Pergamon

Tetrahedron Letters 41 (2000) 7145–7149

TETRAHEDRON LETTERS

Solid-phase synthesis of 1,3-diamino ketones

Chakrapani Subramanyam* and Shang-Poa Chang

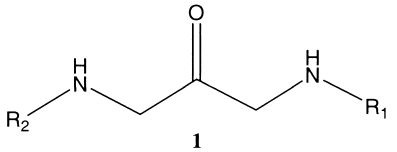
Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, USA

Received 21 July 2000; accepted 25 July 2000

Abstract

A versatile solid-phase methodology for the synthesis of 1,3-diamino ketone class of cysteine protease inhibitors is reported.

Cysteine proteases are ubiquitous in nature and have been implicated in the etiology of a number of disease states.[1] Over the past two decades identification of selective and reversible inhibitors for this class of enzymes has been an area of intense research.[2] These investigations have led to a number of reversible inhibitors such as peptidyl aldehydes, α-ketoamides and α-keto heterocycles.[3] Recently, researchers from SmithKline Beecham have reported the design and synthesis of a novel class of cysteine protease inhibitors based on a 1,3-diamino ketone (**1**) scaffold.[4]



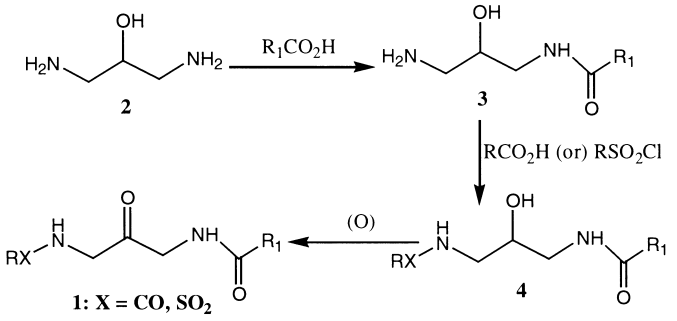
1

The synthesis of these compounds involved selective acylation of diamino propanol (**2**) with various carboxylic acids and amino acids and finally oxidation of the resulting alcohol to the corresponding ketone (Scheme 1).[4]

However, the need to chromatographically purify the acylated intermediates **3** and **4** at each stage would render such a methodology unsuitable for any effort aimed at the synthesis of libraries of 1,3-diamino ketones. Herein, we report a versatile methodology for the solid-phase synthesis of the title compounds.[5] Our approach relies on immobilization of a differentially protected diamino propanol **5** onto a polymer support. Simultaneous modification of the amino termini in **6**, followed by release from the solid support, would provide alcohol **7**, which upon oxidation would provide the title compounds **1** (Fig. 1).

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01262-4



Scheme 1.

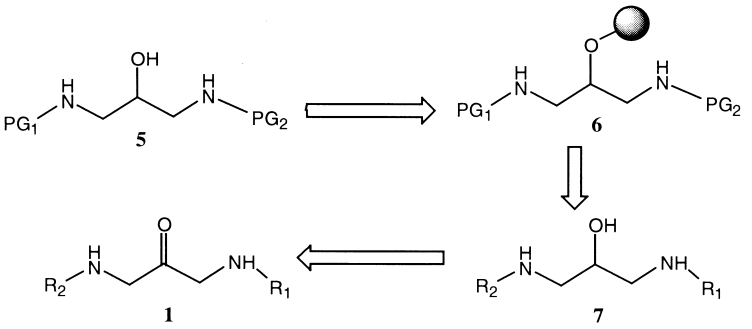
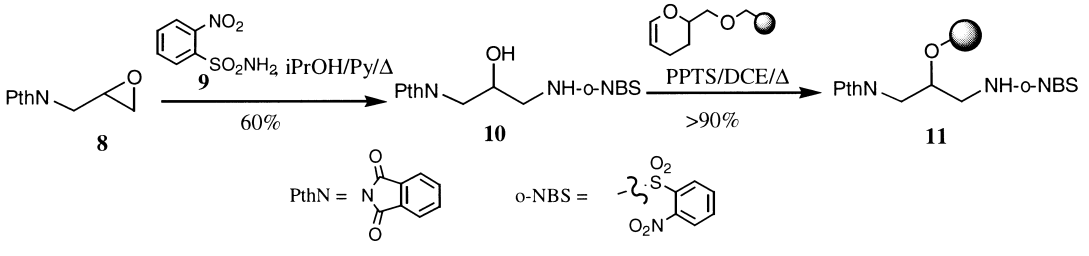


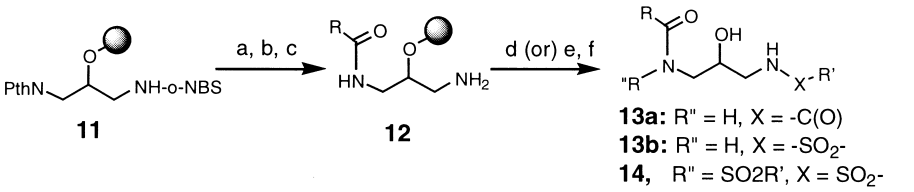
Figure 1.

