Pergamon

Tetrahedron Letters 43 (2002) 8327–8330

TETRAHEDRON LETTERS

Solid phase synthesis of 3,5-disubstituted oxazolidin-2-ones†

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Received 23 July 2002; revised 3 September 2002; accepted 13 September 2002

Abstract—A versatile method for the solid phase synthesis of oxazolidin-2-ones is described. A resin bound phenolic group was treated with (±)-epichlorohydrin followed by opening of the epoxide ring with sodium azide. The resulting 1-azido-3-aryloxypropan-2-ol was treated with *p*-nitrophenylchloroformate and subsequent Staudinger's cyclization using PPh_3 yielded a 5-substituted oxazolidinone. Finally, additional diversity at position 3 was introduced by treating the 5-substituted oxazolidinone with an alkyl halide in the presence of NaH to give the desired compound in high yield and purity.

In recent years solid phase organic synthesis has been recognized as a powerful tool for the preparation of a large number of heterocyclic compounds.[1,2] Several liquid phase methods for the preparation of heterocycles have been transferred to solid phase, however, methodologies pertaining to the synthesis of substituted heterocyclic compounds with high chemical diversity still need to be addressed. One such example among the heterocyclic class of compounds are oxazolidinones, which are particularly attractive since they are known to be the core structural unit of compounds with antibacterial,[3] antiallergy[4] and immunosuppressant[5] activities.

Their synthesis on solid phase has been reported starting from a resin bound tyrosine derivative followed by reduction and reaction with thionyl chloride to give the oxazolidinones.[6] Another strategy involves the reaction of polymer bound diols with *p*-toluenesulfonyl isocyanate and subsequent cyclo-elimination.[7] Since highly substituted heterocyclic compounds offer a high degree of structural diversity and have proved to be broadly and economically useful as therapeutic agents, we focused our efforts to develop a suitable strategy for the solid phase synthesis of oxazolidinones with extensive chemical diversity. These studies are in continuation of our interest in the solid phase synthesis of libraries based on peptides,[8] small organic molecules (heterocyclic and acyclic structures)[9] and natural products[10] of medicinal importance. In this paper we describe a novel method for the solid phase synthesis of oxazolidinones from resin bound epoxides.

The solid phase synthesis of oxazolidinones via a resin bound epoxide is outlined in Scheme 1. Treatment of the Rink Amide AM resin with 4-hydroxybenzoic acid in the presence of DIC/HOBt resulted in the resin bound aromatic hydroxy acid **1**. The polymer bound phenol was characterized by single bead FTIR microscopy, which showed complete disappearance of the NH_2 stretch and the appearance of an O–H stretch at 3138 cm^{-1} and a C=O stretch at 1725 cm^{-1}.

Epoxide **2** was obtained by treating **1** with (±)-epichlorohydrin in the presence of K_2CO_3 in DMF at 50°C. FTIR revealed the disappearance of the OH stretch at 3138 cm^{-1}. Treatment of **2** with sodium azide in DMF:H_2O (9:1; v/v) for 24 h at 120°C yielded **3**. The completion of the reaction was confirmed by FTIR with the appearance of an azide stretch at 2102 cm^{-1} and an O–H stretch at 3139 cm^{-1}. The resin bound 1-azido-3-aryloxy-propan-2-ol **3** was treated with *p*-nitrophenyl chloroformate in the presence of DIPEA and DMAP in THF for 16 h to give **4**. The reaction progress could be qualitatively monitored by analysis of the FTIR by following the broadening of the C=O stretch from 1734 to 1819 cm^{-1}. Finally, Staudinger's cyclization of intermediate **4** with triphenylphosphine in THF for 16 h at 50°C yielded **5**. The formation of **5** was confirmed by FTIR, which showed the appearance of a new cyclic urethane C=O stretch at 1817 cm^{-1} and the disappearance of the azide stretch at 2102 cm^{-1}. Next, the resin bound oxazolidinone **5** so obtained was treated with 50% TFA in DCM to give **6** as a racemic

