Pergamon

Tetrahedron Letters 39 (1998) 1477–1480

TETRAHEDRON LETTERS

The Synthesis of 2-Imidazolidones on Solid Support by Tandem Aminoacylation / Michael Addition

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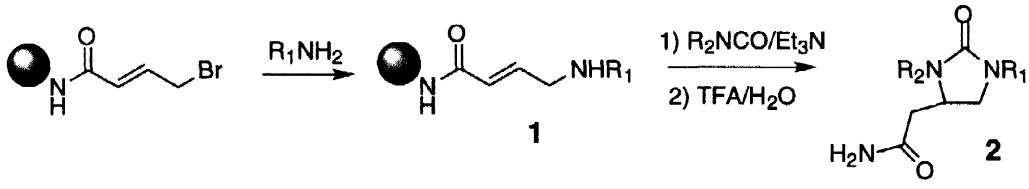
Received 14 October 1997; revised 11 November 1997; accepted 14 December 1997

Abstract. Reaction of isocyanates with unsaturated amines bound to a solid support can lead either to 2-imidazolidones or 2-iminooxazolidinones depending on conditions. The imidazolidones are a useful new framework for combinatorial library synthesis.

We have recently described the synthesis of 2-oxopiperazines on solid support via a tandem SN2 displacement/ Michael addition strategy.[1] This work led us to suppose that five membered ring 2-imidazolidones could be similarly constructed by reaction of a resin bound allylic amine with an isocyanate, followed by intramolecular Michael addition (Scheme 1). A literature search revealed one example of this type of reaction in solution.[2] The cyclic urea moiety provides structural rigidity as well as hydrogen bonding possibilities.[3] Variation of the resin bound amine and the isocyanate can provide large numbers of simple, diverse, low-molecular weight 2-imidazolidone carboxamides (or acids if desired) for biological assay. Furthermore the synthesis can easily include an extended peptoid side chain containing one or more tertiary amides.[4] Finally, the simple reactions involved can be readily done robotically. Six and seven membered ring cyclic ureas have recently gained attention as HIV protease inhibitors[5] and acylic ureas are incorporated in many pharmaceuticals .[6]

When resin bound amine **1** (R_1= iBu) was treated with 1M phenylisocyanate in DMF in the presence of 1M Et_3N at room temperature for 1h, followed by heating overnight at 55° C a single product (70% hplc pure) was produced.[7] 2-Imidazolidone **2** (R_1= iBu, R_2= Ph) gave the correct protonated parent ion (276.2) upon electrospray mass spectrometry. ^{1}H nmr shows a multiplet at 4.6 ppm for the ring methine, multiplets at 3.1 and 3.7 for the ring methylene protons, while the CH_2CONH_2 protons come as two dd at 2.4 and 2.6 ppm.

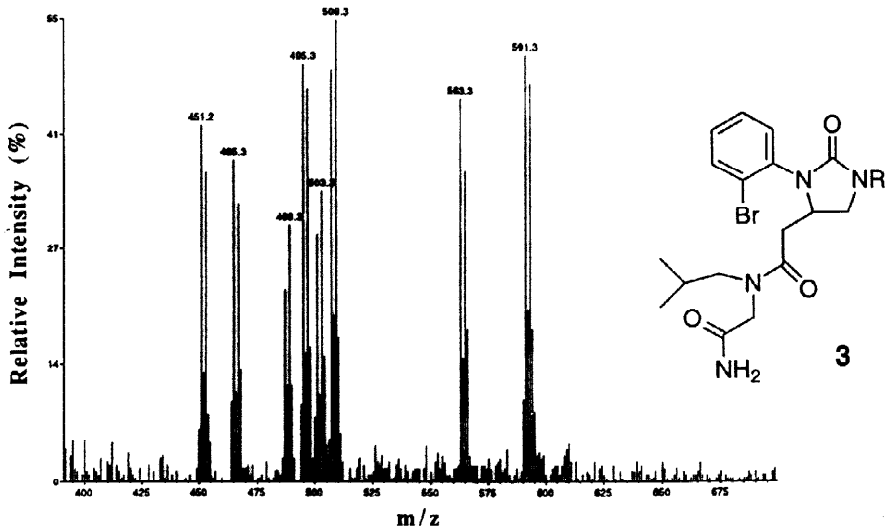
Scheme 1



0040-4039/98/$19.00
PII: S0040-4039(98)00009-4

Encouraged by this result we prepared a mixed amine resin consisting of an equimolar mixture of eight different amines at the terminal position. This mixed resin was then reacted with various isocyanates according to Scheme 1. Figure 1 shows the mass spectrum of the crude product from 2-bromophenylisocyanate. All of the expected products are present and the mass spectrum is clean.

