ORGANIC LETTERS

2002
Vol. 4, No. 7
1167−1170

A New Resin-Bound Universal Isonitrile for the Ugi 4CC Reaction: Preparation and Applications to the Synthesis of 2,5-Diketopiperazines and 1,4-Benzodiazepine-2,5-diones

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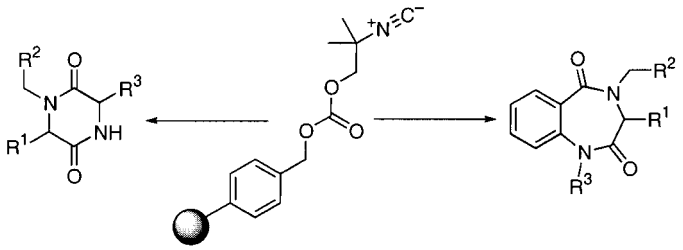
Received January 22, 2002

ABSTRACT



The preparation and synthetic applications of a novel resin-bound isonitrile are described. The resin is an example of a novel convertible isonitrile that can be utilized in the Ugi multicomponent reaction. Base-activation of the resin-bound Ugi product results in cleavage via formation of a *N*-acyloxazolidone that is then trapped as a carboxylic acid ester. This resin and the methodology described are suitable for synthesizing diversity libraries of 2,5-diketopiperazines and 1,4-benzodiazepine-2,5-diones.

Parallel synthesis is at the forefront of organic and medicinal chemistry and is playing an important role in many lead discovery and lead optimization programs in the pharmaceutical industry.[1] 2,5-Diketopiperazines and 1,4-benzodiazepine-2,5-diones are biologically interesting molecules that have been the targets of many lead generation libraries.[2] The multicomponent Ugi reaction[3] provides an attractive method to assemble a broad range of molecular fragments into dipeptide motifs suitable for cyclization into constrained 2,5-diketopiperazines and 1,4-benzodiazepine-2,5-dione targets.[4] However, there is a relatively low number of commercially available isonitriles, a component of the Ugi reaction, and they tend to be malodorous. In addition, the efficiency of Ugi reactions can vary greatly over a large and diverse set of inputs. Convertible isonitriles[5] have been used to remedy

(1) Leading reviews of applications in drug discovery: (a) Dolle, R. E. *Mol. Diversity* **1998**, *3*, 199. (b) Coffen, D. L.; Baldino, C. M.; Lange, M.; Tilton, R. F.; Tu, C. *Med. Chem. Res.* **1998**, *8*, 206. (c) Kerwin, J. F. *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M., Kerwin, J. F., Eds.; Wiley-Liss: New York, 1998; p 475. (d) Weber, L. *Drug Discovery Today* **1998**, *3*, 379. (e) Kubinyi, H. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 16. (f) Plunkett, M. J.; Ellman, J. A. *Sci. Am.* **1997**, *276*, 68.

(2) For biological activity and library generation of 2,5-diketopiperazines and 1,4-benzodiazepine-2,5-diones: (a) Funabashi, Y.; Horiguchi, T.; Iinuma, S.; Tanida, S.; Harada, S. *J. Antibiot.* **1994**, *47*, 1202. (b) Cui, C.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 534. (c) Cui, C.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651. (d) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935. (e) Hulme, C.; Cherrier, M. P. *Tetrahedron Lett.* **1999**, *40*, 5295. (f) Hulme, C.; Morrissette, M.; Volz, F.; Burns, C. *Tetrahedron Lett* **1998**, *39*, 1113.

(3) (a) Ugi, I.; Lohberger, S.; Karl, R. *Comprehensive Organic Synthesis*; Trost, B.M., Ed.; Pergamon Press: New York, 1991; Vol. 2, Part 2, Section 4.6, p 1083. (b) Ugi, I.; Demharter, A.; Horl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657.

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(5) (a) Keating, T.; Armstrong, R. *J. Am. Chem. Soc.* **1995**, *117*, 7842. (b) Keating, T.; Armstrong, R. *J. Am. Chem. Soc.* **1996**, *118*, 2574. (c) Linderman, R.; Binet, S.; Petrich, S. *J. Org. Chem.* **1999**, *64*, 336.

