Reviews

Combinatorial Syntheses of Five-Membered Ring Heterocycles Using Carbon Disulfide and a Solid Support

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Combinatorial chemistry has become an extremely powerful technique for the rapid generation of small, drug-like organic molecule libraries for the purpose of medicinal chemistry programs within the pharmaceutical industry.[1−3] Well over half of all therapeutic agents contain heterocyclic skeletons that serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs.[4,5] In combinatorial synthesis, solid-phase organic synthesis (SPOS) is now routinely used to prepare a large number of small, heterocyclic, drug-like molecules and is especially useful in creating massive numbers of hit and lead compounds as part of high-throughput screening technologies.[5,6] This is especially true for five-membered heterocyclic compounds, which are core components of a large number of substances that possess a wide range of interesting biological activities.[7]

Substituted five-membered ring heterocyclic compounds and their fused counterparts offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. In this respect, various approaches for the preparation of these privileged structures with drug-like properties have been developed on solid-phase strategies.[8,9]

The sulfur atom is the fundamental element of various five-membered ring heterocycles,[10] such as thiophene, thiazole, isothiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, and 1,3,4-thiadiazole, and is the key element of the reaction intermediate and linkers for solid support.[8,11] Several well-known sulfur source reagents, such as carbon disulfide, thiourea, thiophosgene, phosphorus sulfide (P_2S_5), Lawesson's reagent, 1,1-thiocarbonyldiimidazole, di-(2-pyridyl)thionocarbonate (DPT), and isothiocyanate, have been used to synthesize various heterocycles.

Thus, many synthetic methods have been investigated for the synthesis of five-membered ring heterocycles and their fused counterparts using sulfur-containing reagents as a sulfur source, linker, substituted site, or intermediate. Among recent examples, many research groups reported the synthesis of 2,3,4,5-tetrasubstituted thiophenes,[12] 1,3,4-thiadiazoles,[13] and 1,3,4-triazolo[3,4-*b*][1,3,4]thiadiazoles and 1,3,4-triazolo[3,4-*b*]-[1,3,4]thiadiazines,[14] using carbon disulfide as a sulfur source and substituted site in solution-phase. The carbon disulfide was used as a sulfur source in the solution-phase synthesis of arylthiobenzothiazoles,[15] 4,6-dithiopyrazolo[3,4-*d*]-pyrimidines,[16] and 1,2,3,4-tetrahydro-7-thia-6,9,10,11-tetraaza-benzo[*c*]fluorenes.[17] The solution-phase syntheses of 3-alkyldithiocarbonyl-oxazolidines[18] and 5-thia-1,3,8-triaza-cyclopenta[*b*]naphthalen-7-ones[19] were developed by using carbon disulfide as a substituted site. The carbon disulfide was used as useful reagents in the solution-phase synthesis, such as an intermediate of the synthesis of 2-arylamino-2-imidazolines,[20] an intermediate of the formation of isothiocyanate for the synthesis of substituted thienopyrimidine-4-ones,[21] and a ring formation agent of the synthesis of benzimidazoles.[22] In addition, some research groups established the synthesis of 2-amino-5-sulfanylthiazoles using isothiocyanate as a sulfur source,[23] and the synthesis of 1,3,4-thiadiazoles using DPT as a sulfur source[24] or using isothiocyanate as a sulfur source and diversity element[25] on a solid support. The solid-phase synthesis of 5-arylalkylidene rhodanines using 1,1-thiocarbonyldiimidazole as a sulfur source and linker was reported.[26] The flow chemical synthesis of 4,5-disubstituted thiazoles and imidazoles in combination with immobilized base was developed by using isothiocyanate as a sulfur source and substituted site.[27]

Among these sulfur-containing reagents, *carbon disulfide* is a facile, cheap, and versatile reagent and a starting material for the synthesis of various sulfur and heterocyclic compounds.[28] As part of our current interest in SPOS, we examined the efficient and rapid synthesis of nitrogen- or sulfur-containing, five-membered ring heterocycles and their fused counterparts by solid-phase strategies using Merrifield resin **1** and carbon disulfide (Figure 1).[29−38] In addition, many research groups developed the solid-phase synthesis of five-membered ring heterocycles using carbon disulfide

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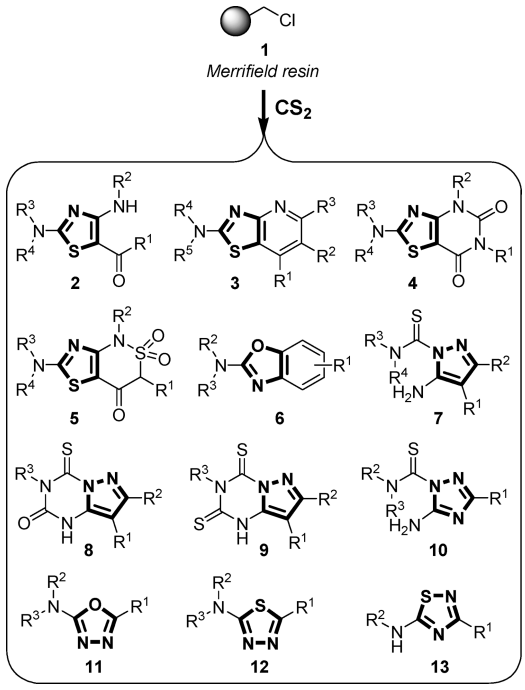


Figure 1. Drug-like five-membered heterocycles and their fused-heterocycles from Merrifield resin and carbon disulfide.

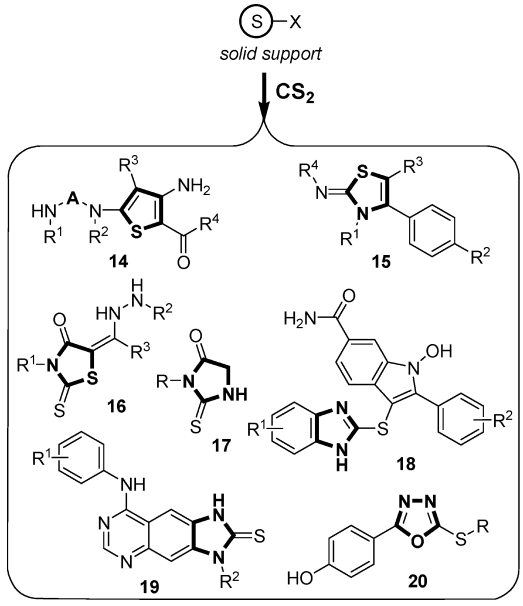


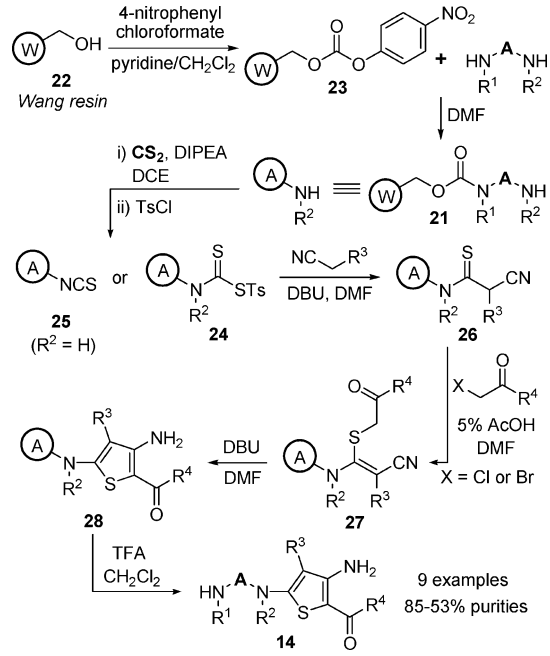
Figure 2. Drug-like five-membered heterocycles and their fused-heterocycles from a solid support and carbon disulfide.

(Figure 2).[39−45] In this paper, we review the synthesis of five-membered ring heterocycles and their fused counterparts on solid support with carbon disulfide. The sections are divided according to the amount of heteroatoms in the core ring and kinds of core heterocycles. Moreover, the compounds are divided into subsections on the basis of the preparation of monocyclic compounds and fused-heterocycles. Publications cited herein are mostly from refereed journals and not from patents.

Solid-Phase Synthesis of Thiophenes

The protocol for the solid-phase synthesis of 3-aminothiophenes **14** with variable substituents was described by

Scheme 1. Solid-Phase Synthesis of 2,4,5-Trisubstituted 3-Aminothiophenes



Zaragoza et al.[39] The reaction sequence was based on resin-bound primary or secondary amines **21**, which were synthesized from Wang resin **22** with two-step reactions.[46] The Wang resin **22** was converted to the *p*-nitrophenyl carbonate intermediate resin **23** by reaction with 4-nitrophenyl chloroformate (Scheme 1).

The carbonate resin **23** was treated with appropriate amines in DMF to give the amine resin **21**. Treatment of resin **21** with carbon disulfide and *p*-toluenesulfonyl chloride (TsCl) in the presence of diisopropylethylamine (DIPEA) led to the formation of thiocarbamoyl derivatives **24** or isothiocyanates **25**. These intermediate resins **24** or **25** were then reacted with various acceptor-substituted acetonitriles, under basic conditions, to yield thioamide resin **26**. S-Alkylation of the latter with α-halo ketones under slightly acidic conditions provided the resin-bound intermediate **27**. When this intermediate resin **27** was treated with a base (DBU or amines) to give the thiophene resin **28** and then cleaved by trifluoroacetic acid (TFA) from the solid support, the desired pure thiophenes **14** were obtained. However, this reaction sequence suffered the following limitations: generally no thiophenes **14** resulted when aliphatic halo ketones or haloacetic esters were used for the S-alkylation of thioamides **27**. On the other hand, a broad range of different acceptor-substituted acetonitriles could be used, such as aliphatic or arene sulfonylacetonitriles, acylacetonitriles, cyanoacetic esters, and malononitrile but not (cyanomethyl)phosphonates. The purities of the crude products **14**, determined by HPLC analysis, ranged from 53% to 85% (9 examples, Figure 3).