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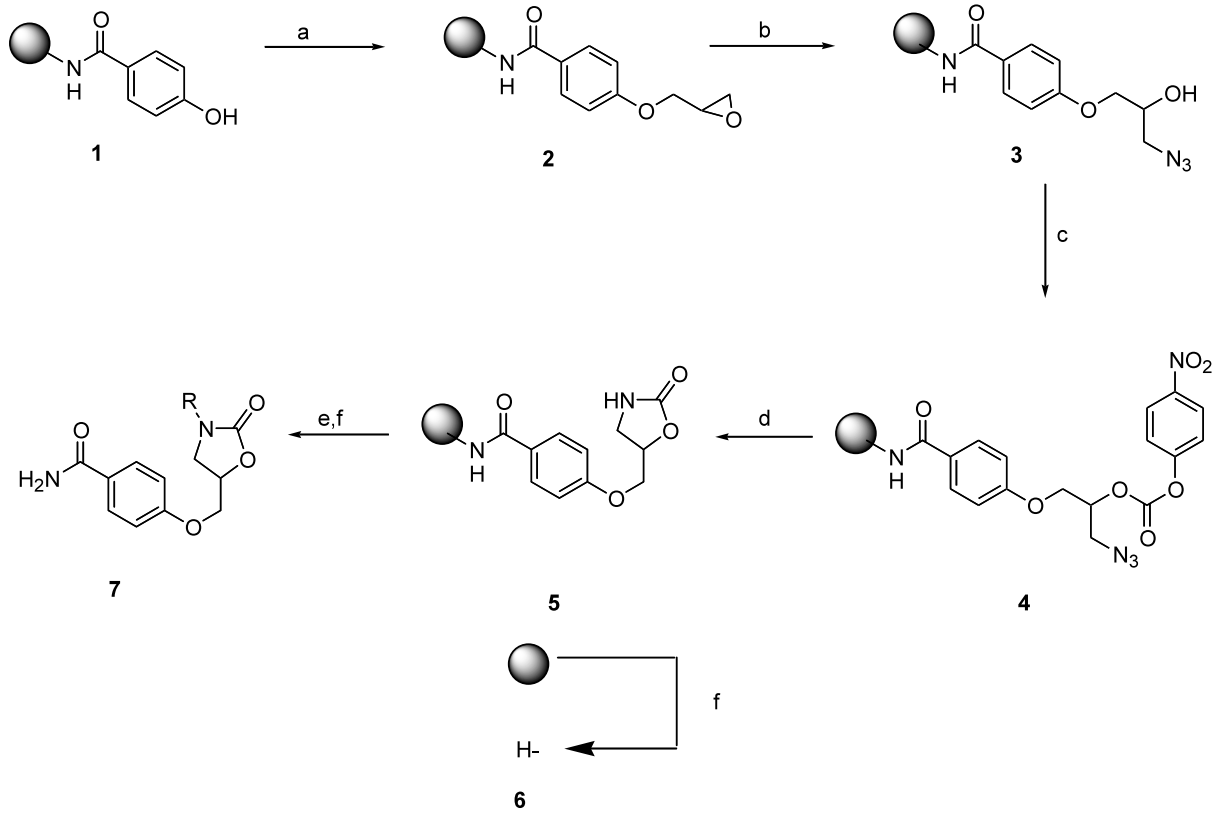
† CDRI Communication No. 6300.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02009-9



Scheme 1. *Reaction conditions*: (a) (±)-epichlorohydrin, K_2CO_3, DMF, 50°C; (b) NaN_3 in DMF:H_2O, (9:1; v/v), 24 h, 120°C; (c) *p*-nitrophenyl chloroformate, DIPEA, DMAP, THF, 16 h; (d) PPh_3, THF:H_2O (1:1), 16 h, 50°C; (e) alkyl bromide, NaH, 80°C; (f) 50% TFA–DCM.

mixture. This was purified by high throughput HPLC-MS and characterized by NMR.[11]

Further in order to introduce diversity in the oxazolidinone ring, the -NH was alkylated using benzyl bromide and NaH in dry DMF for 16 h at 80°C to give the resin bound *N*-alkylated oxazolidinone. This was then treated with 50% TFA in DCM to give **7** (R = Bn) as a racemic mixture which was again purified by high throughput HPLC-MS and characterized by NMR.[12]

The structural identity of the compound 4-(2-oxo-oxazolidin-5-ylmethoxy)benzamide **6** was established using proton NMR studies. The ^1H NMR spectrum along with the ^{13}C chemical shifts of the methylene and methine carbon obtained by spectral editing suggested the formation of 4-(2-oxo-oxazolidin-5-ylmethoxy)-benzamide. It was further confirmed by HSQC and HMBC data using 4-(3-benzyl-2-oxo-oxazolidin-5-ylmethoxy)benzamide **7** (R = Bn) as a representative example. In the HMBC experiment, the benzylic protons showed a strong cross peak with C-4 and the methylene protons of C-4 at 3.47 and 3.67 ppm showed strong cross peaks with C-3 thus ruling out the possibility of the formation of 4-(3-benzyl-2-oxo-oxazolidin-4-ylmethoxy)benzamide.

