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Solid Phase Synthesis of Diverse Isoxazolidines *via* 1,3-Dipolar Cycloaddition

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Abstract: Diverse substituted isoxazolidines **2-4** are assembled on solid phase by condensing hydroxylamines with aldehydes and trapping the resulting nitrones with various dipolarophiles. The one-pot three-component cycloaddition reaction yields the isoxazolidines in good to excellent yield. Three different reaction pathways - each dealing with one of the three components attached to the solid support - are evaluated with respect to versatility and yield of the synthesized isoxazolidines. Structures and relative configurations of representative isoxazolidines are elucidated with ^{1}H-NMR, TOCSY, HSQC and NOESY. The reaction of polymer-bound hydroxylamines with aldehydes and alkenes is found to be the most successful. The kinetics of the solid phase reaction are determined by FT-IR-ATR spectroscopy. Polymer-bound nitrones are stable for the split/combine synthesis. A library of isoxazolidines is synthesized by the split/combine method and analyzed by means of HPLC-MS.

Introduction

The solid phase synthesis provides a rapid method for generating small-molecule libraries by automated split/combine synthesis supporting the lead-finding process as well as lead-refinement.[1] One of the most important reactions for the construction of structurally diverse 5-membered heterocyclic rings is the 1,3-dipolar cycloaddition reaction between an alkene and a nitrone to synthesize isoxazolidines.[2] Hardly any other class of 1,3-dipolar cycloaddition has achieved greater importance to date.[3] If the nitrone is generated by condensing aldehydes with N-substituted hydroxylamines, this reaction can be considered as a one-pot three-component reaction. Due to many commercially available aldehydes and alkenes, diverse isoxazolidines are accessible within a few and fast reaction steps. Furthermore, up to three chiral centers are introduced in the isoxazolidine adduct (Figure 1) and subsequent transformations of the isoxazolidines to amino alcohols[4] or nitrones of the second generation[5] enable the construction of "libraries from libraries".[6] For this reason isoxazolidines are an attractive heterocyclic ring system for combinatorial chemistry focused on lead discovery.

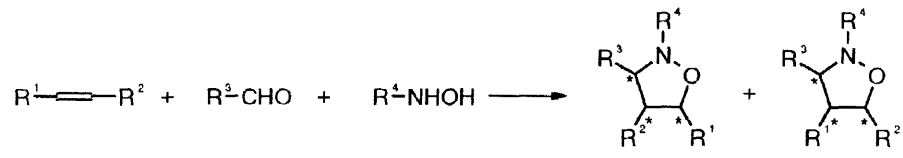

Figure 1

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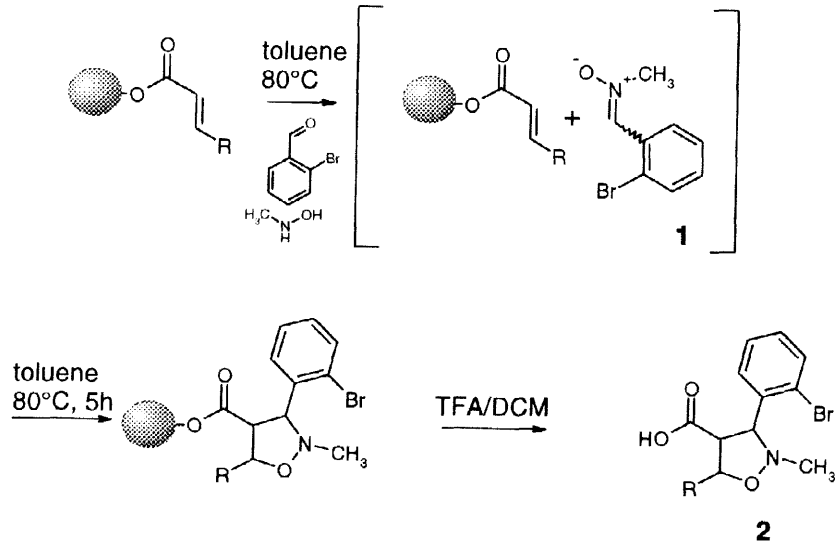
PII: S0040-4020(98)00099-4

Results and Discussion

In order to optimize the reaction conditions for the 1,3-dipolar cycloaddition, we investigated three different reaction pathways each dealing with one of the three components attached to the solid support.

Method I - Synthesis with polymer-bound olefins

First, we studied the reaction of polymer-bound olefins with nitrones generated in solution (Figure 2). Substituted acrylic acids were attached to 2-chlorotrityl resin. Afterwards, nitrone **1** was added to the polymer-bound olefin to react to isoxazolidine **2** under regiochemical control. The electron-withdrawing ester function and the aromatic substituent predominantly lead to 4-carboxy substituted isoxazolidines. The final product **2** was cleaved from the resin with 5 % trifluoroacetic acid (TFA) in dichloromethane.



R = - 4-C_6H_4OMe, -H, - 2-C_6H_4Br, - 4-C_6H_4F, - 2-C_4H_3O

= 2-Chlorotrityl resin

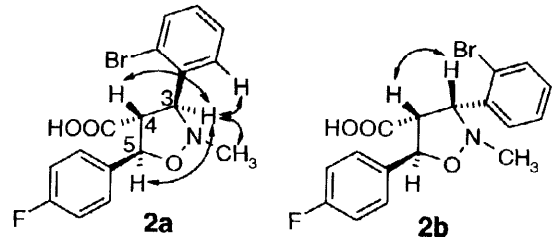
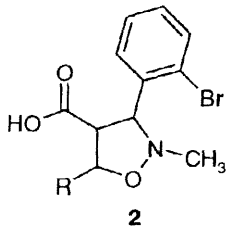


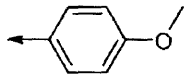
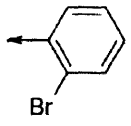
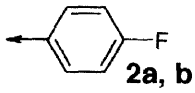
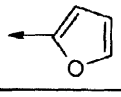
Figure 2

The products were routinely characterized with ESI-MS and RP-HPLC. The RP chromatographic relative yields of the cleaved products are determined at 214 nm and include the sum of the peak areas of all diastereomers. Yields between 24 - 45 % (Table 1) were found. The remainder of the crude products corresponds to the starting material. Significant amounts of by-products are not observed. To drive this reaction to completion the excess of nitrone **1** was enlarged up to 40 equivalents. When the reaction time was extended up to 18 h a thermal cleavage of the acids from the 2-chlorotrityl resin was observed. For this reason, the reaction was carried out on the more stable Wang resin with 40 equiv of nitrone **1**. But even after 18 h at 80°C only marginal improvement of the reaction progress could be achieved.

Table 1: Variation of acrylic acid components in isoxazolidines **2** synthesized with method I (Figure 2). For each synthesis 2-bromobenzaldehyde and N-methylhydroxylamine were used. Total relative yields ([a] determined by analytical HPLC, detection at 214 nm) and found masses of the protonated molecule ions.



2

Entry	R	MH^+ (^{81}Br)	Yield (%) [a]
1		395.0	45
2		288.0	35
3		444.0	30
4	 **2a, b**	382.0	40
5		354.0	24

We confirmed the structures of coeluting **2a** and **2b** (Figure 2) by TOCSY, NOESY and HSQC experiments. The proton 3-H of **2a** showed n.O.e effects to the adjacent protons of the methyl group, 4-H, 5-H and the aromatic proton of the 2-bromophenyl substituent. This implies a cisoid configuration of the 2-bromophenyl and the 4-fluorophenyl group in positions 3 and 5, respectively, whereas the 4-carboxy function is transoid to both phenyl groups. Due to the well known *Z/E*-isomerization of nitrones, [2] the coeluting diastereomer **2b** showed an inversion of the configuration at the C-3 atom. This was confirmed by the observation of only one n.O.e. contact between 3-H and 4-H, but no contact between 3-H and 5-H suggesting a transoid configuration for these two protons. The ratio of **2a:2b** was determined to be 5:1 by integration of the corresponding signals in the proton NMR spectrum.

Method II - Synthesis with polymer-bound aldehydes

In order to raise the yield in the solid phase cycloaddition we evaluated a second reaction pathway starting with polymer-bound aldehydes (Figure 3).