Solid-Phase Synthesis of Related Thiazole Compounds

Solid-Phase Synthesis of 2,4,5-Trisubstituted Thiazoles. Thiazoles are useful heterocycles and building blocks and a prominent structural element of compounds used to treat cancer, bacterial, fungal, and viral infections.[47] Because the thiazole derivatives exhibit a wide range of important

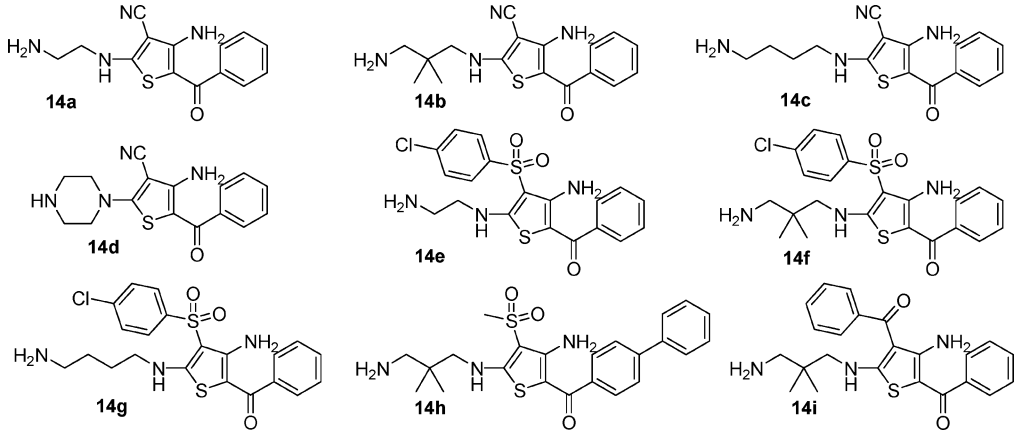
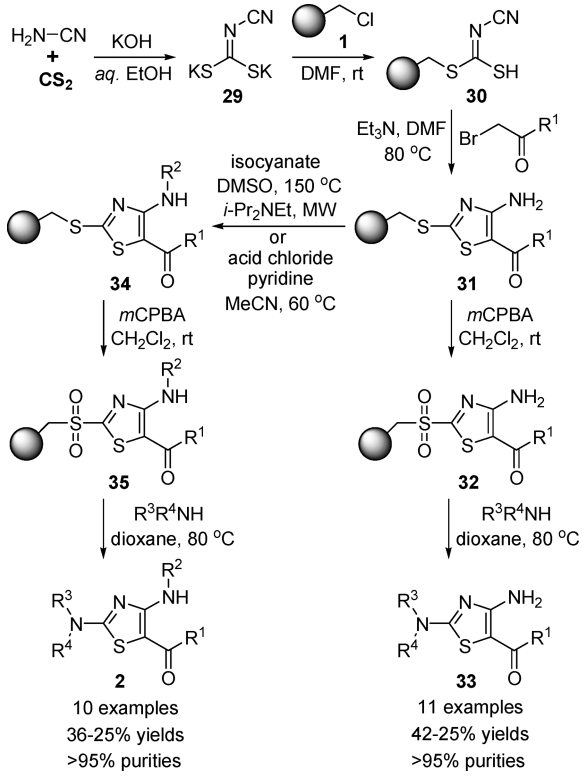


Figure 3. 2,4,5-Trisubstituted 3-aminothiophenes.

Scheme 2. Solid-Phase Synthesis of 2,4,5-Trisubstituted Thiazoles



biological activities, they serve as attractive targets for combinatorial library construction. We have previously described an efficient, facile, and rapid solid-phase synthetic strategy for 2,4,5-trisubstituted thiazoles **2** using a traceless cleavage[48] of the 2-sulfonyl linker of thiazole.[29]

The general solid-phase synthetic procedure for thiazole derivatives started with the reaction of commercial Merrifield resin **1** with dipotassium cyanodithioimidocarbonate **29**,[49] which was prepared from carbon disulfide, cyanamide, and KOH in aqueous ethanol. When DMF was used as a solvent, solid-supported cyanocarbonimidodithioate **30** was obtained with a good loading capacity (Scheme 2). In addition, one-pot three-component reaction of Merrifield resin **1** with carbon disulfide and cyanamide for resin **30** displayed a lower loading capacity of about 40% based on a comparison of the stepwise pathway. The resin **30** was treated with 2-bromoacetophenone (for **31a**) or ethyl 2-bromoacetate (for **31b**) (R^1 diversity element) and triethylamine at 80 °C to give the corresponding thiazole resin **31** via Thorpe−Ziegler cyclization. After the sulfonyl resin **31** was oxidized to form sulfone resin **32** by treatment with *m*-chloroperoxybenzoic acid (*m*CPBA),[50,51] the desired thiazoles **33** were liberated from resin **32** by nucleophilic addition of various amines (R^3R^4N diversity elements: primary and secondary amines and anilines). The isolated overall yields for thiazoles **33** (11 examples, Figure 4) ranged from 25 to 36% from the Merrifield resin **1**.

The acylation with acid chloride and the urea formation with isocyanate of intermediate resin **31** afforded other substituent groups onto 4-aminothiazole. Under microwave (MW) irradiation reaction[52] with isocyanate and acylation reaction with acid chloride, R^2-substituted thiazole resin **28** was obtained. Following conversion of sulfanyl resin **34** to sulfonyl resin **35** (*m*CPBA/CH_2Cl_2) substitution reactions promoted by treatment with appropriate amines (R^3R^4N diversity elements) furnished the 2,4,5-trisubstituted thiazoles **2** (10 examples; 36−25% isolated yields from Merrifield resin **1**, Figure 4).

Solid-Phase Synthesis of 2,5,6,7-Tetrasubstituted Thiazolo[4,5-*b*]pyridine. The fused-thiazole heterocycles are important structural components of bioactive molecules, and as a result, they serve as attractive targets for combinatorial library construction via solution- and solid-phase synthesis.[1,53] Among the fused-thiazoles, thiazolo[4,5-*b*]pyridine derivatives **3** exhibit a wide range of biological properties.[54] Thus, many solution-phase synthetic methods have been documented for thiazolo[4,5-*b*]pyridine derivatives using carbon disulfide as a starting material.[50,55,56] Kirsch and co-workers reported a solution-phase synthesis of 7-aminothiazolo[4,5-*b*]-pyridines and thiazolo[4,5-*d*][1,2,3]triazines using carbon disulfide as a starting material for 4-amino-1,3-thiazole-5-carbonitrile intermediate.[55] Also, Johnson and co-workers developed a synthesis of 7-chloro-2-methylsulfanyl-thiazolo[4,5-*b*]pyridine-6-carbonitrile using carbon disulfide as a starting material for 4-amino-thiazole.[50] We represented the first solid-phase synthesis of 2,5,6,7-tetrasubstituted thiazolo[4,5-*b*]pyridines **3** using thiazole resin **31** from carbon disulfide and Merrifield resin **1**.[30]

The solid-phase synthetic route for the preparation of thiazolo[4,5-*b*]pyridines utilizes appropriate α-bromoacetophenones, ketones, and amines as key building blocks and

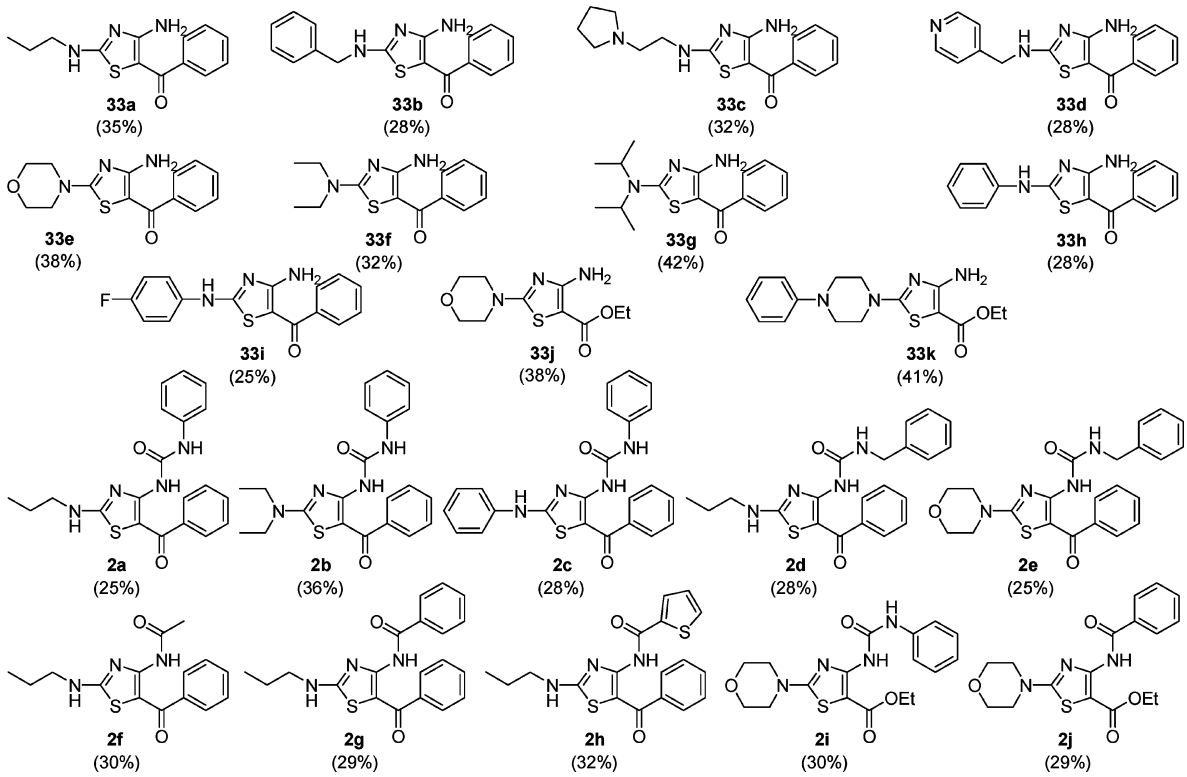


Figure 4. 2,4,5-Trisubstituted thiazoles **2** and **33** and their yields.

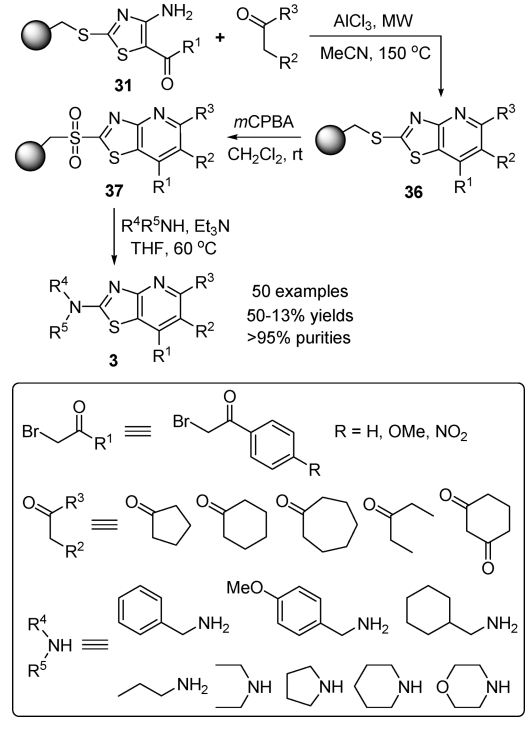
diversity elements. The sequence began on the basis of successful solution-phase synthetic conditions.[30] The known thiazole resin **31** with R^1 diversity element was reacted under optimized Friedländer reaction conditions ($AlCl_3$ and MW irradiation)[55,57] with ketones ($R^2CH_2COR^3$). This process efficiently produced the thiazolo[4,5-*b*]pyridine resin **36** and introduced the second potential diversity elements R^2 and R^3. Treatment of resin **36** with *m*CPBA in CH_2Cl_2 provided the resin-bound sulfone intermediate **37** (Scheme 3).

Finally, the sulfone group on resin **37** was displaced by a desulfonative substitution reaction with the corresponding amines (R^4R^5N diversity elements) in THF. This process, which is accompanied by concurrent cleavage from the resin, furnished the final thiazolo[4,5-*b*]pyridine derivatives **3** (50 examples; 50−13% overall yields from Merrifield resin **1**), which were purified by column chromatography.

