# Molecular Diversity of Hydroxamic Acids: Part I. Solution- and Solid-Phase Synthesis

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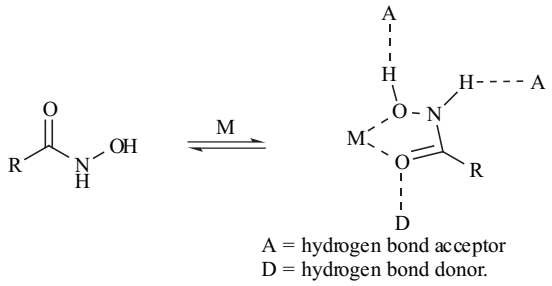
**Abstract:** Hydroxamic acid derivatives are an important class of molecules with a variety of pharmaceutical properties. Over the last decade steady progress has been made in the development of efficient methods for the syntheses of hydroxamic acid derivatives. This mini-review covers the most recent publications that highlight current strategies and syntheses of bioactive molecules containing the hydroxamate moiety in both solution- and solid-phase.

## INTRODUCTION

The ever-increasing importance of hydroxamic acid functionality in the design of a wide spectrum of bioactive agents, especially of highly potent and selective inhibitors of disease-related metalloproteinases, has heightened the interest in the synthesis of hydroxamic acid-based small molecules [1,2]. The hydroxamic acid moiety can serve as a bidentate ligand to chelate metal ions such as $Zn^{++}$ and $Fe^{++}$ at the active site of the enzymes. Very importantly, this metal binding group possesses multiple sites for potential hydrogen bond interaction with the enzyme backbone, which are critical structural elements leading to highly potent metalloproteinase inhibitors (Scheme (1)) [3]. In general, the hydroxamic acid-based metalloproteinase inhibitors, such as matrix metalloproteinase (MMP) inhibitors are significantly more effective than the parent carboxylic acids.




**Scheme 1.** Chelating and hydrogen bonding with hydroxamic acid.

Over the last decade, many highly potent hydroxamic acid-based inhibitors of various matrix metalloproteinases (MMPs) have been developed as potential therapeutic agents for the treatment of cancer and inflammatory diseases [1,4,5]. Some of them, such as Marimastat (**1**) [6], CGS-27023A (**2**) [7], AG-3340 (**3**) [8] and RS-130,830 (**4**) [9], have advanced into human clinical trials (Figure (**1**)). In addition, there is a rapidly growing interest in many other

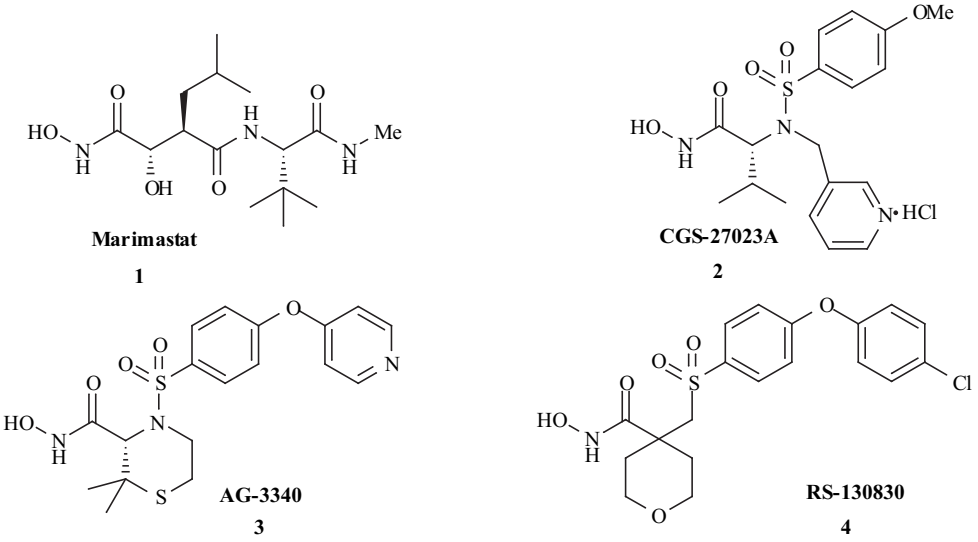



**Fig.** (**1**)**.** Representative examples of MMP inhibitors.

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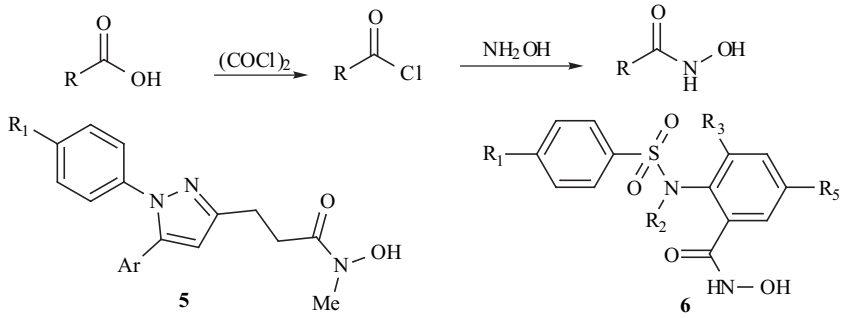
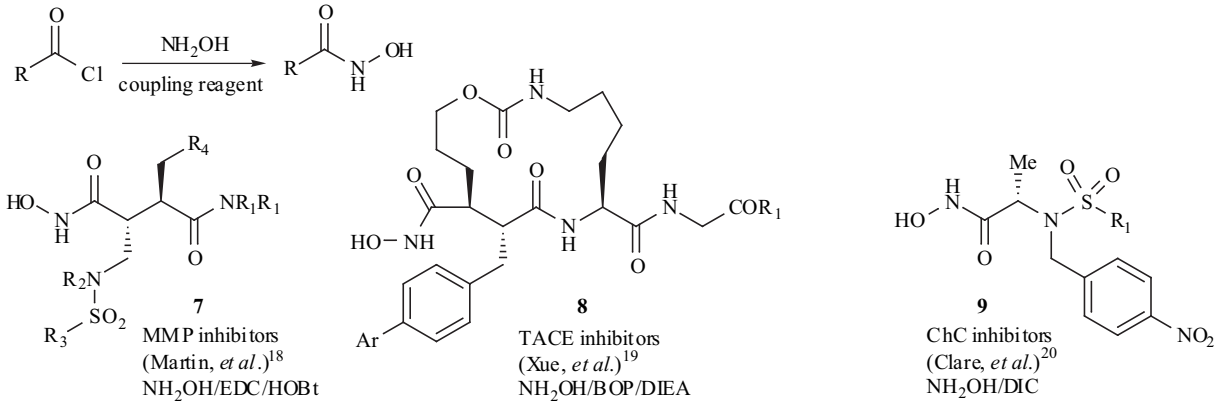


**Scheme 2.** Acylation of hydroxylamine with acid chlorides.

metalloproteinases, such as TNF-α converting enzyme [10], histone deacetylase [11] and peptide deformylase [12]. Therefore, the development of efficient methods for the syntheses of hydroxamic acids have received much attention. Recently, combinatorial synthesis of hydroxamic acid libraries has rapidly expanded the diversity of this important class of molecules [13,14,15]. This mini review highlights the general approaches to solution- and solid-phase synthesis of hydroxamic acids with an emphasis on recent practice in the area of medicinal chemistry.

acylations are usually conducted at a later stage of the synthesis.