Figure 1

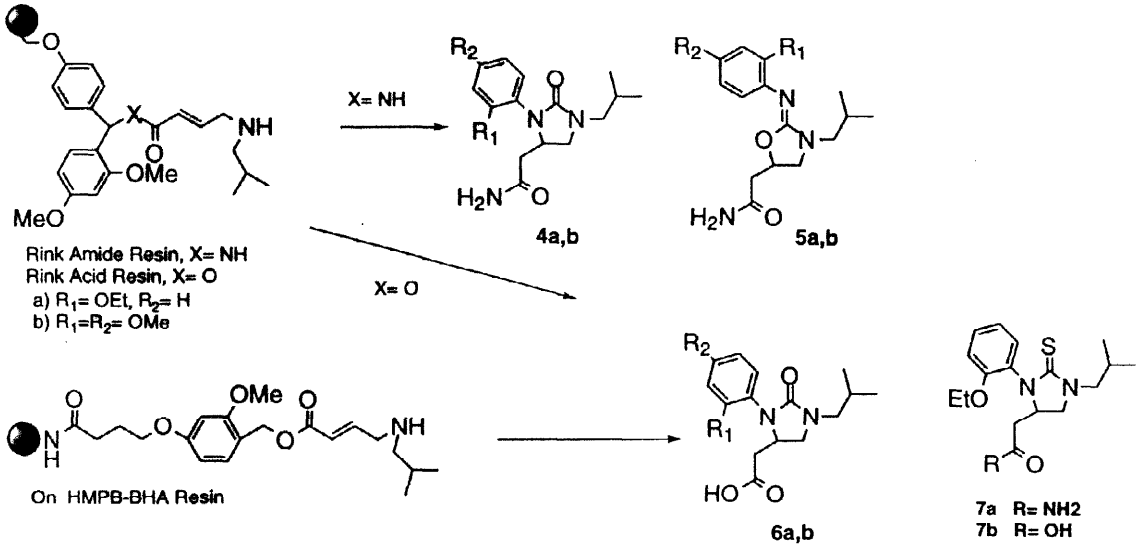


MW	R
450	allyl
464	cyclopropyl methyl
486	phenyl
494	n-hexyl
500	benzyl
506	cycloheptyl
562	4-biphenylyl
590	2,2-diphenylethyl

It appeared from this initial screening of isocyanates and amines that this synthesis could be useful for the production of combinatorial libraries of 2-imidazolidones. However, several of the isocyanates gave unexpectedly complex hplc patterns in which many of the peaks appeared to be doubled (confirmed by ms analysis of individually collected peaks) The ms profile of the crude mixtures in these cases was still, however, quite clean and no extraneous peaks were observed. This effect seemed limited to aliphatic isocyanates or phenyl isocyanates substituted at the ortho position with large groups.

To investigate this effect we carried out the reactions shown in Scheme 2. When the cyclization was carried out with 2-ethoxyphenyl isocyanate , two major peaks were observed in the hplc at 19.5 min (**5a**) and 20.5 min (**4a**) in a 1/1 ratio.[8] The two peaks gave identical electrospray mass spectra (MH^+= 320). Semipreparative hplc gave pure material sufficient for nmr. The main difference between the compounds lay in the chemical shift of the ring methine proton: 5.18 ppm for **5a** and 4.25 ppm for **4a**. [9] The most likely explanation for this dichotomy is N versus O cyclization. On the basis of the greater electronegativity of O, we propose that Fr.1 is the O- cyclized 2-iminooxazolidinone **5a**, while Fr. 2 is the desired N- cyclized 2-imidazolidone **4a**.

