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Solid Phase Synthesis of Oxazolidinones via a Novel Cyclisation/Cleavage Reaction

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Abstract: The solid phase synthesis of oxazolidinones via a novel cylisation/cleavage reaction is described. Resin bound carbamates **2**, which were obtained by reaction of Wang-resin with commercially available isocyanates **1**, were alkylated with glycidyltosylate to the corresponding epoxides **3**. Nucleophilic opening of the epoxides **3** with pyrrolidine and subsequent cyclisation leads to the title compounds in high yield and purity.

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, 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 chemistry accessible on solid phase.

The N-aryloxazolidinone scaffold is a constituent of a number of compounds, which showed interesting biological effects as antibacterial agents[2], MAO inhibitors[3] or neuroleptics.[4] For this reason a versatile method on solid support to generate libraries of compounds including this scaffold is of high interest.

In this paper the synthesis of oxazolidinones via a novel cyclisation/cleavage reaction is reported.

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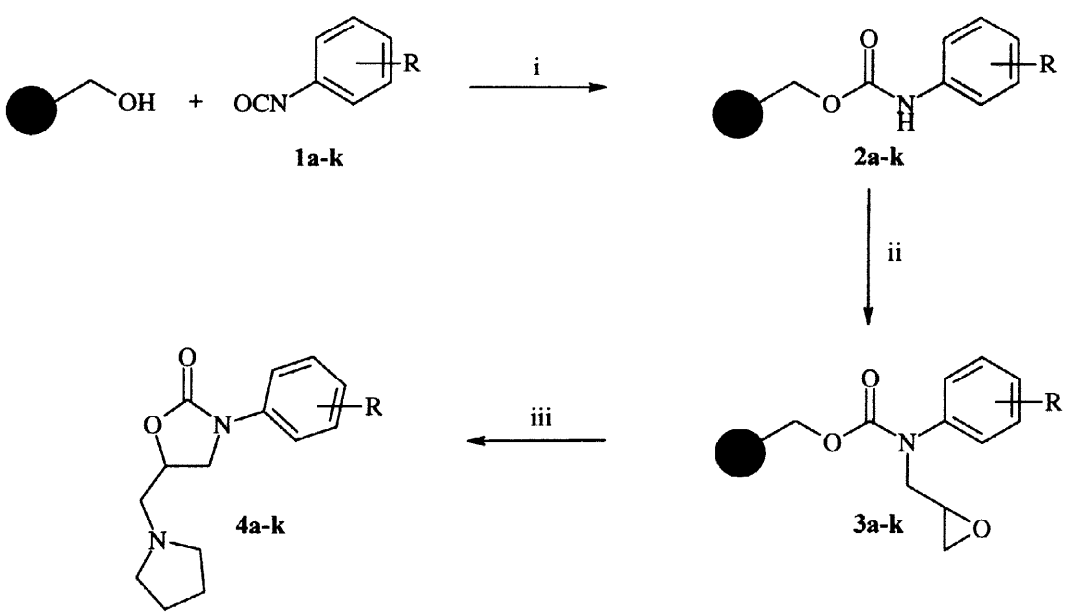
RESULTS AND DISCUSSION

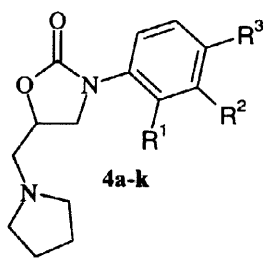
The title compounds were synthesised in three steps as outlined in Scheme 1. The resin bound carbamates **2a-k** were obtained by reaction of Wang resin with commercially available isocyanates **1a-k**. The best results were obtained using 6 equivalents of the respective isocyanate and catalytic amounts of triethylamine in dichloromethane. Even with poorly soluble isocyanates, e.g. **1b** or **1i** the reactions worked well in the employed solvent.[5] In the subsequent alkylation step the well dried resins **3a-k** were treated with 2 equivalents of base ($LiN(Si(CH_3)_3)_2$, 1M solution in THF), 10 equivalents glycidyltosylate and 1 equivalent lithium iodide. In general, the reactions were carried out at ambient temperature under argon atmosphere. In cases were nitro groups were attached to the phenyl moiety (**3i-k**) better yields and purities of the final products were obtained using 1.1 equivalents of base for the deprotonation. Due to 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[6]. In the key step, nucleophilic opening of the epoxides with pyrrolidine leads to the corresponding aminoalcohol intermediates, which cyclised spontaneously and liberated the title compounds from the resin. As described in the literature lithium perchlorate was added to facilitate the ring opening of the epoxide owing to the coordination of the lithium ion with the oxygen atom[7]. Typically a fivefold excess of amine as well as lithium perchlorate was used in this procedure and the reactions were carried out in THF at ambient temperature. After aqueous work up, investigation by HPLC revealed that the



