Solid-Phase Synthesis of Biologically Interesting Compounds Containing Hydroxamic Acid Moiety

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Abstract: Chemical strategies developed for the solid-phase synthesis of hydroxamates are divided into four groups: (i) the traditional synthesis of hydroxamates *via* cleavage of resin-bound esters by hydroxylamine and its derivatives, (ii) introduction of hydroxamic acid moiety on the resin-bound precursor, (iii) transformation of polymer-supported hydroxylamine, attached to a solid supported linker either by oxygen (*O*-linking strategy) or by nitrogen (*N*-linking strategy), and (iv) synthesis of *N*-alkyl hydroxamates. The scope and limitation of individual approaches are discussed.

Keywords: Hydroxamic acid, hydroxamate, solid-phase synthesis.

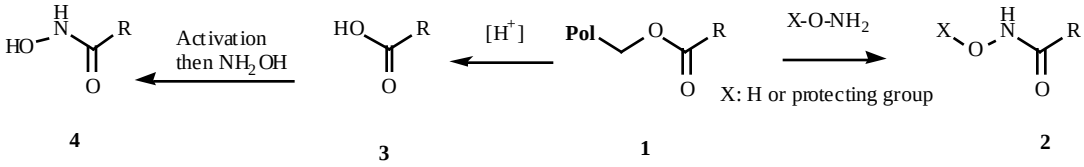
INTRODUCTION

Hydroxamic acid derivatives represent an increasingly important class of biologically active compounds. Hydroxamates serve as ligands to chelate metal ions including Zn(II) and Fe(III) and compounds containing hydroxamic acid moiety are know to inhibit enzymes having metal ion in their active sites. In addition, naturally occurring siderophores containing hydroxamic acid functionality facilitate Fe(III) transport into bacterial cells and are essential for cell survival. The most frequently studied biologically relevant hydroxamates are targeted against inhibition of metal-containing enzymes, particularly matrix metalloproteinases (MMP) and histone deacetylases (HDAC). Biological activities of hydroxamates and their therapeutic applications have been reviewed on numerous occasions [1-6].

For the sake of this review, solid-phase synthesis of hydroxamic acids was divided into four distinct categories, depending on the route the hydroxamate moiety is incorporated into the synthesized compound. The first approach is based on solid-phase synthesis of target compounds, usually on an ester-type linker, followed by transformation of carboxylate to hydroxamate. In the second approach, the hydroxamate is introduced onto a resin-bound intermediate, typically by conversion from a carboxylate. The third strategy builds the target hydroxamate from polymer-supported hydroxylamine. The hydroxylamine can be attached to a polymer-supported linker either by oxygen (*O*-linking strategy), the more common approach, or by nitrogen (*N*-linking strategy). In the last section of this review, four different routes to the synthesis of *N*-alkyl hydroxamic acids are covered.

POST-SYNTHETIC TRANSFORMATION FROM A CARBOXYLATE

The traditional approach, often applied with peptide-derived hydroxamates, relies on synthesis of a carboxylic acid derivative of the target molecule on an ester-type linker



4 **3** **1** **2**

Scheme 1. Synthesis of hydroxamic acids by post-synthetic transformation from a carboxylate.

and conversion of the polymer-supported ester **1** into a hydroxamate only after the entire target molecule is assembled on the solid phase (Scheme **1**). This transformation is achieved in two different ways: the product **2** is cleaved from the ester linkage by hydroxylamine, or, in a two stage procedure, the product is cleaved as a carboxylic acid **3** and converted to a hydroxamate **4** in a subsequent step. *The cleavage of resin-bound esters by hydroxylamine depends on the character of the resin and may not be quantitative*.

The most straightforward route for the solid-phase synthesis of hydroxamic acids appears to be the direct application of the original Merrifield procedure for peptide synthesis, followed by cleavage of the polymer-supported carboxylate by hydroxylamine. Although this procedure is a traditional way to prepare hydroxamic acids in solution and has been applied to the solid phase on several occasions, it was not quantitative on hydrophobic polystyrene resin [7,8]. Substantially more successful results were obtained using PEG grafted polystyrene resins (ArgoGel or TentaGel) with yields above 70%, even for sterically hindered amino acids

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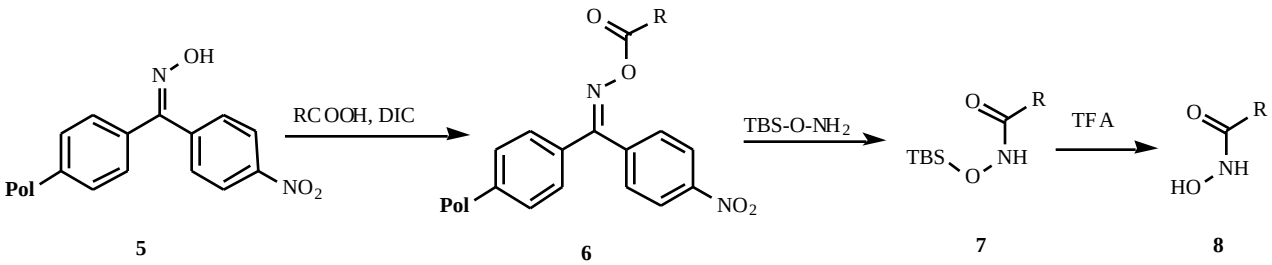


5 **6** **7** **8**

Scheme 2. Synthesis of hydroxamic acids on Kaiser oxime resin.

(50% aqueous hydroxylamine in THF, 2 days) [8]. This method was used to make a library of MMP inhibitors with unspecified better results compared to the trityl *O*-linked hydroxylamine approach [9,10]. Another solution to improve yields of the nucleophilic substitution is to use thioesters on polystyrene resin. This method has been applied to the synthesis of peptide hydroxamic acids [11,12]. Improvement is seen because thioesters are more susceptible to nucleophilic cleavage by hydroxylamine. Because of their acid stability towards trifluoroacetic acid (TFA), Boc-protection strategy can be used for the peptides synthesis. However, the low solubility of hydroxylamine hydrochloride in most organic solvents required the use of DMF as a solvent during cleavage. To avoid evaporation of a high boiling point solvent, cleavage from the resin was carried out by O-trimethylsilyl hydroxylamine in THF, followed by TFA removal of the silyl protecting group [12].

An alternative method is to utilize the Kaiser oxime resin **5** [13]. Oxime resin esters **6** were cleaved by O-*tert*-butyldimethylsilyl hydroxylamine [14] and TBS groups removed with TFA [15] (Scheme **2**). Cleavage with anhydrous hydroxylamine solution was described by Touin and Lubell [15]. Hydroxylamine hydrochloride was dissolved in MeOH, treated with MeONa, and the precipitated NaCl removed by filtration.

