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SOLID PHASE SYNTHESIS OF 2,4,5-TRISUBSTITUTED THIOMORPHOLIN-3-ONES

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Abstract: The solid phase synthesis of 2,4,5-trisubstituted thiomorpholin-3-ones is described. Starting from a resin-bound protected cysteine, and employing reductive alkylation and amide formation, thiomorpholin-3-one derivatives have been synthesized through intramolecular thioether formation in good yield and high purity. © 1998 Elsevier Science Ltd. All rights reserved.

Many studies involving solid phase organic synthesis (SPOS) have been reported over the last five year.[1-3] This technique is a fundamental tool for the generation of organic compound libraries, as is solid phase peptide synthesis from which SPOS originates.[4] We report here the design and solid phase synthesis of thiomorpholin-3-one compounds derived from a resin-bound β-mercaptoalkylamine. Starting from p-methylbenzhydrylamine (MBHA) resin, N-α-Fmoc-S-trityl-L-cysteine is coupled in the presence of diisopropylcarbodiimide (DICI) and hydroxybenzotriazole (HOBt). Following cleavage of the trityl (Trt) group with 5% trifluoroacetic acid (TFA) in DCM in the presence of 5% of $(iBu)_3SiH$, the resin-bound Fmoc-cysteine **1** is treated with a range of different α-bromo, α-alkyl acetic acid derivatives in DMF in the presence of N-methylmorpholine (NMM). When bulky R_1 groups such as isopropyl or phenyl were present, poor purity was obtained for the final product (< 15% by HPLC) due to the difficulty of displacing the bromo group. However, excellent results were obtained with bromoacetic acid (R_1= H), 2-bromopropionic acid (R_1 = Me), and 2-bromovaleric acid (R_1 = Et). Following the removal of the Fmoc protecting group with 20% piperidine in DMF, reductive alkylation of the free amine occurred in the presence of an aldehyde and sodium cyanoborohydrate ($NaBH_3CN$). No racemization was observed when the resulting imine was reduced immediately upon formation.[5] The formation of thiomorpholin-3-one **4** occurred via intramolecular amidation using HATU as the coupling reagent (Scheme 1).[6]

In an attempt to overcome the steric problem related to the bulky α-alkyl substituted bromoacetic acid derivatives, we attempted the synthesis of the thiomorpholin-3-one derivatives **4** by first reductively alkylating the amino group, followed by the coupling of the α-bromo, α-alkyl acetic acid derivatives, and finally, the formation

