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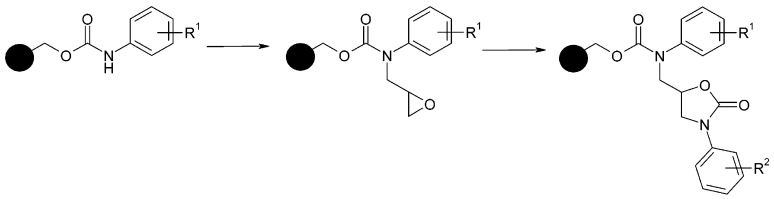

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Solid-Phase Synthesis of Oxazolidinones by Cycloaddition of Resin-Bound Epoxides with Isocyanates

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The first solid-phase synthesis of oxazolidinones by cycloaddition of resin-bound epoxides with isocyanates is described. Synthesis of the title compounds was achieved by alkylation of resin-bound carbamates with glycidyl tosylate, followed by cycloaddition of the resulting epoxides with isocyanates at elevated temperature in high yields and purity. Because *N*-aryloxazolidinones have been known to possess various biological activities, this method is useful from the viewpoint of drug discovery.

Introduction

Solid-phase chemistry has recently gained much interest as an effective synthetic strategy for the preparation of combinatorial libraries of small organic molecules.[1] The suitability for automation, offering the possibility of producing huge numbers of structures as well as the simplification of the workup procedures and avoiding time-consuming intermediate purification are considered the main attractions of this technique. On the other hand, the synthetic repertoire on solid support is still inadequate, especially if compared with the traditional solution-phase chemistry. For this reason, a major effort is currently invested with the aim of increasing the variety of organic transformations achievable on solid phase.

The *N*-aryloxazolidinone scaffold is a constituent of a number of compounds, which show interesting biological effects as antibacterial agents,[2] MAO inhibitors,[3] neuroleptics,[4] or GP IIb/IIIa antagonists.[5] For this reason, versatile methods on solid support to generate libraries of compounds incorporating this scaffold is of high interest.[6] In a recent work, the synthesis of oxazolidinones via a cyclization/cleavage reaction utilizing resin-bound epoxides **3** was reported.[7] Further experiments to examine scope and limitations of this procedure revealed that this approach, including a nucleophilic ring opening, is restricted to primary and secondary aliphatic amines.[8]

When aniline was used as the amine component, the amino alcohol intermediate did not cyclize spontaneously, but required the addition of a strong base, for example, potassium *tert*-butylate, to liberate the oxazolidinone from the resin. Unfortunately, this method is not of general applicability, since almost all substituted aniline derivatives employed gave insufficient results. However, such oxazolidinones bearing an arylamino side chain are accessible through a cycloadditon reaction utilizing the same intermediates **3** as for the cyclization/cleavage approach. In this paper, the solid-phase synthesis of oxazolidinones according to this procedure as well as further derivatizations of appropriately substituted intermediates are reported.

Results and Discussion

The synthesis of the title compounds is outlined in Scheme 1. Formation of resin-bound carbamates **2** was achieved by reaction of commercially available Wang resin[9] with 6 equiv of the respective isocyanate **1** and catalytic amounts of triethylamine in DCM. Even with poorly soluble isocyanates, the reactions worked well in the employed solvent.[10] The subsequent alkylation to resins **3** was accomplished by treating resins **2** with 2 equiv of $LiN(Si(CH_3)_3)_2$ (1 M solution in THF), 10 equiv of glycidyltosylate, and 1 equiv of lithium iodide. These reactions, which in general were carried out at ambient temperature under argon atmosphere, were described in detail previously.[7] Because of the lability of the epoxide functionality under acidic cleavage conditions, it was not possible to determine the loading of the resins at this synthesis step. However, the course of the reactions could easily be monitored by IR spectroscopy owing to the shift of the carbonyl band to lower wavenumbers.[7]

