library, Chem. Commun. 3714 (2007).
23. Jeon M. K., La H. J., Ha D. C. and Gong Y. D., Novel Solid-Phase Synthetic Method for Combinatorial Generation of a 4-Hydroxyquinolin-2(1H)-one-Based Library, Synlett, 1431 (2007).
24. Laustsen L**.** S**.** and Sams C**.** K**.**, Parallel synthesis of 1,3-dihydro-1,4-benzodiazepine-2-ones employing catch and release, J. Comb. Chem. 9, 1094 (2007).
25. Moon-Kook J., Jeong-Jin K., Myung S. and Young-Dae G., A novel Solid-Phase synthetic method for 1,4-benzodiazepine-2,5-dione derivatives, Synlett, 11, 1651 (2008).

26. Brase S., Kirchhoffb J. H. and Kobberlingc J., Palladium catalyzed reactions in solid phase organic synthesis, Tetrahedron 59, 885-939 (2003).
27. Berry J. M., Howard P. W. and Thurston D. E., Solid-Phase Synthesis of DNAInteractive Pyrrolo[2,1-c][1,4]benzodiazepines, Tetrahedron Lett. 41, 6171 (2000).
28. Boojamra C. G., Burow K. M., Thompson L. A. and Ellman J. A., The Solid-Phase Synthesis of 1,4-Benzodiazepine-2,5-diones. Library Preparation and Demonstration of Synthesis Generality, J. Org. Chem. 62, 1240 (1997).
29. Dewitt S. H., Kiely J. S., Stankovic C. J., Schroeder M. C., Cody D. M. R. and Pavia M. R., Diversomers: an approach to nonpeptide, nonoligomeric chemical diversity, Proc. Natl. Acad. Sci. USA 90, 6909-6913 (1993).
30. Franzen R., The Suzuki, Heck, and Still reactions: Three versatile methods for the introduction of C-C bonds on solid support, Can. J. Chem. 78, 957-962 (2000).
31. Adel N., Nhi A. O., Marc A. G., John M. O. and Richard A. H. Solid phase synthesis of 1,4-benzothiazepin-s-one derivatives, Tetrahedron Letters, 40, 4939-4942 (1999).
32. Schwarz M. K., Tumelty D. and Gallop M. A., Solid-phase synthesis of 3,5-disubstituted-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones, J. Org. Chem. 64, 2219 (1999).
33. George C. M., Joseph M. S., Richard F. L. and Timothy F. H., Novel solid-phase synthesis of 1,5-benzothiazepine-4-one derivatives, Tetrahedron Letters 41, 3029-3033 (2000).
34. Farzana L. A., Fatima I., Ihsan-ul-Haq, Bushra M., Mohammad B. and Umer R., Solid-phase synthesis and biological evaluation of a parallel library of 2,3-dihydro-1,5-benzothiazepines, Bioorganic & Medicinal Chemistry 16, 7691-7697 (2008).
35. Ouyang X., Tamayo N. and Kiselyov A. S., Solid support synthesis of 2-substituted dibenz [b,f]oxazepin-11(10H)-ones via SnAr methodology on AMEBA Resin, Tetrahedron, 55, 2827 (1999).
36. Fukuyama T., Jow C. K. and Cheng M., 2-nitrobenzenesulfonamides and 4-nitrobenzenesulfonamides-exceptionally versatile means for preparation of secondary-amines and protection of amines, Tetrahedron Lett. 36, 6373-6374 (1995).
37. Woolard F. X., Paetsch J. and Ellman J. A., A Silicon Linker for the Direct Loading of Aromatic Compounds onto Solid Supports. Traceless Synthesis of Pyridyl-Based Tricyclics, J. Org. Chem., 62, 6102 (1997).