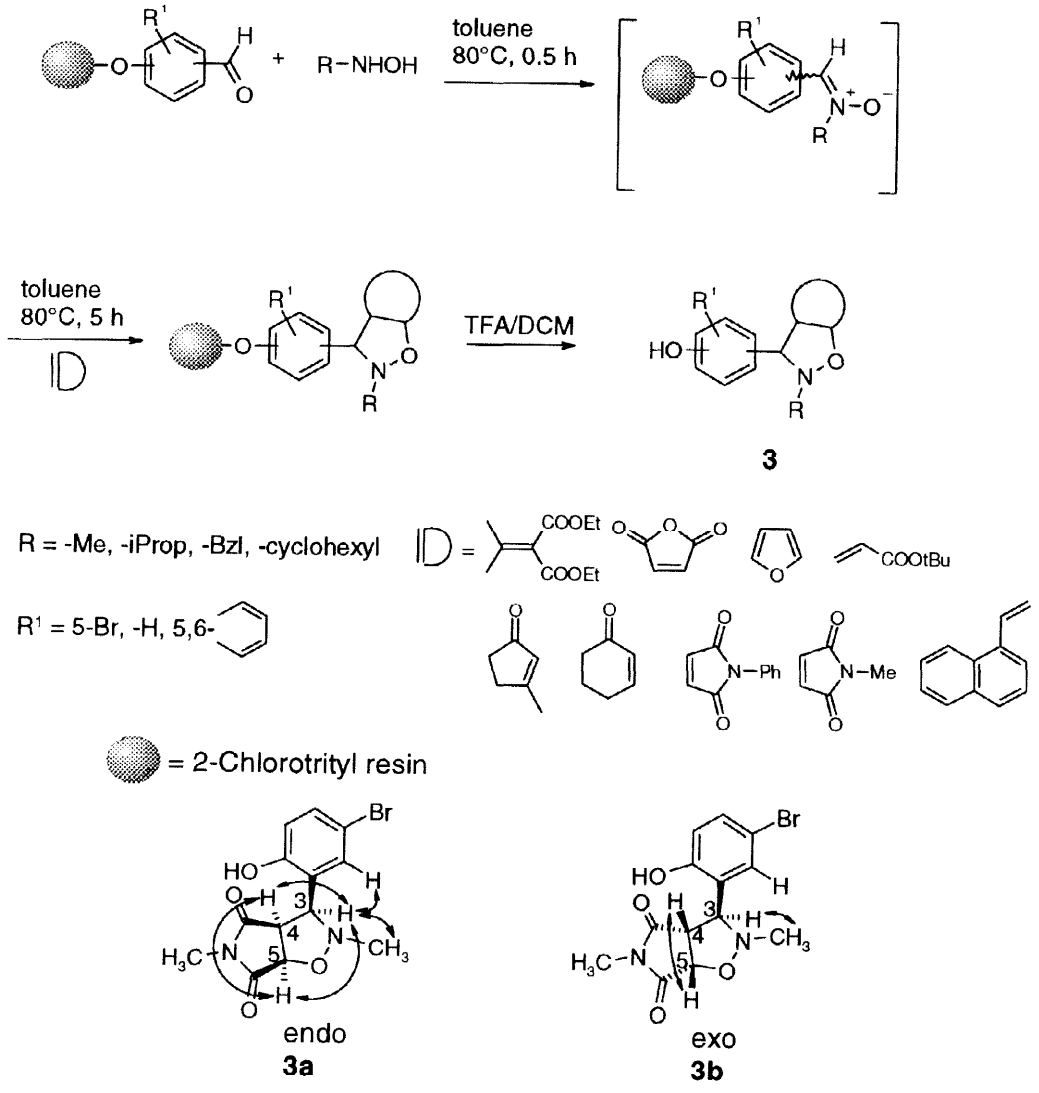


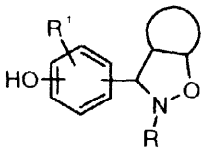
Figure 3

Aromatic hydroxyaldehydes were attached onto 2-chlorotrityl resin and subsequently condensed with N-substituted hydroxylamines. The resulting polymer-bound nitrone was trapped by adding olefins. Cleavage of the products was performed with 5 % TFA in dichloromethane. In order to evaluate the scope and limitations of this pathway all building blocks were varied (Tables 2 and 3).

Obviously, tetra- and trisubstituted alkenes like isopropylidene diethylmalonate (entry 1) and 3-methyl cyclopentenone (entry 5) are sterically too hindered for the cycloaddition because no products were obtained. Moreover, strongly electron deficient or electron rich dipolarophiles such as maleic acid anhydride (entry 2) or

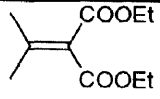
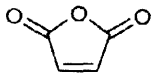
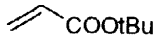
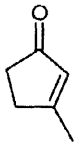
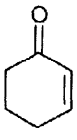
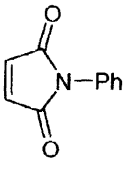
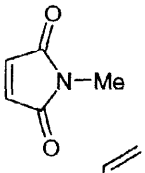
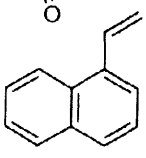
furane (entry 3) also gave no products. Monosubstituted alkenes like acrylic acid *tert.*-butylester (entry 4) or 1-vinylnaphthalene (entry 9) are useful building blocks for the cycloaddition and gave yields of about 70 %. Similar results with 2-cyclohexenone and N-phenylmaleimide were obtained, whereas the reaction with N-methylmaleimide gave highest yield near 90 %.

Table 2: Variation of dipolarophile components in isoxazolidines **3** synthesized with method II (Figure 3). For each synthesis 5-bromosalicylic aldehyde and N-methylhydroxylamine were used. Total relative yields ([a] determined by analytical HPLC, detection at 214 nm) and found masses of the protonated molecule ions.



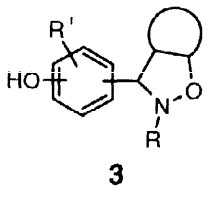
3

Entries 1-9: -OH adjacent to isoxazolidine

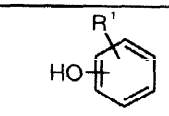
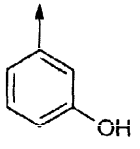
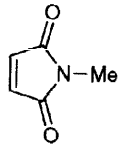
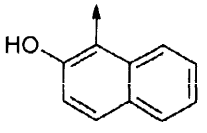
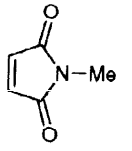
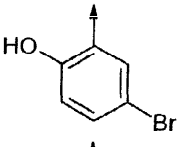
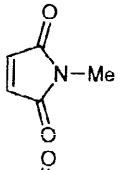
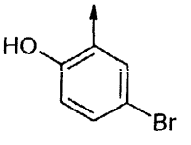
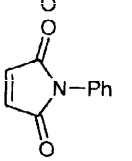
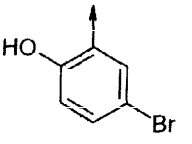
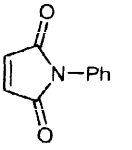
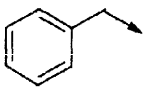
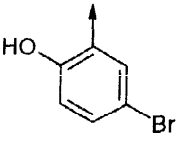
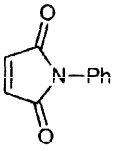
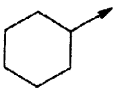
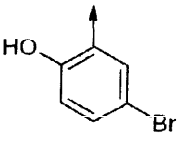
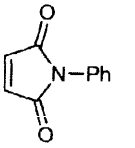
Entry	R	R^1		MH^+ (^{81}Br)	Yield (%) [a]
1	-Me	5-Br		-	0
2	-Me	5-Br		-	0
3	-Me	5-Br		-	0
4	-Me	5-Br		304.0	70
5	-Me	5-Br		-	0
6	-Me	5-Br		328.0	73
7	-Me	5-Br		405.0	68
8 **(3a, b)**	-Me	5-Br		343.0	87
9	-Me	5-Br		386.0	72

Variation of aldehyde and hydroxylamine components (Table 3) showed no dramatical differences of the yields with the exception of N-benzylhydroxylamine (entry 6). The reaction of polymer-bound 5-bromosalicylic aldehyde with N-benzylhydroxylamine and N-phenylmaleimide gave only 50 % yield of the isoxazolidine.

Table 3: Variation of aldehyde and hydroxylamine components in isoxazolidines **3** synthesized with method II (Figure 3). Total relative yields ([a] determined by analytical HPLC, detection at 214 nm) and found masses of the protonated molecule ions.