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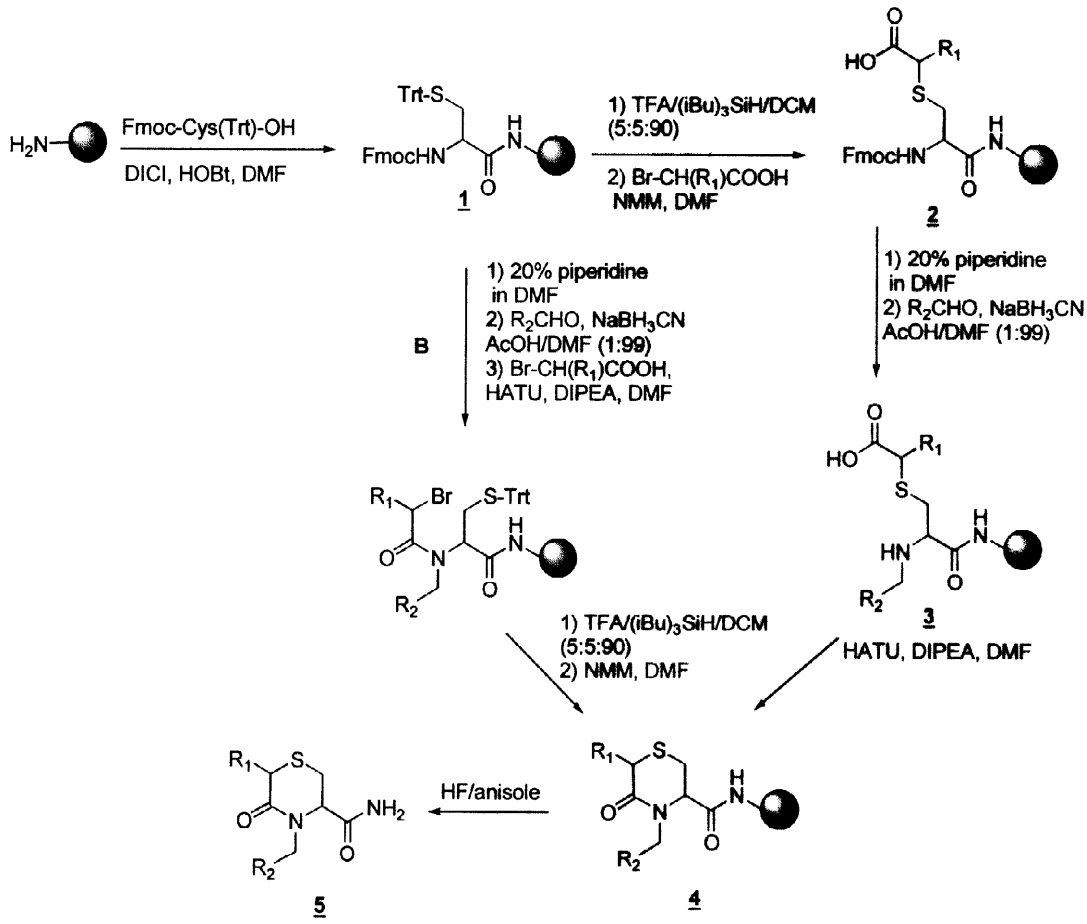
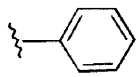
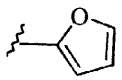
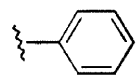
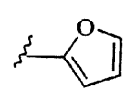
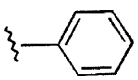
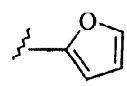
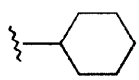
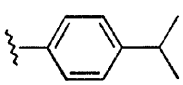
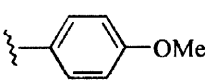
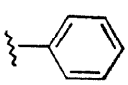


Scheme 1. Solid phase synthesis of 2,4,5-trisubstituted thiomorpholin-3-ones

of the thioether (method B). We expected that after trityl removal, the thermodynamically favorable intramolecular thioether formation would overcome the steric problems. Furthermore, we also encountered problems driving the coupling of the secondary amine with α-bromo, α-alkyl acetic acid derivatives to completion.

Limiting R_1 to Me, Et, H, and using a variety of aldehydes, we were able to carry out parallel syntheses of a number of individual thiomorpholin-3-ones **5** in good yield (Table 1).[7] All compounds prepared were characterized by LC-MS and ^{1}H-NMR. In Figure 1, we show the LC-MS spectra of the diastereomeric mixture of the thiomorpholin-3-one **5e** obtained from benzaldehyde and 2-bromovaleric acid, which is representative of

Table 1. Individual thiomorpholin-3-ones

Compound #	R_1	R_2	HPLC purity (%)
5a	H		92%
5b	H		90%
5c	Me		diastereomeric mixture (80%)
5d	Me		diastereomeric mixture (78%)
5e	Et		diastereomeric mixture (75%)
5f	Et		diastereomeric mixture (80%)
5g	H		>95%
5h	H		>95%
5i	H		>95%
5j			diastereomeric mixture (15%)

The products were run on a Vydac column, gradient 5 to 95% of 0.05% TFA in ACN in 7 min. The purity was estimated on analytical traces at λ=214 nm.

the purities obtained. This is an example of our ongoing efforts directed toward the solid phase synthesis of small molecule and heterocyclic compounds and the generation of combinatorial libraries of organic compounds using amino acids and peptides as starting materials.[8,9]