INTRODUCTION OF A HYDROXAMATE ON RESIN-BOUND INTERMEDIATE

In the second approach, the hydroxamate group was introduced onto the side-chain carboxylate of Asp and Glu. A peptide was synthesized on MBHA resin using Fmoc-Asp(O*t*Bu) or Fmoc-Glu(O*t*Bu). The *tert*-butyl protecting group was removed by TFA. The acid was then activated with BOP and coupled with NH_2OBn [16]. The benzyl protecting group was removed by HF, simultaneously with cleavage of the peptide from the MBHA resin. An analogous strategy was used for installation of a hydroxamate using *O*-2-methoxypropanehydroxylamine on the carboxylic acid of resin-bound HDAC inhibitors [17] and also using *O-tert*-butylhydroxylamine on glutamate [18].

The traditional solid-phase peptide synthesis immobilizes the carboxy terminal of an amino acid and the synthesis follows along the "C to N" direction. In order to convert the carboxy terminus to a hydroxamate, the inverse solid-phase synthesis was used that links the peptide backbone to the solid support *via* its amino group, leaving the carboxy terminus available for further modification. Among other classes of compounds, hydroxamic acids were prepared by activating the carboxylate **9** and coupling with O-*tert*-butyl protected hydroxylamine to yield **10** [19]. Simultaneous cleavage of peptide hydroxamic acids from the resin and *tert*-butyl protecting groups were affected by 10 % TFA to yield peptide hydroxamic acids **11**.

The use of Barany's backbone amide linker (BAL) [20] should represent an alternative strategy for the synthesis of amino acid-related hydroxamates, although this application of the BAL linker has not yet been reported.

SYNTHESIS FROM POLYMER-SUPPORTED HYDROXYLAMINE

This synthetic strategy takes advantage of polymer-supported hydroxylamine, attached to a solid support either

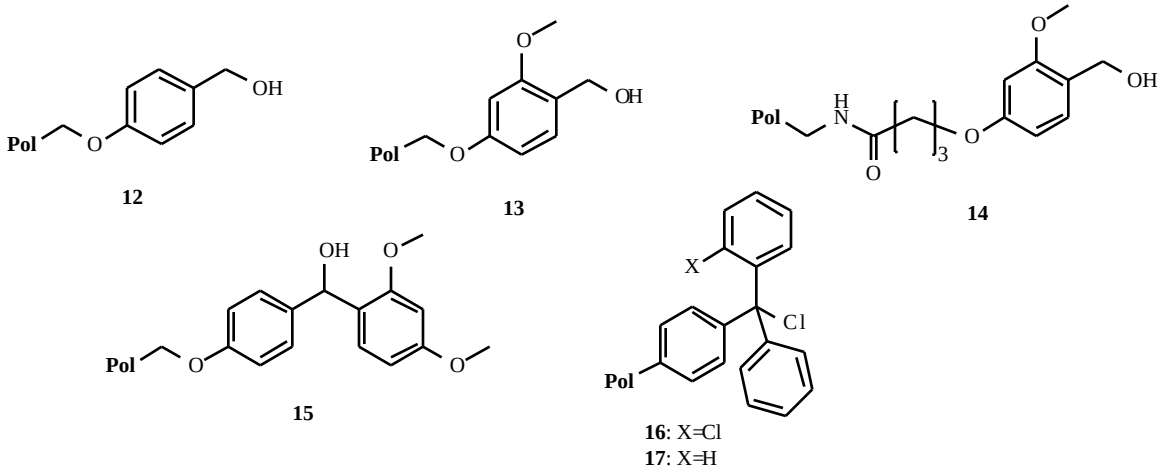
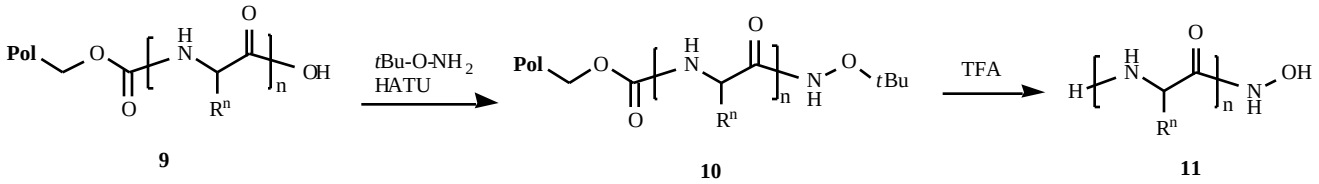


Fig. (1). Linkers used for the synthesis of hydroxamic acids.



Scheme 3. Transformation of resin-bound carboxylate to hydroxamate.

by oxygen (*O*-linking strategy) or by nitrogen (*N*-linking strategy). The *O*-linking approach has been used almost exclusively. *Two potential problems are (i) the presence of an NH group on the hydroxamate and (ii) side-product contamination and incomplete cleavage when using* a *Wang linker.*

O-Linking Strategy

Protected hydroxylamine was immobilized on a suitable linker either by Mitsunobu reaction of a resin-supported alcohol with *N*-hydroxyphthalimide or by nucleophilic substitution of a resin-bound electrophile with *N*-protected hydroxylamine. Mitsunobu reaction of *N*-hydroxyphthalimide with Wang [7] **12**, Sasrin [21,22] **13** or 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyrate (HMPB) [7] **14** resin was carried out with triphenylphosphine and azodicarboxylate in anhydrous THF (Sasrin and HMPB differ only by the attachment of the linker to the solid support.) (Fig. **1**). The reaction course can be monitored by the presence of ν_{max} 1770 and 1726 cm^{-1} bands in the infrared spectrum [7].

In an alternative route to the Mitsunobu reaction, hydroxymethyl resins Wang **12**, Sasrin **13**, and Rink acid **15** were converted to a mesylate and then reacted with *N*-hydroxyphthalimide [23]. The 2-chlorotrityl chloride resins **16** were treated with *N*-hydroxyphthalimide (TEA in DMF at ambient temperature) [24] analogously to trityl chloride resin **17** [25]. Synthesis of hydroxamates were described on modular solid-phase supports, Mimotope's SynPhase crowns derivatized with trityl chloride [26] or α-chloroethyl linker on polystyrene grafted SynPhase crowns [27]. Chlorotrityl chloride resin **16** was also derivatized by *N*-Fmoc hydroxylamine [28]. The advantage of the Fmoc derivative is its simple and fast cleavage. The disadvantage is the need to synthesize the derivative. Any unreacted resin-bound bound trityl chloride was capped by methanol [28]. Fig. (**1**) shows structures of linkers used to *O*-tether the hydroxylamine. The selection of the linker seems to be important. Several reports indicated lower yields and the presence of impurities when using a Wang linker [7,29] and recommend the use of a more acid-labile linker.