3

Entry	R			MH^+	Yield (%)[a]
1	-Me			263.0	63
2	-Me			313.0	75
3 (**3a, b**)	-Me			343.0 (^{81}Br)	87
4	-Me			405.0 (^{81}Br)	68
5				433.0 (^{81}Br)	77
6				481.0 (^{81}Br)	49
7				473.0 (^{81}Br)	70

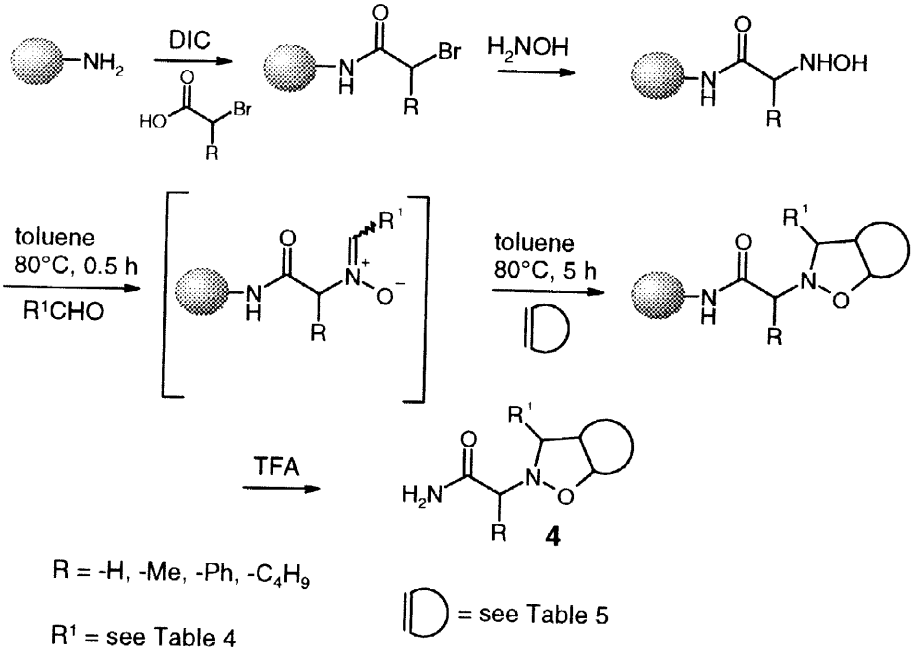
Reaction of 5-bromosalicylic aldehyde with N-methylhydroxylamine and N-methylmaleimide yields a mixture of **3a** and **3b** (Figure 3). In order to assign the configuration of **3a** and **3b** n.O.e. difference spectra have been recorded. Compound **3a** showed strong n.O.e. contacts between 3-H, 4-H, and 5-H, whereas in the case of **3b** only a contact between 4-H and 5-H could be observed. Together with the proton coupling constants of 4-H

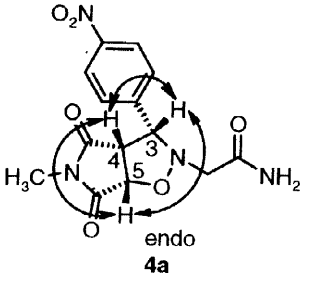
(**3a**: 7.6/8.8 Hz; **3b**: 5.3/7.3 Hz) the configurations of **3a** and **3b** could be clearly determined to *endo* and *exo*, respectively. The *endo:exo* ratio was estimated by integration of the corresponding signals to be 1:1.

Method III - Synthesis with polymer-bound hydroxylamines

Due to the limited number of commercially available N-substituted hydroxylamines and hydroxy aldehydes a third reaction pathway, allowing the synthesis of much more diverse isoxazolidines, was established using Rink amide resin (Figure 4).

α-Bromo carboxylic acids were coupled onto Rink resin with N,N′-diisopropylcarbodiimide. Substitution of bromine with hydroxylamine resulted in polymer-bound N-substituted hydroxylamine. After condensation of an aldehyde the resulting nitrone was trapped with an olefin to yield isoxazolidines.





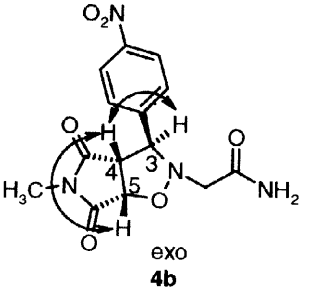
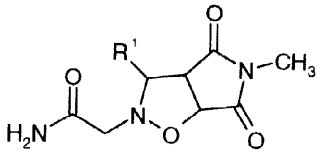
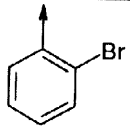
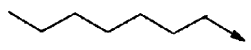
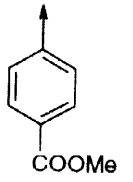
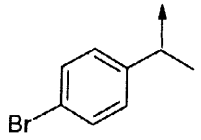
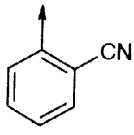
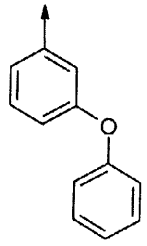
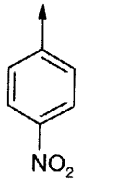
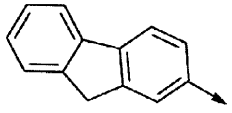
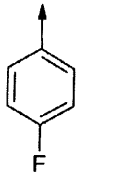
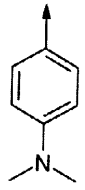
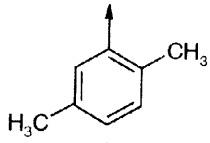
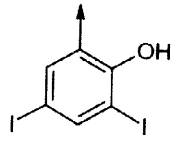
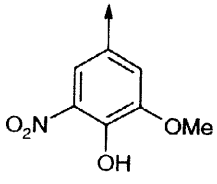
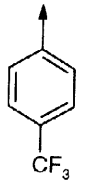
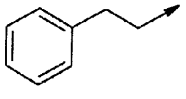
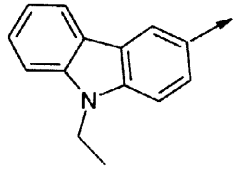


Figure 4

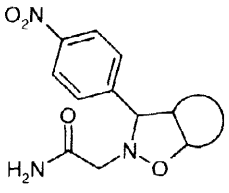
Table 4: Variation of aldehyde components in isoxazolidines **4** synthesized with method III (Figure 4). For each synthesis bromo acetic acid (R = H) and N-methylmaleimid were used, whereas the aldehyde component was varied. Total relative yields ([a] determined by analytical HPLC, detection at 214nm) and found masses of the protonated molecule ions.



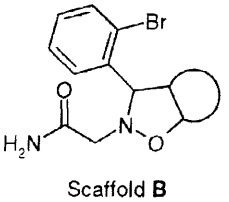
Entry	R^1	Yield (%)[a] MH^+	Entry	R^1	Yield (%)[a] MH^+
1		83; 370.0 (^{81}Br)	9		81; 312.0
2		89; 348.5	10		-; 0
3		66; 315.0	11		73; 382.0
4 (**4a, b**)		91; 335.0	12		65; 378.0
5		84; 308.0	13		84; 333.0
6		84; 318.0	14		72; 557.5
7		81; 381.0	15		71, 358.0
8		48; 318.0	16		86, 407.0

The influence of the substitution pattern and the electronic properties of the aromatic aldehydes on product yield is less than expected (Table 4). For instance, the isoxazolidines containing the nitro group (entry 4; 91 %) or the N,N-dimethylamino group (entry 13; 84 %) in position 4 have similar yields. Different substitution patterns had also no significant effect on this reaction. Hence, an immense variety of aromatic aldehydes is applicable for this cycloaddition. Aliphatic aldehydes (entry 8 and 9) showed a different behavior. For example the long-chained octanal (entry 9) gave a product of 81 % yield, however, 3-phenylpropanal gave only 48 % yield of the heterocycle (entry 8). The synthesis of isoxazolidines derived from ketones was not possible in the case of 3-bromoacetophenone (entry 10). Nitrones derived from ketones are known to be more unstable against hydrolysis than those derived from aldehydes.[2]

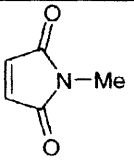
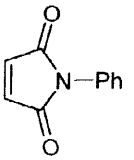
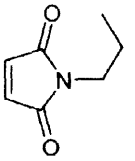
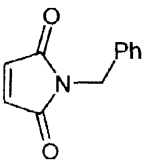
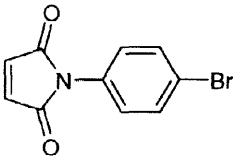
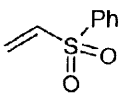
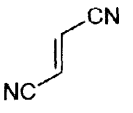
Table 5: Variation of dipolarophile components in isoxazolidines **4** synthesized with method III (Figure 4). For each synthesis bromo acetic acid (R = H) and 4-nitro benzaldehyde (Scaffold **A**) or 2-bromo benzaldehyde (Scaffold **B**) were used. Total realtive yields ([a] determined by analytical HPLC, detection at 214 nm) and found masses of the protonated molecule ions.