One of the first syntheses of oxazolidinones in solution by cycloaddition was published by Herweh and Kauffman.[11] They investigated the reaction of phenyl glycidyl ether with isocyanates in various hydrocarbon solvents. Lithium bromide, which was added in catalytic amounts to facilitate the ring opening of the epoxide, was solubilized in the nonpolar solvents as an adduct with tributyl phosphine oxide. Although the obtained yields were good, the reported reaction conditions with elevated temperatures could not be applied to epoxides on solid support. Thus, for the adaptation of the key step to solid-phase synthesis, it was inevitable to decrease the reaction temperature. Several experiments with resin-bound epoxide **3** and phenylisocyanate in various solvents at 95 °C revealed that this is not detrimental to yield and purity of the final product. Similarly to the synthesis in solution, the best results were obtained in xylene (Table 1). However, NMP could be used as an alternative solvent in those cases in which the isocyanate is poorly soluble in xylene. It has been described in the literature that any side reaction could be avoided by adding the reactants to an azeotropically dried solution of the catalyst in refluxing

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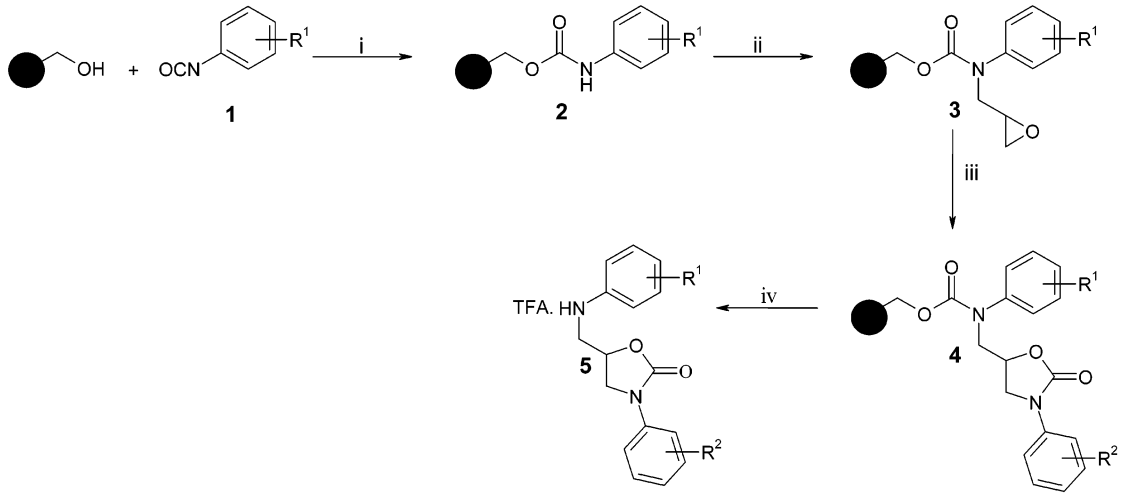
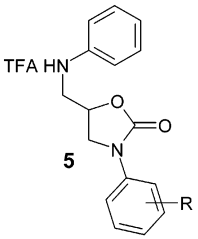
Scheme 1. Synthetic Route to Substituted 3-Phenyl-5-phenylaminomethyloxazolidin-2-ones



Reagents and conditions:(i) Et_3N (cat.), dichloromethane, 6.5 h; (ii) $LiN(Si(CH_3)_3)_2$, LiI, glycidyltosylate, NMP/THF, 24 h; (iii) 10 equiv $R_2-Ph-NCO$ **1a**−**i**, 0.5 equiv LiBr/Bu_3PO, xylene, 95 °C, 4 h; (iv) TFA/DCM = 1:1, 30 min, r.t.