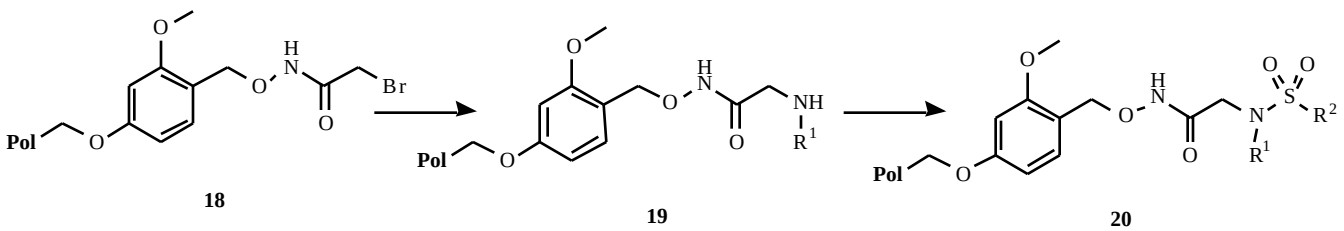
The phthaloyl protecting group was typically cleaved using 15% hydrazine in THF/ethanol [7] at ambient temperature overnight or with 22% hydrazine hydrate in DMSO at 60 ºC for 2 h [26]. For large scale synthesis, methylaminolysis in THF was advocated, offering significant safety advantages [30]. Quantification of the loading level was measured by reading the absorbance at 346 nm (ε = 3615) [26].

After cleavage of the phthaloyl group, the resin-bound hydroxylamine was acylated by activated carboxylic acid derivatives to afford resin-bound hydroxamates. The carboxylic acid side-chain was then further derivatized in order to arrive at the target compounds.

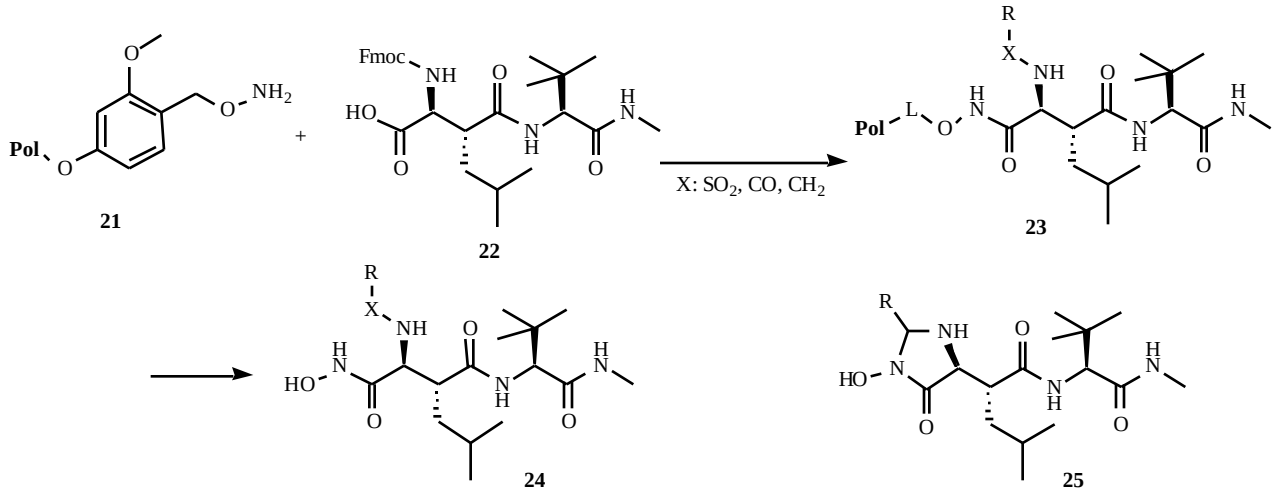
Release of hydroxamates from the solid support was carried out by reaction with TFA. The Wang linker is the most acid stable linker used for the synthesis of hydroxamates. Cleavage of the product from this linker was effected by 90% TFA [23,31], 80% TFA provided "fair to good yields" [7], and 50% TFA cleaved 80% of the hydroxamic acid in 30 min [32]. The HMPB linker is more acid labile and hydroxamic acids were quantitatively released by 10% TFA in 30 min [29]. Release from the chlorotrityl linker was achieved by treatment with 5% TFA in dichloromethane (DCM) for 1h [24,28]. Cleavage from the highly acid labile trityl linker was achieved by formic acid/THF (1:3) for 1 h [25] or 1% TFA in DCM [26].

Synthetic Applications

The *O*-linking strategy is the most often used method for the synthesis of hydroxamates. The Wang-derived benzyloxyamine resin was used to prepare the peptide Z-Pro-Leu-Ala-NHOH, a known MMP inhibitor, and a set of analogs [7]. The authors observed the presence of non-peptidic contaminants that depended on resin batches. This problem was solved by using the more labile HMPB linker, attached to MBHA resin. This allowed the concentration of TFA in the cleavage cocktail to be decreased and provided crude product of higher purity and yield. The HMPB linker-based resin was used for the preparation of a set of known MMP inhibitors. The polymer-supported benzyloxyamine was acylated with bromoacetic acid, the bromide of **18** was



Scheme 4. Synthesis of sulfonamide hydroxamates.

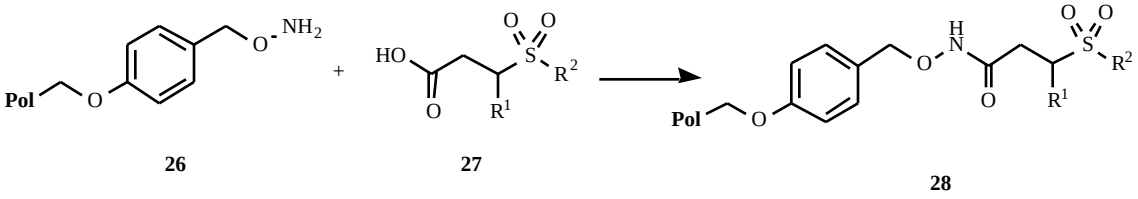


Scheme 5. Synthesis of marimastat related MMP inhibitors.

replaced by amines, and the secondary amine **19** reacted with sulfonyl chlorides to provide the target compounds **20** [7] (Scheme **4**). Similar chemistry was reported for a trityl linker immobilized on Synphase crowns [26].