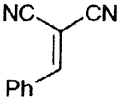
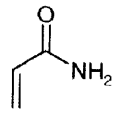
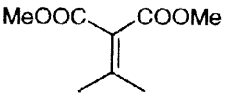
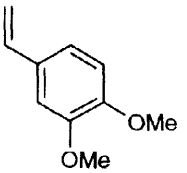
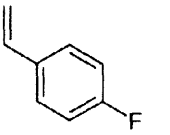
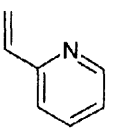


Scaffold **A**



Scaffold **B**

Entry		Yield (%)[a]; MH^+
1		**A**: 91; 335.0
2		**A**: 85; 397.0
3		**A**: 83; 363.0
4		**A**: 81; 411.0
5		**A**: 78, 477.0
6		**A**: 75; 392.0
7		**B**: 31; 337.0 (^{81}Br)

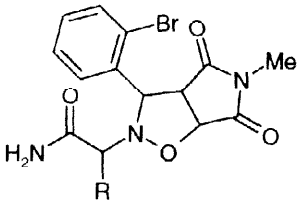
Entry		Yield (%)[a]; MH^+
8		**A**: -; 0
9		**A**: 46; 294.0
10		**A**: -; 0
11		**B**: 80; 422.5 (^{81}Br)
12		**B**: 52; 380.5 (^{81}Br)
13		**B**: 66; 363.5 (^{81}Br)

In Table 5 the yields of isoxazolidines obtained from various dipolarophiles are listed. Different N-substituted maleimides (entries 1-5) gave the best results with 78-85 % yield. Again, strongly electron deficient dipolarophiles like fumaric acid dinitrile (entry 7) or tri- and tetrasubstituted dipolarophiles like phenylene malondinitrile or isopropylidene dimethylmalonate (entries 8 and 9) reacted in low yields or not at all. Monosubstituted electron deficient olefins like phenylvinylsulfone (entry 6) and acryl amide (entry 9) gave different results. Whereas the product obtained with the sulfone showed a yield of 75 % the acryl amide gave only 46 % due to its tendency to polymerize. Furthermore, styrenes (entries 11-13) are also useful building blocks. Hereby, the reaction time had to be extended to 18 h at 80°C to drive the reaction to completion. The electron rich styrenes like the 2,3-dimethoxystyrene (entry 11) gave the best results.

The influence of the variation of bromo carboxylic acids on product yield is shown in Table 6. As expected, the bulkiest substituent, the phenyl group (entry 3), gave the lowest yield with 71 %.

We elucidated the structures of the diastereomers **4a** and **4b** (Figure 4) by means of the NMR techniques mentioned above. The n.O.e difference spectra of **4a** showed strong contacts between 3-H, 4-H and 5-H. The corresponding *exo* adduct **4b** only showed a strong contact of 4-H with 5-H and a weak contact of 3-H with 4-H. The integration of the corresponding signals of **4a** and **4b** gave an *endo:exo* ratio of 3:2.[7]

Table 6: Variation of carboxylic acid components in isoxazolidines **4** synthesized with method III (Figure 4). For each synthesis 2-bromo benzaldehyde and N-methylmaleimide were used. Total relative yields ([a] determined by analytical HPLC, detection at 214 nm) and found masses of the protonated molecule ions.



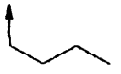
Entry	R	MH^+ (^{81}Br)	Yield (%) [a]
1	H	370.0	93
2	Me	384.0	95
3	Ph	446.0	71
4		426.0	83

Figure 5 shows a HPLC-ESI-MS run of the crude product mixture **4a** and **4b**. Only two peaks are detected in the total ion chromatogram (TIC) as well as in the UV trace at 214 *nm*. The extracted ESI mass spectra showed the masses of the protonated molecule ions (*m/z* 335.0) of the diastereomers, the ammonium adduct (*m/z* 352.0), the corresponding dimer and fragments. Due to the high ionization energy, the carboxamide group is cleaved (loss of *m/z* 45) to form the fragment with *m/z* 290.0 and a *retro* 1,3-dipolar cycloaddition leads to the fragment with *m/z* 224.0 under elimination of N-methylmaleimide. In this case, the *endo*-adduct is eluted earlier than the *exo*-adduct from the HPLC column.

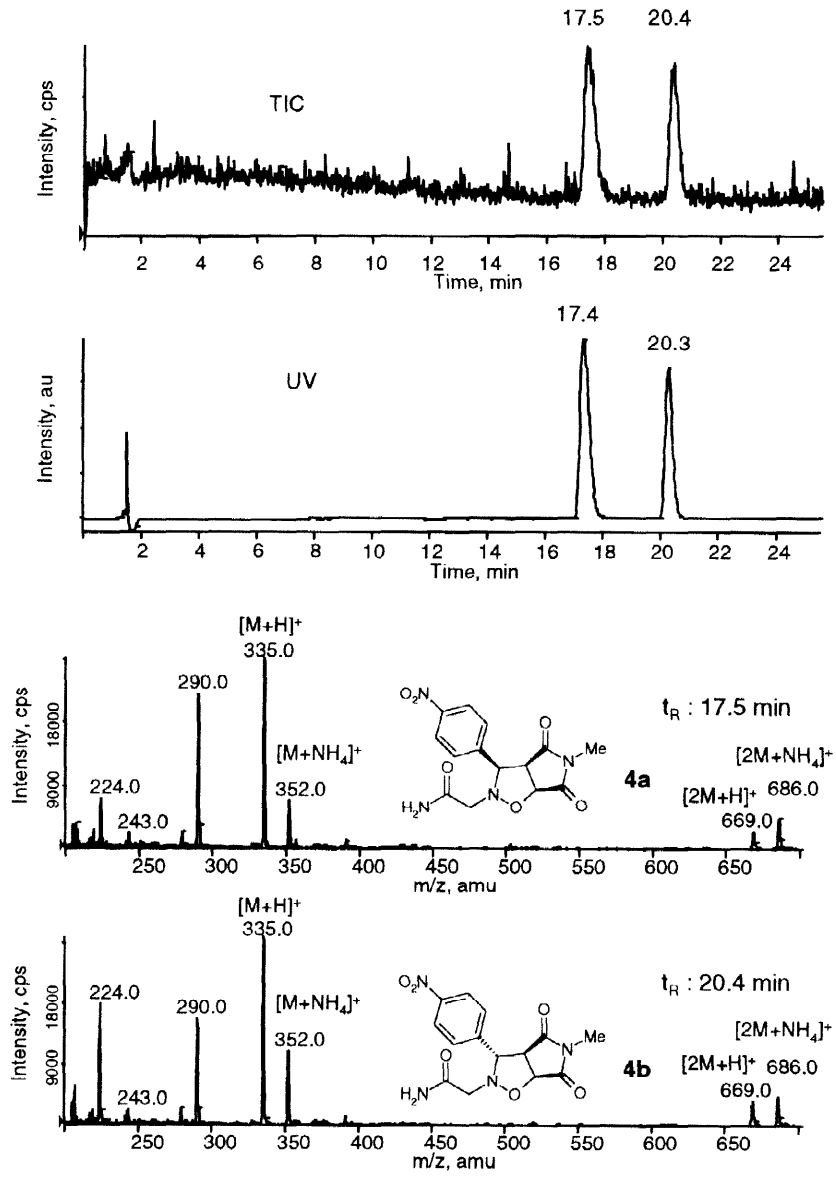


Figure 5: HPLC-MS analysis of crude product mixture **4a** and **4b**. above: total ion current and UV trace at 214 nm; below: extracted ESI-mass spectra of **4a** and **4b**.