Table 1. Assessment of Cycloaddition Reaction Conditions



entry	R	solvent	yield (%)[a]	purity (%)[b]
	H	DMF	89	93
	H	NMP	93	98
5a	H	xylene	98	100
5b	2-NO_2	xylene	99	98.5
5c	3-NO_2	xylene	95	99
5d	4-NO_2	xylene	94	96
5e	4-CN	xylene	98	99
5f	4-Br	xylene	88	92
5g	4-COOEt	xylene	92	97
5h	4-Ph	xylene	96	92.5
5i	2-Cl, 4-NO_2	xylene	93	98

[a] Yields of cleaved products are based on the theoretical loading of commercial resins. [b] For details, see the Experimental Section.

xylene. However, in contrast to that and in order to make this reaction feasible for parallel synthesis, it was necessary to change the mode of addition of the reactants. Accordingly, the catalyst was prepared by heating lithium bromide and tributyl phosphine oxide in xylene for 1 h at 140 °C, and the appropriate amount of the resulting solution was added to a mixture of the epoxide resin **3** and the respective isocyanate in xylene at 65 °C. This temperature was absolutely necessary to keep the catalyst adduct in solution. After complete addition, the temperature was raised to 95 °C, and the reaction mixture was kept for 4 h at this temperature. It was then cooled to ambient temperature, and the resin was successively washed with DMF and DCM. Acidic cleavage (TFA/DCM = 1:1) afforded oxazolidinone **5a** in high yield and purity (determined by LC analysis). The NMR and mass spectra of a sample of **5a** revealed the product to be identical to that isolated by the cylization/cleavage approach. Assessment of the reaction conditions with a set of substituted isocyanates revealed them to be compatible with various functional groups, for example, ester or nitro groups, and compounds **5b**−**i** could be isolated in high yields and purities (Table 1).

To demonstrate the versatility of this procedure, 12 different isocyanates, **1j**−**u** (Figure 1), were selected and used for carbamate synthesis and cycloaddition, thus generating a 144-member library. Although carbamate and epoxide resins were prepared in batches manually, most of the cycloaddion and cleavage reactions were performed in a semiautomated fashion using the Quest 210 synthesizer. Moreover, the automated synthesizers (ACT 496, Advanced Chemtech; ASW 2000, Chemspeed) were tested for their suitability for this type of chemistry. It was interesting to see that compounds of comparable quality could be isolated with all three systems.[12] After acidic cleavage, the products were obtained in high yields as well as high purities (LC/MS analysis). The overall results are outlined in Figure 2 and show that over 70% of the synthesized compounds had purities >90%.

Furthermore, this approach allowed the introduction of various functional groups, which gave access to further synthetic transformations, as outlined in Scheme 2. Reduction of the nitro group of resin-bound intermediate **4c** with $SnCl_2$ applying standard reduction conditions resulted in the resin-bound aniline **7**. This intermediate could be further derivatized by reaction with various acyl chlorides to compounds **8** or with isocyanates to compounds **9**. Yields and purities of the resulting oxazolidinone derivatives **8** and **9** are summarized in Table 2.

Conclusion

In summary, the presented four-step procedure, including a cycloaddition reaction of epoxides with isocyanates, is an effective method for the synthesis of arylamino-substituted oxazolidinones on solid support. Isolated yields of these compounds were good, and the purities were high. The procedure is quite general, thus allowing the introduction of a variety of functional groups. Moreover, the intermediates generated by this approach offer themselves for further synthetic transformations. The mild reaction conditions are

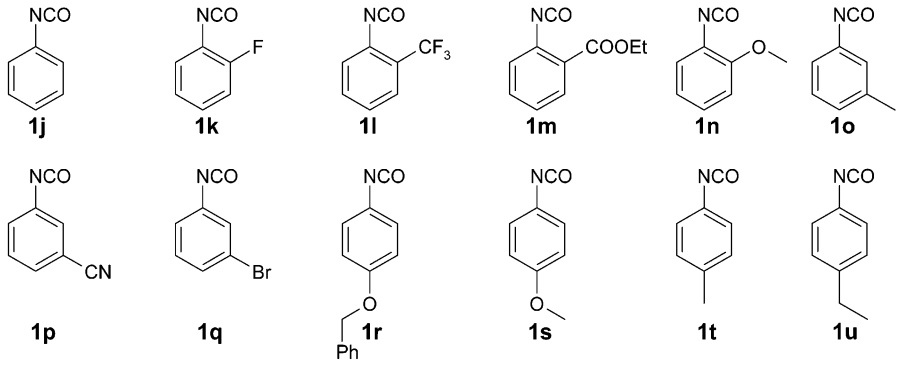


Figure 1. Isocyanates for 144-member library.