Solid-Phase Synthesis of 2,4,6-Trisubstituted Thiazolo[4,5-*d*]pyrimidine-5,7-diones. Thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives **4**, congeners of xanthine and uracil (pyrimidinedione), exhibit a wide range of important biological properties[58] and, as a result, are attractive targets for combinatorial library construction. In view of these diverse properties, an expedient, traceless, solid-phase synthesis of 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives was developed.[31] The key step of a solid-phase synthetic route is urea formation by the microwave irradiation[52] promoted reaction of a thiazole amino ester resin **31b** (R^1 = OEt) with an isocyanate and base-catalyzed cyclization, which were optimized in solution-phase chemistry (Scheme 4).

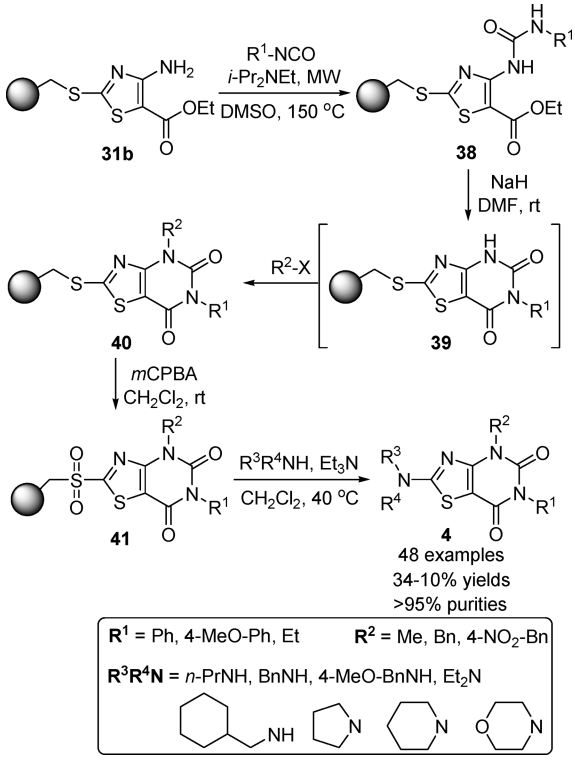
The solid-phase synthesis of thiazolo[4,5-*d*]pyrimidine-5,7-diones **4** utilizes appropriate isocyanates, alkyl halides, and amines as key building blocks and diversity elements.

Scheme 3. Solid-Phase Synthesis of 2,5,6,7-Tetrasubstituted Thiazolo[4,5-*b*]pyridines

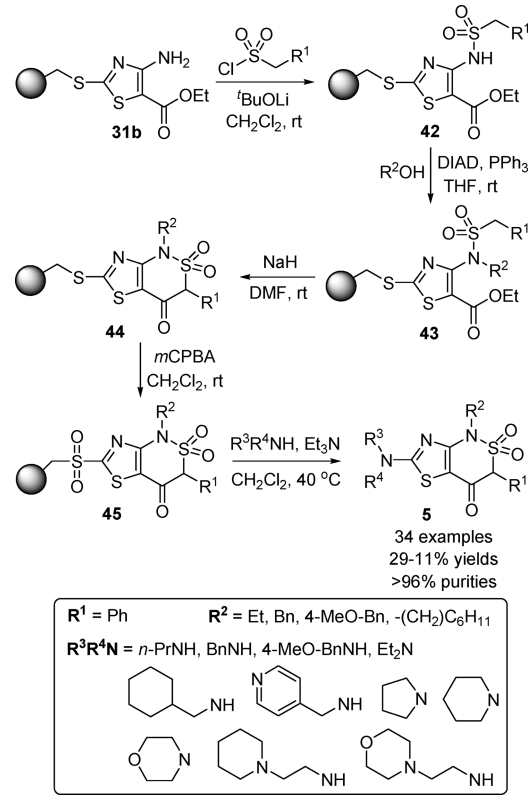


The sequence was started with the formation of thiazole amino ester resin **31b** through reaction of the solid supported cyanocarbonimidodithioate **30** with ethyl 2-bromoacetate. The amino ester resin **31b** was treated under MW irradiation conditions with isocyanate (R^1 diversity element) to give the corresponding thiazolourea resin **38**. The one-pot cyclization/*N*-alkylation of thiazolourea resin **38**, using sodium hydride as a base and alkyl halide (R^2 diversity element) was carried

Scheme 4. Solid-Phase Synthesis of 2,4,6-Trisubstituted Thiazolo[4,5-*d*]pyrimidine-5,7-diones



Scheme 5. Solid-Phase Synthesis of 1,3,6-Trisubstituted 1*H*-Thiazolo[4,5-*c*][1,2]-4(3*H*)one-2,2-dioxides



out in DMF at room temperature. Accordingly, treatment of resin **38** with NaH in DMF provided the intermediate **39**, which underwent in situ N-alkylation with alkyl halide to provide the desired thiazolo[4,5-*d*]pyrimidine-5,7-dione resin **40** containing two diversity elements at N-4 and N-6. After the oxidation of resin **40** to form the sulfone group on resin **41**, nucleophilic C-2 substitution with the corresponding amines (R^3R^4N diversity elements) afforded the target 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimide-5,7-dione derivatives **4**. This process, which was accompanied by concurrent cleavage from the resin, furnished the final thiazolo[4,5-*d*]-pyrimidine-5,7-diones **4** (48 examples). The isolated overall yields for thiazolo[4,5-*d*]pyrimidine-5,7-diones ranged from 10 to 34% for the six-step linear pathway (the average yield for each step was 69 to 84%) from the Merrifield resin **1**.

Lipinski's rule[59] and similar formulations serve as guides to an estimation of the physicochemical properties of the 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives **4**. Most of the key parameters for members of the library fall within the range of those predicted for reasonable oral bioavailable drugs by using the commonly known guidelines.[31]

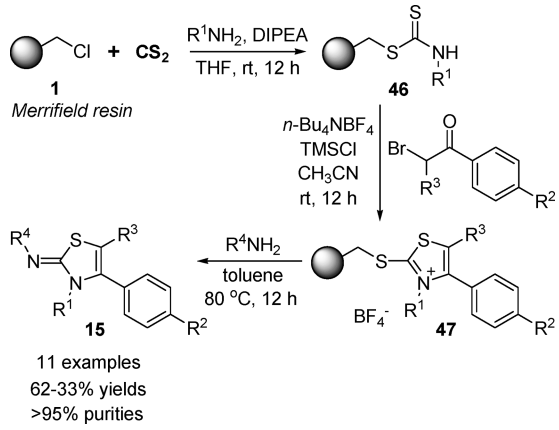
Solid-Phase Synthesis of 1,3,6-Trisubstituted 1*H*-Thiazolo[4,5-*c*][1,2]thiazin-4(3*H*)one-2,2-dioxides. We previously described the first solid-phase route for the preparation of 1,3,6-trisubstituted 1*H*-thiazolo[4,5-*c*][1,2]thiazin-4(3*H*)one-2,2-dioxide derivatives.[32] The initial solid-phase synthetic route we developed to prepare substances containing the thiazole scaffold involved the formation of the intermediate thiazole resin **31b** (Scheme 5).

Resin **31b** was first swollen in CH_2Cl_2 and, in a manner that parallels the route employed in the solution-phase synthesis, was reacted with a selected benzylsulfonyl chloride and *t*-BuOLi as a base to give the corresponding sulfonamide resin **42**, containing the first diversity element R^1. The sulfonamide resin **42** was then reacted under Mitsunobu conditions (PPh_3, DIAD, THF, room temperature)[60,61] with the appropriate alcohols. This process efficiently produced resin **43** and introduced the second diversity element R^2. Cyclization reaction of resin **43** was promoted by sodium hydride in DMF and led to the formation of the desired thiazolo[4,5-*c*][1,2]thiazine resin **44**. Treatment of resin **44** with *m*CPBA in CH_2Cl_2 generated the resin-bound cyclic sulfonamide **45**. Finally, the thiazolo[4,5-*c*][1,2]thiazine derivatives **5** were formed and cleaved from the resin (in a traceless manner[48]) by treatment of resin **45** with the corresponding amines (R^3R^4N diversity elements) in respectable yields (34 examples, from 11 to 29% for seven linear steps starting with Merrifield resin **1**).

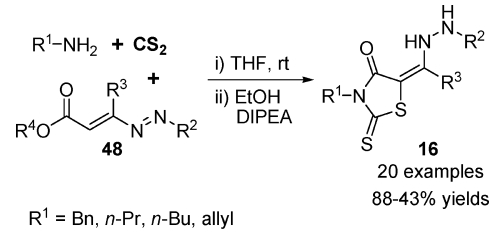
When the R^1 on resin **43** was hydrogen or ethyl, reaction of intermediate resins **43** under the optimal conditions failed to produce precursors of the respective target compounds and only noncyclized products were isolated. This problem is probably because of the lower acidity of the C-3 α-protons in resins **43** (R^1 = H or Et). In cases where the R^2 substituent was an electron-withdrawing benzyl (4-NO_2-Bn), the sequence also failed to produce the desired target. It appeared that the acidic proton present in **43** (R^2 = 4-NO_2-Bn) renders ineffective the cyclization to produce **44**.[60]

Solid-Phase Synthesis of Tetrasubstituted 2-Imino-1,3-thiazolines. Gomez and co-workers developed the solid-phase synthesis of tetrasubstituted 2-imino-1,3-thiazolines **15** using carbon disulfide and Merrifield resin **1**.[40] The key strategy is a functionalizing cleavage of the thiazolium salt with various amines (Scheme 6).

Scheme 6. Solid-Phase Synthesis of 2-Imino-1,3-thiazolines



Scheme 7. Solution-Phase Synthesis of 5-Hydrazinoalkylidene Rhodamines Using a Three-Component Reaction



R^1 = Bn, *n*-Pr, *n*-Bu, allyl
$CH_3CHOHCH_2$-, $(EtO)_2CHCH_2$-
R^2 = CO_2t-Bu, CO_2Et, CO_2Me, CO_2Bn, Ph
R^3 and R^4 = Me or Et

The resin-bound dithiocarbamate **46**[62] was prepared by the three-component reaction of the Merrifield resin **1** and a primary amine (R^1 diversity element) in the presence of carbon disulfide under basic conditions. The key thiazolium intermediate resin **47** was obtained by the reaction of dithiocarbamate resin **46** with α-bromoketones (R^2 and R^3 diversity elements) using the combination of chlorotrimethylsilane (TMSCl) and tetrabutylammonium tetrafluoroborate. These reaction conditions prevented the formation of two byproduct, namely, imidazolininone and imidazolinethione, which were obtained by the cleavage hydrolysis and nucleophilic attack of the bromide at the benzylic position of the thiazolium resin respectively. Treatment of thiazolium resin **47** with a primary amine (R^4 diversity element) in toluene at 80 °C provided the target 2-imino-1,3-thiazolines **15** in good overall yields (Figure 5, 11 examples; 62−33% isolated yields from Merrifield resin **1**).