We also analyzed the formation of all possible isomers including the enantiomers. For this purpose, we transferred the enantiomers into diastereomers by introducing a defined chiral center in the isoxazolidines. The synthesis protocol as described in Figure 4 was extended with the coupling of Fmoc-L-alanine onto the Rink resin as the first reaction step. After Fmoc-cleavage, the synthesis was carried out using bromo acetic acid, hydroxylamine, 2,5-dimethyl benzaldehyde and N-methylmaleimide. The final product was cleaved as described above and the crude product was analyzed by means of HPLC-MS (Figure 6). Mainly four peaks are detected which correspond directly to all possible diastereomers of **5**. L-Alanine showed nearly no racemization (0.58 % D-Ala). The extracted ESI mass spectra (Figure 7) showed exactly the same pattern including the protonated molecule ion (*m/z* 389.0), fragments at *m/z* 372.0 (loss of NH_3), at *m/z* 344.0 (loss of carboxamide) and at *m/z*

273.0 (loss of Ala-NH-CO). An unequivocal assignment of the configuration of the diastereomers was not possible so far.

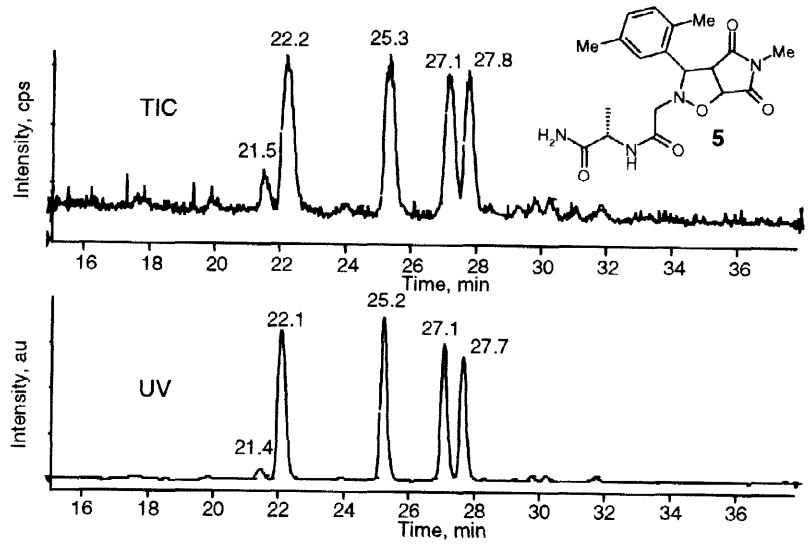


Figure 6: HPLC-MS analysis of crude isoxazolidine **5**. Total ion current and UV trace at 214 nm.

A by-product eluted at 21.4 min with 2 % was due to incomplete coupling of bromo acetic acid. The free amino group of the amino acid reacts in this case first with the aldehyde to an azomethine ylide. This 1,3-dipole adds to N-methylmaleimide to build the pyrrolidine **6** (Figure 8).

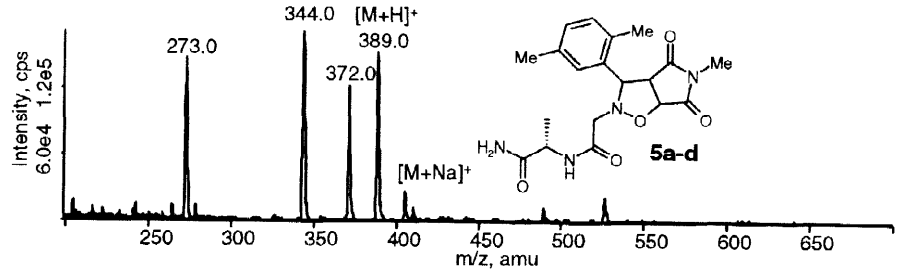


Figure 7: Extracted ESI-mass spectrum from HPLC-MS analysis of isoxazolidines **5a-d** (t_R = 22.2, 25.3, 27.1, and 27.8 min). Each compound showed exactly the same mass spectrum.

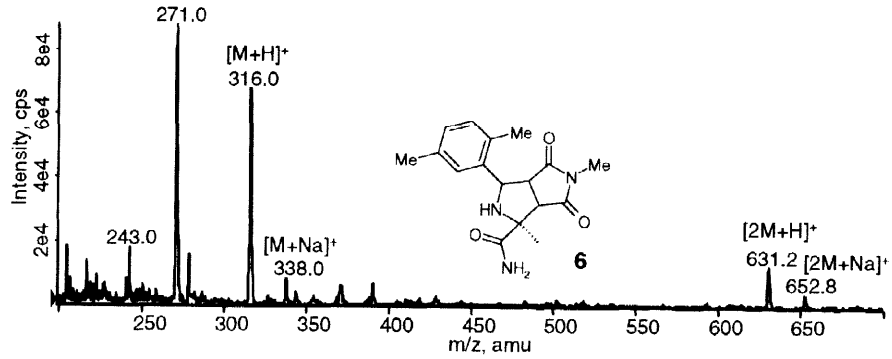


Figure 8: Extracted ESI-mass spectrum of by-product **6** from HPLC-MS analysis (t_R = 21.4 min) in Figure 6.

To determine the kinetics of the solid phase cycloaddition we initiated the reaction described in Figure 9 by adding N-methylmaleimide to the polymer-bound nitrone **7**. Small amounts of resin beads were taken out of the reaction mixture after defined time intervals. After washing and drying *in vacuo* FT-IR-ATR spectra were acquired of each resin sample by means of Harrick's SplitPea® ATR accessory. The spectra were normalized to the constant amide absorption at 1682 cm^{-1} (Figure 9).

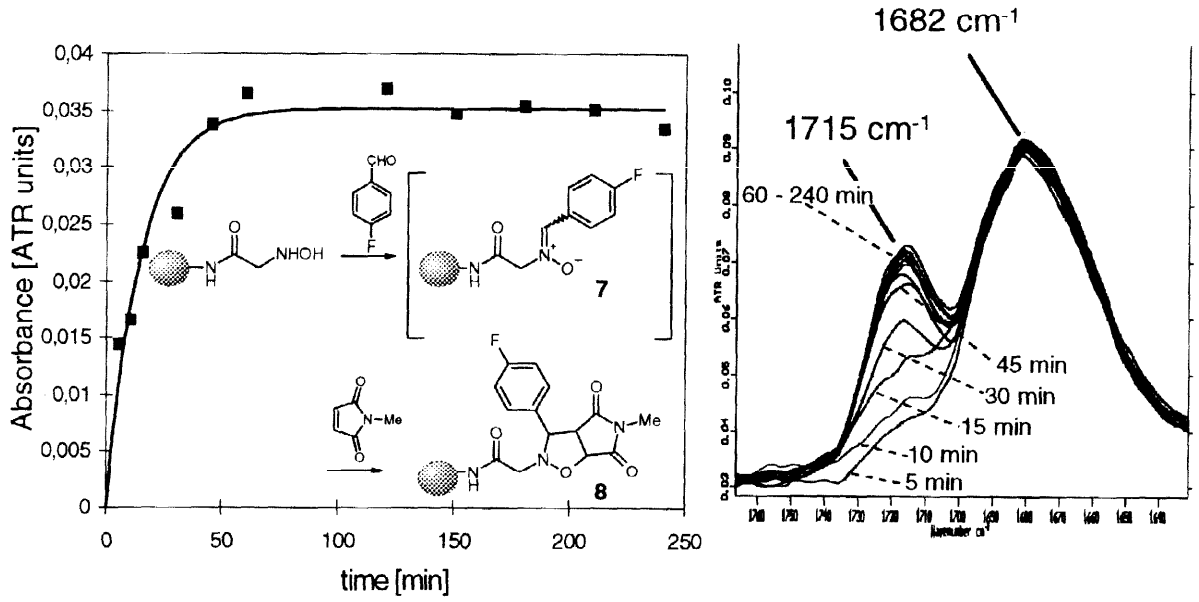


Figure 9: Kinetics of solid phase cycloaddition reaction determined by FT-IR-ATR spectroscopy. The relative peak heights of the imide absorption (1715 cm^{-1}) is depicted against time. The ATR-spectra are normalized to the amide absorption at 1682 cm^{-1}. $t_{1/2}$ = 10.3 min; steady state (99.9 %) = 103 min.