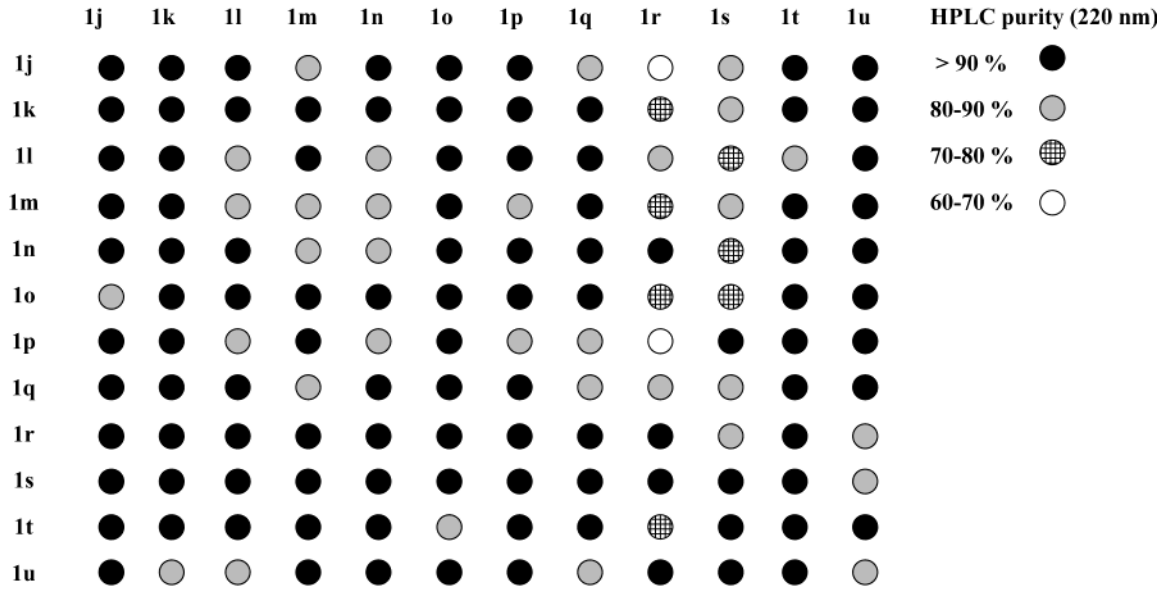
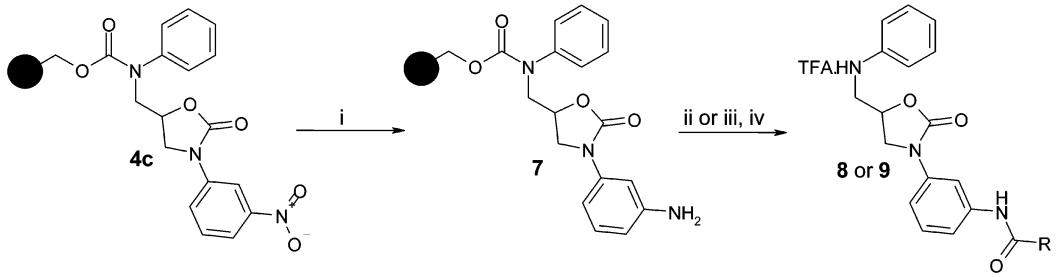


Figure 2. Purities of a 144-member library.

Scheme 2. Further Derivatizations of Resin-Bound Oxazolidinones



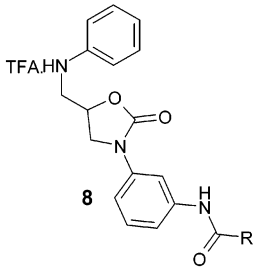
Reagents and conditions: (i) 10 equiv $SnCl_2 \cdot 2H_2O$, DMF/EtOH = 4:1, 50 °C, 2 h; (ii) 20 equiv R−NCO, DCM, r.t., 15 h; (iii) 10 equiv R−COCl, DMAP (cat.), DCM/pyridin = 1:1, r.t., 18 h; (iv) TFA/DCM = 1:1, r.t., 30 min.