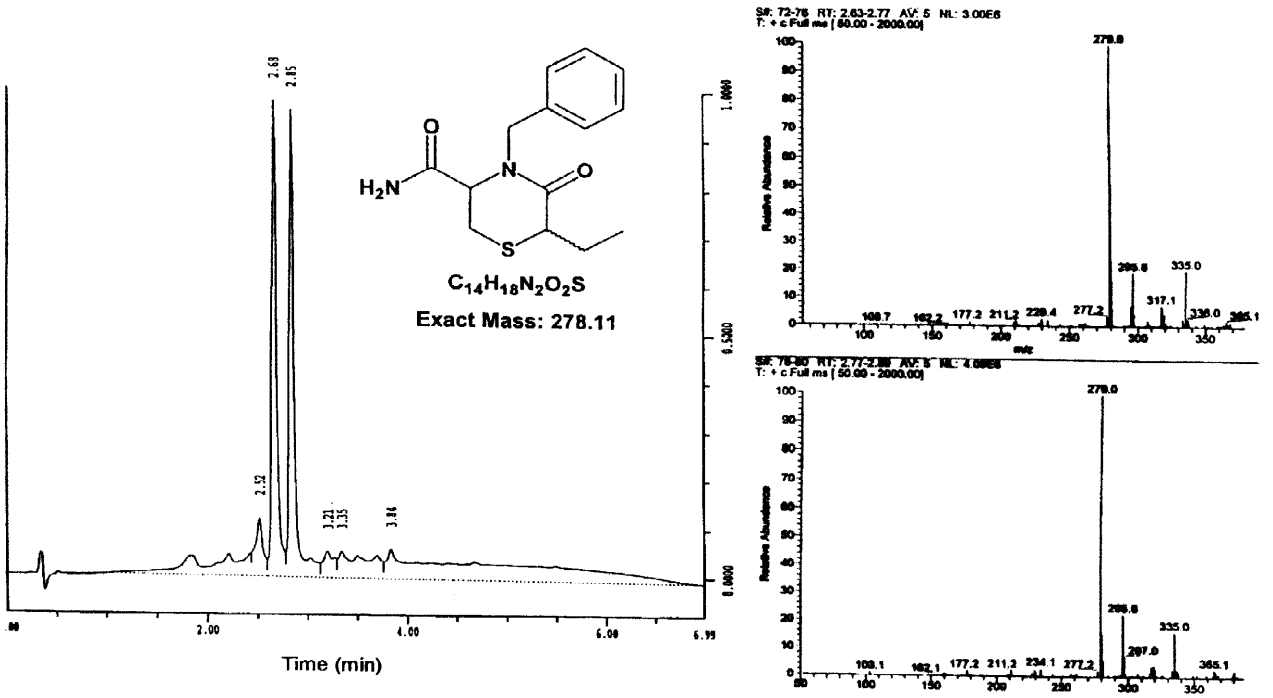


Figure 1. LC-MS of the diastereomeric mixture of the thiomorpholin-3-one **5e**.

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

1. Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, 97, 449.
2. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, 96, 555.
3. Fruchtel, J. S.; Jung, G. *Chem Rev.* **1996**, 35, 17.
4. Merrifield, R. B. *Science.* **1986**, 232, 341.
5. Ho, P. T.; Chang, D.; Zhong, J. W. X.; Musso, G. F. *Pep. Res.* **1993**, 6, 10.
6. Carpino, L. A.; El-Faham, A.; Minor, C. A.; Albericio, F. *J. Chem. Soc.; Chem. Commun.* **1994**, 201.
7. Typical procedure for the individual synthesis of thiomorpholin-3-one **5**: 100 mg p-methylbenzhydrylamine (MBHA) resin (0.81 meq/g, 100-200 mesh) was contained within a sealed polypropylene mesh packet. Reactions were carried out in a 10 ml polyethylene bottle. Following neutralization with 5% DIEA in DCM, the resin was washed with DCM. Fmoc-Cys(Trt)-OH was coupled using the conventional reagents HOBt and DICI. Following removal of the Trt group with TFA/$(iBu)_3SiH$/ DCM (5:5:90), the resin was treated overnight with 15-fold excess of α-bromo, α-alkyl carboxylic acid derivatives in DMF in the presence of NMM. Following the removal of Fmoc with 20% piperidine in DMF, benzaldehyde (5 eq, 0.07M) was added in 1% AcOH in DMF, followed immediately by the addition of $NaBH_3CN$ (5 eq). The mesh packet was shaken overnight in a solution of HATU (5eq) and DIPEA (5eq) in DMF. Following cleavage from the resin with anhydrous HF in the presence of anisole,[10] the desired product **5** was extracted, lyophilized and analyzed.
8. Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Tedrahedron Lett.* **1997**, 38, 4943.
9. Nefzi, A.; Ostresh, J. M.; Meyer, J-P.; Houghten, R. A. *Tedrahedron Lett.* **1997**, 38, 931.
10. Houghten, R. A.; Bray, M. K.; DeGraw, S. T.; Kirby, C. J. *Int. J. Pep. Prot. Res.* **1986**, 27, 673.