Solid-Phase Synthesis of 2-Thioxothiazolidin-4-ones. Among 4-thiazolidinone heterocycles, the rhodanine A (2-thioxothiazolidin-4-ones) motif represents an important medicinal scaffold and rhodanine-based molecules are biologically active and inhibit numerous targets.[63] Recently, Alizadeh and co-workers reported a simple and effective approach to the synthesis of rhodanine derivatives via three-component reactions with primary amines, carbon disulfide, and dialkyl acetylenedicarboxylate in water[64] and also developed a novel multicomponent method for the synthesis of 2-thioxothiazolidin-4-ones using three-component reactions with primary amines, carbon disulfide, and fumaryl chloride.[65] In addition, Favi's research group reported a novel three-component synthesis under both solution- and solid-phase conditions of 5-hydrazinoalkylidene rhodanine derivatives **16** starting from aliphatic primary amines, carbon disulfide, and 1,2-diaza-1,3-dienes.[41] The three-component solution reaction is illustrated in Scheme 7.

To obtain the relative rhodanine **16a** from the reagent [benzylamine (R^1 = Bn)], carbon disulfide, and 1,2-diaza-1,3-diene **48a** (R^2 = CO_2t-Bu, R^3 = Me, and R^4 = Et), the various reaction conditions were screened. A reagent ratio of 1.5/1/3 (benzylamine/carbon disulfide/**48a**) in THF afforded the desired rhodanine **16a** in the best yield (83%). Having established the optimal conditions, the 5-hydrazinoalkylidene rhodamines **16** were synthesized in one-pot three-component reaction providing 88−43% yields (20 examples). DIPEA must be added at the disappearance of the 1,2-diaza-1,3-dienes **48** to drive the process to completion by conversion of the dithiocarbamate acyclic intermediate **49B** (see Scheme 8) into the final 5-hydrazinoalkylidene rhodanines **16**. The structures of **16** were obtained exclusively in the hydrazino isomer with *E* configuration by the X-ray crystal structure analysis of one compound **16b** (R^1 = *n*-Pr, R^2 = CO_2Bn, and R^3 = Me).

A plausible mechanism for the formation of hydrazinoalkylidene rhodanines **16** is presented in Scheme 8. Initially, the intermediate **49A** is produced by nucleophilic

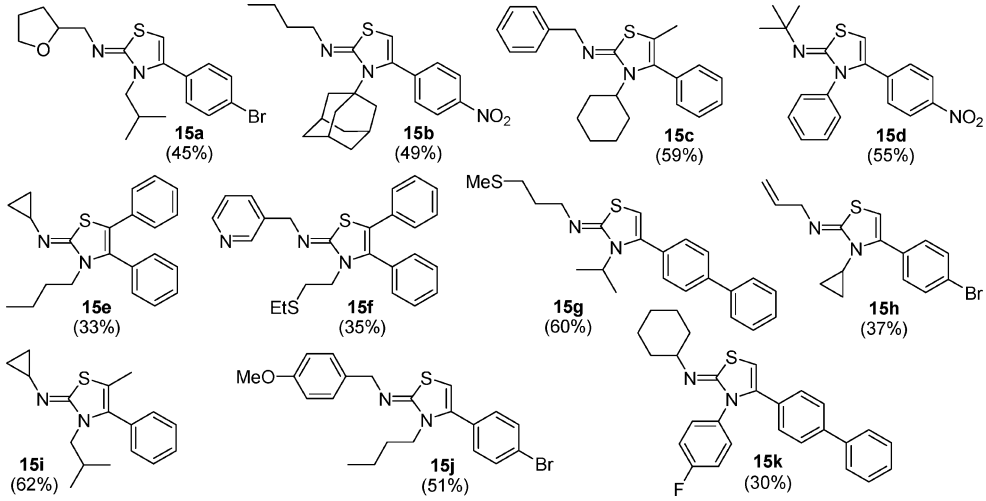
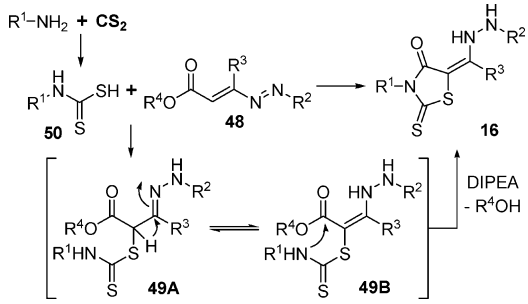
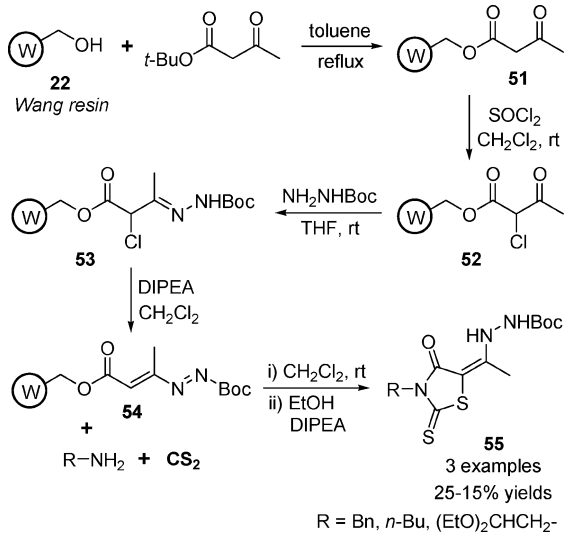


Figure 5. 2-Imino-1,3-thiazolines **15** and their yields.

Scheme 8. Plausible Mechanism for the Formation of 5-Hydrazinoalkylidene Rhodanine Derivatives



Scheme 9. Solid-Phase Synthesis of 5-Hydrazinoalkylidene Rhodamines



attack of the in situ generated dithiocarbamic acid **50** to the azo-ene system of the 1,2-diaza-1,3-diene **48** via a Michael-like 1,4-addition reaction. Successively, hydrazono−hydrazino tautomerization of intermediate **49A** produces **49B**, followed by base-promoted intramolecular nucleophilic attack of the NH dithiocarbamic group at the ester moiety with loss of the alcohol molecule and formation of compound **16**.

On the basis of successful solution-phase synthesis, the solid-phase version of this methodology was investigated. Wang resin **22** was treated with *tert*-butyl acetoacetate (toluene, reflux) to give the polymer-bound β-ketoester **51**. The chlorination of resin **51** with thionyl chloride led to the polymer-bound α-chloro-β-ketoester **52** that was subjected to reaction with Boc-protected hydrazine affording the polymer-bound hydrazone **53**. Treatment of resin **53** with DIPEA provided Wang resin polymer-bound 1,2-diaza-1,3-diene **54** obtained.[66] The resin **54** reacted with carbon disulfide and amines (R-NH_2) in dichloromethane at room temperature to afford directly hydrazinoalkylidene rhodanines **55** (Scheme 9). The overall yields for the multistep process of these solid-phase reactions were in the range of 15−25% (3 examples).

Solid-Phase Synthesis of Benzoxazoles

Benzoxazoles are privileged structures of particular interest in medicinal chemistry[67] and, consequently, have been the target of a number of solution- and solid-phase synthetic studies.[68] We have employed a carbon disulfide-mediated thioether linker methodology (i.e., safety-catch linker methodology[69]) in a procedure for efficient solid-phase synthesis of 2-aminobenzoxazole derivatives.[33] The sequence used to prepare the target 2-aminobenzoxazole derivatives **6** started with the Merrifield resin **1** as the polymer support. The benzyl chloride groups can be used to produce thioether linkages by reaction with the thiol formed in the cyclization reaction of carbon disulfide and aminophenol (Scheme 10).

Specifically, the intermediate benzoxazole resin **56** was generated by treatment of aminophenol **57** with carbon disulfide and Merrifield resin **1** in the presence of triethylamine in acetonitrile, but the resin was obtained in very low yield under this condition. The inefficiency of this process is due to rapid release of 2-mercaptobenzoxazole **58** from the intermediate **59** during the cyclization reaction (Scheme 11, path a). We attempted to circumvent this cleavage process by preforming 2-mercaptobenzoxazole **58**; however, reaction of aminophenol with carbon disulfide for 6 h at 80 °C gave 2-mercaptobenzoxazole **58** in a low yield (Scheme 11, path b).

We reasoned that a possible solution to this problem would be to accelerate the cyclization reaction. Therefore, we examined the effects of various additives, including *N*,*N*′-diisopropylcarbodiimide (DIC), *N*,*N*′-dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI), and TsCl. It resulted that the addition of DIC markedly increased the yield of the desired resin **56**. This intermediate is subsequently cyclized to yield 2-mercaptobenzoxazole **58**, which combines with the Merrifield resin **1** to give the polymer-bound benzoxazole **56** (Scheme 11, path c).

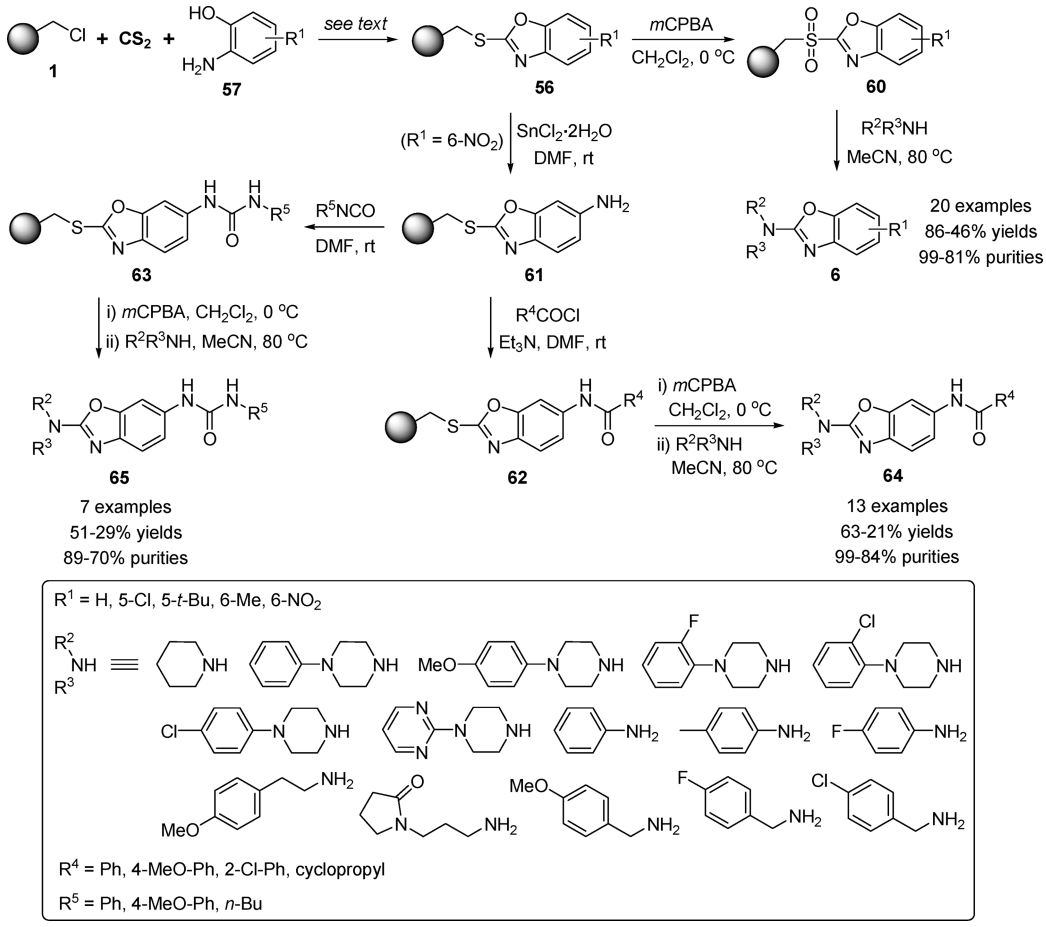
The resins **56** were transformed to the corresponding sulfone derivatives **60** by treatment with *m*CPBA in CH_2Cl_2 at 0 °C. To explore the versatility of this methodology, various amines (R^3R^4N diversity elements) were reacted with the sulfone-containing resins to generate the corresponding benzoxazole derivatives **6**. These cleavage reactions generally proceeded in high yields and high purities (20 examples, 86−46% yields, 99−81% purities).