The *N*-acylation of hydroxylamine can be achieved by using acid chlorides which can be readily generated from the corresponding carboxylic acids under the standard conditions. As shown in Scheme (2), Murray reported the preparation of anti-inflammatory agents (**5**) by the coupling of hydroxylamine or *N*-methyl hydroxylamine with acid chlorides, which were derived from the corresponding acids



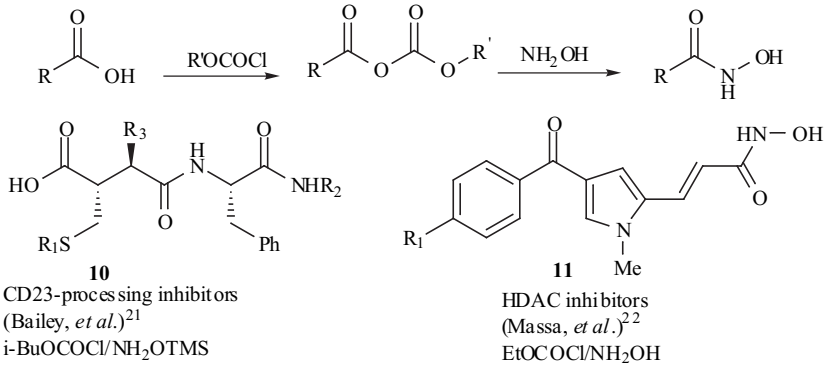
**Scheme 3.** Preparation of hydroxamic acids from the corresponding acids.

## SOLUTION-PHASE SYNTHESIS

### Acylation of Hydroxylamine

The most straightforward route to hydroxamic acids is the direct *N*-acylation of hydroxylamine. In order to circumvent potential undesired side reactions with chemical reagents encountered during synthetic transformations, the with the treatment of oxalyl chloride [16]. More recently, Levin *et al.*[17] successfully employed the same method to prepare a series of highly potent and selective anthranilic acid-based MMP inhibitors (**6**).

The acylation of hydroxylamine with carboxylic acids can also be accomplished in the presence of appropriate coupling reagents such as EDC, BOP and DIC. Applications



**Scheme 4.** Preparation of hydroxamic acids via mixed anhydrides.

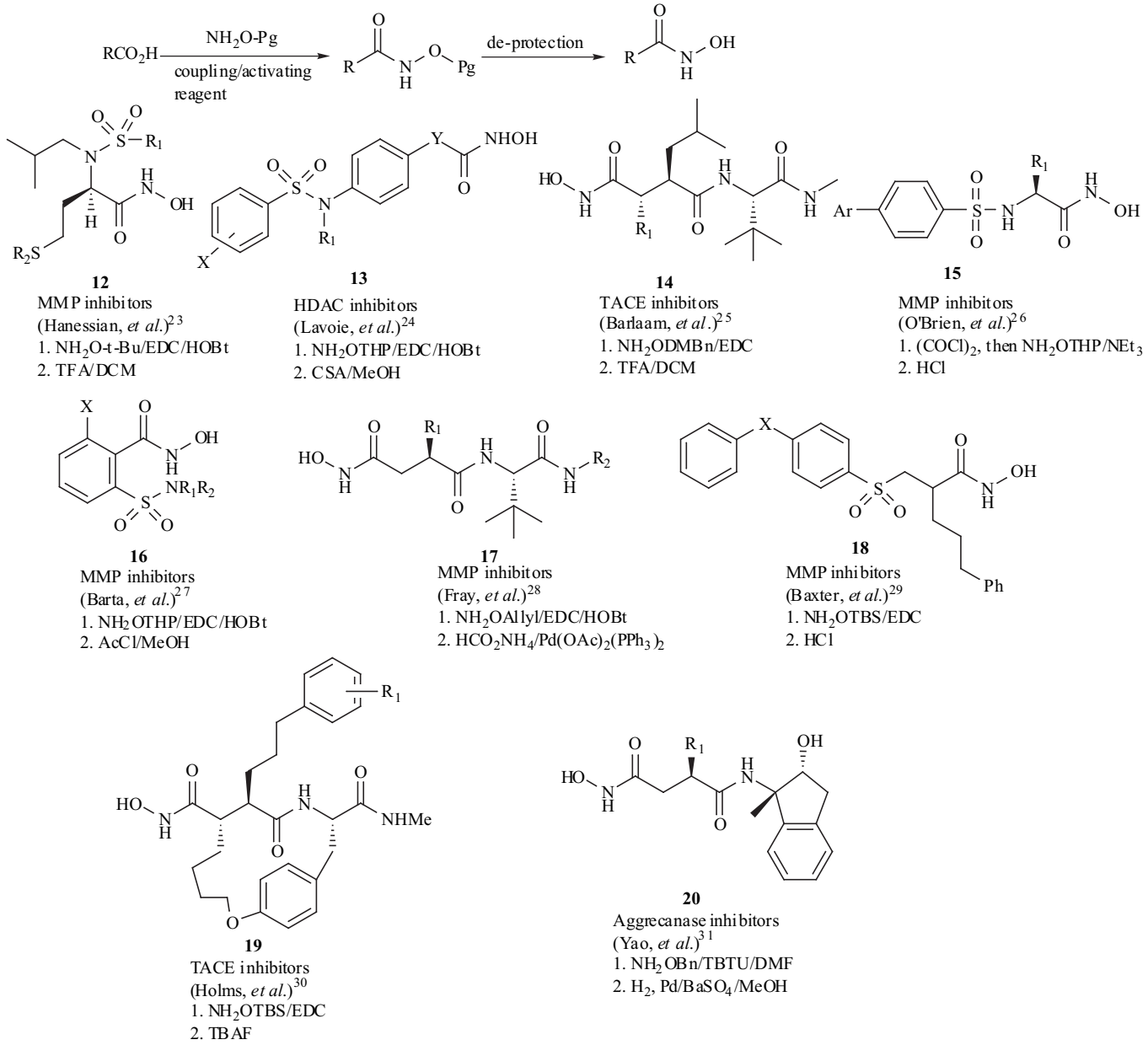
of this strategy have been found in the syntheses of many biologically important molecules such as MMP inhibitors (**7**) [18], TACE inhibitors (**8**) [19], and *Clostridium histolyticum* collagenase (ChC) inhibitors (**9**) [20] as shown in Scheme (3).

Carboxylic acids can be activated using appropriate chloroformates to form mixed anhydrides which are then treated with hydroxylamine to give the corresponding hydroxamic acids. This method has been applied in the synthesis of CD23-processing inhibitors (**10**) [21] and histone deacetylase (HDAC) inhibitors (**11**) [22] as shown in Scheme (4).