10.1021/ol0256015 CCC: $22.00
Published on Web 03/07/2002

the lack of readily available isonitrile inputs. Convertible isonitriles provide a method of transforming the secondary amide of the Ugi products into a carboxylic acid, ester, or thioester suitable for further elaboration. A resin-bound convertible isonitrile[6] appeared to be an ideal solution to the shortcomings. Our endeavors in this area are the subject of this report.

During our investigation of synthetic methods that would be applicable for making a 4000 member (2,5-diketopiperazine) library, we found that the known resin-bound convertible isonitriles, depicted in Figure 1, were expensive or labor

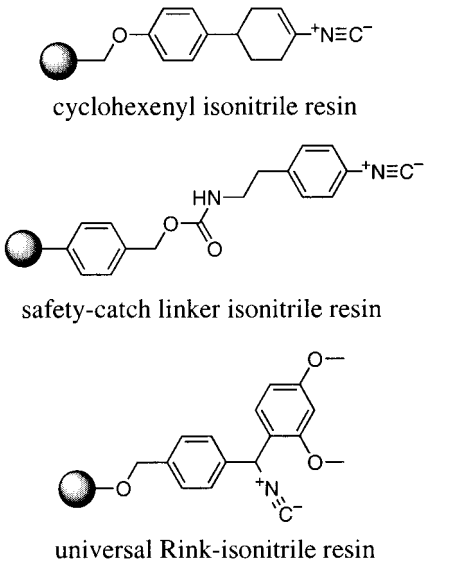
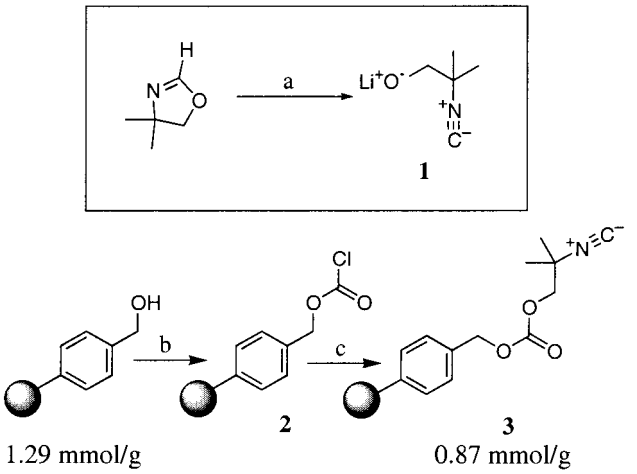


Figure 1. Universal isonitrile resins.

intensive to prepare on the scale required for a library of this size. Furthermore, the synthetic plan required the generation of an activated ester equivalent either during or after cleavage of the Ugi product to promote cyclization to the desired 2,5-diketopiperazine products. We developed a novel resin-bound carbonate convertible isonitrile (CCI resin) as an extension of a class of convertible isonitriles reported by Ugi et al.[7]

The CCI resin was synthesized in two steps (Scheme 1). Resin-bound chloroformate **2** was generated by treating hydroxymethyl polystyrene resin twice with a 20% phosgene/toluene solution and washing extensively. Simultaneously, lithium alkoxide **1** was generated and transferred via cannula into the freshly prepared resin **2** suspended in THF at 0 °C to afford resin-bound isonitrile **3**. The resin is stable at room

Scheme 1[a]



[a] Reagents and conditions: (a) 4,4-dimethyl-2-oxazoline, ^{n}BuLi, THF, −78 °C, 1 h; (b) 2 × 20% phosgene/toluene, toluene, rt, 30 min; (c) **1**, THF, 0 °C, 5 min.

temperature, and the process has been executed reproducibly on 200 g scale to provide resin **3** with a loading of 0.87 mmol/g.[8]

It was envisioned that α-aminoacylamides such as **4** (Scheme 2) could be built up on this resin and then cleaved with base to generate the *N*-acyloxazolidone **5**. Indeed, resin **3** acts as an efficient isonitrile in solid-phase multicomponent condensations with a wide variety of amines, acids, and aldehydes to generate the desired Ugi products **4** (vida infra).