To introduce additional diversification, the nitro group containing resin **56** (R^1 = 6-NO_2) was reduced to generate 6-aminobenzoxazole resin **61** by treatment with $SnCl_2 \cdot 2H_2O$. Functionalization of the amino group was promoted with acid chlorides (R^4COCl) or isocyanates (R^5NCO) to generate the corresponding amide resins **62** and urea resins **63**. In each case, the desired products **64** and **65** were cleaved by sequential treatment with *m*CPBA and various amines (R^2R^3N diversity elements) (for **64**: 13 examples, 63−21% yields, 99−84% purities, and for **65**: 7 examples, 51−29% yields, 89−70% purities).

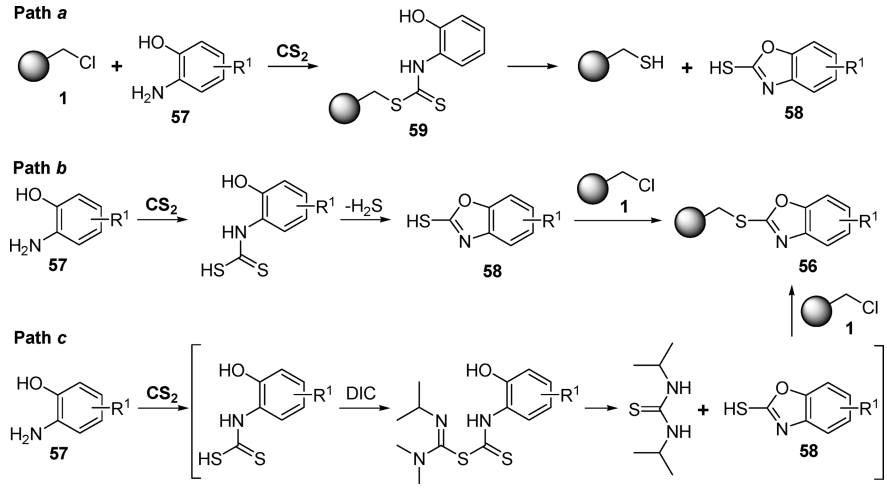
Solid-Phase Synthesis of Related Imidazole Compounds

Solid-Phase Synthesis of 2-Thioxoimidazolidin-4-ones. Chen group described a novel method for the liquid-phase combinatorial synthesis of 3-substituted-2-thiohydantoins using poly(ethyleneglycol) supported isothiocyanate.[42] Synthetic approaches that utilize soluble polymers, termed "liquid-phase" chemistry or soluble polymer-supported chem-

Scheme 10. Solid-Phase Synthesis of 2-Aminobenzoxazoles



Scheme 11. Plausible Mechanism for the Formation of Benzoxazole Resin **56**

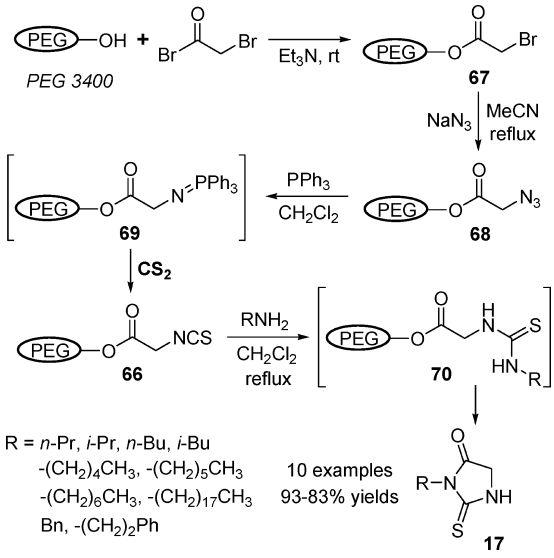


istry, couple the advantages of homogeneous solution chemistry with those of solid-phase methods.[70] Liquid-phase combinatorial chemistry has advantages, such as high reactivity, lack of diffusion phenomena, and ease of analysis. In particular, among the soluble supports, poly(ethyleneglycol) (PEG) is the most studied soluble polymer for organic synthesis.

The biological activities of thiohydantoin (2-thioxoimidazolidin-4-one) derivatives have been known for a long time.[71] The chemistry of thiohydantoin derivatives has been well developed in the past few years.[72] Chen's research group presented a new method to prepare thiohydantoin **17** using PEG-supported isothiocyanate **66**, which was formed by aza-Wittig reaction of bromoacetate resin **67**, followed by a cyclization-cleavage reaction with a primary amine.

As shown in Scheme 12, to achieve a reasonable balance between loading and good precipitation properties, a solid support comprising bifunctional PEG 3400-OH was used as a soluble polymer support. The PEG 3400 reacted with an excess of 2-bromoacetyl bromide in the presence of triethylamine in CH_2Cl_2 at room temperature to give PEG-bound bromoacetate **67**. After purification, resin **67** was treated with an excess of sodium azide to afford PEG-supported azide **68**. Triphenylphosphine reacted with polymer-bound azide

Scheme 12. Solid-Phase Synthesis of 2-Thiohydantoins



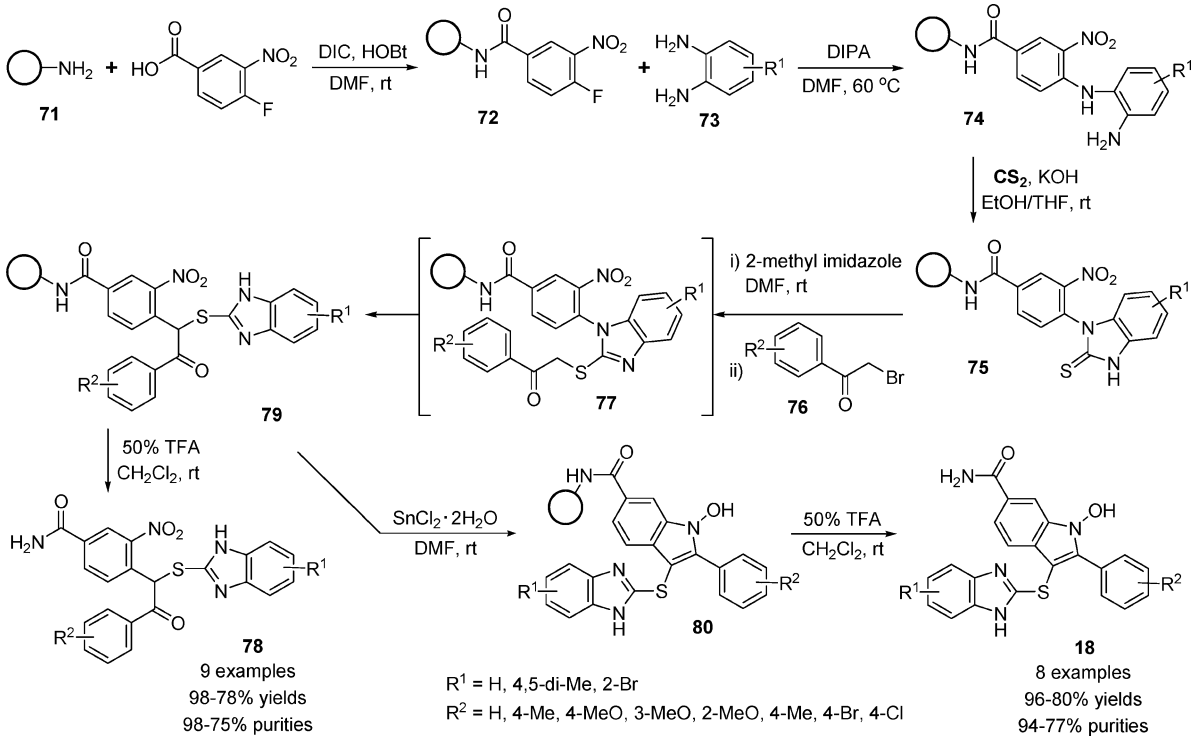
68 in an almost quantitative formation of the PEG-bound phosphorane **69**, and this compound underwent an aza-Wittig reaction[73] with carbon disulfide to produce PEG-bound isothiocyanoacetate **66** under reflux in dry CH_2Cl_2. Subsequently, polymer-bound isothiocyanoacetate **66** was coupled with various aliphatic amines (R diversity elements) to give the corresponding thiourea intermediate **70**, which was cyclized and cleaved at reflux in acetonitrile to afford the crude 3-substituted 2-thiohydantoin **17**. The purification of crude products by column chromatography gave the desired 3-substituted 2-thiohydantoins **17** in excellent yields (10 examples, 93−83% yields).

Solid-Phase Synthesis of Sulfanyl Benzimidazoles and Indole-Benzimidazoles. The research groups led by Kundu and Roy have developed an efficient method for the synthesis of a new benzimidazole-based intermediate that resulted from an unusual rearrangement on solid-phase.[43] A novel intramolecular SNAr rearrangement, observed during the S-alkylation of benzimidazole-2-thione with α-haloacetophenone, led to the formation of a new benzimidazole-based intermediate, which was further used for the generation of new biheterocyclic indole-benzimidazole derivatives with a two-point diversity.

The synthetic methodology started with the anchoring of 4-fluoro-3-nitrobenzoic acid to Rink amide resin **71** (Scheme 13) by the help of the coupling agents DIC/HOBt. The fluorine atom on resin **72** was replaced with 1,2-benzenediamine (**73a**) (R^1 diversity element) in the presence of diisopropylamine (DIPA) in DMF at 60 °C to give resin **74a** (R^1 = H). The resulting diamine resin **74a** was then treated with carbon disulfide and KOH in a mixture of THF/EtOH to give the intermediate 1,3-dihydrobenzoimidazole-2-thione resin **75a** (R^1 = H).