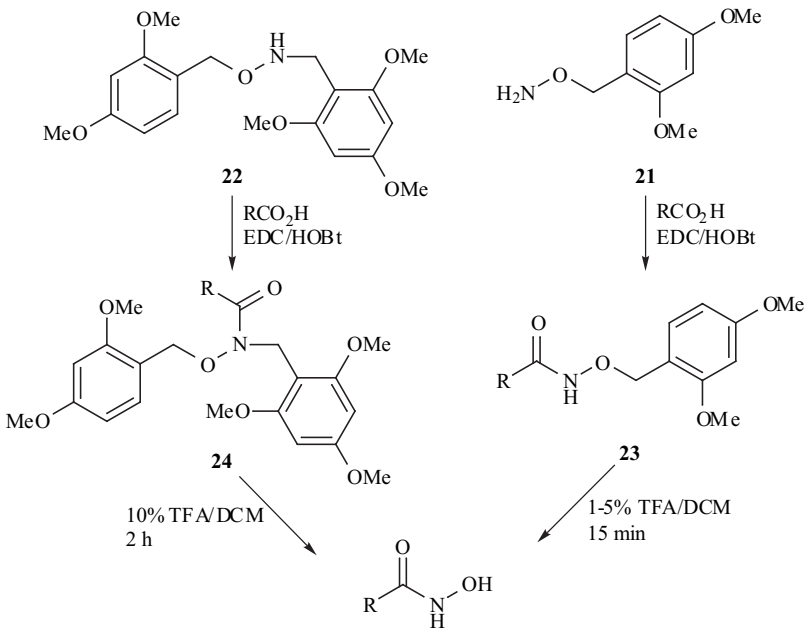
## Acylation of Protected Hydroxylamine

Protected hydroxylamines are frequently used in order to prevent potential *O*-acylation or other undesirable side reactions with the acidic NH or OH groups during subsequent chemical manipulations. Common protecting groups, such as benzyl, allyl, trityl, THP and silyl group, are often used for the *O*-protection of hydroxylamine. They can be removed by applying the standard de-protection protocols. A set of representative examples with coupling/deprotection conditions are shown in Scheme (5) [23-31].

Barlaam *et al.* recently reported a method for the preparation of *O*-protected or *O,N-bis*-protected hydroxamic acids that can be subsequently deprotected under mild acidic conditions [32]. *O*-2,4-dimethoxybenzyl hydroxylamine (**21**) or *O*-2,4-dimethoxybenzyl-*N*-2,4,6-trimethoxybenzyl hydroxylamine (**22**) was coupled with various carboxylic acids in the presence of EDC to give (**23**) or (**24**) in good yield. Both protecting groups could be removed by treatment of 10% TFA in DCM. But the selective deprotection of *O*-dimethoxybenzyl group of (**24**) was




**Scheme 5.** Preparation of hydroxamic acids from *O*-protected hydroxylamine.



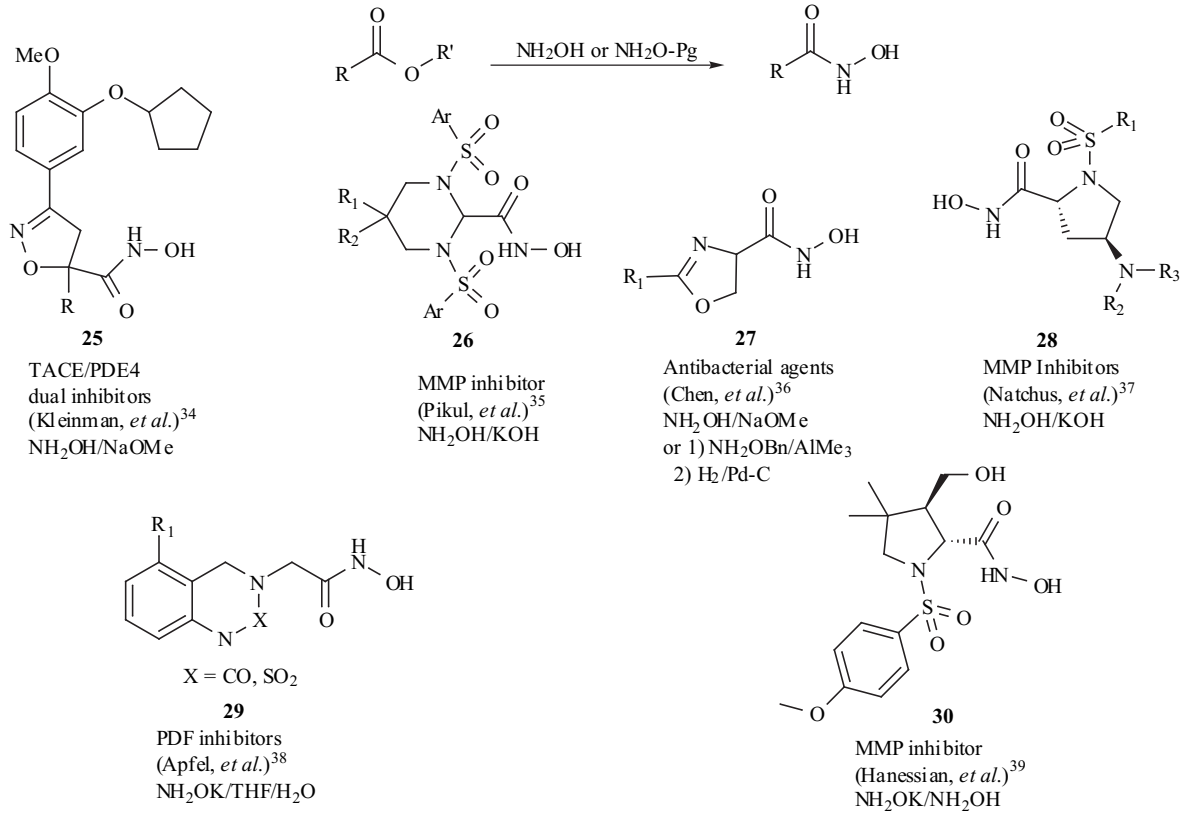

**Scheme 6.** Preparation of hydroxamic acids from *N*, *O*-protected hydroxylamine.

achieved by using 1% TFA without affecting the *N*-protection.

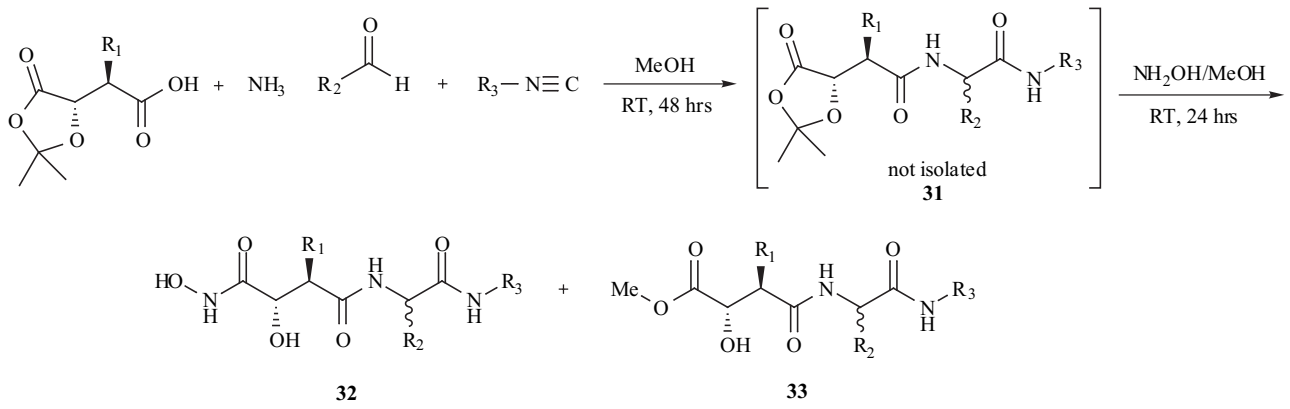
## Nucleophilic Displacement of Esters

Hydroxamic acids can be generated from carboxylic acid esters by treatment with hydroxylamine under basic conditions. Since the first example reported by Renfrow and Hauser in 1937 [33], this method and its modified versions have been widely used in the preparation of bioactive hydroxamic acids. Scheme (7) illustrates recent examples synthesized based on this approach. Their specific reaction conditions are also included therein [34-39].