Scheme 1: i) Et_3N (cat.), dichloromethane, 6,5 h; ii) $LiN(Si(CH_3)_3)_2$, LiI, glycidyltosylate, NMP/THF, 24 h; iii) pyrrolidine, $LiClO_4$, THF;

oxazolidinones, with the exception of **4k**, were obtained as essentially pure compounds (Table 1). The structures were confirmed by MS and NMR spectra. These results emphasise the versatility of the described procedure. The reaction conditions are compatible with a variety of functional groups attached to the phenyl moiety, which allow further synthetic transformations.

Table1. Oxazolidinone Synthesis on Solid Support



4a-k

Entry	R^1	R^2	R^3	Yield (%)[a]	Purity (%)[b]
4a	H	H	H	94	98.4
4b	H	H	CN	71	96.9
4c	H	CN	H	100	98.1
4d	H	H	OCH_3	100	98
4e	OCH_3	H	H	74	97.1
4f	OCH_3	H	OCH_3	99	98.6
4g	H	H	Br	95	97.8
4h	H	H	COOEt	73	93
4i	H	H	NO_2	74	96.9
4j	NO_2	H	H	100	82.5
4k	Cl	H	NO_2	90	53.8

[a]Yields of the cleaved products are based on the theoretical loading of commercial resins;
[b]For details see experimental section.

CONCLUSION

In summary, the presented three step procedure is an effective method for the synthesis of oxazolidinones on solid support with high yields and purities. The mild reaction conditions are viewed as being well suited for automated synthesis. Preliminary experiments indicate, that the cyclisation/cleavage sequence is not restricted

to pyrrolidine as the amine component and further work is in progress to extend the diversity of the title compounds using different amines for this cyclisation/cleavage procedure.

EXPERIMENTAL

General. All reagents and solvents were obtained from commercial suppliers and used without further purification. Wang resin was purchased from Rapp Polymere GmbH, Ernst-Simon-Str. 9, D-72072 Tübingen, Germany. Proton magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker am 250 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm) or DMSO (2.49 ppm) 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 and aqueous workup 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 (0.1 % TFA)/acetonitrile (0.08 % TFA) were used as eluent in mixtures (unlinear gradient) as follows: 0 min, 10 % ACN; 14 min, 50 % ACN; 20 min, 100 % ACN; 23 min, 100 % ACN; 26 min, 10 % ACN; 30 min, 10 % ACN.

Resin bound carbamates 2a-k: To a suspension of Wang resin (1g, loading 1.11 mmol/g) in dry dichloromethane (8 ml) phenyl isocyanate **1a-k** (6 mol eq.) and a catalytic amount of triethylamine were added and the reaction mixture stirred for 6.5 h. The resins were filtered, washed[5] with DMF (5x 20 ml), DMF/dichloromethane (1/1; 3x 20 ml) and dichloromethane (5x 20 ml) and dried thoroughly under vacuum.

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

Alkylation of 2i-k: Resins **2i-k** (1 g), lithium iodide (1 mol eq.) and glycidyltosylate (10 mol eq.) were suspended in dry NMP (8 ml) and stirred for 10 min at ambient temperature under argon atmosphere. Lithium bis(trimethylsilyl)amide (1.1 mol eq., 1M solution in THF) was added dropwise and the reaction mixture stirred overnight. The resins were filtered, washed with DMF (10x 20 ml), DMF/dichloromethane (1/1; 5x 20 ml) and dichloromethane (5x 20 ml) and dried under vacuum.

3-Phenyl-5-(pyrrolidinylmethyl)oxazolidin-2-one (4a): Resin **3a** (150 mg, 0.14 mmol) and lithium perchlorate (74 mg, 0.7 mmol) were suspended in dry THF (1.5 ml) and stirred for 5 min at ambient temperature.