Relative peak intensities of imide absorption at 1715 cm^{-1} are depicted against time. The reaction was considered as pseudo-first-order due to the large excess (10 equiv) of the maleimide. We calculated $t_{1/2}$ to 10.3 min with the parameters obtained after a curve fit with the equation f(t) = a[1-exp(-bt)]. The reaction reaches the steady state (99.9 % yield) after 103 min. This reaction time differs considerably if other dipolarophiles are used. Thus, for styrenes reacted with the polymer-bound nitrone **7** the reaction time had to be extended up to 18 h.

Library synthesis

Small molecule libraries are typically synthesized with the split/combine method. We wanted to know if polymer-bound nitrones are stable 1,3-dipoles for this approach. Thus, bromo acetic acid was attached to the Rink amide resin and reacted with hydroxylamine. The resin was divided into five portions (Figure 10) to condense five aromatic aldehydes with the hydroxylamine to their corresponding nitrones.

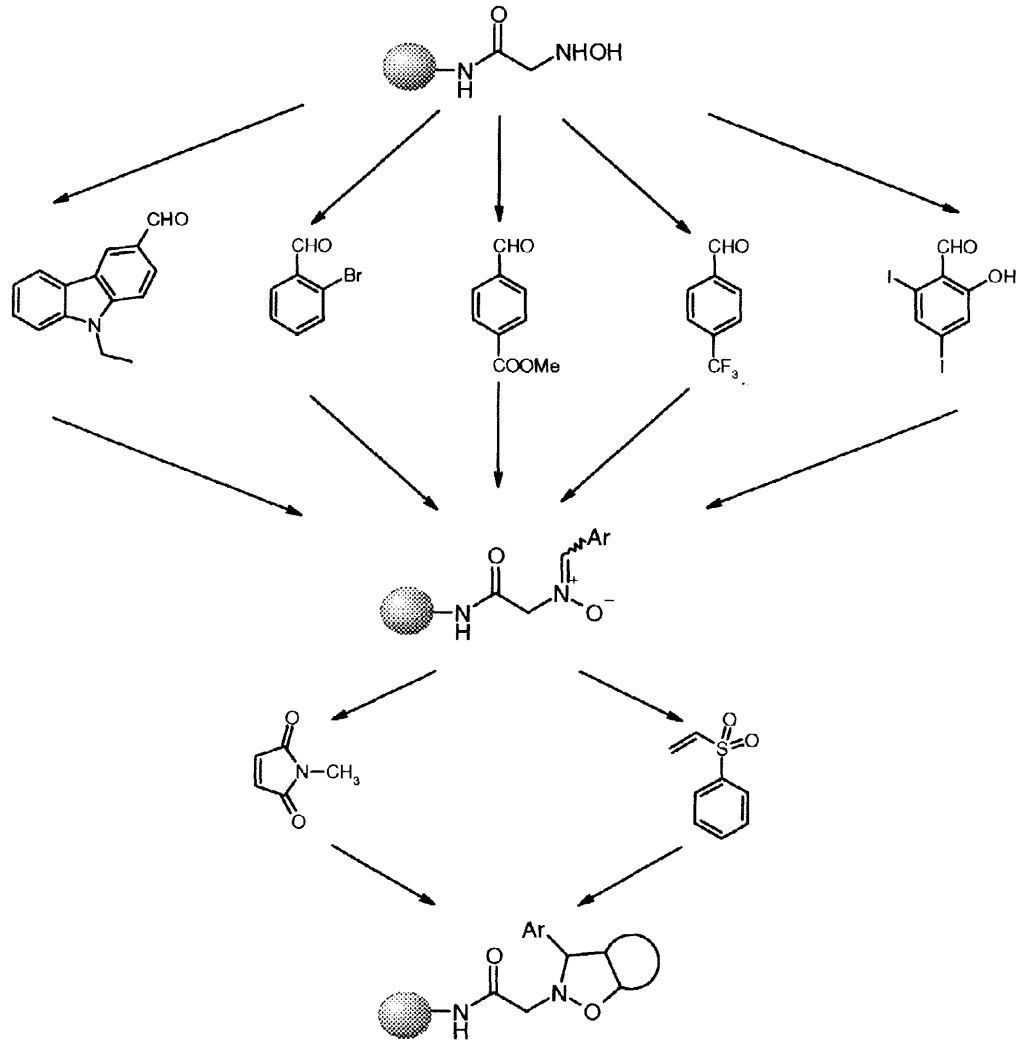


Figure 10: Split/combine synthesis of isoxazolidines synthesized as described in Figure 4.

After washing and drying the combined resin was split into 2 portions. The nitrones were trapped with N-methylmaleimide or phenylvinylsulfone in toluene (80°C, 5 h). The resin was combined again, washed and dried. The isoxazolidine collection containing 10 compounds and corresponding isomers was finally cleaved from the solid support. HPLC-MS analysis (Figure 11) detected nearly all compounds with the exception of the combination of N-ethylcarbazole and N-methylmaleimide (A2). Interestingly, the combination of N-ethylcarbazole and vinylsulfone (A1) was found to be present in a considerable amount. The polymer-bound nitrone derived from N-ethylcarbazole is in principle stable enough for the library synthesis but did not react with N-methylmaleimide. All other compounds are mainly eluted as "*endo/exo*-double peaks" from the HPLC column beginning with the most polar compounds C2 followed by compounds B2. In addition, compounds C1 and E2 coeluted from the column.

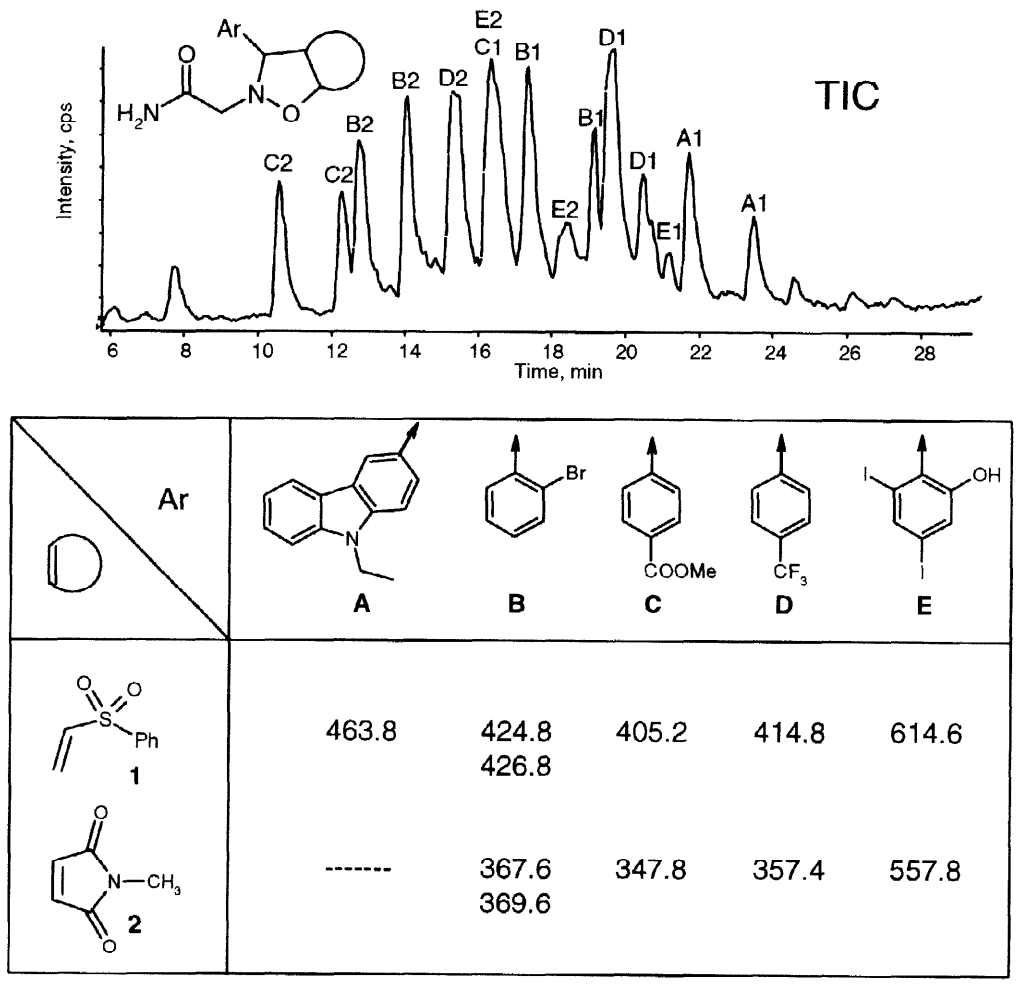


Figure 11: Total ion chromatogram of the HPLC-MS analysis of the split/combine library shown in Figure 10. Found masses of the protonated molecule ions A1-E2.

