ORGANIC LETTERS

2002
Vol. 4, No. 4
597−598

# A Solid-Phase Route to *N*-Cyanoamides

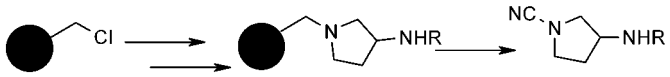
**Trevor Morgan, Nicholas C. Ray,* and David M. Parry**

*Celltech R&D Ltd., Granta Park, Great Abington, Cambridge CB1 6GS, U.K.*

*nick.ray@cam.celltechgroup.com*

**Received December 10, 2001**

## ABSTRACT




**A new method for the solid-phase synthesis of cyanamides is described. The attachment of a secondary amine to solid support is accomplished using Merrifield resin. After functionalization, cleavage is readily achieved with cyanogen bromide to afford the desired cyanamide.**

The cysteine proteinases are one of four major classes of proteinase enzymes[1] that selectively catalyze the hydrolysis of polypeptide bonds. They are involved in a variety of physiological processes such as apoptosis, inflammation, and cell signaling and migration. Inhibitors of such enzymes therefore have promising therapeutic application in the treatment of, for instance, tumor metastasis, myocardial infarction, inflammation, and bone disease. Most cysteine proteinase inhibitors contain electrophilic isosteres (the "warhead") that interact with the cysteine thiol group at the enzyme catalytic site, and a key feature in the development of inhibitors to this enzyme class has been the design of warheads that react selectively without the toxicity problems associated with alkylation/acylation of other functionalities. Nitrile groups are known to be suitable warheads with selectivity toward cysteine proteinases over other classes,[2] and recently workers at Merck have disclosed *N*-cyanamides (Figure 1) as inhibitors of the cysteine proteinases cathepsins

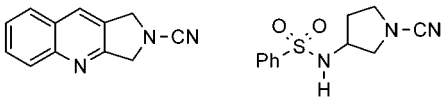



**Figure 1.** Merck cathepsin inhibitors.

K and L.[3] Herein we disclose our work toward the preparation of such compounds on the solid phase.

We hypothesized that secondary amines loaded onto suitable resins should be cleavable through quaternization with cyanide and loss of a benyzl group (from the linker) in one step (the von Braun reaction[4]). To test this methodology we prepared suitably substituted 1-cyano-3-aminopyrrolidines and 1-cyano-4-aminopiperidines as disclosed by the Merck workers.

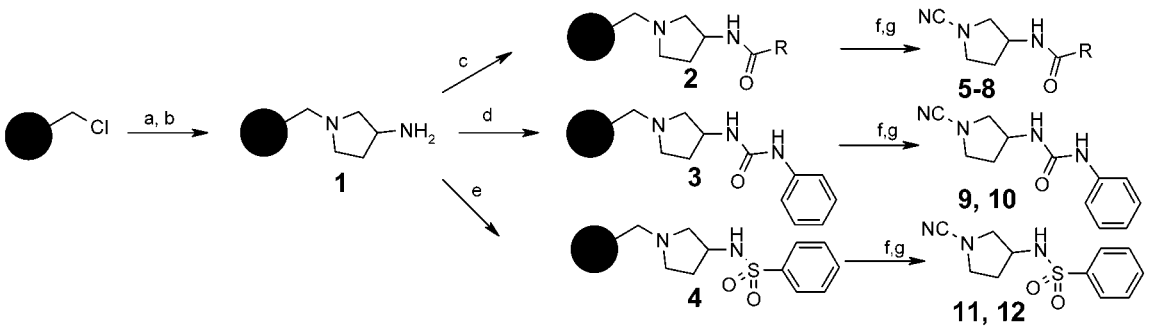
Thus Merrifield resin[5] was loaded with 3-(*tert*-butoxycarbonylamino)pyrrolidine (Scheme 1) in DMF with catalytic tetrabutylammonium iodide. Loading was judged qualitatively by IR (carbonyl stretch at 1650−1680 cm). Deprotection with 20% trifluoroacetic acid in dichloromethane followed by a triethylamine wash afforded compound **1** as the free base. Disappearance of the carbonyl stretch indicated complete deprotection of the primary amine. At this point the amino group was derivatized in a number of ways. Carboxylic acids were coupled using an HBTU protocol to afford compounds **2a**,**b**, while the urea was prepared through reaction with excess phenyl isocyanate to yield **3**. To prepare sulfonamide **4**, pyridine was chosen as the base rather than triethylamine or diisopropylethylamine, as the latter often led to the formation of significant amounts of the bis-sulfonamide. The chemistry was repeated using 4-(*tert*-butoxycarbonylamino)piperidine attached to the resin to give the appropriately functionalized aminopiperidines.