As shown in Scheme 2, our initial plan entailed base-induced generation of the *N*-acyloxazolidone **5,** which would then be trapped by the resulting resin alkoxide **6** to afford the resin-bound ester **7**.[9] This would allow one to wash away the 4,4-dimethyloxazolidone and convert ester **7** to the product **8** cleanly in a subsequent cyclative cleavage. Utilizing KO^{t}Bu, this approach was unsuccessful, affording none of the desired diketopiperazine **8**. However, a trace amount of intermediate **5** was obtained, presumably, left behind from insufficient washing of the resin. This lead us to believe that the multicomponent condensation had been successful and that KOtBu had induced the generation of *N*-acyloxazolidone, **5**. However, the resulting resin alkoxide **6** was not a sufficient nucleophile for formation of **7** from **5**.

However, treatment of **4** with NaOMe gave a low yield of **8**, but afforded the amide **9** as a major component (50% by HPLC/UV/MS analysis), apparently arising from direct hydrolysis of the carbonate. This again indicated that the multicomponent condensation was proceeding well. The challenge remained to induce formation of *N*-acyloxazolidone **5** followed by trapping with a more efficient nucleophile than resin **6**. A two-step, one pot procedure was developed where

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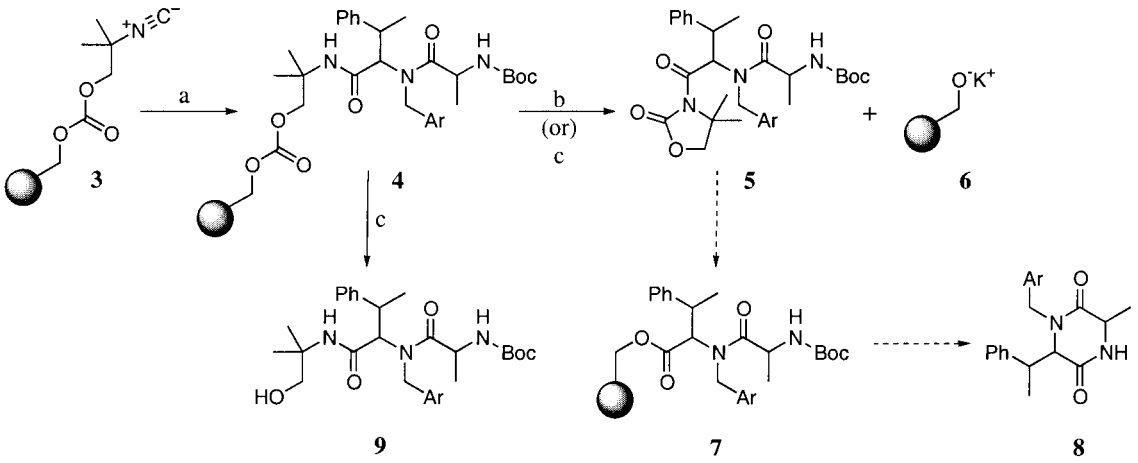
(7) Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, *55*, 7411.

(8) Loading determined by combustion analysis of % nitrogen.