Patel *et al.* reported a five-component synthesis of Marimastat analogues as potential MMP inhibitors [40]. As shown in Scheme (8), three diversity elements were




**Scheme 7.** Displacement of carboxylic acid esters with hydroxylamines.




**Scheme 8.** A five-component synthesis of hydroxamic acids.

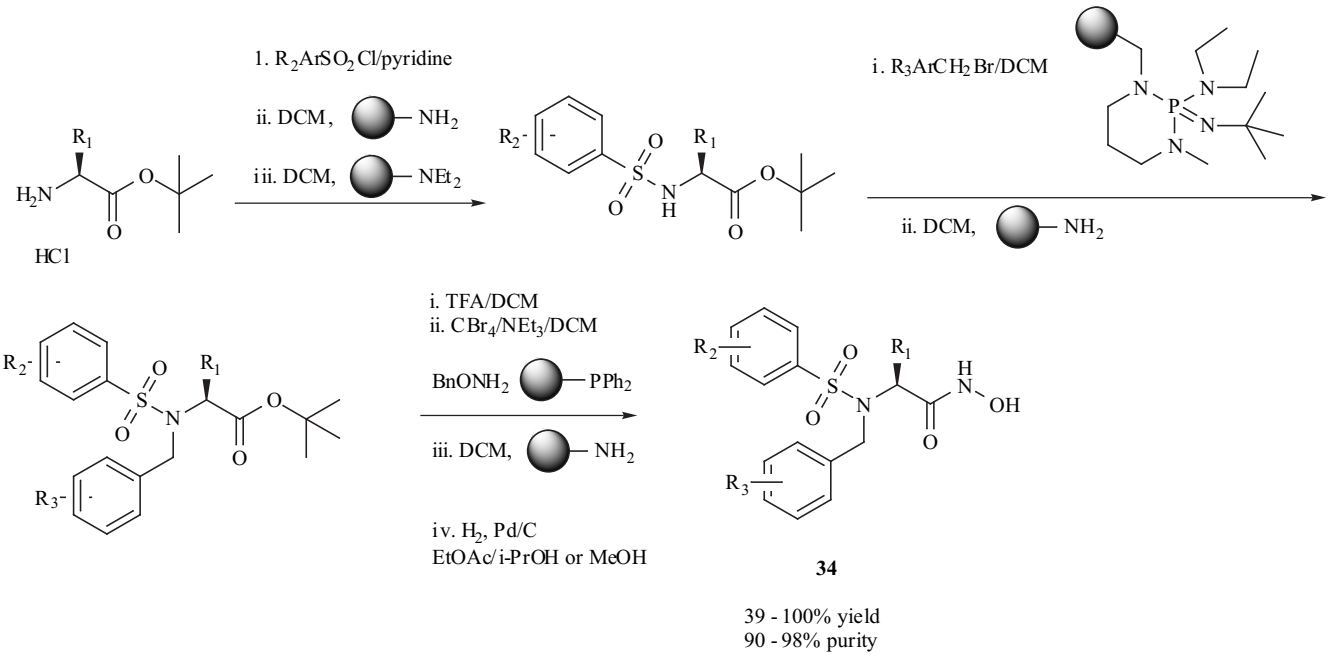
introduced simultaneously in a one-pot Ugi condensation reaction, followed by a methanolic hydroxylamine treatment to open the acetonide-ester (**31**) to furnish the hydroxamic acids (**32**). It was found that preforming imines with a limited amount of ammonia suppressed the competing reaction leading to methyl ester by-products (**33**). However, it was not mentioned whether the methyl ester (**33**) could be converted to the product (**32**) by the treatment of hydroxylamine.

## Solution-Phase Parallel Synthesis of Hydroxamic Acids

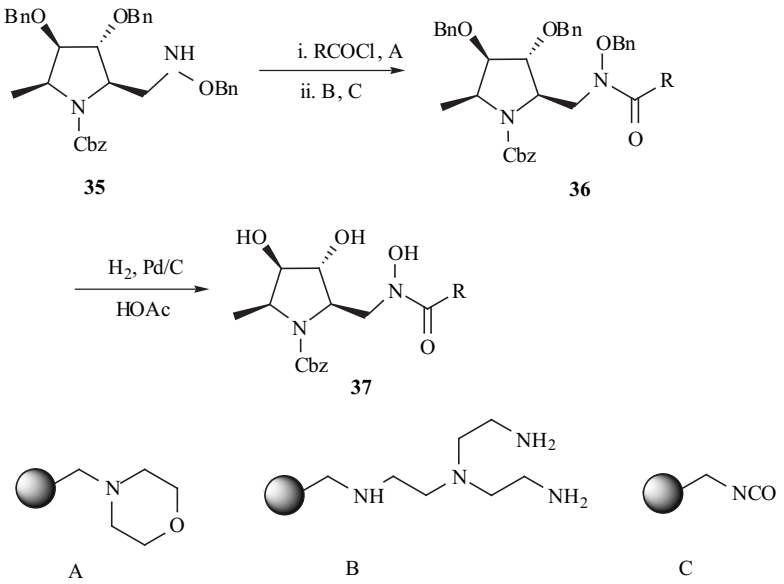
Enormous progress has been made towards developing efficient methods for the syntheses of hydroxamic acids as discussed above, however, most of them are not suitable for multiple parallel synthesis (MPS) of hydroxamic acid libraries due to tedious purification and isolation/deprotection steps.

Remarkably, Caldarelli *et al.* recently reported a practical protocol for solution-phase synthesis of combinatorial libraries of α-sulfonamido-hydroxamic acids [41]. As shown in Scheme (9), a series of polymer supported reagents were used to assist synthetic transformations and remove excess reactants and by-products. The final desired products, MMP inhibitor-like compounds (**34**), were obtained in good yield (39~100%) with excellent purity (90~98%).

