Molecular Diversity via a Convertible Isocyanide in the Ugi Four-Component Condensation

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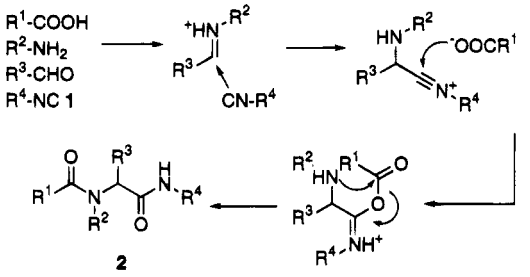
Large chemical libraries represent a new way of thinking about both targeted drug design and the search for new lead compounds.[1] Traditionally, combinatorial synthesis has exploited methodologies that are well adapted to the twin aims of automated synthesis and diversity of library inputs, such as automated peptide[2] and nucleic acid[3] synthesis, although substantial recent progress has been made in the area of small organic molecules.[4,5]

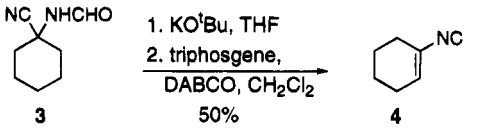
Multiple component condensation (MCC) reactions are an excellent tool for the generation of chemical libraries.[6] In particular, the Ugi reaction[7] (eq 1), which generates an α-acylaminoamide (**2**) in a one-pot, four-component condensation (4CC), is well suited for the construction of arrays of compounds based on a common core and displaying varied functionality.



(1)

However, perusal of commercially available inputs for these reactions reveals about two dozen isocyanides **1**. Thus the diversity of products from these reactions is restricted by isocyanide availability. Methodology for isocyanide synthesis is well developed but involves at least two steps from an amine. Moreover, isocyanides are nontrivial to work with, due to their reactivity, toxicity, and odor. We therefore set out to develop a single, "universal" isocyanide that could be converted, after a 4CC reaction, to a wide variety of functionalities in simple one- or two-step procedures.[8] This would free condensation product **2** from the restraints of the isocyanide input R^4. We present here our results and procedures for converting α-acylaminoamides (**2**) produced from a convertible isocyanide into esters, thioesters, acids, and primary amides. Our route to a convertible isocyanide uses 1-isocyanocyclohexene (**4**). Ugi has

Scheme 1



(2)

synthesized 1-isocyanocyclohexene and demonstrated its use in the 4CC and subsequent hydrolysis to the primary amide.[9,10] Synthesis of **4**[11] proceeded according to the procedure of Ugi[9] from cyclohexanone, except that it was found that elimination and dehydration of formamide **3** gave better yields when performed as separate steps and that triphosgene[12] as a dehydrating agent was superior to the phosphorus oxychloride called for by Ugi (Scheme 1). **4** was found to be stable for at least 2 months at −30 °C under argon; its immediate precursor, 1-formamidocyclohexene, is a stable white crystalline solid.

Shown in Table 1 are the results of several 4CCs using **4** and a variety of other inputs. (In general, the carboxylic acid [1.25 equiv], amine [1.25 equiv], and aldehyde [1.0 equiv] were dissolved in methanol to 1 M in each. This solution was stirred for 10 min and then added in one portion to a flask containing the isocyanide [1.0 equiv]. The resulting solution was stirred at room temperature for 12 h, and the product was purified by chromatography.) After isolation and characterization, the products were subjected to the acidic conditions detailed in the table footnote. The results of these conversions are also tabulated in Table 1.

In earlier work by Ugi, hydrolysis of *N*-(1-cyclohexenyl)-1-(*N'*-benzylformamido)cyclohexanecarboxamide in 1.7% HCl/THF yielded only the expected[13] primary amide, presumably through an *N*-acyliminium intermediate. Remarkably, when cyclohexenamides **5** and **6** were subjected to the same reaction conditions, we obtained carboxylic acids **8** and **9**. Products **10**−**12** and **14** demonstrate alcoholysis of the 4CC product to a variety of esters. Product **13** illustrates conversion to a thioester. No primary amide products were observed in any of these examples. A possible mechanism for hydrolysis is presented in Scheme 2. Protonation of **5** or **6** provides the *N*-acyliminium species **20** and **21**, which can cyclize and eliminate to give the münchnones[14] **22** and **23**, which are typically generated from tertiary *N*-acylamino acids in the presence of acetic anhydride.[15] The acid and ester products can arise from subsequent ring opening by water and alcohol, respectively.