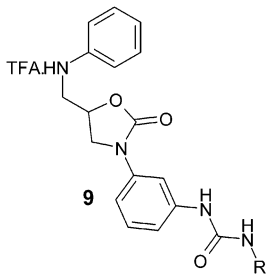
regarded as being well-suited for the preparation of combinatorial libraries, even in an automated fashion.

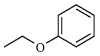
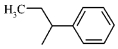
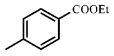
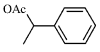
Experimental Section

General. All reagents and solvents were obtained from commercial suppliers and were used without further purification. Proton magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AM 250 spectrometer or a Bruker DRX 500 spectrometer. All samples were dissolved in DMSO containing CF_3COOD. Chemical shifts are reported in parts per million (δ) relative to DMSO as internal reference. Mass spectra were recorded on a Varian 70-SE spectrometer (FAB) or a VG Analytical 7070E spectrometer (EI), respectively. Analytical HPLC of the products after cleavage from the resin were recorded on a La Chrom (Merck Hitachi) system (interface L-7000, pump L-7100, auto sampler L-7200, diode array detector L-7450) using a LiChrospher 60 RP-select B (5-μm) column. Water (0.01% TFA)/acetonitrile (0.008% TFA) was used as eluent in mixtures (unlinear gradient) as follows: 0 min, 20% ACN; 7 min, 100% ACN; 10 min, 100% ACN; 10.5 min, 20% ACN; 12 min, 20% ACN; UV detection, 220 nm. HPLC/MS of the products after cleavage from the resin were recorded on an Agilent 1100 HPLC system (1100 high-pressure gradient pump, 1100 diode array detector) interfaced to an Agilent 1100 mass spectrometer detector using a Chromolith SpeedROD RP 18e50-4.6

Table 2. Further Derivatizations: Yields and Purities of Amides and Ureas





Entry	R	Yield (%)[a]	Purity (%)[b]	Entry	R	Yield (%)[a]	Purity (%)[b]
8a		98	95	**9a**		76	95
8b		88	86	**9b**		88	93
8c		95	64	**9c**		89	92
8d		90	69	**9d**		84	95
8e		85	81	**9e**		98	93
8f		92	70	**9f**		98	95
8g		93	68	**9g**		98	84
8h		95	67	**9h**		92	90
8i		84	76	**9i**		90	95
8j		92	61	**9j**		83	84

[a] Yields of cleaved products are based on the theoretical loading of commercial resins. [b] For details, see the Experimental Section.

column. Water (0.01% TFA)/acetonitrile (0.008% TFA) was used as eluent in mixtures as follows: 0 min, 20% ACN; 2.8 min, 100% ACN; 3.3 min, 100% ACN; 3.4 min, 20% ACN; 3.6 min, 20% ACN; UV detection, 220 nm.

Resin-Bound Carbamates 2. To a suspension of Wang resin (1 g, loading 1.11 mmol/g) in dry DCM (8 mL), phenyl isocyanates **1** (6 mol equiv) and a catalytic amount of triethylamine were added, and the reaction mixture was stirred for 6.5 h. The resins were filtered; washed with DMF (5 × 20 mL), DMF/DCM (1/1; 3 × 20 mL), and DCM (5 × 20 mL); and dried thoroughly under vacuum.[10]

Alkylation of Resins 2. Resin **2** (1 g), lithium iodide (1 mol equiv), and glycidyltosylate (10 mol equiv) were suspended in dry NMP (8 mL) and stirred for 10 min at ambient temperature under argon atmosphere. Lithium bis-(trimethylsilyl)amide (2 mol equiv, 1 M solution in THF) was added dropwise, and the reaction mixture was stirred overnight. The resins were filtered; washed with DMF (10 × 20 mL), DMF/DCM (1/1; 5 × 20 mL), and DCM (5 × 20 mL); and dried under vacuum.