The scope and limitation of the method was established by introducing an amino acid as an additional diversity element between the resin and the aromatic hydroxy acid. Thus, in the first instance, the synthesis of 4-(3-benzyl-2-oxo-oxazolidin-5-ylmethoxy)-*N*-carbamoylmethyl-benzamide (**8**, $R^1 = CH_2$, $n = 0$, $R^2 = Bn$, Fig. 1) was accomplished by loading Fmoc-glycine on to the Rink amide resin followed by loading of 4-hydroxybenzoic acid and steps thereafter as depicted in Scheme 1. The final compound **8** obtained after the acidolytic cleavage from the resin was purified by high throughput HPLC-MS and characterized by NMR.[13] This was followed by the generation of a library of 24 compounds using 6 amino acids (Fmoc-Gly, Fmoc-Ala, Fmoc-Leu, Fmoc-PABA, Fmoc-Trp and Fmoc-βAla), 2 aromatic hydroxy acids (*p*-hydroxybenzoic acid and *p*-hydroxyphenylacetic acid) and 2 alkyl halides (benzyl bromide and phenacyl bromide) using an automated multiple organic synthesizer (Advanced Chemtech). The compounds **8** were obtained in good yields with purities ranging from 70 to 92% (Fig. 1, Table 1).

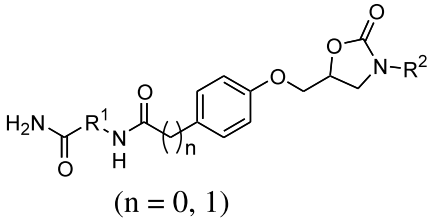
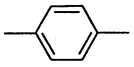
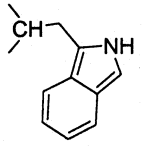
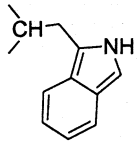


Figure 1. Library based on general structure **8**.

Table 1. Purity and ES MS of some representative compounds based on **8**

R^1	n	$-R^2$	ESMS $[M+H]^+$	Yield*/Purity# (%)
$>CH_2$	0	$-CH_2C_6H_5$	384.06	65/72
$>CHCH_3$	0	$-CH_2C_6H_5$	398.02	70/80
$>CHCH_2CH(CH_3)_2$	1	$-CH_2COC_6H_5$	482.34	70/82
	0	$-CH_2C_6H_5$	446.78	62/76
	1	$-CH_2C_6H_5$	527.78	75/80
	0	$-CH_2COC_6H_5$	541.03	70/90
$—CH_2CH_2—$	0	$-CH_2COC_6H_5$	426.87	71/92
$>CHCH_3$	1	$-CH_2COC_6H_5$	426.0	72/88

** Isolated yields following purification by LC-MS; # purity of crude products based on analytical HPLC*

In summary, an efficient route has been developed for the synthesis of oxazolidinones on solid phase. The procedure allows the construction of the 3,5-disubsituted oxazolidin-2-one scaffold with two-point diversity at positions 3 and 5.

Acknowledgements

The authors wish to thank Dr. A. K. Mandwal for his technical assistance for providing ES MS and FTIR data.

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11. **A typical procedure for the preparation of individual 4-(3-benzyl-2-oxo-oxazolidin-5-ylmethoxy)-benzamide 7**: To 100 mg of Rink Amide resin (0.74 mmol/g) was added *p*-hydroxybenzoic acid (30.6 g, 3 equiv., 0.222 mmol) dissolved in dry DMF, HOBt (60.6 mg, 6 equiv., 0.444 mmol) dissolved in 500 μl of dry DMF and 34.8 μl of DIC (3 equiv., 0.222 mmol). The reaction was allowed to stir at room temperature for 16 h. The resin was washed sequentially with DMF (5×2 ml), methanol (2×2 ml), DCM (3×2 ml), ether (5×2 ml) and dried in vacuo. To the

resin **1** in 1000 μl of dry DMF was added 204.5 mg of fused potassium carbonate (20 equiv., 1.48 mmol) and 173.7 μl (30 equiv., 2.22 mmol) of (±)-epichlorohydrin; the reaction mixture was stirred at 50°C for 24 h. Finally, the resin was washed sequentially with dry DMF (5×2 ml), methanol (3×2 ml), DCM (3×2 ml) and ether (3×2 ml). After drying under vacuum, the resin **2** was treated with sodium azide (48.1 mg, 10 equiv., 0.74 mmol) in 900 μl of dry DMF and 100 μl of triple distilled water at 120°C for 24 h. The resulting resin **3** was washed sequentially with DMF (5×2 ml), methanol (2×2 ml), water (5×2 ml), methanol (2×2 ml), DCM (3×2 ml), ether (3×2 ml) and dried in vacuo overnight. To the resin **3** was added *p*-nitrophenylchloroformate (74.6 mg, 5 equiv., 0.37 mmol) in 6.3 mg DMAP (0.7 equiv., 0518 mmol) and 88.6 μl of DIPEA (7 equiv., 518 mmol) using 1000 μl of THF as solvent and the reaction mixture was shaken at 0°C for 2 h and 16 h at room temperature. After being washed with THF, methanol, DCM and ether, the resin **4** was dried under high vacuum, and treated with triphenylphosphine (194.1 mg, 10 equiv., 0.74 mmol) in 1 ml of THF:H_2O mixture (1:1) for 16 h at 50°C. Finally the resulting resin **5** was treated with 17.7 mg of sodium hydride (10 equiv., 0.74 mmol) and 175.6 μl of benzyl bromide (20 equiv., 1.48 mmol) in dry DMSO (1000 μl) at 80°C. The resin was then washed successively with DMSO (5×2 ml), methanol (2×2 ml), DCM (3×2 ml), ether (3×2 ml) and dried in vacuo overnight. The compound was cleaved using 50% TFA in DCM for 2 h followed by lyophilization in ^{t}BuOH:H_2O mixture (4:1) to afford the pure compound as a white powder.