The second generation of marimastat related MMP inhibitors, **24**, were prepared by acylating the resin **21** with a succinate derived acid **22**, cleaving the Fmoc group, and derivatization through sulfonamide formation (in DCM-pyridine 4:1), acylation, and reductive alkylation (resin **23**) [22] (Scheme **5**). Interestingly, the reaction with a few aldehydes provided imidazolone derivatives **25** that could not be reduced by $NaBH_3CN$ to the corresponding amine.

The benzyloxyamine **26** derived from Wang resin was used to convert a small combinatorial library of arylsulfone carboxylic acids **27** to hydroxamates **28** [33] (Scheme **6**).



Scheme 6. Synthesis of arylsulfone hydroxamates.

Solid-phase synthesis of sulfones **27** was carried out on a Wang linker. The library compounds were cleaved from the polymer support and used to acylate the Wang resin based

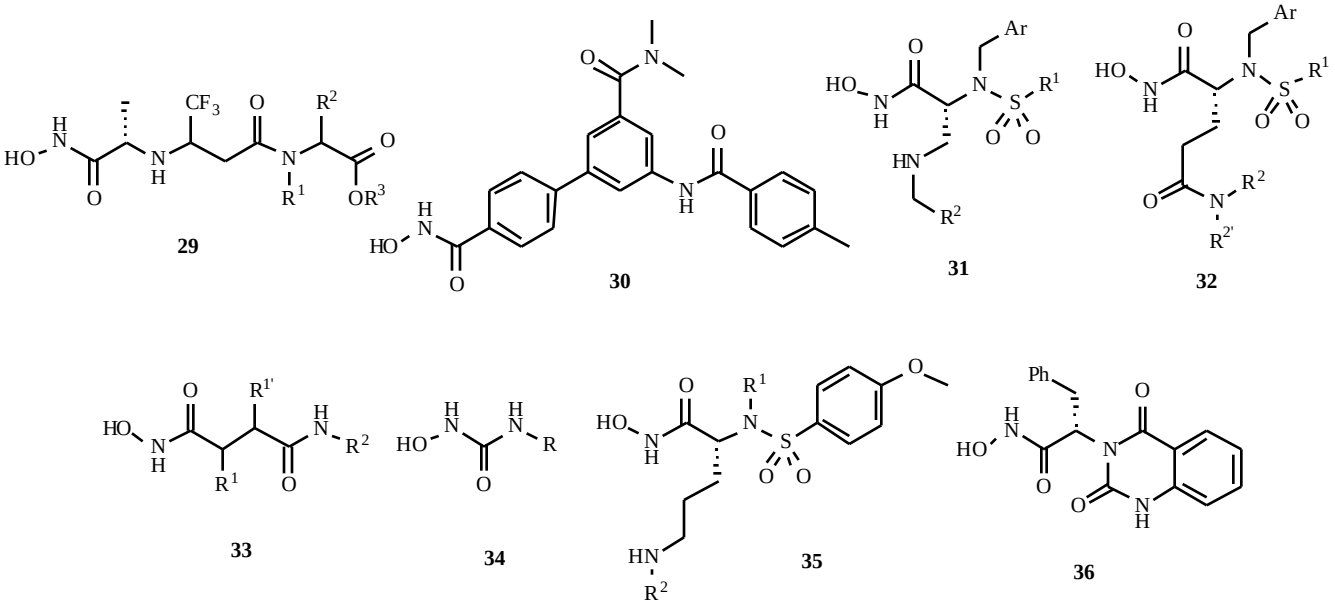
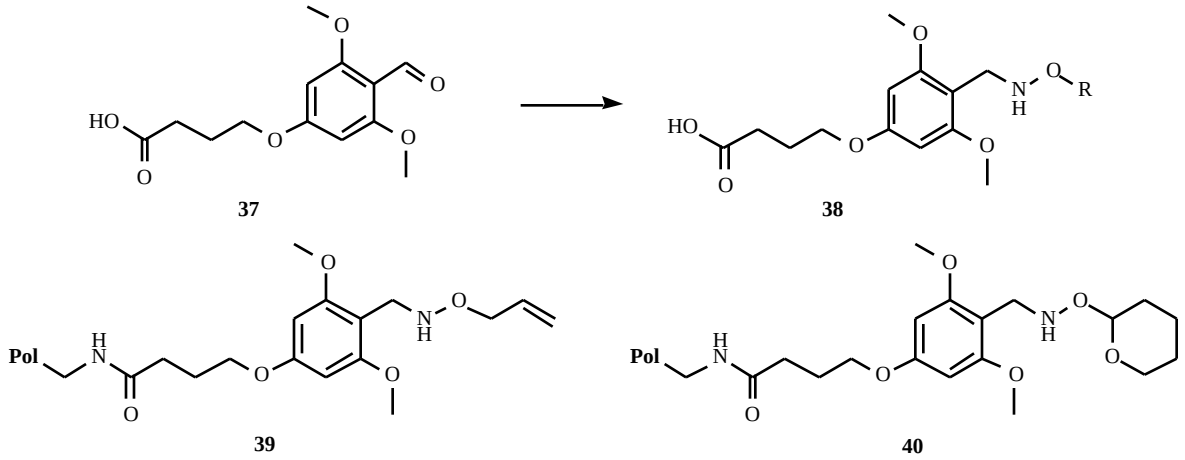


Fig. (2). Representative hydroxamates prepared on solid phase.



Scheme 7. Synthesis of hydroxamic acids via *N*-linking strategy.

hydroxylamine **26**. Cleavage by TFA yielded the target arylsulfone hydroxamate library of MMP inhibitors.