A parallel synthesis of *N*-(pyrrolidinylmethyl)-hydroxamic acids (**37**) as potential glycosyltransferase inhibitors was recently reported by Takayanagi *et al.* [42]. Multiple polymer supported reagents were used in the *N*-acylation step (Scheme (10)). The acylation of (**35**) was first carried out in the presence of polymer-bound morpholine (**A**). Subsequently, a polyamine scavenger resin (**B**) was used to trap the excess acyl chloride. An isocyanate scavenger resin (**C**) was then employed to remove unreacted hydroxylamine derivatives. This sequential work-up protocol with the aid of the multiple polymer-bound reagents afforded




**Scheme 9.** Solution-phase parallel synthesis of potential MMP inhibitors.




**Scheme 10.** Solution-phase parallel synthesis of glycosyltransferase inhibitors.

the final products (**37**) in excellent yields (82 ~ 90%) and high purity (77 ~ 93%).

### Other Methods

Braslau *et al.* reported an intramolecular ligation process for the preparation of hydroxamic acid peptides as shown in Scheme (11) [43]. For this approach, a bulky *N*-substituent, *t*-butyl group, was needed to ensure the exclusive *O*-acylation with amino acids to form (38) under the EDC/DCM coupling conditions. However, due to the increased steric hindrance, the subsequent *N*-acylation of (38) was performed at elevated reaction temperature using amino acid chloride (39).

## SOLID-PHASE SYNTHESIS

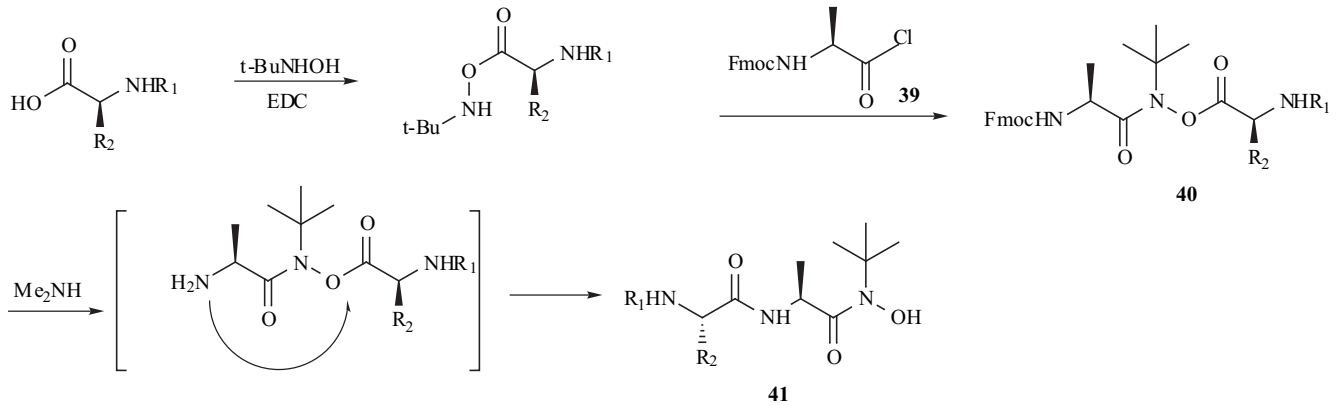
Solid-phase synthesis has emerged as an important tool for rapid generation of hydroxamic acid libraries. Many methods for the syntheses of hydroxamic acids on solid support have been reported. The strategies for the synthesis can be categorized as follows: (1) the use of hydroxylamine resins; (2) the use of ester linkers that are cleavable by hydroxylamine or its derivatives.

### Use of Hydroxylamine Resins

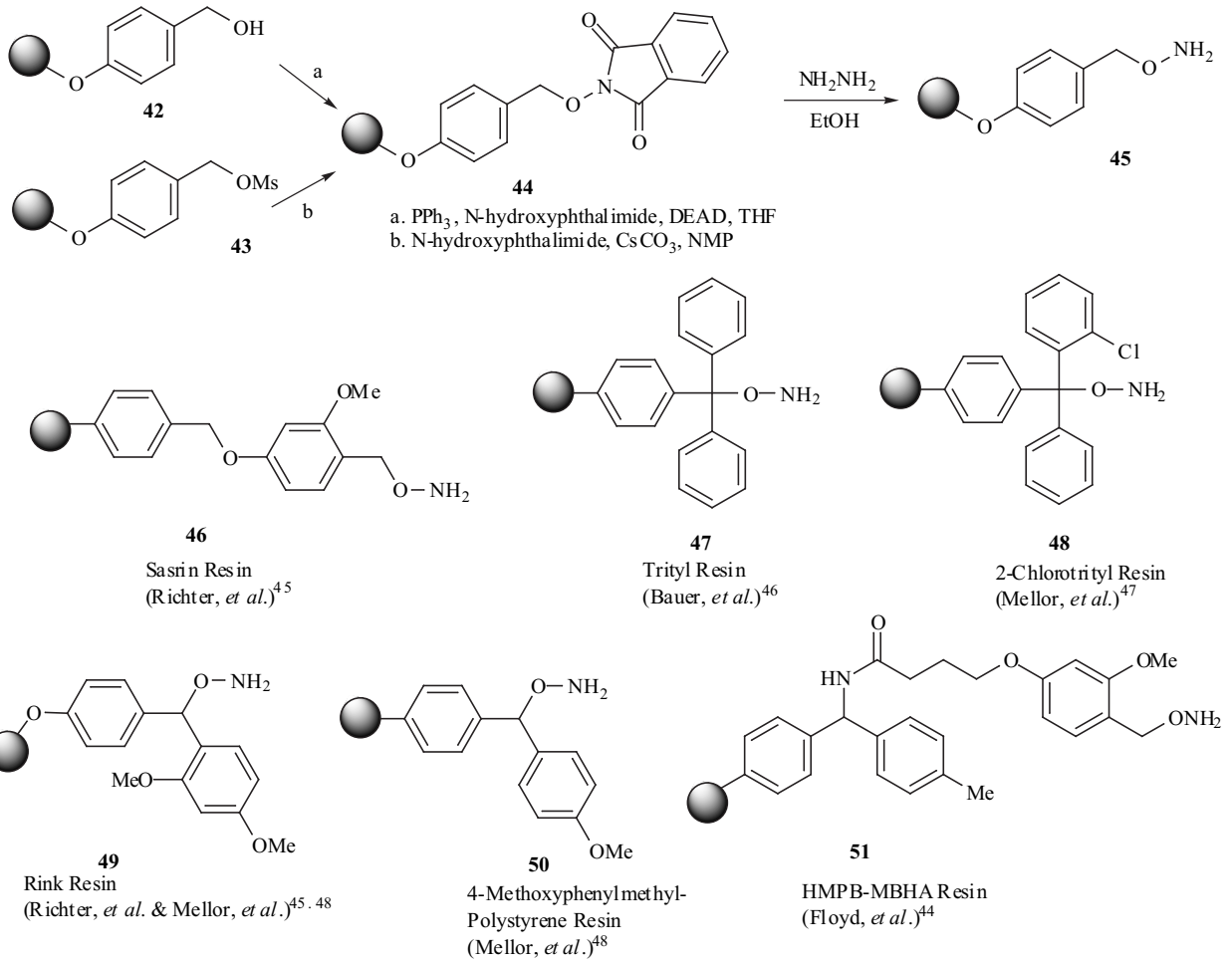
Hydroxylamine can be attached onto the polymer support via either *O*- or *N*-linkage. A subsequent *N*-acylation of the hydroxylamine resins followed by various chemical transformations leads to the target compounds which are usually cleaved from the resins under acidic conditions. These methods have a limitation in that they may not be applicable to the synthesis of hydroxamic acids containing acid-labile building blocks or functional groups.