Next, the resin-bound 1-(2-nitrophenyl)-1,3-dihydrobenzimidazole-2-thione **75a** (R^1 = H) was treated with 2-bromo-4′-methylacetophenone (**76a**) (R^2 diversity element) in the presence of triethylamine as a base in DMF for 24 h at room temperature to generate the *S*-alkylated product resin **77a** (R^1 = H, R^2 = 4-Me). The final product was then washed and cleaved from the intermediate resin **77a** by treatment with 50% TFA/CH_2Cl_2. However, TLC analysis of the crude final product revealed two major spots, indicating the formation of two compounds. One revealed the formation of the *S*-alkylated product from the resin **77a** and in an unexpected result the other revealed 4-[1-(1*H*-benzimidazol-2-ylsulfanyl)-2-(4-methyl-phenyl)-2-oxo-ethyl]-3-nitrobenzamide (**78a**, R^1 = H, R^2 = 4-Me) by spectroscopic analyses of one- and two-dimensional NMR and MS. On the basis of

Scheme 13. Solid-Phase Synthesis of 1*H*-Benzimidazol-2-yl-sulfanyl Derivatives and Indole-Benzimidazole Derivatives



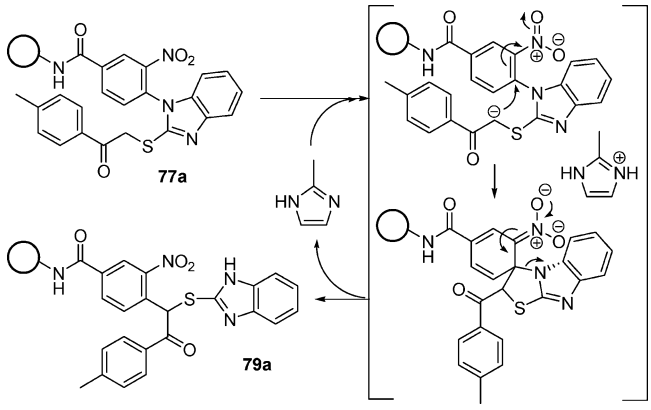


Figure 6. Proposed mechanism for a base-catalyzed intramolecular SNAr reaction.

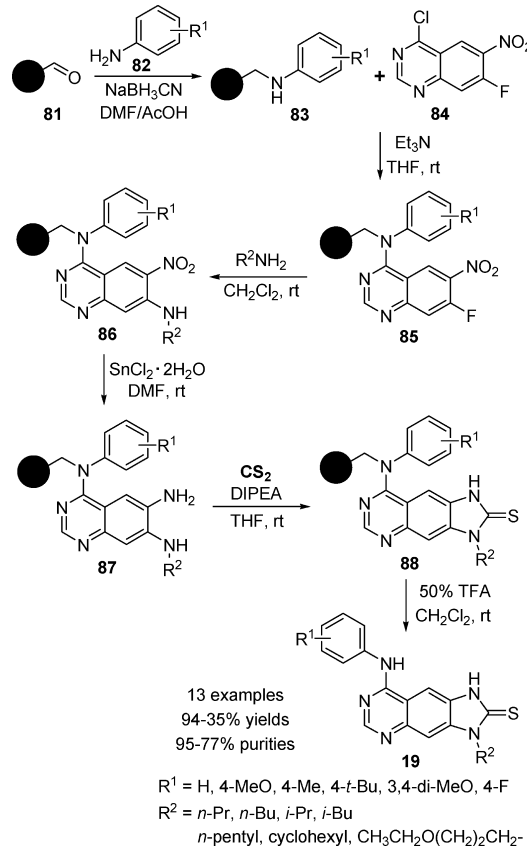
these observations, a plausible mechanism for the rearrangement was proposed, as shown in Figure 6.

The first step of the reaction is the usual dehydration of the benzimidazole ring proton, followed by *S*-alkylation, leading to formation of the expected resin-bound product **77a**. An excess of base present in the system then abstracts the activated methylene proton to generate a nucleophile, followed by its attack on the electrophilic carbon (C-13) that affords a five-membered ring transition state. This results in substitution of the nucleophilic methine carbon (C-11) at the C-13 quaternary carbon, thereby replacing the benzimidazole ring via an intramolecular SNAr mechanism in order to obtain the resin **79a**.

The presence of the electron-withdrawing nitro group may contribute to the stabilization of the cyclic transition state through charge dispersion, which may facilitate the reaction. Interestingly, the entity **78** appeared to be a useful template for the generation of a novel benzoannelated heteroatom ring system through the reduction of the nitro group to an amino group in the aromatic ring, which may then undergo spontaneous intramolecular cyclization with the keto group at the γ-position. For further application of the resin **79**, various bases, such as DIPEA, DMAP, imidazole, 2-methylimidazole, 1-methylimidazole, and DIPA, were screened for this reaction. The optimal condition that led to the selective synthesis of **78** in high yield and purity was the treatment of resin **75** with 2-methylimidazole as a base for 4 days in DMF at room temperature.

Once the reaction conditions for the selective synthesis of **79** were optimized, the reaction then proceeded using **79** to generate a novel heteroatom ring system. For this, the resin-bound 4-[1-(1*H*-benzimidazol-2-ylsulfanyl)-2-oxo-2-phenylethyl]-3-nitrobenzamide **79** was then treated with $SnCl_2 \cdot 2H_2O$ in DMF for 5 h to give the *N*-hydroxyindole-benzimidazole resin **80**.[74] The final product indole-benzimidazole **18** was cleaved with 50% TFA in CH_2Cl_2. The resulting product was then purified using column chromatography. To probe the versatility and limitation of this strategy, a mini-library of 17 compounds with two-point diversity having general structures **78** and **18** was synthesized (for **78**, 9 examples, 98−78% yields, 98−75% purities; for **18**, 8 examples, 96−80% yields, 94−77% purities).

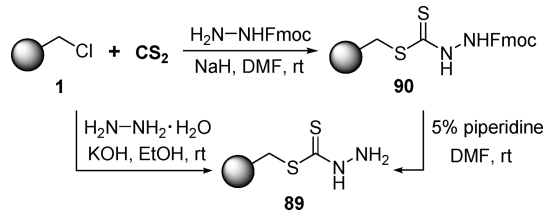
Scheme 14. Solid-Phase Synthesis of 3-Alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones



Solid-Phase Synthesis of 1*H*-Imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones. Quinazoline compounds have been well-recognized for their pharmacological properties and their imidazoquinazoline derivatives, such as 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones, have been reported as biologically active inhibitors.[75] The Yu group developed an efficient solid-phase synthesis of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones.[44] The quinazoline core structure of the target compounds was introduced by using the 4-chloro-7-fluoro-6-nitroquinazoline scaffold. The parallel solid-phase synthesis of these compounds was carried out on the solid phase using the "tea-bag"[3] methodology. The reaction sequence is illustrated in Scheme 14.

Starting from 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin **81**, in the presence of $NaBH_3CN$ in DMF, an arylamine **82** (R^1 diversity element) was attached to the resin by reductive amination. The resin-bound arylamine **83** was then reacted with 4-chloro-7-fluoro-6-nitroquinazoline (**84**)[76] to yield the corresponding highly chemoselective resin-bound quinazoline **85**, which was then treated with a primary alkylamine (R^2NH_2, R^2 diversity element) to give resin-bound compound **86**. The resin-bound compound **87** was formed through the reduction of resin-bound compound **86** by $SnCl_2 \cdot 2H_2O$ in DMF. Thionylation of resin-bound compound **87** with carbon disulfide in THF afforded resin-bound compound **88**. The desired 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones **19** were obtained in good yield and purity after cleavage of the resin-bound

Scheme 15. Synthesis of Dithiocarbazate Linker



compound **88** by TFA/CH_2Cl_2 (1:1) (13 examples, 94−35% yields, 95−77% purities).

The yields and purities of products **19** were found to depend on the nature of the substituent R^1 of the arylamines **82**. Arylamines bearing electron-donating groups and aniline gave satisfactory results, whereas those bearing electron-withdrawing groups or ortho-substituents gave low yields.

Solid-Phase Synthesis of Related Pyrazole Compounds and 1,3,4-Triazoles via Dithiocarbazate Linker

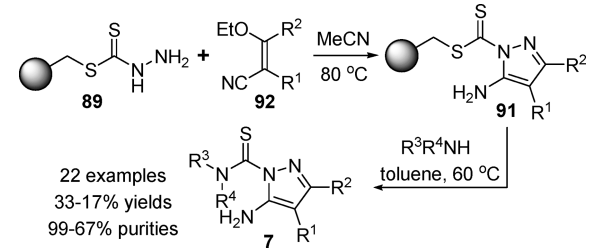
Synthesis of a Dithiocarbazate Linker on Solid Support. Thioureas with heterocycle have scarcely been reported in the research field of drug-like library construction by solid-phase synthesis, as compared with their ureas and simple aromatic thiourea analogues. We have previously described the dithiocarbazate linker **89** and its application to drug-like heterocycle formation.[34−36] The key intermediate, the polymer-bound dithiocarbazate **89**, was prepared in a one- or two-step procedure starting from the Merrifield resin **1** as shown in Scheme 15.

In the first step, Fmoc-protected dithiocarbazate resin **90** was prepared by a three-component reaction of Merrifield resin **1** and carbon disulfide with Fmoc-protected hydrazine in the presence of sodium hydride in DMF at room temperature. Deprotection of the Fmoc group of resin **90** with 5% piperidine produced the corresponding free dithiocarbazate resin **89**.[34] In this step, the use of 5% piperidine was essential because a higher concentration caused loss of the desired substrate from resin **90**. In addition, we have developed a more convenient synthetic route to the resin **89** compared to the previous report using hydrazine monohydrate and carbon disulfide with potassium hydroxide in ethanol solvent.[36] Under these reaction conditions, we obtained the polymer-bound dithiocarbazate **89** without the Fmoc-protection step of the hydrazine.

Solid-Phase Synthesis of Pyrazoles via Dithiocarbazate Linker. For heterocycle diversification of the hydrazine in the dithiocarbazate system, 5-aminopyrazoles **91** on dithiocarbazate resin **89** (by two-step sequence from Fmoc-hydrazine) were introduced by nucleophilic cyclization reactions with substituted 3-ethoxyacrylonitriles **92** (R^1 and R^2 diversity element) in acetonitrile (Scheme 16 and Figure 7).[34]

The desired 5-amino-1-(substituted-thiocarbamoyl)pyrazoles **7** were finally liberated from resin **91** using various amines (Figure 7) by thermal cleavage reaction in toluene at 60 °C. Various types of amines (R^3R^4N diversity elements) gave the 5-amino-1-(substituted-thiocarbamoyl)pyrazole derivatives **7** in good four-step overall yields (22 examples, 33−17% yields, 99−67% purities) from Merrifield resin **1**

Scheme 16. Solid-Phase Synthesis of Pyrazoles via Dithiocarbazate Linker



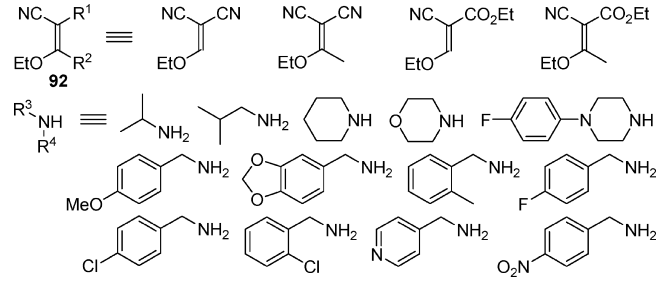
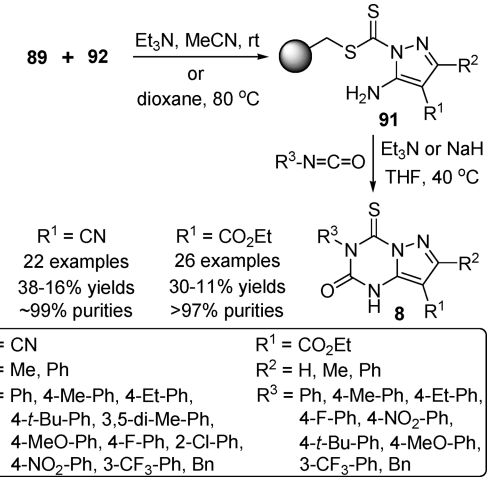


Figure 7. Substituted 3-ethoxyacrylonitriles **92** and amines used for pyrazoles **7**.