The successful implimentation of this approach is shown in Schemes 2 and 3. Thus, treatment of commercially available epoxide **8** with sulfonamide **9**[6] in refluxing 2-propanol containing a catalytic amount of pyridine[7] provided alcohol **10** in excellent yield. Immobilization of **10** onto Ellman's THP linker[8] was achieved without incident to yield resin bound diamino propanol **11** in good yield.[9]

With **11** in hand, we turned our attention towards selective modification of either of the amino termini. Removal of the phthalimide protecting group provided the intermediate amine which was coupled with appropriate acids to give resin bound amides which, after treatment with mercaptoethanol/DBU, yielded the corresponding amines **12**. Reaction of **12** with either another carboxylic acid or a sulfonyl chloride followed by release from solid support (6:1 TFA:H_2O) yielded alcohols **13a**–**b**. Analysis of crude product by MS and NMR indicated that the product **13b** was contaminated by substantial amount of the bis-sulfonylated material **14**. This probably

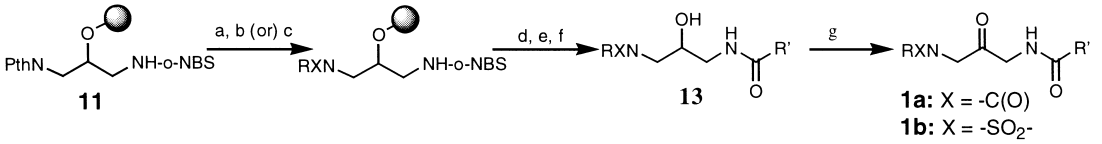


Scheme 2.



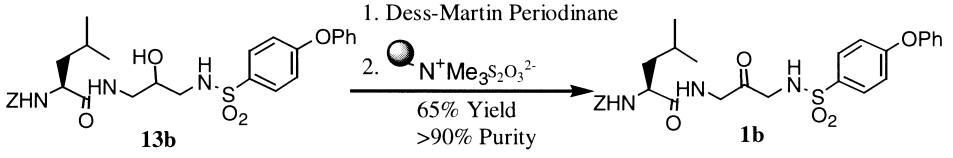
Scheme 3. (a) $N_2H_4{\cdot}xH_2O$/THF/DMF; (b) RCO_2H/DIC/HOB*t*/DMF; (c) β-mercaptoethanol/DBU/DMF; (d) $R''CO_2H$/DIC/HOBt/DMF; (e) $R'SO_2Cl$/DIEA/DCE; (f) 6:1 TFA/H_2O 70–75% overall yield

arises by sulfonylation not only of the amine functionality in **12** but also of the amide. The ratio of the desired product to the bis-sulfonylated material was also dependent on the nature of the acid used in the first coupling step. With more sterically hindered acids, the amount of **14** was reduced considerably. The undesired formation of **14** was easily overcome by reversing the order of amide and sulfonamide formation (Scheme 4), resulting in alcohols **13** in very good yield and high purity.[10] Finally, oxidation of **13** under the SKB protocol[4] provided the desired diamino ketones **1**.



Scheme 4. (a) $N_2H_4{\cdot}xH_2O$/THF/DMF; (b) RCO_2H/DIC/HOBt/DMF; (c) RSO_2Cl/DIEA/DCE; (d) β-mercaptoethanol/DBU/DMF; (e) $R'CO_2H$/DIC/HOBt/DMF; (f) 6:1 TFA/H_2O; (g) Jones' reagent, acetone

To help ease the purification of the final products, we also carried out oxidation of one of the alcohols (**13b**) with Dess–Martin periodinane. Scavenging of excess periodinane reagent with the recently disclosed thiosulfate resin[11] provided the target ketone **1b** in excellent yield and purity (Scheme 5).

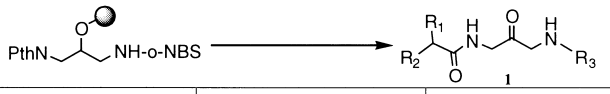


Scheme 5.

As shown in Table 1, a number of 1,3-diamino ketones **1** was synthesized via this SPS approach. In all instances, the product was obtained in good overall yield and purity.[12]

In summary, a versatile solid-phase methodology has been developed for synthesis of the 1,3-diamino ketone class of cysteine protease inhibitors. This method should allow simultaneous variation of functional groups at either end of the diamino ketone scaffold and should find wide spread use in synthesis of this class of protease inhibitor libraries.

Table 1



Compound[a]	R1 =	R2	R3	% Yield[b]
1a	H	4-BP	4-Ph-O-Ph-SO_2-	25
1b	i-Bu	Z-NH	4-Ph-O-Ph-SO_2-	30[c], 60[d]
1c	i-Bu	Z-NH	4-Ph-O-Ph-CO-	45
1d	CH_2Ph	Z-NH	4-Me-Ph-SO_2-	35
1e	CH_2Ph	Z-NH	4-tBu-Ph-SO_2	20

[a]Compounds 1a-c have been reported to be potent Cathepsin-K inhibiotrs by researchers at SmithKline and Beecham (SeeRef:4) [b]Yield is for purified material. [c]Used Jones reagent for oxidation. [d]Used periodinane/thiosulfate method for oxidation

Acknowledgements

The author would like to thank Dr. Christopher Poss for stimulating discussions and Drs. Mikel P. Moyer and Steven J. Brickner for encouragement and support.