4-(2-Oxo-oxazolidin-5-ylmethoxy)benzamide 6: LC MS purity 92% (C18 reverse–phase column (10×50 mm, 5 μm) with a linear gradient 10–100% MeOH in water (v/v) over 11 min, flow rate 6.0 ml/min), $t_R = 3.4$ min; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.34 (dd, 1H, $J = 6.6$, 9.1 Hz, CH_2NH), 3.62 (t, 1H, $J = 9.1$ Hz, CH_2NH), 4.16 (dd, 1H, $J = 5.9$, 11.0 Hz, CH_2OPh), 4.23 (dd, 1H, $J = 3.3$, 11.0 Hz, CH_2OPh), 4.92 (m, 1H, CH), 7.0 (d, 2H, $J = 8.9$ Hz, 2×Ar-H), 7.18 (s br, 2H, $CONH_2$), 7.59 (s, 1H, NH), 7.85 (d, 2H, $J = 8.9$ Hz, 2×Ar-H), ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.4, 68.7, 73.3, 113.9, 126.9, 129.3, 158.5, 160.4, 167.2. ESI MS: $m/z = 259.54$ $[M+Na]^+$.

12. **4-(3-Benzyl-2-oxo-oxazolidin-5-ylmethoxy)benzamide 7**: R = Bn: LC MS purity 95% (C18 reverse-phase column (10×50 mm, 5 μm) with a linear gradient 10–100% MeOH in water (v/v) over 11 min, flow rate 6.0 ml/min), $t_R = 6.5$ min; ^{1}H NMR (300 MHz, CD_3OD) δ: 3.47 (dd, 1H, $J = 6.0$, 9.2 Hz, CH_2N), 3.67 (t, 1H, $J = 9.2$ Hz, CH_2N), 4.12 (dd, 1H, $J = 11.1$, 4.1 Hz, OCH_2), 4.27 (dd, 1H, $J = 11.1$, 3.1 Hz, OCH_2), 4.36 (d, 1H, $J = 15.2$ Hz, NCH_2), 4.54 (d, 1H, $J = 15.2$ Hz, NCH_2), 4.92 (m, 1H, CH), 6.94 (d, 2H, $J = 8.9$ Hz, 2×Ar-H), 7.30–7.41 (m, 5H, 5×Ar-H), 7.83 (d, 2H, $J = 8.91$ Hz, 2×Ar-H). ^{13}C NMR (75 MHz, CD_3OD) δ: 46.7, 48.9, 69.7, 73.3, 115.4, 127.8, 130.7, 137.3, 160.2, 171.9. ESI-MS: $m/z = 349.13$ $[M+Na]^+$.
13. **4-(3-Benzyl-2-oxo-oxazolidin-5-ylmethoxy)-*N*-carbamoylmethylbenzamide 8**: $n = 0$; $R^1 = CH_2$, R^2 = Bn: LC MS purity 88% (C18 reverse-phase column (10×50 mm, 5 μm) with a linear gradient 10–100% MeOH in water (v/v) over 11 min, flow rate 6.0 ml/min), $t_R = 9.5$ min; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.60$ (d, 2H, $J = 5.1$ Hz, CH_2N), 3.77, 3.75 (d, 2H, $J = 5.4$ Hz, $COCH_2$), 4.24–4.08 (dd, 2H, $J = 11.1$, 3.3 Hz, OCH_2), 4.25 (s, 2H, $PhCH_2$) 4.92–4.89 (m, 1H, CH), 7.03, 7.00 (d, 2H, $J = 8.7$ Hz, 2×Ar-H), 7.10 (m, 5H, 5×Ar-H), 7.31 (bs, 2H, $CONH_2$), 7.85, 7.82 (d, 2H, $J = 8.7$ Hz, 2 Ar-H), ESI-MS: $m/z = 406.20$ $[M+Na]^+$.