Scheme 17. Solid-Phase Synthesis of Pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazines via Dithiocarbazate Linker

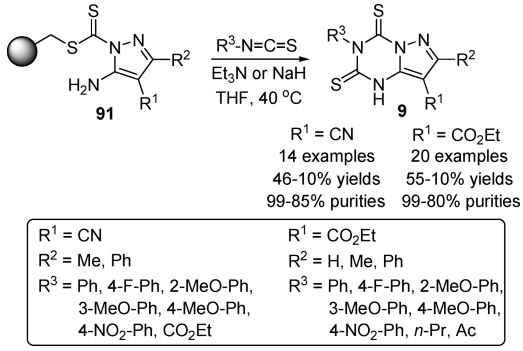


with high purities, except for sterically hindered secondary amines, such as DIPA and diisobutylamine.

Solid-Phase Synthesis of Pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazines. We have described studies that have led to the development of an efficient procedure for the synthesis of novel 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives **8** (Scheme 17) that involves solid-phase cyclization reactions of resin-bound 3,4-functionalized-5-amino-1-dithiocarboxy-pyrazoles **91** with various isocyanates.[35] These key intermediates then serve as precursors for the target 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazines **8**.

When R^1 was a nitrile group on the 3-ethoxyacrylonitriles **92**, the pyrazole ring formation of hydrazine dithiocarbazate resin **89** (by a two-step sequence from Fmoc-hydrazine) was accomplished in acetonitrile. In contrast, cyclization reactions of resin **89** with 3-ethoxyacrylonitriles **92** ($R^1 = CO_2Et$) did not run smoothly in acetonitrile. Instead, among various solvents, 1,4-dioxane was used to generalize the process

Scheme 18. Solid-Phase Synthesis of Pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazines



leading to resin **91**. The concurrent cyclization-resin cleavage reactions of the 5-aminopyrazole resins **91** were explored in more detail to determine the optimal conditions. The results showed that reactions of the 4-cyano-5-aminopyrazole resin **91** (R^1 = CN) with isocyanates take place in the presence of triethylamine (THF, 40 °C). On the other hand, the reactions of the 4-ethylcarboxy-5-aminopyrazole resin **91** (R^1 = CO_2Et) required the strong base sodium hydride (THF, 40 °C). Variously substituted aryl isocyanates (R^3 diversity element) reacted to generate the target 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives **8** with good, five-step overall yields starting from the Merrifield resin **1** and in high purities (R^1 = CN 22 examples, 38−16% yields; R^1 = CO_2Et 26 examples, 30−11% yields).

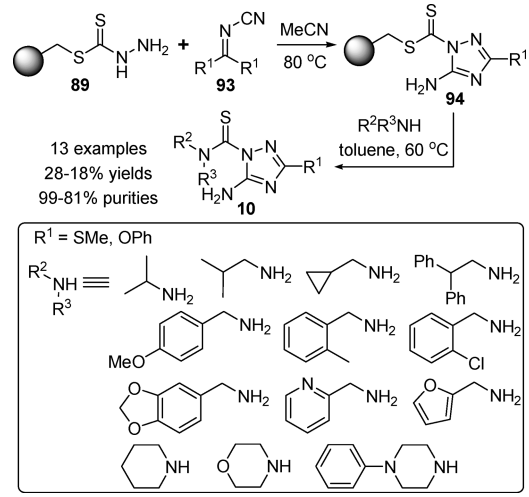
Solid-Phase Synthesis of Pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazines. We also have described the development of an efficient procedure for the synthesis of novel 7,8-functionalized-pyrazolo-[1,5-*a*][1,3,5]-2,4-dithioxotriazine derivatives **9** (Scheme 18) using a similar method to the synthesis of pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazines **8**, except for the cyclization by various isothiocyanates.[36]

The polymer-bound 5-amino-1-dithiocarboxypyrazole resin **91** was obtained by the reaction of dithiocarbazate resin **89** (by a one-step sequence from hydrazine monohydrate) with 3-ethoxyacrylonitriles **92** (R^1 and R^2 diversity elements) using previously reported methods. Finally, the desired target 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazine derivatives **9** were obtained from the respective 5-aminopyrazole resins **91** through a reaction sequence involving the intermediate formation of a solid-supported thiourea with various isothiocyanates (R^3 diversity element) and the intramolecular cyclization reaction of the resulting intermediate.

We could obtain various 7,8-functionalized-pyrazolo[1,5-*a*]-[1,3,5]-2,4-dithioxotriazine derivatives **9** by the concurrent reaction of 5-aminopyrazole resin **91** with aryl isothiocyanates in good, three-step overall yields starting from the Merrifield resin **1** with high purities (R^1 = CN 14 examples, 46−19% yields; R^1 = CO_2Et 20 examples, 55−10% yields).

Solid-Phase Synthesis of 1,3,4-Triazoles. A general method has been reported for the parallel solid-phase synthesis of 1,2,4-triazole derivatives based on the cyclization of polymer-bound dithiocarbazate **89** (by a two-step sequence from Fmoc-hydrazine) with electrophiles using a similar route to the formation of pyrazole **7**.[34] The linker **89** served as a nucleophile for the cyclization reactions with electrophiles, such as cyanocarboimidates **93** (R^1 diversity elements) (Scheme 19).

Scheme 19. Solid-Phase Synthesis of 1,3,4-Triazoles via Dithiocarbazate Linker



Further nucleophilic substitution on these polymer-bound 1,2,4-triazoles **94** with various amines (R^2R^3N diversity elements) under thermal cleavage conditions produced the desired 5-amino-1-(substituted thiocarbamoyl)-1,2,4-triazoles **10**. The final compounds **10** were obtained in good four-step overall yields and high purities upon cleavage from the resins (13 examples, 28−18% yields, 99−81% purities).

Solid-Phase Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles

In the five-membered ring heterocyclic compound family, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles have been used as privileged scaffolds to produce substances of interest in numerous therapeutic areas.[77] In addition, these heterocycles serve as intermediates in the preparation of various biologically important compounds.[78] As a result of these applications, 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives have been targets of a number of solution- and solid-phase synthetic studies.[24a,25]

Solid-Phase Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles via Selective Cyclization. In a recent investigation, described below, we expanded the utility of the carbazate resin by applying it to the efficient solid-phase syntheses of 1,3,4-oxadiazole derivatives **11** and 1,3,4-thiadiazole derivatives **12** via selective, reagent-based cyclization of an acyldithiocarbazate.[37] The process employs an acyldithiocarbazate resin, from which the respective targets are generated by cyclodesulfurization (route a) or cyclodehydration (route b) (Figure 8).

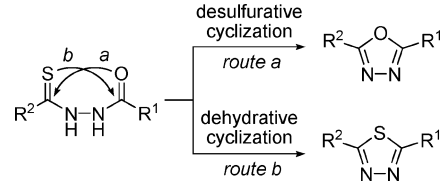
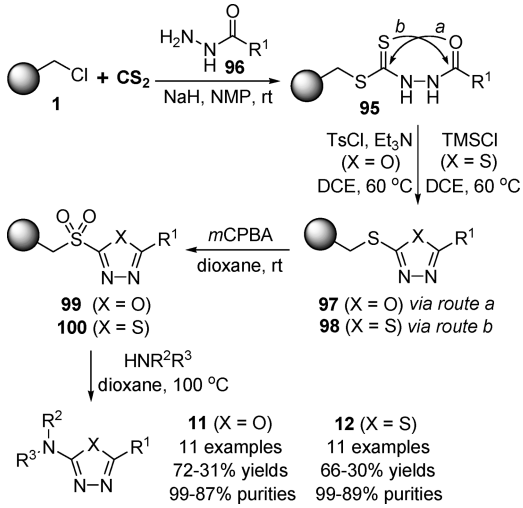


Figure 8. Synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles using an acyldithiocarbazate.

Scheme 20. Solid-Phase Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles



The sequence used to prepare the acyldithiocarbazate resins **95** (Scheme 20) employs the Merrifield resin **1** as a polymer support. Treatment of **1** with carbon disulfide and various hydrazides **96** in the presence of sodium hydride at room temperature led to production of the corresponding acyldithiocarbazate resins **95**.[62b]

To investigate suitable methods for the reagent-based, skeletal, diversity-oriented synthesis of 1,3,4-oxadiazoles or 1,3,4-thiadiazoles, cyclization reactions of the acyldithiocarbazate resin **95** were investigated by using various reagents, including EDCI, DCC, TMSCl, TsCl, PPh_3, $SOCl_2$, PCl_5, and diphenyl chlorophosphate. The desired products **11** (X = O) and **12** (X = S) were cleaved from the resins **97** (X = O) and **98** (X = S) by sequential treatment with *m*CPBA and NaOH in aqueous dioxane [producing the sulfones **99** (X = O) and **100** (X = S)] and piperidine in 1,4-dioxane at 100 °C.

Reactions of the acyldithiocarbazate resin **95** with EDCI and DCC both gave 1,3,4-oxadiazole **11a** (X = O, R^1 = 4-CF_3-Ph, R^2R^3NH = piperidine) as the major product, but in a low yield, whereas the use of $SOCl_2$ led to promote the desulfurative cyclization process to a 1,3,4-oxadiazole as the major product with high chemoselectivity (99:1) and a moderate yield (28%) via route a. Reaction of the resin **95** with TsCl as a reagent for cyclization via route a in the presence of triethylamine generated the 1,3,4-oxadiazole **11a** in a high yield (50%) and high chemoselectivity (98:2). The 1,3,4-thiadiazole **12a** (X = S, R^1 = 4-CF_3-Ph, R^2R^3NH = piperidine) was produced in a high yield (53%) and excellent chemoselectivity (99:1) by the dehydrative cyclization upon treatment of the resin **95** with TMSCl as a reagent for cyclization via route b. Similarly, reaction of the resin **95** with diphenyl chlorophosphate also gave **12a** in a good yield (51%) and high chemoselectivity (98:2) via route b. However, PCl_5 and PPh_3 treatment of **93** produced **12a**, but with low chemoselectivity.

To explore the diversity of this methodology, various amines (R^2R^3N diversity elements) were used to liberate the 1,3,4-oxadiazoles **11** and 1,3,4-thiadiazoles **12** (Figure 9) from the functionalized sulfone-containing resin. Cleavage reactions with amines generally gave the desired products in high yields (22 examples, 72−30% yields).