### *O*-linked Hydroxylamine Resins

Several methods for the preparation of hydroxylamine resins via the *O*-linkage have been reported. *N*-Hydroxyphthalimide was coupled with Wang resin under the Mitsunobu conditions to give the resin (**44**) (Scheme (12))



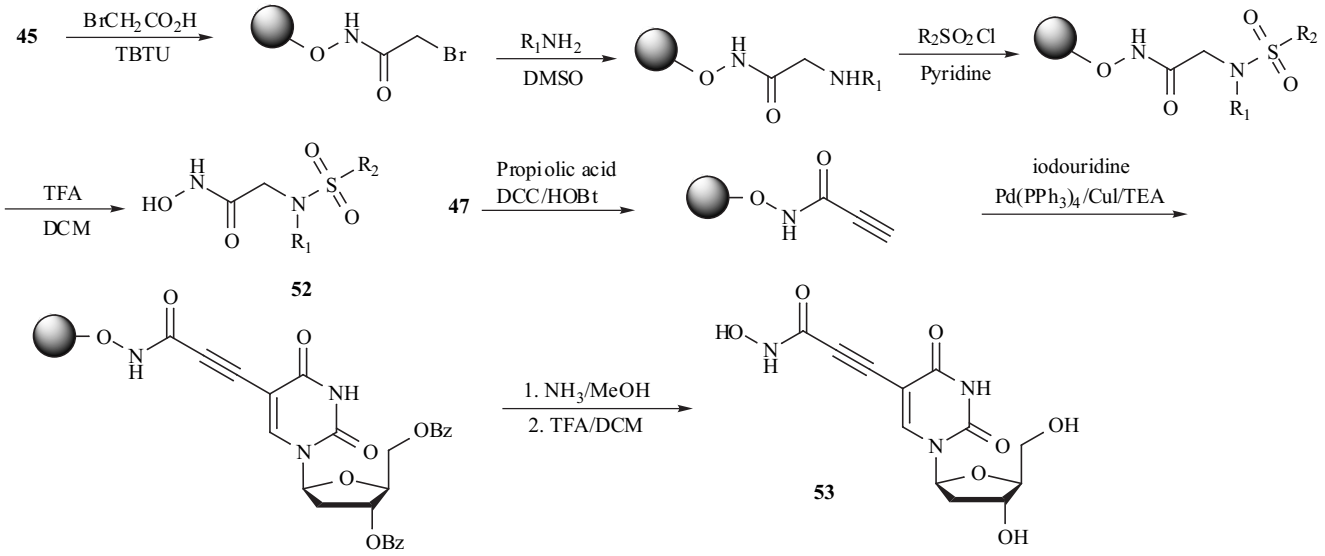

**Scheme 11.** Synthesis of hydroxamic acids via an intramolecular ligation process.



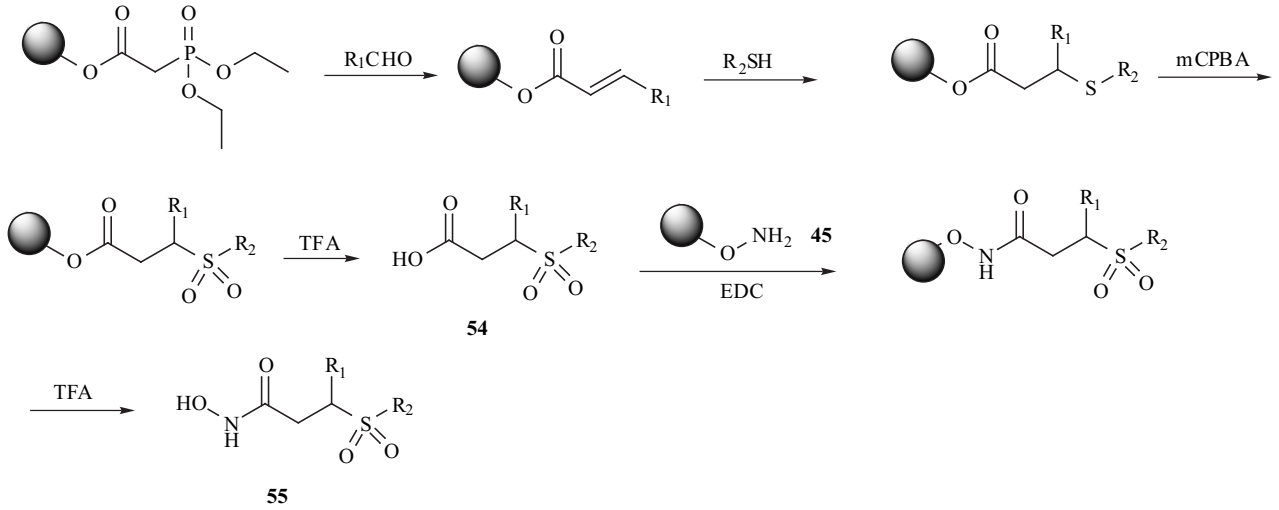

**Scheme 12.** Various *O*-linked hydroxylamine resins.

[44]. Alternatively, it can also be obtained by nucleophilic displacement reaction of mesylate Wang resin (**43**) with *N*-hydroxyphthalimide under mild basic conditions [45]. Subsequent treatment of the resin (**44**) with hydrazine gave the desired *O*-linked hydroxylamine Wang resin (**45**). Similarly, more acid-labile hydroxylamine resins were prepared, such as Sasrin, Rink, HMPB-MBHA and Trityl resins, as shown in Scheme (12) [44-48].

Numerous hydroxamic acids have been prepared from these resins. For example, starting from hydroxylamine Wang resin (**45**), Floyd *et al.* synthesized a series of