Cycloaddition Reaction with Resins 3. The lithium bromide adduct was prepared by refluxing a 0.1 M solution of lithium bromide and tributyl phosphine oxide in xylene for 1 h. Resins **3** (100 mg) and phenyl isocyanates **1** (10 mol equiv) were suspended in dry xylene (0.5 mL) and warmed to 65 °C. A 0.5 mol equiv of the freshly prepared catalyst solution in xylene was added, and the reaction mixtures were stirred for 4 h at 95 °C. The reaction mixtures were cooled to ambient temperature, and the resins were filtered; washed with DMF (10 × 2 mL), DMF/DCM (1/1; 3 × 2 mL), and DCM (5 × 2 mL); and dried under vacuum.

Cleavage. The resins were treated with 50% TFA/CH_2Cl_2 for 30 min and filtered. The resins were washed two times with CH_2Cl_2, and the combined filtrates were concentrated.

3-Phenyl-5-[(phenylamino)methyl]oxazolidin-2-one (5a). ^{1}H NMR (DMSO, 250 MHz) δ 7.65−7.52 (m, 2H); 7.48−7.32 (m, 4H); 7.27−7.08 (m, 4H); 5.05−4.91 (m, 1H, 5-H); 4.24 (t, J = 9.1 Hz, 1H, 4-H_a); 3.89 (dd, ^2J = 9.1 Hz, ^3J = 6.5 Hz, 1H, 4-H_b); 3.82−3.6 (m, 2H, CH_2); mass spectrum (EI) m/z 268 (M^+).

3-(2-Nitrophenyl)-5-[(phenylamino)methyl]oxazolidin-2-one (5b). ^{1}H NMR (DMSO, 250 MHz) δ 8.09 (dd, 1H); 7.81 (dt, 1H); 7.68 (dd, 1H); 7.56 (dt, 1H); 7.38 (t, 2H); 7.2 (d, 2H); 7.1 (t, 1H); 5.14−4.98 (m, 1H, 5-H); 4.33 (t, J = 8.8 Hz, 1H, 4-H_a); 3.97 (dd, ^2J = 8.8 Hz, ^3J = 5.9 Hz, 1H,

4-H_b); 3.81−3.62 (m, 2H, CH_2); mass spectrum (FAB) *m/z* 627 $(2M + H)^+$, 314 $(M + H)^+$.

3-(3-Nitrophenyl)-5-[(phenylamino)methyl]oxazolidin-2-one (5c). ^{1}H NMR (DMSO, 250 MHz) δ 8.59 (t, 1H); 8.0 (dd, 1H); 7.91 (dd, 1H); 7.71 (t, 1H); 7.28 (t, 2H); 7.02 (d, 2H); 6.93 (t, 1H); 5.07−4.89 (m, 1H, 5-H); 4.31 (t, $J = 9$ Hz, 1H, 4-H_a); 3.97 (dd, $^2J = 9$ Hz, $^3J = 6.4$ Hz, 1H, 4-H_b); 3.74−3.52 (m, 2H, CH_2); mass spectrum (EI) *m/z* 313 (M^+).

3-(4-Nitrophenyl)-5-[(phenylamino)methyl]oxazolidin-2-one (5d). ^{1}H NMR (DMSO, 250 MHz) δ 8.31 (d, 2H); 7.83 (d, 2H); 7.32 (t, 2H); 7.08 (d, 2H); 6.97 (t, 1H); 5.19−4.93 (m, 1H, 5-H); 4.31 (t, $J = 9.2$ Hz, 1H, 4-H_a); 3.96 (dd, $^2J = 9.2$ Hz, $^3J = 6.5$ Hz, 1H, 4-H_b); 3.76−3.57 (m, 2H, CH_2); mass spectrum (FAB) *m/z* 314 $(M + H)^+$.