Conclusions

We established the solid phase synthesis of diverse isoxazolidines as a one-pot three-component cycloaddition reaction. The versatility of the cycloaddition and yields of the isoxazolidines is strongly dependent on the resin-bound component. Isoxazolidines obtained by the reaction of polymer-bound hydroxylamines with aldehydes and olefins showed the highest yields and are accessible in high diversity, whereas the synthesis with polymer-bound olefins is less practicable due to the low yields. Similar regio- and stereochemical results of the solid phase nitrone-olefin cycloaddition compared to solution phase reactions were observed. The construction of isoxazolidine libraries by the split/combine method *via* polymer-bound nitrones is possible.

EXPERIMENTAL

All chemicals and resins were obtained from commercial suppliers and used without further purifications. Syntheses were carried out in plastic syringes equipped with a frit. FT-IR-ATR spectra were recorded on a Bruker Vector 22 (Opus-Software 2.2) in combination with Harrick's SplitPea® ATR-unit. HPLC analysis was performed with a Beckman System Gold (autosampler 507, solvent module 126, diode array detector 168) equipped with a Grom Nucleosil C18 column (5 µm; dim. 250 × 2 mm) and a binary linear gradient (solvent A = water/0.1 % TFA, solvent B = acetonitrile/0.1 % TFA, 10 % B - 100 % B in 45 min.). Positive ion ESI-MS and HPLC-MS data were recorded on a Perkin Elmer Sciex API III mass spectrometer (Toronto, Canada) equipped with a nebulizer-assisted electrospray source in combination with an ABIMED Autosampler (model 231). ESI-mass spectra were acquired at unit resolution scanning with a step size of 0.5 *u* and a dwell time of 1 ms. Five to ten spectra were summed. HPLC chromatograms for HPLC-MS were obtained on an Applied Biosystems 140 A Delivery System (Weiterstadt, Germany) equipped with a Gromsil ODS 5-ST 5 µm C18 column (Grom, Herrenberg, Germany) (column dimension 100 × 2 mm, flow rate 200 µl/min, split of 40 µl/min into ESI source) and a Linear UVis 204 detector (Reno, Nevada). Binary linear gradients were used (solvent A = water/0.1 % TFA, solvent B = acetonitrile/0.1 % TFA). NMR-spectra were recorded on a Bruker AMX2-600 spectrometer.

General procedure for preparing isoxazolidines using method I (Table 1; entries 1-5)

To 2-chlorotrityl chloride resin (50 mg, 0.065 mmol) one of the acrylic acids (entries 1-5, Table 1; 0.325 mmol, 5 equiv), DIEA (0.325 mmol, 5 equiv) and a catalytical amount of DMAP in DCM (1.5 ml) were added. The mixture was agitated for 18 h at 25°C. After intensive washing with DMF, the resin was capped with methanol and DIEA within 30 min. After washing with DMF, methanol, DCM and diethyl ether and drying *in vacuo* a solution of N-methylhydroxylamine hydrochloride (0.65 mmol; 10 equiv), DIEA (0.65 mmol; 10 equiv) and 2-bromobenzaldehyde (10 equiv) in toluene (2 ml) was added to the resin. After heating for 5 h at 80°C and washing the isoxazolidines were cleaved from the resin with 5 % TFA in DCM (1.5 ml) for 3 h. The cleavage solution was evaporated under reduced pressure and the crude products were lyophilized out of *tert.*-butyl alcohol/water (4:1).

All compounds were analyzed with ESI-MS and HPLC (for analytical data see Table 1). Compounds **2a** and **2b** (Table 1, entry 4) were further analyzed by NMR spectroscopy.

3-(2-Bromophenyl)-4-carboxy-5-(4-fluorophenyl)-2-methylisoxazolidine (2a and 2b)

mixture of diastereomers and enantiomers; NMR (CD_3CN): **2a**: δ (^1H): 2.81 (-CH_3, s) 3.34 (4-H, dd, J = 6.9/4.7 Hz), 4.78 (3-H, d, J = 4.7 Hz), 5.51 (5-H, d, J = 6.9 Hz), 7.11 (Ar-F), 7.22 (Ar-Br), 7.39 (Ar-Br) 7.44 (Ar-F), 7.61 (Ar-Br), 7.64 (Ar-Br)

δ (^{13}C, HSQC): 44.3 (-CH_3) 66.1 (4-H), 75.5 (3-H), 83.7 (5-H), 116.7 (Ar-F), 131.0 (Ar-Br), 129.3 (Ar-Br) 130.0 (Ar-F), 134.2 (Ar-Br), 130.6 (Ar-Br)

n.O.e: contacts between 3-H, 4-H and 5-H; contacts between 3-H, -CH_3 and -Ar-Br

2b: NMR (CD_3CN): δ (^{1}H): 2.68 (-CH_3, s) 3.67 (4-H, broad, dd, J = 7.4/7.4 Hz), 4.52 (3-H, d, J = 7.4 Hz), 5.42 (5-H, d, J = 7.4 Hz), 7.15 (Ar-F), 7.23 (Ar-Br), 7.38 (Ar-Br) 7.49 (Ar-F), 7.56 (Ar-Br), 7.61 (Ar-Br)

δ (^{13}C, HSQC): 44.1 (-CH_3) 61.0 (4-H), 75.6 (3-H), 82.5 (5-H), 116.9 (Ar-F), 131.1 (Ar-Br), 129.3 (Ar-Br) 130.0 (Ar-F), 131.4 (Ar-Br), 134.4 (Ar-Br)

n.O.e: contacts only between 3-H and 4-H

ESI-MS: *m/z* 382.0/380.0 (^{81}Br/^{79}Br)

General procedure for preparing isoxazolidines using method II (Table 2, entries 1-9; Table 3, entries 1-7)

A solution of a hydroxybenzaldehyde (0.325 mmol, 5 equiv), DIEA (0.325 mmol, 5 equiv) and a catalytical amount of DMAP in dry DCM (1.5 ml) was added to 2-chlorotrityl chloride resin (50 mg, 0.065 mmol). After agitation at 25°C for 18 h the resin was washed and capped with methanol. A suspension of N-substituted hydroxylamine hydrochlorides (0.65 mmol, 10 equiv) and DIEA (0.65 mmol; 10 equiv) in toluene (0.75 ml) was added to the polymer-bound aldehyde and heated at 80°C for 0.5 h. To this mixture, a solution of a dipolarophile (0.65 mmol, 10 equiv) in toluene (0.75 ml) was added. The cycloaddition reaction was carried out within 5 h at 80°C. After washing the resin as described above, the isoxazolidines were cleaved with 5 % TFA in DCM (1.5 ml) within 3 h. The cleavage solution was evaporated under reduced pressure and the crude products were lyophilized out of *tert.*-butyl alcohol/water (4:1).

All compounds were analyzed with ESI-MS and HPLC (for analytical data see Tables 2 and 3). Compounds **3a** and **3b** (Table 2, entry 8) were further analyzed by NMR spectroscopy.