Pyrrolidine (58 µl, 0.7 mmol) was added and the reaction mixture stirred overnight. The resin was filtered, washed with dichloromethane several times and the filtrate washed with water. The aqueous layer was extracted twice with dichloromethane, the combined organic layers were dried (Na_2SO_4) and evaporated to dryness to give 34 mg (94 %) of **4a**. ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, 2'-H); 7.37 (t, 2H, 3'-H); 7.13 (t, 1H, 4'-H); 4.84-4.7 (m, 1H, 5-H); 4.18 (t, 1H, 4-H_a); 3.87 (dd, 1H, 4-H_b); 2.97-2.77 (m, 2H, N-CH_2-CH); 2.75-2.55 (m, 4H, N-C$\underline{H_2}$-CH_2); 1.88-1.72 (m, 4H, N-CH_2-C$\underline{H_2}$). MS (EI) *m/z* 246 (M^+).

3-(4-Cyanophenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4b) was prepared from resin **3b** (150 mg) according to **4a** to give 28 mg (71 %) of **4b**. ^{1}H NMR ($CDCl_3$) δ 7.76-7.62 (m, 4H, 2'-H, 3'-H); 4.88-4.74 (m, 1H, 5-H); 4.09 (t, 1H, 4-H_a); 3.92 (dd, 1H, 4-H_b); 3.01-2.79 (m, 2H, N-CH_2-CH); 2.76-2.57 (m, 4H, N-C$\underline{H_2}$-CH_2); 1.9-1.72 (m, 4H, N-CH_2-C$\underline{H_2}$). MS (EI) *m/z* 271 (M^+).

3-(3-Cyanophenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4c) was prepared from resin **3c** (100 mg) according to **4a** to give 26 mg (100 %) of **4c**. ^{1}H NMR ($CDCl_3$) δ 7.9 (d, 1H, 6'-H); 7.84 (s, 1H, 2'-H); 7.48 (t, 1H, 5'-H); 7.41 (d, 1H, 4'-H); 4.87-4.73 (m, 1H, 5-H); 4.07 (t, 1H, 4-H_a); 3.91 (dd, 1H, 4-H_b); 2.99-2.79 (m, 2H, N-CH_2-CH); 2.75-2.54 (m, 4H, N-C$\underline{H_2}$-CH_2); 1.91-1.71 (m, 4H, N-CH_2-C$\underline{H_2}$). MS (EI) *m/z* 271 (M^+).

3-(4-Methoxyphenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4d) was prepared from resin **3d** (150 mg) according to **4a** to give 37.5 mg (100 %) of **4d**. ^{1}H NMR ($CDCl_3$) δ 7.44 (d, 2H, 2'-H); 6.9 (d, 2H, 3'-H); 4.85-4.7 (m, 1H, 5-H); 4.06 (t, 1H, 4-H_a); 3.83 (dd, 1H, 4-H_b); 3.81 (s, 3H, OCH_3); 3.02-2.8 (m, 2H, N-CH_2-CH); 2.79-2.6 (m, 4H, N-C$\underline{H_2}$-CH_2); 1.9-1.76 (m, 4H, N-CH_2-C$\underline{H_2}$). MS (EI) *m/z* 276 (M^+).

3-(2-Methoxyphenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4e) was prepared from resin **3e** (150 mg) according to **4a** to give 27.5 mg (74 %) of **4e**. ^{1}H NMR ($CDCl_3$) δ 7.35 (dd, 1H, 6'-H); 7.32-7.23 (m, 1H, 4'-H); 7.03-6.9 (m, 2H, 3'-H, 5'-H); 4.9-4.75 (m, 1H, 5-H); 4.04 (t, 1H, 4-H_a); 3.86 (s, 3H, OCH_3); 3.76 (dd, 1H, 4-H_b); 3.02-2.82 (m, 2H, N-CH_2-CH); 2.8-2.62 (m, 4H, N-C$\underline{H_2}$-CH_2); 1.88-1.77 (m, 4H, N-CH_2-C$\underline{H_2}$). MS (FAB) *m/z* 277 $(M+H)^+$.