**Scheme 13.** Application of *O*-linked hydroxylamine resins.




**Scheme 14.** A catch-release strategy.

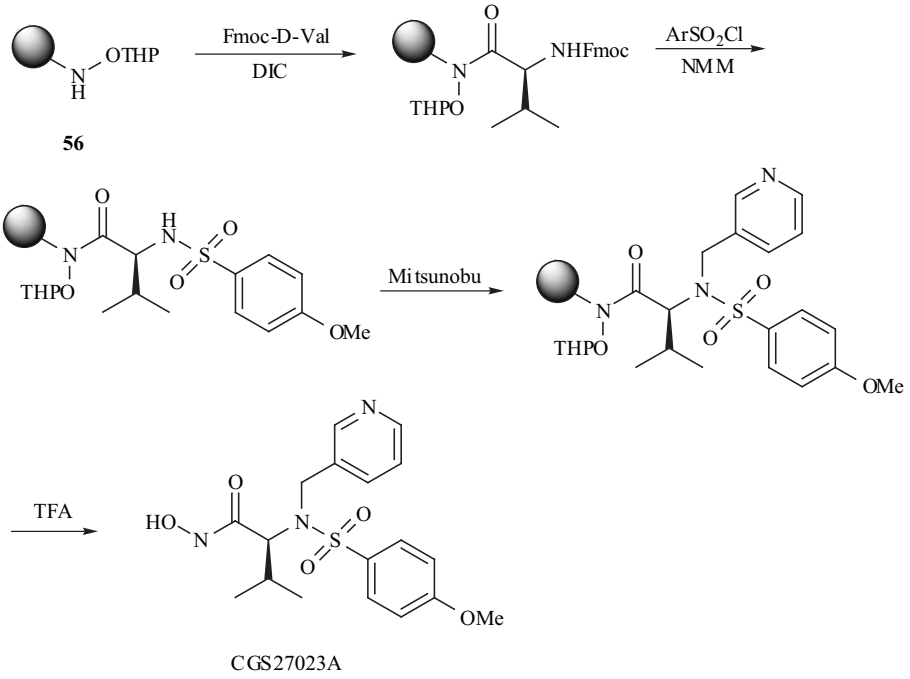
tripeptide hydroxamic acids based on the standard Fmoc-chemistry protocol in 25~88% yields [44]. They also employed the same resin to prepare an array of sulfonamide hydroxamic acid type MMP inhibitors (**52**) as shown in Scheme (13) [44]. Using hydroxylamine trityl resin, Khan and Grinstaff synthesized a nucleoside hydroxamic acid derivative (**53**) as shown in Scheme (13) [49].

Salvino reported a catch-release strategy for the preparation of an arylsulfone hydroxamic acid library, in which a library of the intermediate carboxylic acids (**54**) were first synthesized and then cleaved from the solid support. Subsequently, a polymer-bound hydroxylamine was used to catch these acids under EDC-assisted coupling conditions.

The final hydroxamic acids (**55**) were released from resin by TFA/DCM treatment with >80% purity as shown in Scheme (14) [50].

## Use of *N*-linked Hydroxylamine Resins

The use of the *O*-linked hydroxylamine resins for the multi-step synthesis of hydroxamic acids may result in undesired by-products derived from side reactions of the NH-group of the hydroxamate. Ngu and Patel developed *N*-linked *O*-protected hydroxylamine resin (**56**) [51]. In this case, the linker group served not only as a cleavage site of attachment for the molecule to a solid support, but also as a nitrogen protecting group for the hydroxamate functionality. The versatility of the resin was demonstrated in its application to the successful synthesis of a broad-spectrum MMP inhibitor, CGS 27023A (**2**), as shown in Scheme (15) [51]. The *O*-protecting group, tetrahydropyran group, was removed by 2.5% TFA and 1% $H_2O$ in DCM. The final product (**2**) was then cleaved from the resin by 50% TFA treatment in 66% overall yield [51].




**Scheme 15.** Synthesis of CGS27023A from an *N*-linked hydroxylamine resin.

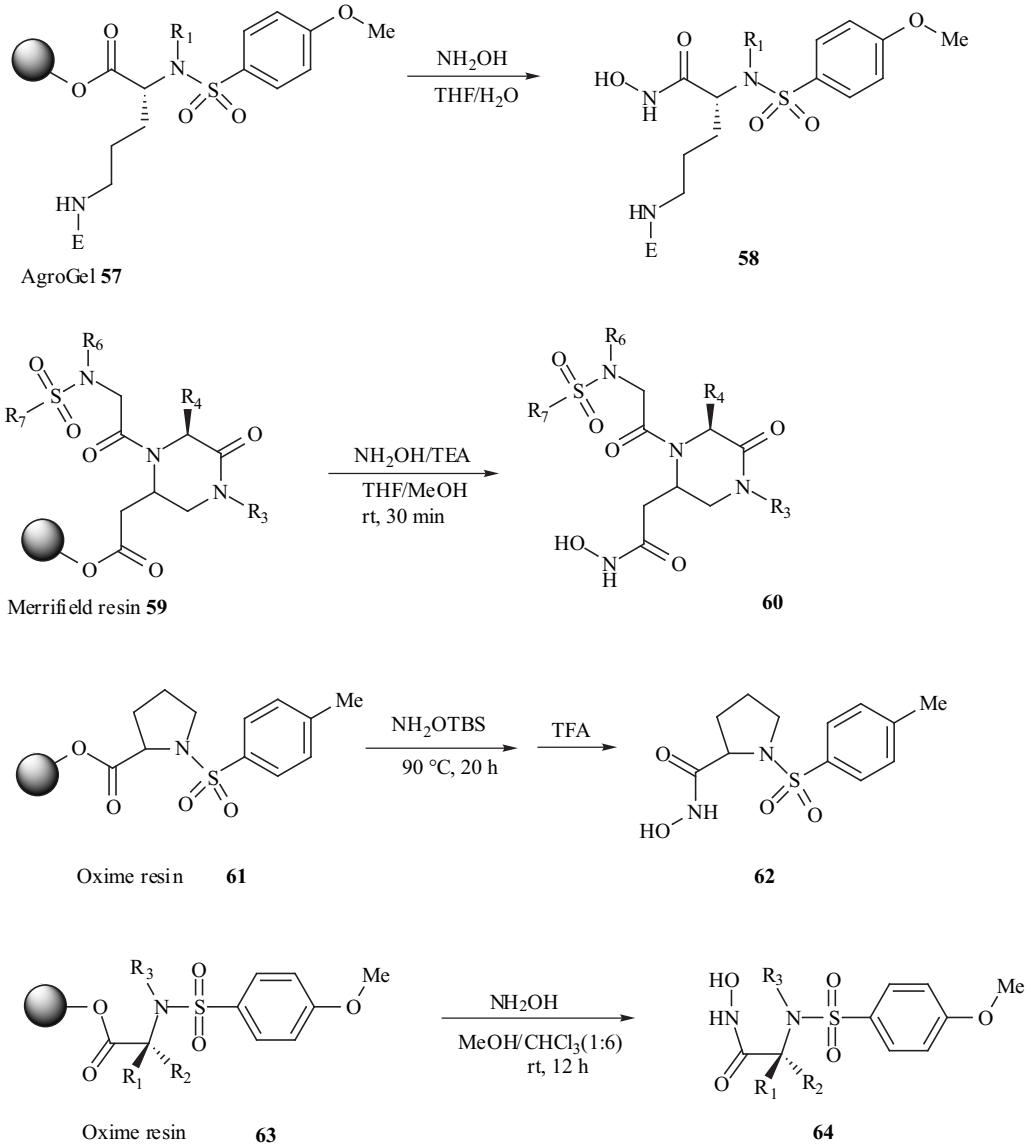
## Use of Hydroxylamines as Cleavage Reagents

Similar to the solution-phase nucleophilic displacement of esters by hydroxylamine and its derivatives, hydroxamic acids can also be obtained from resin-bound carboxylic acid esters using hydroxylamines as cleavage reagents. This strategy offers several advantages over the other methods discussed above because it avoids the formation of potential by-products derived from functionalization of the NH group of the *O*-linked hydroxylamine resin during the multi-step synthesis, and it is compatible with acid-labile functional groups and building blocks.