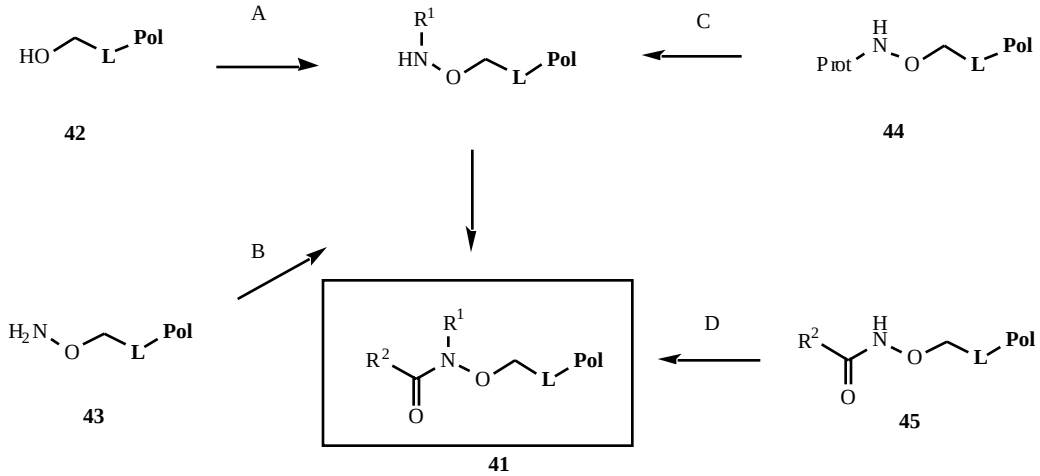
Solid-phase synthesis of hydroxamates via *O*-linking strategy has frequently been used for the synthesis of pharmacologically relevant compounds, including MMP inhibitors **29** [34,35] and HDAC inhibitor **30** [36] using a Wang linker or diamino acid and glutamic acid based MMP inhibitors **31** and **32** using a chlorotrityl resin [37,38] (Fig. **2**). The trityl linker was used in a model syntheses of succinimide derived MMP inhibitors **33** [25]. In addition to hydroxamates, the hydroxylamine resin was also converted to *N*-hydroxyurea derivatives **34** using isocyanates [25]. The same linker was used for synthesis of sulfonamide derived procollagen C-proteinase inhibitors **35** [9]. Quinazoline-2,4-dione derivatized hydroxamic acids **36** were prepared on the Sasrin resin [21].

N-Linking Strategy

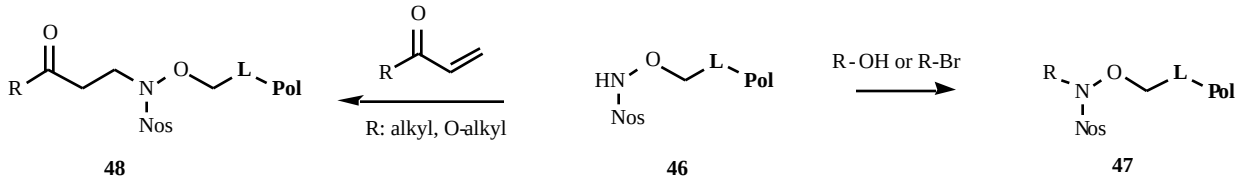
The alternative approach of tethering the hydroxylamine *via* its nitrogen was designed to prevent potential side-reactions caused by the NH group of hydroxamates present in the previous *O*-linking strategy. Ngu and Patel [39] linked the hydroxylamine to Barany's BAL linker **37** [20], while the oxygen was protected by the acid labile tetrahydropyran (THP) group or acid stable allyl group [39] (Scheme **7**). The BAL linker **37** was used to reductively alkylate NH_2-OTHP or $NH_2OCH_2CH{=}CH_2$ in solution. The resulting *N,O*-derivatized hydroxylamines **38** were protected with an Fmoc group and attached to an aminomethyl polystyrene type resin by acylation. After cleavage of the Fmoc group, the resin-supported hydroxylamines **39** and **40** were used for the synthesis of hydroxamate based MMP inhibitors.

SYNTHESIS OF *N*-ALKYL HYDROXAMIC ACIDS

Four synthetic strategies are available to access *N*-alkyl hydroxamates **41** (Scheme **8**): (i) *N*-alkyl hydroxylamine derivatives were prepared in solution and then immobilized on the resin **42** (route A), (ii) direct *N*-alkylation of resin bound hydroxylamine **43** (route B), (iii) *N*-alkylation of *N*-protected resin-bound hydroxylamine **44** followed by cleavage of the protecting group (route C), and (iv) *N*-alkylation of acylated hydroxylamine **45** (route D). *Route C is the most versatile method amenable to combinatorial synthesis with a large selection of synthons (building blocks) while not prone to side-reactions. Also note, if R^2 of route D is not OR (ie, carbamate) but is instead a simple alkyl or aryl group, then this route is prone to competitive*



Scheme 8. Four routes for access to *N*-alkyl hydroxamic acids.



Scheme 9. *N*-alkylation of 2-nitrobenzenesulfonyl-derivatized resin-bound hydroxylamine.

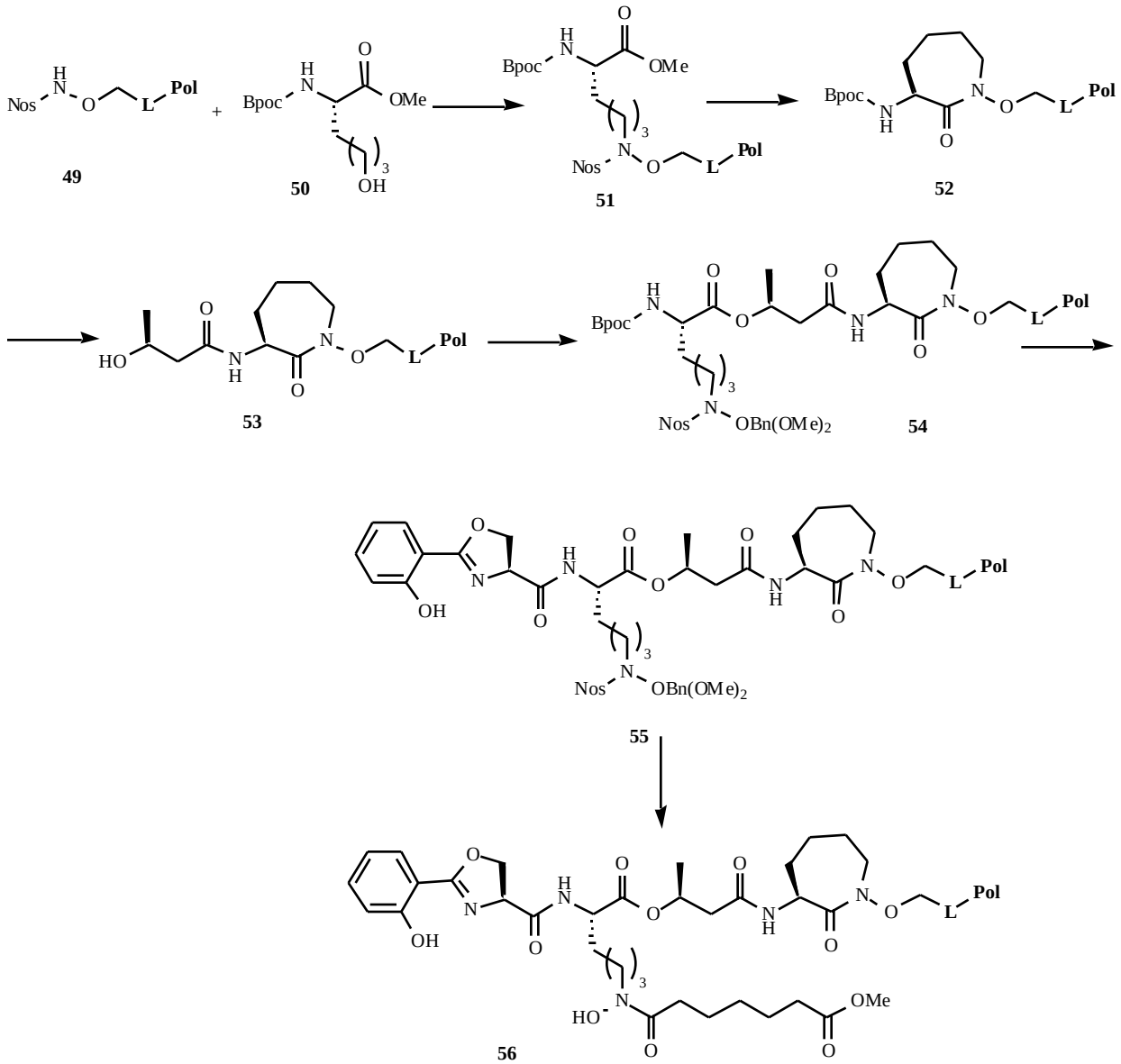
N- and carbonyl O-alkylations and generally gives mixtures that are very difficult, if not impossible to separate.