3-(2,4-Dimethoxyphenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4f) was prepared from resin **3f** (150 mg) according to **4a** to give 42.5 mg (99 %) of **4f**. ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 1H, 6'-H); 6.54-6.45 (m, 2H, 3'-H, 5'-H); 4.88-4.74 (m, 1H, 5-H); 3.92 (t, 1H, 4-H_a); 3.84 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.69 (dd, 1H, 4-H_b); 3.02-2.83 (m, 2H, N-CH_2-CH); 2.81-2.64 (m, 4H, N-C$\underline{H_2}$-CH_2); 1.91-1.76 (m, 4H, N-CH_2-C$\underline{H_2}$). MS (FAB) *m/z* 307 $(M+H)^+$.

3-(4-Bromophenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4g) was prepared from resin **3g** (150 mg) according to **4a** to give 40.1 mg (95 %) of **4g**. ^{1}H NMR ($CDCl_3$) δ 7.52-7.41 (m, 4H, 2'-H, 3'-H); 4.84-4.69 (m, 1H, 5-H); 4.04 (t, 1H, 4-H_a); 3.85 (dd, 1H, 4-H_b); 2.97-2.76 (m, 2H, N-CH_2-CH); 2.74-2.55 (m, 4H, N-C$\underline{H_2}$-CH_2); 1.88-1.73 (m, 4H, N-CH_2-C$\underline{H_2}$). MS (FAB) *m/z* 325 $(M+H)^+$.

4-[2-Oxo-5-(pyrrolidinylmethyl)-3-oxazolidinyl]benzoic Acid Ethylester (4h) was prepared from resin **3h** (150 mg) according to **4a** to give 30.5 mg (73 %) of **4g**. ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 2H, 3'-H); 7.64 (d, 2H, 2'-

H); 4.86-4.71 (m, 1H, 5-H); 4.37 (q, 2H, $OC\underline{H}_2CH_3$); 4.11 (t, 1H, 4-H_a); 3.92 (dd, 1H, 4-H_b); 2.98-2.77 (m, 2H, $N\text{-}CH_2\text{-}CH$); 2.75-2.55 (m, 4H, $N\text{-}C\underline{H}_2\text{-}CH_2$); 1.86-1.74 (m, 4H, $N\text{-}CH_2\text{-}C\underline{H}_2$); 1.41 (t, 3H, $OCH_2C\underline{H}_3$). MS (FAB) *m/z* 319 $(M+H)^+$.

3-(4-Nitrophenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4i) was prepared from resin **3i** (100 mg) according to **4a** to give 20.7 mg (74 %) of **4i**. ^1H NMR (DMSO-d_6) δ 8.28 (d, 2H, 3'-H); 7.83 (d, 2H, 2'-H); 4.94-4.78 (m, 1H, 5-H); 4.24 (t, 1H, 4-H_a); 3.89 (dd, 1H, 4-H_b); 2.92-2.74 (m, 2H, $N\text{-}CH_2\text{-}CH$); 2.68-2.5 (m, 4H, $N\text{-}C\underline{H}_2\text{-}CH_2$); 1.8-1.61 (m, 4H, $N\text{-}CH_2\text{-}C\underline{H}_2$). MS (EI) *m/z* 291 (M^+).

3-(2-Nitrophenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4j) was prepared from resin **3j** (150 mg) according to **4a** to give 41.4 mg (100 %) of **4j**. ^1H NMR ($CDCl_3$) δ 8.01 (dd, 1H, 3'-H); 7.65 (t, 1H, 5'-H); 7.52-7.4 (m, 2H, 4'-H, 6'-H); 4.92-4.83 (m, 1H, 5-H); 4.13 (t, 1H, 4-H_a); 3.92 (dd, 1H, 4-H_b); 3.07-2.85 (m, 2H, $N\text{-}CH_2\text{-}CH$); 2.81-2.53 (m, 4H, $N\text{-}C\underline{H}_2\text{-}CH_2$); 1.82-1.73 (m, 4H, $N\text{-}CH_2\text{-}C\underline{H}_2$). MS (FAB) *m/z* 292 $(M+H)^+$.

3-(2-Chloro-4-nitrophenyl)-5-(pyrrolidinylmethyl)oxazolidin-2-one (4k) was prepared from resin **3k** (150 mg) according to **4a** to give 40.5 mg (90 %) of **4k**. MS (EI) *m/z* 325 (M^+).

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5. In these cases (**1b**, **1i**) the washing procedure described above was slightly modified starting with DMSO.
6. Alkylation of **3c** to **4c** e.g. caused a shift of the carbonyl band from 1733 cm^{-1} to 1701 cm^{-1}.
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