Solid-Phase Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles. *N*-Acylhydrazines are a versatile class of nitrogen-substituted molecules with a high degree of chemical reactivity and are used as precursors and intermediates of many important organic molecules, such as heterocycles, pharmaceuticals, polymers, dyestuffs, and photographic products.[79] Only a few papers have described the preparation of combinatorial libraries of heterocyclic compounds on solid supports using this chemistry.[80]

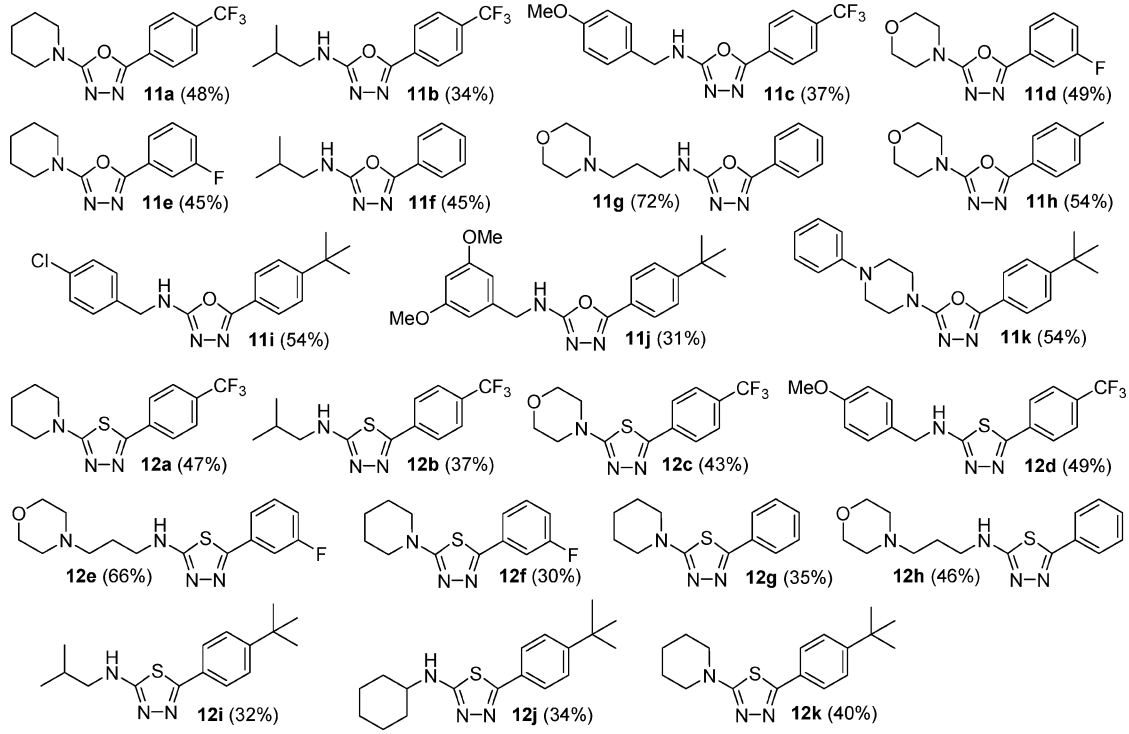
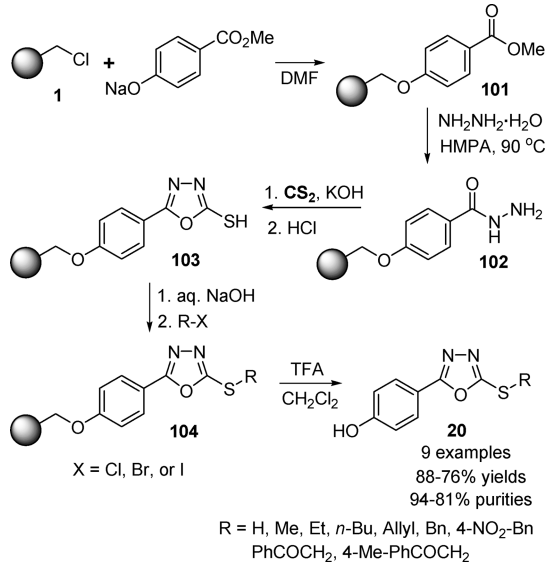


Figure 9. 1,3,4-Oxadiazoles **11** and 1,3,4-thiadiazoles **12** and their yields.

Scheme 21. Solid-Phase Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles



Liu and Huang described the solid-phase synthesis of 2-aryl-5-alkylthio-1,3,4-oxadiazoles from resin-bound acylhydrazines.[45] The Merrifield resin **1** was first converted to the polymer-supported methyl ester resin **101** by reacting it with excess methyl 4-hydroxybenzoate (Scheme 21). The methyl ester resin **101** was treated with hydrazine hydrate in HMPA at 90 °C for several hours to give the corresponding hydrazide resin **102**. In this step, HMPA was essential for reaction completion. The resin **102** was then reacted with carbon disulfide and KOH at reflux to afford the 2-mercapto-1,3,4-oxadiazole resin **103**.

Further reaction with NaOH and a variety of electrophilic reagents (RX), such as alkyl halides, allyl bromide, benzyl halides, and phenylacyl bromide as an R diversity element, gave the corresponding resin **104**. Release of the final 2-aryl-5-alkylthio-1,3,4-oxadiazoles **20** was achieved after cleavage by treatment with 10% TFA in CH_2Cl_2. The compounds **20** were obtained after simple filtration and evaporation of the solvent. The products generally did not require further purification and showed good purity by HPLC analysis. The 1,3,4-oxadiazoline-5-thione derivatives **20** were synthesized from resin-bound acylhydrazines **102** in several steps providing 78−88% overall yields and excellent purity (9 examples, 94−81% purities).

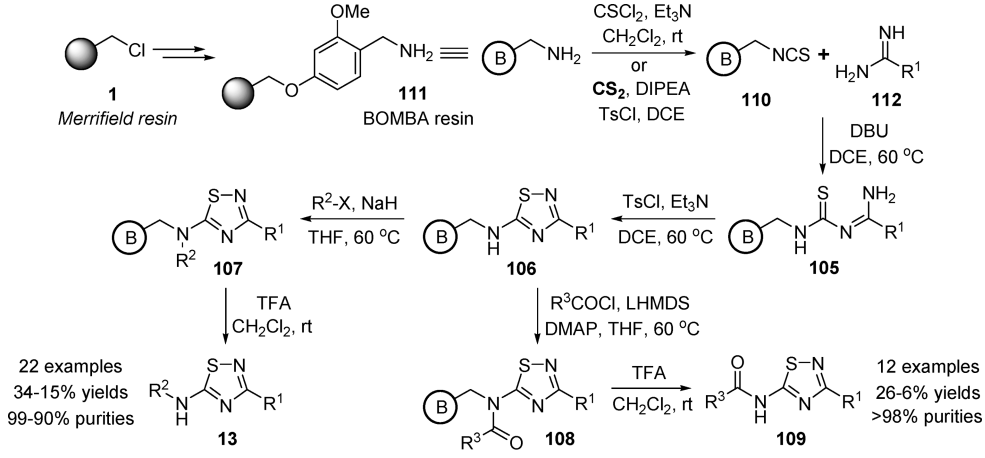
Solid-Phase Synthesis of 1,2,4-Thiadiazoles

As a member of the thiadiazole family, which is a privileged structure for the generation of drug-like libraries, 1,2,4-thiadiazoles have been used as the basic framework for substances of interest in numerous therapeutic areas.[81] Recently, we reported the results of a study that led to the development of a solution-phase parallel synthesis of various drug-like 5-amino-1,2,4-thiadiazoles via a three-component nucleophilic substitution reaction between carbon disulfide, benzamidine, and benzyl chloride, using a key cyclization reaction of a carboxamidine dithiocarbazate induced by TsCl.[82] Also, we developed a simple and efficient solid-phase parallel synthetic method able to facilitate production of a variety of 5-amino- and 5-amido-1,2,4-thiadiazoles derived from a common intermediate.[38]

The strategy for the efficient solid-phase synthesis of various 5-amino- and 5-amido-functionalized 1,2,4-thiadiazole derivatives is given in the sequence illustrated in Scheme 22. Resin-bound carboxamidine thioureas **105** were used as key intermediates and underwent cyclization to produce the 1,2,4-thiadiazole resin **106**. *N*-Alkylation and *N*-acylation reactions of the resin **106** then yielded the respective resins **107** and **108**, which were transformed to the 5-amino- and 5-amido-1,2,4-thiadiazoles **13** and **109**, respectively.

The isothiocyanate-terminated resin **110** was prepared from the amine resin **111** (the BOMBA resin was synthesized by a two-step sequence from Merrifield resin **1**) by the reaction with thiophosgene in the presence of triethylamine or with carbon disulfide and TsCl in the presence of DIPEA in CH_2Cl_2. The resin-bound isothiocyanate **110** reacted with carboxamidine **112** in the presence of DBU in dichloroethane at 60 °C to give the resin-bound carboxamidine thiourea **105**. To develop methods for the solid-phase synthesis of various

Scheme 22. Solid-Phase Synthesis of 1,2,4-Thiadiazoles



5-functionalized 1,2,4-thiadiazoles, cyclization of the carboxamidine thiourea resin **105** was investigated using a number of different activating agents, including EDCI, DCC, TMSCl, TsCl, Ph_3P, $SOCl_2$, PCl_5, and diphenyl chlorophosphate. This investigation demonstrated that the best cyclization condition involved the use of TsCl in the presence of triethylamine in dichloroethane at 60 °C. This process led to the formation of the 3-substituted 5-amino-1,2,4-thiadiazole resin **106**.

Alkylation reactions of 5-amino resin **106** with alkyl halides (R^3 diversity element) provided the desired 3-substituted 5-(*N*-alkylamino)-1,2,4-thiadiazole resin **107**. In a similar manner, 3-substituted 5-(*N*-acylamino)-1,2,4-thiadiazole resin **108** was produced by acylation reactions of resins **106** with acid chlorides (R^3 diversity element). Importantly, resins **107a** (R^1 = Ph, R^2 = Bn) and **108a** ($R^1 = R^2$ = Ph) underwent smooth reactions to yield 5-amino-functionalized 1,2,4-thiadiazoles **13a** (R^1 = Ph, R^2 = Bn) or 5-amido-functionalized 1,2,4-thiadiazoles **109a** ($R^1 = R^2$ = Ph), respectively, in high yields and purities, when treated with TFA in CH_2Cl_2 at room temperature. Various 5-amino-1,2,4-thiadiazoles **13** and 5-amido-1,2,4-thiadiazoles **109** could be produced by this five-step route in high overall yields and purities (for **13** 22 examples, 34−15% yields, 99−90% purities; for **109** 12 examples, 26−6% yields, 89−70% purities).

Summary

The combinatorial synthesis of heterocyclic small organic molecules plays a significant role in the area of drug discovery. Especially, substituted and fused five-membered ring heterocycles acting as bioactive molecules have proven to be broadly useful as therapeutic agents, because of their high degree of structural diversity. In this respect, many synthetic methods for synthesizing these privileged five-membered heterocyclic ring structures with drug-like properties using carbon disulfide have been developed using solid-phase strategies. Carbon disulfide is a facile, cheap, and versatile reagent capable of acting as a sulfur source, traceless linker, substitution site, diversity element, and intermediate in the synthesis of five-membered ring heterocycles and their fused counterparts on a solid support. In this article, we have introduced the preparation of diverse and drug-like five-membered ring heterocycles as thiophenes, thiazoles, imidazoles, benzoxazoles, pyrazoles, triazoles, oxadiazoles, thiadiazoles, and their related compounds. Following further studies in this field, more experimental conditions with carbon disulfide and a solid support will be reported for medicinal chemistry and drug discovery.

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