Route A

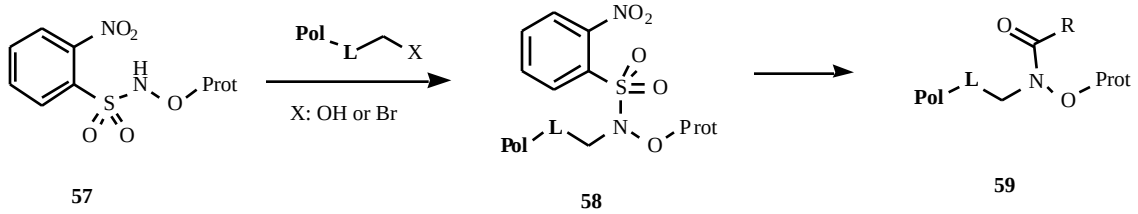
The first approach takes advantage of immobilization of *N*-alkylated hydroxylamine derivatives. With chlorotrityl resin, Fmoc-NMe-OH could be attached and Fmoc cleaved, but the authors were unable to acylate the secondary hydroxylamine, probably due to severe steric constraints [28]. This prompted the authors to prepare and immobilize *N*-alkyl-*N*-Fmoc-hydroxylamine to the sterically less demanding Rink linker [40]. Acylation of the *N*-alkyl hydroxylamine tethered to this linker was achieved by the HATU method [41].

Route B

On resin *N*-alkylation eliminated the need for synthesis of *N*-alkylated building blocks in solution. However, attempts to *N*-alkylate Wang-*O*-hydroxylamine resin were not successful [30]. Direct alkylation resulted in either poor



Scheme 10. Synthesis of carboxymycobactin T 7.



Scheme 11. Immobilization of *O*-protected *N*-(2-nitrophenylsulfonyl)hydroxylamine.

alkylation or overalkylation. Reductive alkylation yielded incomplete reduction or cleavage of the product from the resin. An independent report described a detailed optimization of reaction conditions for reductive alkylation and resulted in a practical procedure that uses BH_3·pyridine in the presence of trichloroacetic acid [42].

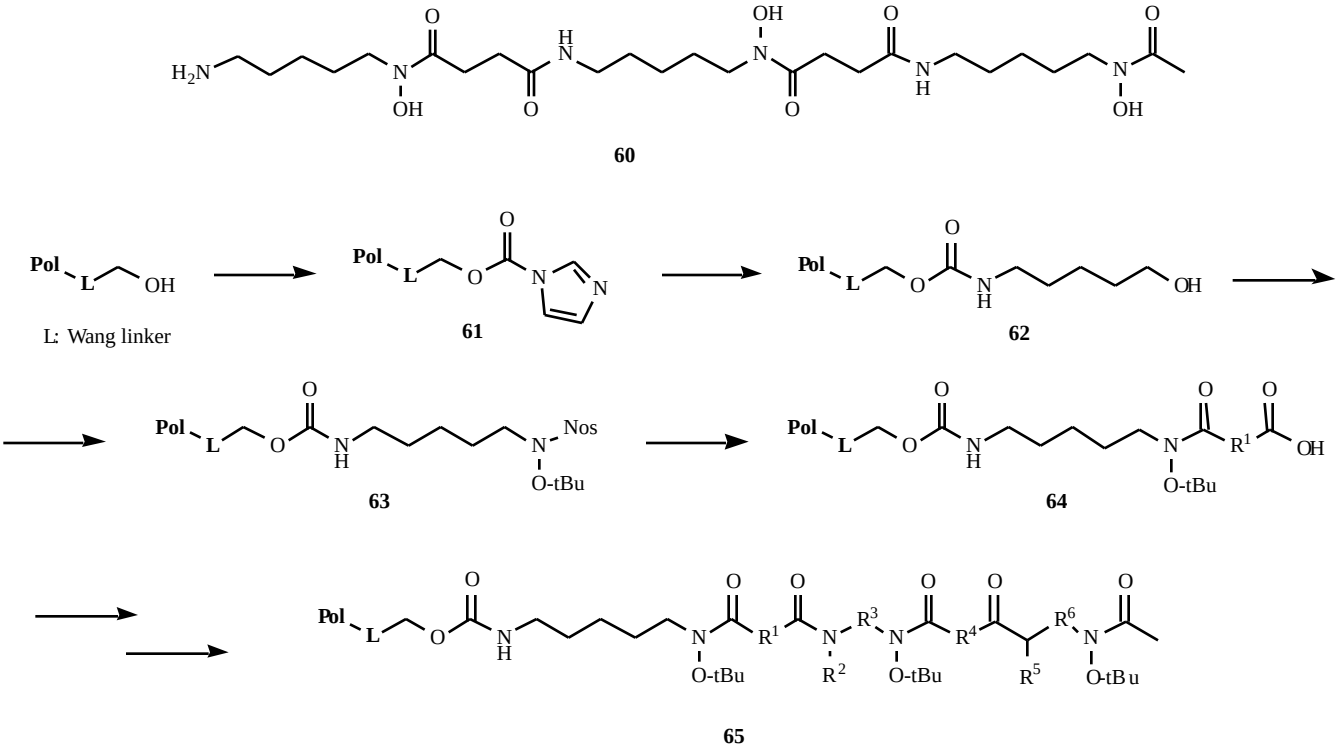
Route C

Successful *N*-alkylation was achieved by introduction of an *N*-protecting group. Alkylation of allyloxycarbonyl (Alloc) protected amino groups with alkyl bromide in the presence of DBU is straightforward [30]. The Alloc group was cleaved and the amino group acylated by carboxylic acids to prepare solid-phase equivalents of Weinreb amides for the synthesis of aldehydes.