Cleavage from the resin was achieved with a slight excess of cyanogen bromide, the excess of which was then scavenged out from solution using polymer-supported trisamine

(1) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305−341.
(2) Hanzlik, R. P.; Zygmunt, J.; Moon, J. B. *Biochim. Biophys. Acta* **1990**, *1035*, 62−70.
(3) Falgueyrat, J.-P.; Oballa, R. M.; Okamoto, O.; Wesolowski, G.; Aubin, Y.; Rydzewski, R. M.; Prasit, P.; Riendau, D.; Rodan, S. B.; Percival, M. D. *J. Med. Chem.* **2001**, *44*, 94−104.
(4) For a review, see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.
(5) Merrifield resin from Novabiochem, loading 1.19 mmol/g.

10.1021/ol0172020 CCC: $22.00 
**Published on Web 01/29/2002**

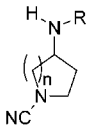
**Scheme 1**[a]




[a] Conditions: (a) 3-(*tert*-butoxycarbonylamino)pyrrolidine, 3 equiv; $Et_3N$, 3 equiv; $Bu_4NI$ (cat.), DMF, 80°, 16 h. (b) 20% TFA in $CH_2Cl_2$, 2 h. (c) $RCO_2H$, 3 equiv; HBTU, 3 equiv; DIPEA, 3 equiv; DMF, rt, 16 h. (d) PhNCO, 4 equiv; $CH_2Cl_2$, rt, 16 h. (e) $PhSO_2Cl$, 4 equiv; pyridine, 8 equiv; $CH_2Cl_2$, rt, 16 h. (f) BrCN, 1.5 equiv; $CH_2Cl_2$, rt, 2 h; (g) PS-trisamine, 3 equiv; $CH_2Cl_2$, rt, 1 h.

(PS-trisamine)[6] to afford compounds **5**−**12** after filtration and evaporation. The resulting compounds listed in Table 1 show the excellent purities and satisfactory yields obtained in most of the reactions.

**Table 1.** Cyanamide Yields and Purities




| | R | n | yield[b] (%) | purity[a] |
|---|---|---|---|---|
| **5** | Ph-C(O)- | 1 | 50 | 95 |
| **6** | 4-biphenyl-C(O)- | 1 | 40 | 95 |
| **7** | Ph-C(O)- | 2 | 48 | 95 |
| **8** | 4-biphenyl-C(O)- | 2 | 55 | 95 |
| **9** | PhNHC(O)- | 1 | 50 | 95 |
| **10** | PhNHC(O)- | 2 | 50 | 95 |
| **11** | $PhSO_2$- | 1 | 45 | 60 |
| **12** | $PhSO_2$- | 2 | 50 | 85 |

[a] Purities from diode array LC. [b] Yields are of the entire sequence based on theoretical loading of the Merrifield resin.

In conclusion, it has been demonstrated that cyanamides of generally excellent purity can be produced from this novel solid-phase method. The robustness of the Merrifield linker allows potential for the application of diverse chemistries without premature cleavage from the resin. We will report on the application of this methodology to our own library designs in due course.

**Acknowledgment.** The authors thank Steve Lloyd and members of the Analytical Chemistry department for LC−MS analysis.

**Supporting Information Available:** Full experimental data and LC−MS analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0172020

(6) Commercially available from Argonaut Technologies Inc.