3-(4-Cyanophenyl)-5-[(phenylamino)methyl]oxazolidin-2-one (5e). ^{1}H NMR (DMSO, 250 MHz) δ 7.85 (d, 2H); 7.76 (d, 2H); 7.28 (t, 2H); 7.03 (d, 2H); 6.84 (t, 1H); 5.05−4.9 (m, 1H, 5-H); 4.26 (t, $J = 9.2$ Hz, 1H, 4-H_a); 3.91 (dd, $^2J = 9.2$ Hz, $^3J = 6.5$ Hz, 1H, 4-H_b); 3.72−3.53 (m, 2H, CH_2); mass spectrum (FAB) *m/z* 587 $(2M + H)^+$, 294 $(M + H)^+$.

3-(4-Bromophenyl)-5-[(phenylamino)methyl]oxazolidin-2-one (5f). ^{1}H NMR (DMSO, 250 MHz) δ 7.63−7.49 (m, 4H); 7.31 (t, 2H); 7.08 (d, 2H); 6.99 (t, 1H); 5.01−4.87 (m, 1H, 5-H); 4.2 (t, $J = 9.1$ Hz, 1H, 4-H_a); 3.86 (dd, $^2J = 9.1$ Hz, $^3J = 6.5$ Hz, 1H, 4-H_b); 3.72−3.52 (m, 2H, CH_2); mass spectrum (FAB) *m/z* 347 $(M + H)^+$.

4-[2-Oxo-5-(phenylamino)methyloxazolidin-3-yl)benzoic Acid, Ethyl Ester (5g). ^{1}H NMR (DMSO, 250 MHz) δ 8.02 (d, 2H); 7.72 (d, 2H); 7.33 (t, 2H); 7.19−6.91 (m, 3H); 5.06−4.91 (m, 1H, 5′-H); 4.32 (q, 2H, CH_2CH_3); 4.27 (t, $J = 9.1$ Hz, 1H, 4′-H_a); 3.98 (dd, $^2J = 9.1$ Hz, $^3J = 6.5$ Hz, 1H, 4′-H_b); 3.78−3.55 (m, 2H, CH_2); 1.34 (t, 3H, CH_2CH_3); mass spectrum (FAB) *m/z* 341 $(M + H)^+$.

3-Biphenyl-4-yl-5-[(phenylamino)methyl]oxazolidin-2-one (5h). ^{1}H NMR (DMSO, 500 MHz) δ 7.73−7.57 (m, 6H); 7.46−7.34 (m, 4H); 7.33−7.22 (m, 3H); 7.17 (t, 1H); 5.02−4.91 (m, 1H, 5-H); 4.24 (t, $J = 8.9$ Hz, 1H, 4-H_a); 3.89 (dd, $^2J = 8.9$ Hz, $^3J = 6.6$ Hz, 1H, 4-H_b); 3.75 (dd, $^2J = 13.6$ Hz, $^3J = 8.3$ Hz, 1H, CH_2); 3.66 (dd, $^2J = 13.6$ Hz, $^3J = 3.1$ Hz, 1H, CH_2); mass spectrum (FAB) *m/z* 345 $(M + H)^+$.

3-(2-Chlor-4-nitrophenyl)-5-[(phenylamino)methyl]-oxazolidin-2-one (5i). ^{1}H NMR (DMSO, 250 MHz) δ 8.38 (d, 1H); 8.27 (dd, 1H); 7.84 (d, 1H); 7.27 (t, 2H); 7.15−6.88 (m, 3H); 5.09−4.92 (m, 1H, 5-H); 4.2 (t, $J = 8.7$ Hz, 1H, 4-H_a); 3.85 (dd, $^2J = 8.7$ Hz, $^3J = 6.2$ Hz, 1H, 4-H_b); 3.74−3.53 (m, 2H, CH_2); mass spectrum (FAB) *m/z* 348 $(M + H)^+$.