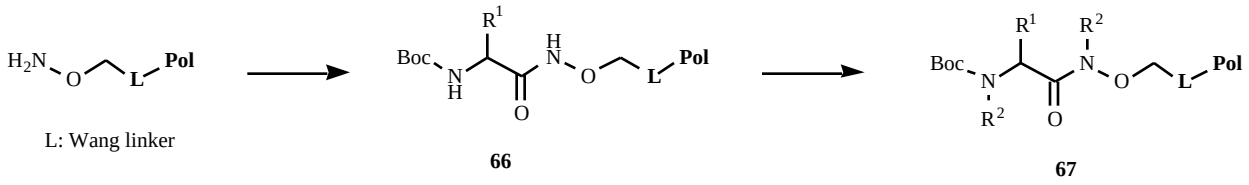
An alternative route takes advantage of alkylation of *O*-linked *N*-(2-nitrobenzenesulfonyl)hydroxylamines **46** [31] (Scheme **9**). Polymer-supported *N*-benzyloxy-2-nitrobenzenesulfonamide was *N*-alkylated using three different routes: *via* Fukuyama variation of the Mitsunobu reaction with alcohols (resin **47**), by *N*-alkylation with alkylbromides (resin **47**), and by Michael addition reaction with α,β-unsaturated carbonyl compounds (resin **48**) [29]. After cleavage of the 2-nitrobenzenesulfonyl (Nos) group (thiol/base) the amino group was acylated.

Synthetic Applications

Applications of this method have been documented in the synthesis of a siderophore mycobactin. Siderophores are complex natural products facilitating Fe(III) transport into bacterial cells, essential for cell survival. Methyl carboxymycobactin T 7 and its analogues were assembled on the solid support according to Scheme **10**. [43]. The Wang resin-supported Nos-protected hydroxylamine **49** was alkylated with alcohol **50** under Mitsunobu conditions, the Nos group of the resin-bound lysine derivative **51** was cleaved using a thiolate and the methyl ester hydrolyzed with LiOH/THF. The carboxylate salt was activated and cyclized to the azopine **52**. The Bpoc-group was cleaved and the resin-bound azepane derivative was coupled with sodium (S)-3-hydroxybutyrate in the presence of HOBT/HBTU. The polymer-supported alcohol **53** was acylated with the lysine derivative. Several methods for esterification were tested and the Mitsunobu reaction was selected because of better yields of the product **54**. The Bpoc protected intermediate **54** was treated with TFA to cleave the Bpoc group, neutralized and



Scheme 12. Synthetic scheme for Desferrioxamine B.



Scheme 13. Double alkylation of Boc amino acid hydroxamates.

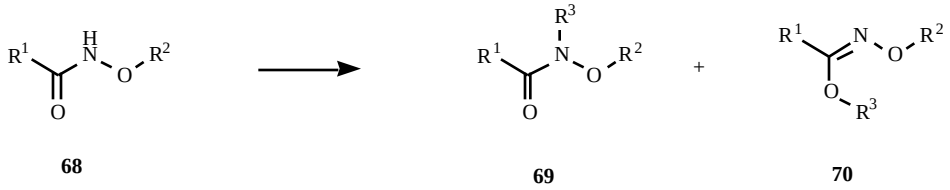
coupled with oxazoline derivative. After deprotection of the Nos group from **55**, the resulting hydroxylamine was acylated with the monoester of the dicarboxylic acid. Cleavage from the resin **56** with simultaneous cleavage of the 2,4-dimethoxybenzyl group afforded crude methyl carboxymycobactin T 7 (~50% purity).

A very useful reagent for the synthesis of *N*-alkyl hydroxamates is the *O*-protected *N*-(2-nitrophenylsulfonyl)hydroxylamine **57**, developed by Slomczynska's group [31] (Scheme **11**). The reagent was attached to solid supports using either a Mitsunobu alkylation of resin-bound alcohols or a base-catalyzed reaction with polymer-supported electrophile to yield resin **58**. After cleavage of the 2-nitrobenzenesulfonyl (Nos) group (thiol/base), the amino group was acylated providing the protected *N*-alkyl hydroxamic acid resin **59**.

carbonyldiimidazole (resin **61**) and reacted with 5-amino-1-pentanol. The polymer-supported alcohol **62** was reacted with *O-tert*-butyl-*N*-2-nitrobenzenesulfonyl-hydroxylamine under Mitsunobu conditions (resin **63**), the Nos group was cleaved using 2-mercaptoethanol and DBU, and the liberated amino group acylated with dicarboxylic acid anhydrides or with activated dicarboxylic acids to finish the incorporation of the first hydroxamate (resin **64**). The sequence was repeated to assemble the target compounds **65**. The products were cleaved from the solid support using 90% TFA in DCM.

Route D

The last route, alkylation of polymer-supported *N*-acylated benzyloxyamine, has limited applicability due to a side-reaction, and its use is restricted to acyl groups

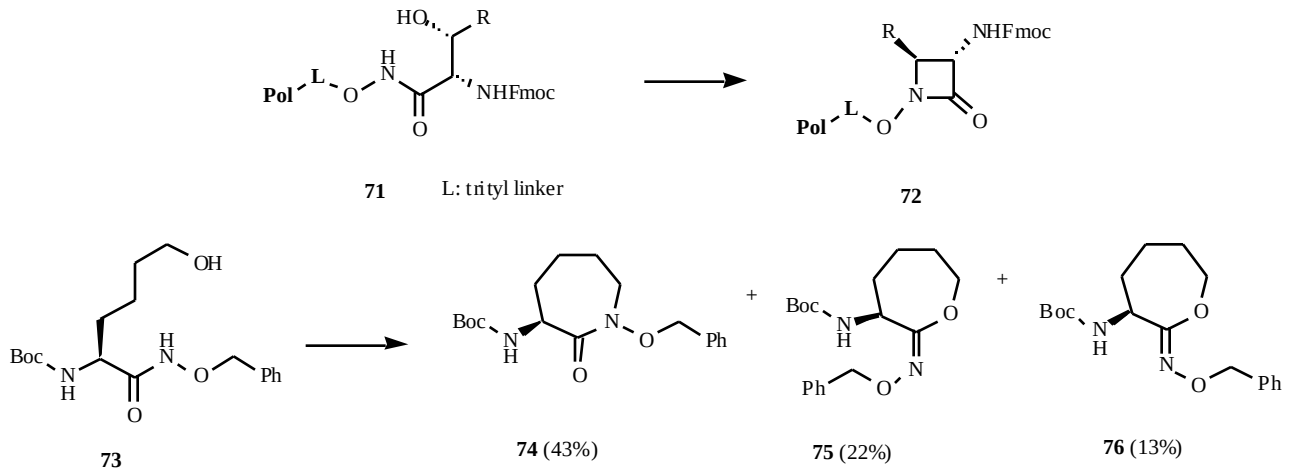


Scheme 14. Competing *N*- and *O*-alkylations.