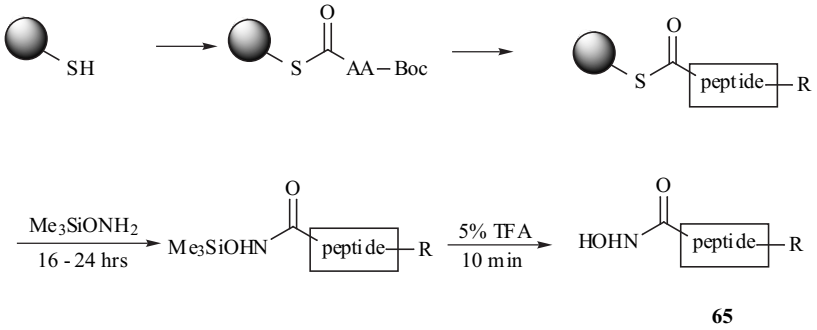
Dankwardt reported that AgroGel-bound Cbz-amino acids were treated with an aqueous hydroxylamine solution for two days to give corresponding hydroxamic acids in good yields [52] Recently the same group applied this method to the synthesis of ornithine-based sulfonamide hydroxamic acids (**58**) as inhibitors of procollagen C-proteinase (PCP) as shown in Scheme (16) [53].

Lou and Mjalli disclosed that a mixture of freshly prepared hydroxylamine, $Et_3N$ and THF served as an effective cleavage reagent for synthesis of highly functionalized hydroxamic acids, such as MMP inhibitors (**60**) as shown in Scheme (16) [54]. They claimed that the cleavage of the ester linker on Merrifield resin proceeded smoothly, and the reactions were usually complete in 30 minutes at room temperature.

Alternatively, Golebiowski *et al.* reported that oxime resin-bound carboxylic acids could be cleaved by an excess of *O*-*t*-butyldimethylsilylhydroxylamine to give *O*-silyl hydroxamic acid intermediates [55]. The silyl protecting group was readily removed by subsequent TFA treatment leading to the desired hydroxamic acids such as (**62**) in 96% yield as shown in Scheme (16) [55]. As shown in Scheme (16), Thouin and Lubell found that anhydrous unprotected hydroxylamine in a $MeOH/CHCl_3$ solution smoothly cleaved the oxime resin-bound α-amino esters to give enantiopure hydroxamic acids (**64**) possessing a variety of functional groups [56]. They confirmed that no




**Scheme 16.** Cleavage of resin-bound esters by hydroxylamines.



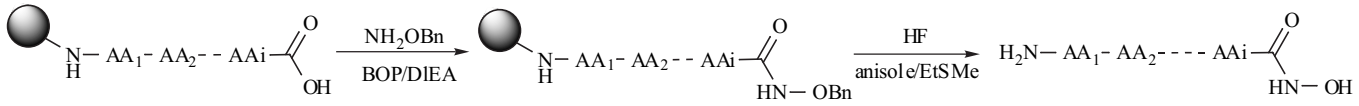

**Scheme 17.** Cleavage of resin-bound thioesters by hydroxylamine.

epimerization at the α-position of (**64**) occurred during the cleavage process.

A resin-bound thioester linker was also cleavable under similar conditions to generate hydroxamic acids as reported by Zhang *et al.* (Scheme (17)) [57]. Remarkably, *O*-(trimethylsilyl)hydroxylamine selectively cleaved the thioester without affecting the carboxylate functionality on the side chain. The use of this reagent led to the better results and was much easier for work-up compared to that of *O*-TBS, *O*-trityl or *O*-benzyl hydroxylamine.

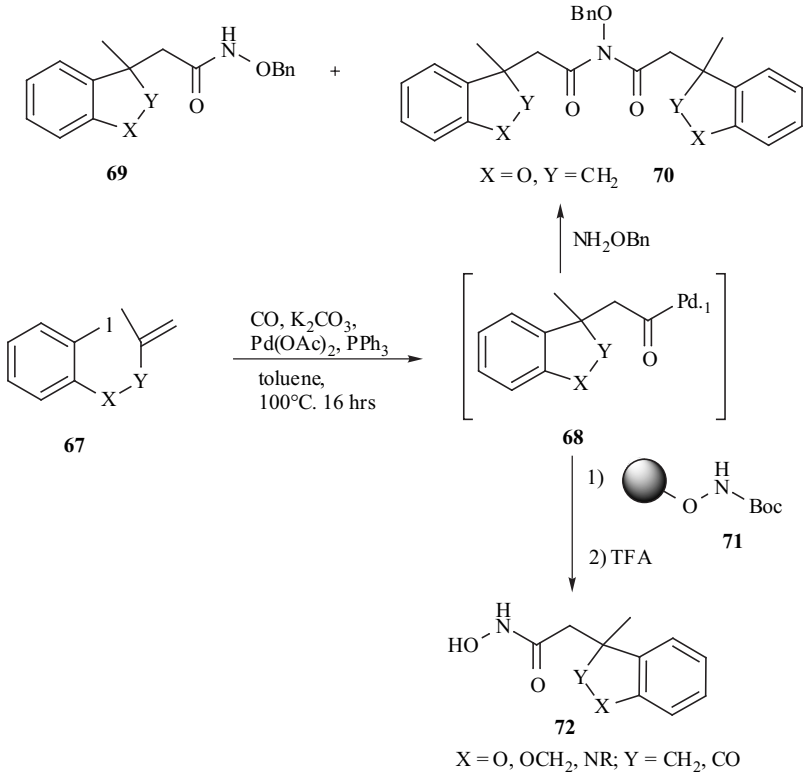
## Other Methods

Hydroxamic acids can be formed by the coupling of free carboxylates on solid support with *O*-protected hydroxylamines. Chen and Spatola reported the transformation of aspartic and glutamic acid side carboxylate moiety into a hydroxamic acid functional group on a resin-bound peptide as shown in Scheme (18) [58].




**Scheme 18.** The formation of hydroxamic acid moiety on side chains.

Grigg *et al.* described a new method for the construction of hydroxamic acid derivatives via an acyl-palladium intermediate (**68**) generated by a palladium-mediated




**Scheme 19.** Pd-mediated synthesis of hydroxamic acids.

carbonylation of aryl iodides (**67**) as shown in Scheme (19) [59]. The formation of a bis-acylated product (**70**) was suppressed using an excess of *O*-benzylhydroxylamine or *N*-Boc-*O*-benzylhydroxylamine. This approach was then adapted in the solid-phase synthesis of the hydroxamic acids (**72**) by using polymer-bound *N*-Boc-hydroxylamine (**71**).

## CONCLUSIONS

Tremendous progress has been made over the last decade in exploiting chemistry and therapeutic applications of hydroxamic acids. This mini-review covers only the most recent publications to illustrate current approaches toward syntheses of this important class of molecules in both solution- and solid-phase. In the next decade novel hydroxamic acid-based drug-like molecules will be increasingly needed in searching for new medicines as many new therapeutic targets, especially disease-relevant metalloproteinases, will be identified and validated. Combinatorial synthesis is the most powerful approach to access diverse and novel small molecules containing the hydroxamic acid moiety for lead discovery. The main synthetic effort in this area will be directed towards the development of highly efficient methods that are versatile, robust and adaptable for automated synthesis.

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