References

1. Aoyagi, T.; Umezawa, H. In *Proteases and Biological Control*; Reich, E.; Rifkin, D. B.; Shaw, E., Eds.; Cold Spring Harbor Press: Cold Spring Harbor, 1975; pp. 429–454.
2. For a recent review on the synthesis of small molecule inhibitors of cysteine proteases, see: Rasnick, D. *Perspect. Drug Discovery Des.* **1996**, 647.
3. (a) Mehdi, S. *Biorg. Chem.* **1993**, *21*, 249. (b) Li, Z.; Patil, G. S.; Golubski, Z. E.; Hori, H.; Tehrani, K.; Foreman, J. E.; Evelth, D. D.; Bartus, R. T.; Powers, J. C. *J. Med. Chem.* **1993**, *36*, 3472. (c) Tao, M.; Bihovsky, R.; Kauer, J. C. *Biorg. Med. Chem. Lett.* **1996**, *6*, 3009.
4. Yamashita, D. S., et al. *J. Am. Chem. Soc.* **1997**, *119*, 11351. (b) LaLonde, J. M., et al. *J. Med. Chem.* **1998**, *41*, 4567.
5. While this work was in progress, an alternate method for solid-phase synthesis of 1,3-bis(acylamino)-2-butanones was reported by researchers from SmithKline Beecham Pharmaceuticals and the University of California, Berkley: Yamashita, D. S.; Dong, X.; Oh, H.-J.; Brook, C. S.; Tomaszek, T. A.; Szewczuk, L.; Tew, D. G.; Veber, D. F. *J. Comb. Chem.* **1999**, *1*, 207. Lee, A.; Huang, L.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 9907. Also, for an earlier work on the synthesis of diamino alcohol-based aspartic acid protease inhibitors, using a similar approach, see: Keck, E. K.; Ellman, J. A. *J. Med. Chem.* **1995**, *38*, 1427.
6. For use of *o*-nitrobenzene sulfonamide as a protecting group for amines, see: Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. Also for use of this protecting group in SPOS, see: Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301.
7. Baker, B. R.; Querry, M. V.; Kadish, A. F. *J. Org. Chem.* **1950**, 15
8. The polymer-bound THP linker was purchased from Nova Biochem and alcohol **10** was immobilized as described in: Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333.
9. The loading was determined to be >90% of theory by cleavage of an aliquot of **11** (6:1 TFA: H_2O) to provide alcohol **10**.
10. General procedure for the synthesis of **1**: To a suspension of 2.4 g of resin **11** (0.63 mmol/g, 1.5 mmol) in 3:1 DMF:THF (15 mL) was added hydrazine hydrate (10 mL). After shaking at rt for 16 h, the resin was collected by filtration, washed (DMF, THF, MeOH) and dried. To 0.4 g of the resulting resin (0.25 mmol based on 0.63 mmol/g

loading) in 2:1 DCE:DIEA (12 mL) was added 4-phenoxy benzenesulfonyl chloride (1.25 mmol, 5 equiv.). After stirring at rt overnight, the resin was collected by filtration, washed and dried. It was resuspended in NMP (2 mL) and DBU (5 mmol,) and β-mercaptoethanol (3 mmol, 12 equiv.) were added and gently stirred at rt for 20 h. The resin was filtered washed and dried. DMF (4 mL) was added followed by Z-Leu-OH (5 equiv.), HOBt (5 equiv.) and DIC (5 equiv.). The resulting mixture was shaken at rt for 20 h, filtered, washed and dried. To the resulting resin was added 6:1 TFA:H_2O (5 mL) and the reaction mixture was stirred for 15 min. The resin was filtered off and washed with CH_3CN (5 mL). The combined filtrates were combined and evaporated to dryness in vacuo. The residue was suspended in acetone (5 mL), Jones reagent (1.5 mL) was added and the mixture stirred at rt overnight. *i*-PrOH (1 mL) was added and the solids filtered off. The filtrate was concentrated in vacuo, dissolved in DCE (5 mL) and satd. $NaHCO_3$ (2 mL) was added. After shaking at rt for 10 min, the biphasic mixture was loaded onto a Chemelut® cartridge, allowed to stand for 5 min and eluted with DCE (10 mL). The combined eluents were concentrated in vacuo and the residue purified by preparative TLC (100% EtOAc) to give 0.04 g (30% of theory) of ketone **1b** as a white solid.

11. Parlow, J. J.; Case, B. L.; South, M. S. *Tetrahedron* **1999**, 6785.
12. All compounds were characterized by a combination of ^1H NMR, MS and the purity determined by a reverse phase HPLC.