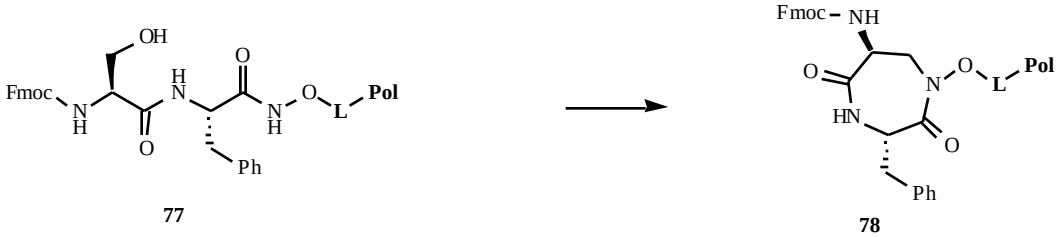
This reagent has been used for combinatorial solid phase synthesis of Desferrioxamine B (DFO) **60** and analogs [44,45]. Desferrioxamine B is a siderophore originating from *Streptomyces pilosis* that contains three *N*-alkyl hydroxamates and is used for treatment of iron overload. The synthesis of a 92 member library is described in Scheme **12**. The Wang resin (L = Wang linker) was activated by 1,1'-

compatible with alkylation [30]. Alkylation (electrophile and DBU in toluene) of benzyloxyamine **66** acylated with Boc-protected amino acids suffered from double alkylation (resin **67**) (Scheme **13**).

In several instances, *N*-alkylation of hydroxamic acids **68**, either by reactions with electrophiles [46,47] or using Mitsunobu alkylation of alcohols [48-52], was accompanied



Scheme 15. Intramolecular alkylations of hydroxamate.



Scheme 16. Solid-phase synthesis of 1,4-diazepan-2,5-dione hydroxamates.

by carbonyl *O*-alkylation and provided both alkylated products **69** and **70** (Scheme **14**). Experiments in solution have shown that the outcome of alkylation is substrate sensitive. Free hydroxamic acids alkylated with an electrophile provided a mixture of *O*- and *N*-alkyl products [46]. *O*-alkyl hydroxamates alkylated with an alcohol under Mitsunobu conditions afforded *N*-alkyl derivatives [51,52]. *O*-Acylhydroxamates gave a mixture of *N*- and *O*-alkylkated products [51]. However, a recent report described an *O*-alkyl derivative as a major product in alkylation of *O*-benzylhydroxamates [48].

The intramolecular Mitsunobu *N*-alkylation of *O*-protected hydroxamic acids derived from serine is the key step in Miller's synthesis of β-lactams [51]. This route was successfully used in solid-phase combinatorial synthesis of β-lactams **72** from linear precursors **71** [53] (Scheme **15**). The formation of a six-membered ring under the same conditions in solution has been accompanied by carbonyl *O*-alkylation [48]. A mixture of *N*- and *O*-alkyl derivatives was also reported by Miller's group during the formation of a seven-membered ring from hydroxamate **73** [49,50]. In addition to the *N*-alkyl derivative **74**, both isomers of hydroximates **75** and **76** were isolated and characterized.

However, no carbonyl *O*-alkylation was observed during solid-phase synthesis of 1,4-diazepan-2,5-dione derivatives **78** on 2-chlorotrityl linker (L = 2-chlorotrityl) by cyclization of a linear dipeptide **77** [54] (Scheme **16**). Interestingly, the cyclization by Mitsunobu reaction was carried out under microwave irradiation in a sealed tube.

CONCLUSIONS

Diverse chemical routes developed for the solid-phase synthesis of hydroxamates enable incorporation of the hydroxamic acid moiety into almost any part of a target molecule. The success of traditional synthesis of hydroxamates *via* cleavage of resin-bound esters by hydroxylamine depends on resin type and careful selection of both resin and linker is advised in order to obtain quantitative cleavage. The most frequently used methodology, *O*-immobilization of hydroxylamine, may suffer from two potential problems (i) the presence of an NH group on the hydroxamate and (ii) side-product contamination and incomplete cleavage when using a Wang linker. For the synthesis of *N*-alkyl hydroxamates, alkylation of *N*-protected resin-bound hydroxylamine followed by removal of the protecting group is the most versatile route. It is amenable to combinatorial synthesis with a large selection of synthons (building blocks) and is not prone to side-reactions. For this synthetic strategy, trityl linkers should be avoided due to problematic acylation of the alkylated species.

Recent developments in the application of solid-phase reagents and scavengers [55], render solid-phase synthesis competitive with solution chemistry in terms of both speed and operational simplicity. However, neither solid- nor solution-phase synthesis is superior. Both methodologies are indispensable tools enabling access to synthetic hydroxamates, and the needs of a particular project should determine the meaningful selection of a synthetic strategy. Indeed, often a combination of both may be the method of choice.

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ABBREVIATIONS

BAL = backbone amide linker

DCM = dichloromethane

Boc = *tert*-butyloxycarbonyl

Bn = benzyl

BOP = benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DFO = desferrioxamine B

DMF = *N*,*N*'-dimethylformamide

DMSO = dimethylsulfoxide

Fmoc = fluorenylmethyloxycarbonyl

HBTU = 2-(1*H*-henzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HDAC = histone deacetylases

HOBT = *N*-hydroxebenzotriazole

MBHA = methylbenzhydrylamine

MMP = metalloproteinase

Nos = 2-nitrobenzenesulfonyl

HMPB = 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyrate

PEG = polyethyleneglycol

Sasrin = Super Acid Sensitive Resin

*t*Bu = *tert*-butyl

TBS = *tert*-butyldimethylsilyl

TEA = triethylamine

TFA = trifluoroacetic acid

THP = tetrahydropyran

THF = tetrahydrofuran

Z = benzyloxycarbonyl

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