2-Oxa-3,7-diaza-4-(5-bromo-2-hydroxyphenyl)-3,7-dimethyl-bicyclo[3.3.0]octa-6,8-dione (3a and 3b)

mixture of diastereomers and enantiomers; NMR (CD_3CN, 315 K): **3a** *endo* δ (^{1}H): 2.63 (CH_3, s); 2.83 (CH_3, s); 3.82 (4-H, dd, J = 7.6/8.8 Hz), 4.07 (3-H, d, J = 8.8 Hz), 4.91 (5-H, d, J = 7.6 Hz), 6.83 (Ar); 7.31 (Ar); 7.36 (Ar)

δ (^{13}C, HSQC): 43.1 (-CH_3); 25.1 (-CH_3); 53.8 (4-C), 72.2 (3-C); 77.4 (5-C); 118.9; 132.5; 133.0 (Ar)

n.O.e: contacts between 3-H, 4-H and 5-H; contacts between 3-H, -CH_3 and -Ar-Br

3b *exo* δ (^{1}H): 2.54 (-CH_3, s); 2.94 (-CH_3, s); 3.75 (4-H, dd, J = 5.3/7.3 Hz), very broad (3-H), 4.95 (5-H, d, J = 7.6 Hz), 6.74; 7.21; 7.30 (Ar)

δ (^{13}C, HSQC): 42.2 (-CH_3, broad); 25.5 (-CH_3) 56.7 (4-C): very broad (3-C); 77.5 (5-C); 118.5; 131.5; 132.5 (Ar)

n.O.e: contacts between 4-H and 5-H; contacts between 3-H and -CH_3

MH^+: *m/z* 343.0/341.0 ($^{81}Br/^{79}Br$)

General procedure for preparing isoxazolidines using method III (Table 4, entries 1-16; Table 5, entries 1-13; Table 6, entries 1-4)

Fmoc protected Rink amide resin (50 mg, loading 0.68 mmol/g; 0,034 mmol) was deprotected with piperidine/DMF (1:1) (1 ml) for 0.5 h. After washing with DMF a solution of a bromo carboxylic acid (0,17 mmol, 5 equiv) and DIC (0,20 mmol, 6 equiv) in DMF (1 ml) was added to the resin. The resin was agitated 3 h at 25°C, washed with DMF and treated with a concentrated solution of hydroxylamine hydrochloride (0.34 mmol, 10 equiv) and DIEA (0.34 mmol, 10 equiv) in DMF (1.5 ml). After nucleophilic substitution within 3 h at 25°C the resin was washed with DMF, methanol, DCM and diethyl ether and dried *in vacuo*. The polymer-bound hydroxylamine was afterwards condensed with an aldehyde (0.34 mmol; 10 equiv) in toluene (0.75 ml) at 80°C within 0.5 h. The obtained nitrone was then trapped by adding a solution of dipolarophiles (0.34 mmol, 10 equiv) in toluene (0.75 ml) to the mixture. After heating at 80°C for 5 h or 18 h in the case of styrenes, the resin was intensively washed with DMF, methanol, DCM and diethyl ether. After drying *in vacuo* the isoxazolidines were cleaved from the resin by TFA/water (95:5, 1.5 ml) within 3 h at 25°C. The filtrate was evaporated under reduced pressure and the crude products were lyophilized out of *tert.*-butyl alcohol/water (4:1).

All compounds were analyzed with ESI-MS and HPLC (for analytical data see Tables 4, 5 and 6). Compounds **4a** and **4b** (Table 4, entry 4) were further analyzed by NMR spectroscopy.

2-Oxa-3,7-diaza-3-carboxamidomethyl-7-methyl-4-(4-nitrophenyl)-bicyclo[3.3.0]octa-6,8-dione (4a and 4b)

mixture of diastereomers and enantiomers; NMR (CD_3CN): **4a** *endo* δ (^1H): 2.89 (-CH_3, s); 3.90 (4-H, dd, *J* = 7.5/8.8 Hz), 4.30 (3-H, d, *J* = 8.8 Hz), 5.01 (5-H, d, *J* = 7.5 Hz), 3.32 (-CH_2-, *J* = 16.4 Hz); 3.17 (-CH_2-, *J* = 16.4 Hz) 7.51 (Ar, *J* = 8.8 Hz), 8.17 (Ar, *J* = 8.8 Hz)

δ (^{13}C, HSQC): 26.6 (-CH_3); 55.9 (4-C), 73.2 (3-C), 79.5 (5-C), 59.8 (-CH_2); 131.5 (Ar), 125.9 (Ar)

n.O.e: contacts between 3-H, 4-H and 5-H

4b *exo* δ (^1H): 2.98 (-CH_3, s); 3.80 (4-H, dd, *J* = 3.7/7.5 Hz), 4.51 (3-H, broad), 5.09 (5-H, d, *J* = 7.5 Hz), 3.22 (-CH_2-, *J* = 16.4 Hz); 2.97 (-CH_2-, very broad) 8.24 (Ar, J = 8.4 Hz), 7.61 (Ar, J = 8.4 Hz)

δ (^{13}C, HSQC): 26.8 (-CH_3); 58.3 (4-CH), 72.0 (3-CH, broad), 79.0 (5-CH), 58.9 (-CH_2-,) 126.0 (Ar), 131.9 (Ar)

n.O.e: contacts between 4-H and 5-H; weak contact between 3-H and 5-H

MH^+: *m/z* 335.0

General procedure for preparing isoxazolidine collections using method III

Fmoc-protected Rink amide resin (200 mg; loading 0.68 mmol/g; 0.34 mmol) was deprotected with piperidine within 0.5 h. The resin was washed and acylated with bromoacetic acid (1.7 mmol, 5 equiv) by DIC activation (2.0 mmol, 6 equiv) in DMF (4 ml). After washing, the resin was treated with a solution of hydroxylamine hydrochloride (3.4 mmol, 10 equiv) and DIEA (3.4 mmol, 10 equiv) in DMF (6 ml). The washed and dried resin was split into 5 portions. Each resin sample was condensed with an aromatic aldehyde (2-formyl-N-ethylcarbazole, 2-bromobenzaldehyde, 4-formylmethylbenzoate, 4-trifluoromethylbenzaldehyde and 2,4-diiodosalicylic aldehyde; each 3.4 mmol, 10 equiv) in toluene (1 ml) within 0.5 h at 80°C. The resin was combined, washed and split into 2 portions. The polymer-bound nitrones were trapped with dipolarophiles (N-methylmaleimide and phenylvinylsulfone; each 3.4 mmol, 10 equiv) in toluene (4 ml) at 80°C in 5 h. The resin was combined and intensively washed. The compound collection was cleaved with TFA/water (95:5, 4 ml) and the filtrate was evaporated. The crude mixture was lyophilized out of *tert.*-butyl alcohol/water (4:1).

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REFERENCES

1. (a) Thompson, L.A., Ellman, J.A. *Chem. Rev.* **1996**, 96, 555-600. (b) Nefzi, A.; Ostresh, J. M.; Houghton, R. A. *Chem. Rev.* **1997**, 97, 449-472. (c) Lam, K. S.; Lebl, M.; Krchnak, V. *Chem. Rev.* **1997**, 97, 411-448. (d) Jung, G., (Ed.): *Combinatorial Peptide and Non-peptide Libraries*, Verlag Chemie, Weinheim 1996. (e) Gordon, E. M.; Gallop, M. A.; Patel, D. V., *Acc. Chem. Res.* **1996,** 29, 144-154. (f) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C., *Angew. Chem.* **1996,** 108; 2436-2488.; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2289-2337. (g) Früchtel, J. S.; Jung, G., *Angew. Chem.* **1996**, 108, 19-46; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 17-42. (h) Hermkens, P.H.H; Ottenheijm, H.C.J.; Rees, D.C., *Tetrahedron*, **1996**, 52, 4527-4554. (i) Hermkens, P.H.H; Ottenheijm, H.C.J.; Rees, D.C., *Tetrahedron*, **1997**, 53, 5643-5678.
2. (a) Tuffariello, J. J. in *"1,3-Dipolar Cycloaddition Chemistry"*. A. Padwa Ed., Wiley, New York, **1984**, p. 83-168. (b) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, 36, 1-173.
3. Giera, H.; Huisgen, R. *Liebigs. Ann./Recueil* **1997**, 8,1685-1689.
4. Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, 31, 3351-3354.

5. (a) LeBel, N. A.; Post, M. E.; Hwang, D. *J. Org. Chem.* **1979**, 44, 1819-1823. (b) De March, P.; Figueredo, M.; Font, J.; Milán, S.; Alvarez-Larena, A.; Piniella, J. F.; Molins, E. *Tetrahedron* **1997**, 53, 2979-2988.
6. Houghten, R. A.; Blondelle, S. E.; Dooley, C. T.; Dorner, B.; Eichler, J.; Ostresh, J. M. *Mol. Div.* **1996**, 2, 41-45.
7. Similar results were reported in Grigg, R.; Markandu, J.; Surendrakumar, S. *Tetrahedron Lett.* **1990**, 31, 1191-1194.