Reduction of Resin 4c. Resin **4c** (200 mg) and $SnCl_2 \cdot 2H_2O$ (10 mol equiv) were suspended in DMF/EtOH, 4:1 (1.6 mL), and stirred at 50 °C for 2 h. The reaction mixture was cooled to ambient temperature, and the resin was filtered; washed with MeOH (3 × 4 mL), MeOH/H_2O (1/1, 2 × 4 mL), MeOH (2 × 4 mL), DMF (5 × 4 mL), and DCM (5 × 4 mL); and dried under vacuum.

Amide Synthesis. Resin **7** (50 mg) and catalytic amounts of DMAP were suspended in DCM/pyridin, 1:1 (1 mL). Acyl chlorides (10 mol equiv) were added at room temperature, and the reaction mixtures were stirred overnight. The resins were filtered; washed with DCM (3 × 1 mL), MeOH (3 × 1 mL), DMF (3 × 1 mL), DMF/DCM (1/1, 3 × 1 mL), DCM (5 × 1 mL); and dried under vacuum.

Cleavage of the compounds **8a**−**j** was performed as described above.

Urea Synthesis. Resin **7** (50 mg) was suspended in DCM (1 mL) and treated with isocyanates (20 mol equiv) at room temperature, and the reaction mixtures were stirred overnight. The resins were filtered; washed with DCM (3 × 1 mL), MeOH (3 × 1 mL), DMF (3 × 1 mL), DMF/DCM (1/1, 3 × 1 mL), and DCM (5 × 1 mL); and dried under vacuum.

Cleavage of the compounds **9a**−**j** was performed as described above.

Supporting Information Available. ^{1}H NMR and LC/MS spectra of selected library members. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527−4554. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643−5678. (c) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385−15443. (d) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581. (e) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202. (f) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214.

(2) (a) Brickner, S. J. *Curr. Pharm. Des.* **1996**, *2*, 175−194. (b) Ford, C. W.; Hamel, J. C.; Stapert, D.; Moerman, J. K.; Hutchinson, D. K.; Barbachyn, M. R.; Zurenko, G. E. *Trends Microbiol.* **1997**, *5*, 196−200. (c) Zurenko, G. E.; Gibson, J. K.; Shinabarger, D. L.; Aristoff, P. A.; Ford, C. W.; Tarpley, W. G. *Curr. Opin. Pharmacol.* **2001**, *1*, 470−476.

(3) (a) Dostert, P. L.; Strolin Benedetti, M.; Tipton, K. F. *Med. Res. Rev.* **1989**, *9* (1), 45−89. (b) Norrby, R. *Exp. Opin. Pharmacother.* **2001**, *2*, 293−302.

(4) Prücher, H.; Gottschlich, R.; Haase, A.; Stohrer, M.; Seyfried, C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 165−170.

(5) Dasenbrock, J.; Tsaklakidis, C.; Wurziger, H.; Barnes, C.; Buehring, K.-U. Ger. Offen. 2001, DE 19958153.

(6) For an alternative approach to 3,5-disubstituted 1,3-oxazolidin-2-ones, see: (a) ten Holte, P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 7407−7410. (b) ten Holte, P.; van Esseveldt, B. C. J.; Thijs, L.; Zwanenburg, B. *Eur. J. Org. Chem.* **2001**, 2965−2969.

(7) Buchstaller, H.-P. *Tetrahedron* **1998**, *54*, 3465−3470.

(8) Buchstaller, H.-P. Gordon Research Conference 1999: Combinatorial Chemistry; Tilton School, New Hampshire.

(9) Wang resin was purchased from Rapp Polymere GmbH, Ernst-Simon-Str. 9, D-72072 Tübingen, Germany.

(10) In these cases (**1b**−**e**), the washing procedure described above was slightly modified, starting with DMSO.

(11) Herweh, J. E.; Kauffman, W. J. *Tetrahedron Lett.* **1971**, *12*, 809−812.

(12) Initially, it was difficult to add the hot catalyst solution to the reaction vessels without precipitation in the transfer needle. However, we could circumvent this problem by dispensing the first portion of catalyst solution to the waste without any subsequent washing step.

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