Scheme 2



We have also observed that the type of linkage to the polystyrene support can significantly affect the chemistry. When we performed the same cyclization using either ester linked HMPB-BHA resin or ester linked Rink resin we obtained a single 2-imidazolinone carboxylic acid **6a.**[10] (Scheme 2, bottom). The ring methine of **6a** comes at 4.25 ppm and the rest of the spectrum is almost identical to that of **4a**. Thus it would appear that O cyclized product is completely eliminated when the α,β- unsaturated ester replaces the α,β- unsaturated amide. A similar effect was observed with (2,4-dimethoxy)phenylisocyanate which gave **4b** and **5b** in a 1.2/1 ratio on Rink amide resin, while only a single product **6b** was obtained on HMPB-BHA resin or Rink acid resin.

These results suggest that the thermodynamic product of the cyclization is the imidazolidone . Apparently when certain bulky isocyanates are used with the amide linked resin, any O- cyclized oxazolidinone which is formed does not completely re-equilibrate to the N- cyclized imidazolidinone. It is possible that the Michael addition could be made freely reversible by changing the reaction conditions.[11] The intramolecular cyclization of a thiourea to an α,β- unsaturated ketone has been reported to be reversible, the kinetic product of cyclization on sulfur could be converted to the thermodynamically more stable cyclic thiourea.[12] Interestingly, when we reacted 2-(ethoxy)phenyisothiocyanate only a single product was observed either on Rink amide or Rink acid resin (Scheme 2). The ^{1}H nmr of **7a** and **7b** are very similar except for the appearance of the

CH_2COX side chain methylene. The ring methine proton comes at 4.4 ppm for both compounds, suggesting that they are N-cyclized thioureas.

In conclusion, a new solid-phase synthesis of 2-imidazolidones has been described which provides an interesting framework for combinatorial libraries using the diverse pools of amines and isocyanates. Isocyanates are a particularly attractive building block since they can be derived from amines which do not work well in SN 2 displacement reactions (anilines, aminoheterocycles) and thus effectively increase the pool of amines at our disposal.

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6) For some interesting recent examples: Forbes, I.T., Ham, P., Booth, D., Martin, R.T., Thompson, M., Baxter, G.S., Blackburn, T.P., Glen, A., Kennett, G.A., Wood, M.D., *J. Med. Chem.*, **1995**, *38*, 2524-2530. Lewis, R.T., Macleod, A.M., Merchant, K.J., Kelleher, F., Sanderson, I., Herbert, R.H., Cascieri, M.A., Sadowski, S., Ball, R.G., Hoogsteen, K., *J. Med. Chem.*, **1995**, *38*, 923-933.

7) Typical Experimental procedure: 100 mg of resin **1** (R_1= iBu, approx. 0.5 mMol/grn substituton) , prepared by the submonomer method as described in Ref. 1, was treated with a solution of phenylisocyanate (3 mMol) and Et_3N (3 mMol) in DMF (3 mMol) with mixing at room temperature for 1 h. The temperature was then increased to 55° C overnight. The resin was filtered off, washed with DMF and CH_2Cl_2 and the product cleaved from the Rink amide resin with 95/5 TFA/H_2O (20 min, room temperature). The resin was filtered off and washed with HOAc. The filtrate was diluted with H_2O and then lyophilized. Relyophilization twice from 1/1 HOAc/H_2O gave crude **2** (R_1= iBu, R_2= Ph) as a solid , 4.1 mg. Control experiments showed that both the added Et_3N and heating were required to get clean reaction.

8) C-18 RP HPLC, linear gradient 0-80% acetonitrile with H_2O containing 1 mL/L TFA in 40 min.

9) The proton connectivities for **4a** and **5a** were completely assigned by DQ-COSY experiments.

10) The Rink amide resin was obtained from Advanced ChemTech, Louisville, KY, while the HMPB-BHA resin was obtained from Novabiochem, San Diego, CA.

11) For example: a) Arunachalam, T., Fan, H., Pillai,, K.M.R., Ranganathan, R.S., *J. Org. Chem.*, **1995**, *60*, 4428-4438 b) Filippini, M.H., Faure, R., Rodriguez, J., *J. Org. Chem.*, **1995**, *60*, 6872-6882.

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