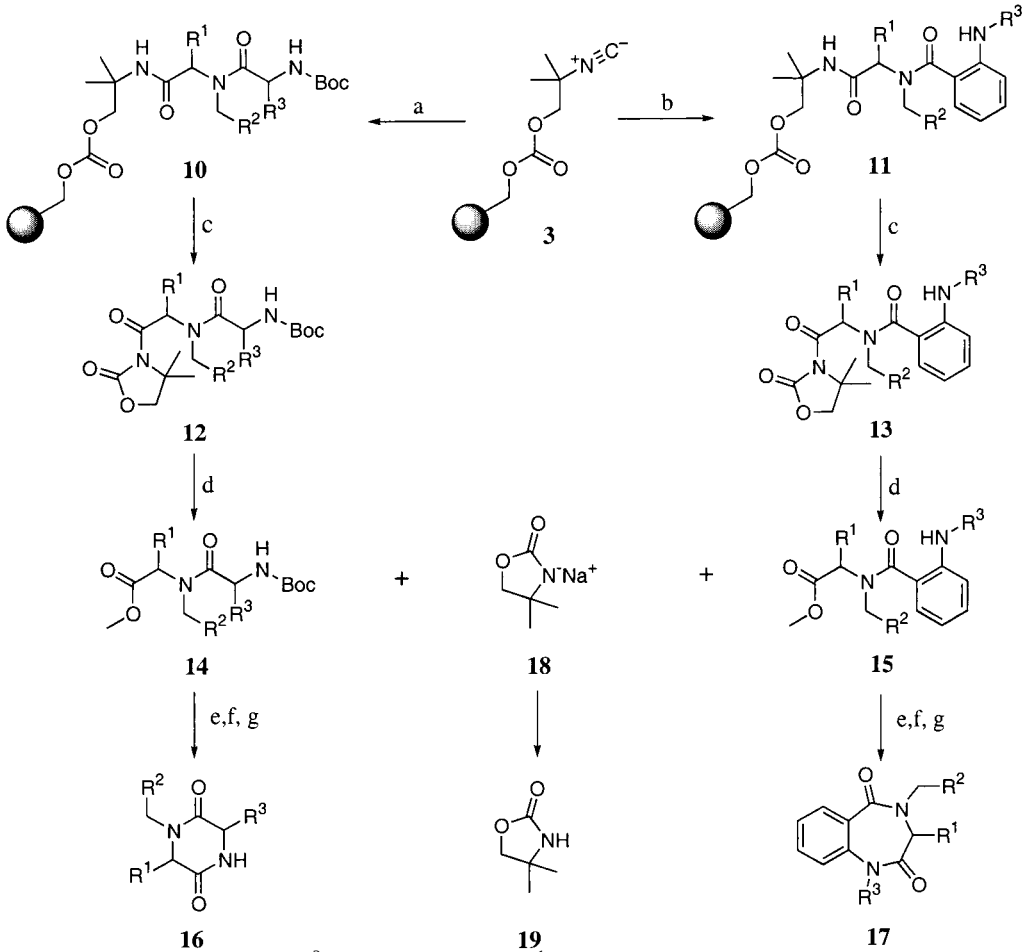
(9) For an example of successful application of this capture technique as applied to the Curtius rearrangement, see: Sunami, S.; Sagara, T.; Ohkubo, M.; Morishima, H. *Tetrahedron Lett.* **1999**, *40*, 1721−1724.

Scheme 2[a]



[a] Reagents and conditions. (a) **3** (110 μmol), 2-chlorobenzylamine (10 equiv), 2-phenylpropionaldehyde (10 equiv), Boc-D,L-alanine (10 equiv), trimethylorthoformate, trifluoroethanol, CH_2Cl_2, rt, 3 days; (b) KO^{t}Bu, THF, rt, 16 h; (c) NaOMe, THF, rt, 16 h.

Scheme 3[a]



[a] Reagents and conditions. (a) **3** (110 μmol), $R^2CH_2NH_2$ (10 equiv), R^1CHO (10 equiv), Boc-D,L-amino acids (10 equiv), trifluoroethanol, 4 Å mol sieves, CH_2Cl_2, rt, 3 days; (b) same as (a) except *N*-R^3-anthranilic acids (10 equiv) used and THF instead of CH_2Cl_2; (c) KO^{t}Bu (2 equiv, 1 M solution in THF), THF, rt, 16 h; (d) NaOMe (1.2 equiv, 0.65 M solution in MeOH), THF, rt, 48 h; (e) 70/30 hexafluoroisopropanol, TFA, rt, 48 h; (f) Silicycle TMA-Carbonate, THF, 6 h; (g) Silicycle Isocyanate-3, THF, 16 h.

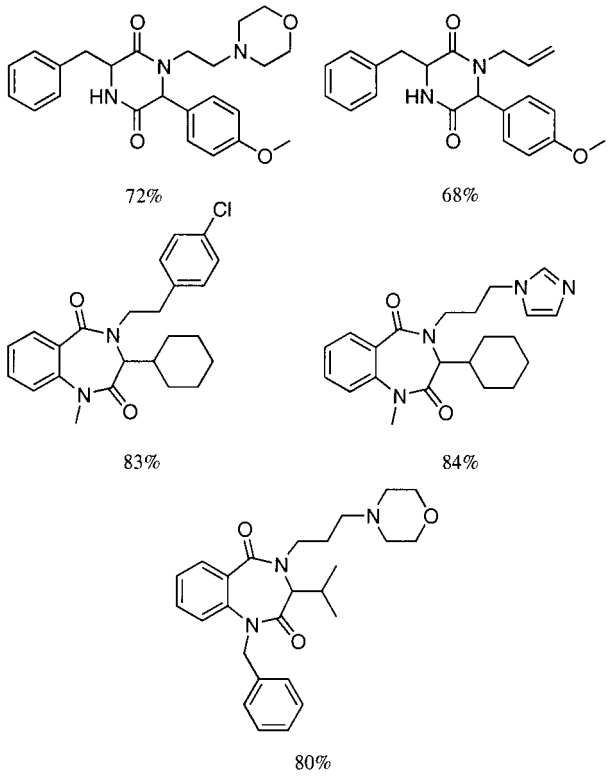


Figure 2. Representative 2,5-diketopiperazines and 1,4-benzodiazepine-2,5-diones (% purity by HPLC/UV 220 nm).

resin **4** was first treated with KO^{t}Bu to induce formation of **5**, which was then converted to the methyl ester by treatment with NaOMe (Scheme 3).

Following the sequence shown in Scheme 3, we were able to synthesize 2,5-diketopiperazine and 1,4-benzodiazepine-2,5-dione libraries in parallel 80-well format. The sequence included Ugi reaction, cleavage to the methyl esters, post-cleavage cyclization, and the application of silica-based scavengers[10] to remove impurities.[11,12] The Ugi products **10** and **11** were cleaved from the carbonate resin with KO^{t}Bu forming the *N*-acyloxazolidone intermediates **12** and **13**. Subsequent treatment with NaOMe gave the esters **14** and **15**, which were ultimately cyclized to the desired products **16** and **17** under acidic conditions. Some representative products and their identity/purity as judged by HPLC/UV/MS data are shown in Figure 2. For a 2,5-diketopiperazine plate where 80 compounds were made in parallel format the average mass recovery was 83%. Alternatively, a 1,4-benzodiazepine-2,5-dione plate where 80 compounds were made in parallel format had an average mass recovery of 95%.

In conclusion, a novel CCI resin has been made cost-effectively in three steps on a 200 g scale. It has been used to synthesize diversity libraries of 2,5-diketopiperazines and 1,4-benzodiazepine-2,5-diones using the Ugi multicomponent reaction in good purities and yields. Base-activation of the resin bound multicomponent reaction product cleaves the product to form an *N*-acyloxazolidone intermediate that can be further elaborated.

Supporting Information Available: Detailed experimental procedures for resin **3**. Detailed experimental procedures for the preparation of diketopiperazines and benzodiazepinediones via resin **3**, including spectral data. General procedure for preparation of diketopiperazines and benzodiazepinediones in parallel format, 80 compounds at a time. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgment. The authors would like to thank Kevin Litwiler, Christy Abbas-Hawks, and Rob Rieger for analytical assistance; also, thanks to Peter Stengel and Gregory Miknis for scientific discussions.

OL0256015

(10) Silicycle's TMA-Carbonate and Isocyanate-3 were used to free base amine and scavenge uncyclized product, respectively.

(11) Some of the open chain products analogous to **9** were formed but easily removed after TFA treatment by scavenging the resulting amine byproduct.

(12) **19** bp = 152−154 °C at 10 Torr was removed during evaporation of solvent.