Little success in esterification was achieved with less nucleophilic alcohol substrates: phenol, 2,4,5-trichlorophenol, and 1-hydroxybenzotriazole all failed to give the desired ester product. Apparently, the alcohol must be sufficiently nucleophilic to accomplish esterification. However, these activated esters can be made in one step from the acid.

Direct transformation to new amide products has not been accomplished under the acidic conditions described. However, access to the acids and esters obviates this need, since both

(1) For background material, see: (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1251. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385−1401.

(2) For a review of methods, see: Jung, G.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 367−383.

(3) (a) Latham, J. A.; Johnson, R.; Toole, J. J. *Nucleic Acids Res.* **1994**, *22*, 2817−2822. (b) Chen, H.; Gold, L. *Biochemistry* **1994**, *33*, 8746−8756.

(4) (a) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171−11172. (b) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4708−4712. (c) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997−10998.

(5) (a) Chen, C.; Ahlberg Randall, L. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661−2662. (b) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909−6913.

(6) Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115−123.

(7) For a review, see: Gokel, G.; Lüdke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; pp 145−199.

(8) For a previous attempt, see: (a) Geller, J.; Ugi, I. *Chem. Scr.* **1983**, *22*, 85−89. (b) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810−819.

(9) Rosendahl, F. K.; Ugi, I. *Ann. Chem.* **1963**, *666*, 65−67.

(10) The cleavage of a cyclohexenamide to a methyl ester has been previously observed: Fukuyama, T. Presented at the 35th Annual Buffalo Medicinal Chemistry Symposium, Buffalo, NY, May 1994.

(11) For other syntheses, see: (a) Barton, D. H. R.; Bowles, T.; Husinec, S.; Forbes, J. E.; Llobera, A.; Porter, A. E. A.; Zard, S. Z. *Tetrahedron Lett.* **1988**, *29*, 3343−3346. (b) Baldwin, J. E.; Yamaguchi, Y. *Tetrahedron Lett.* **1989**, *30*, 3335−3338.

(12) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894−895.

(13) Brossi, A.; Dolan, L. A.; Teitel, S. *Organic Syntheses*; Wiley: New York, 1988; Collective Volume VI, pp 1−4.

(14) (a) Coppola, B. P.; Noe, M. C.; Schwartz, D. J.; Il Abdon, R. L.; Trost, B. M. *Tetrahedron* **1994**, *50*, 93−116. (b) Dalla Croce, P.; La Rosa, C. *Heterocycles* **1988**, *27*, 2825−2832. (c) Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. *J. Org. Chem.* **1982**, *47*, 786−791.

(15) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefer, F. C. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 136−137.

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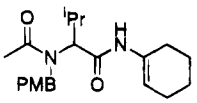
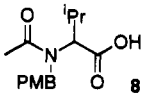
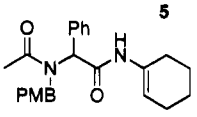
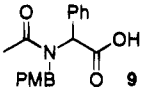
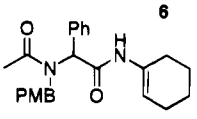
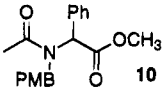
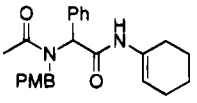
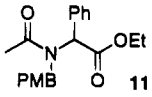
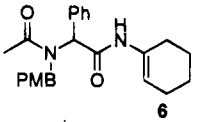
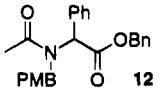
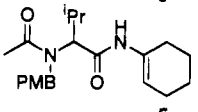
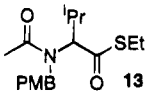
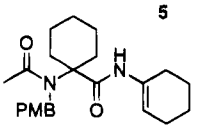
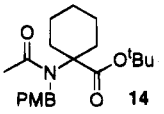
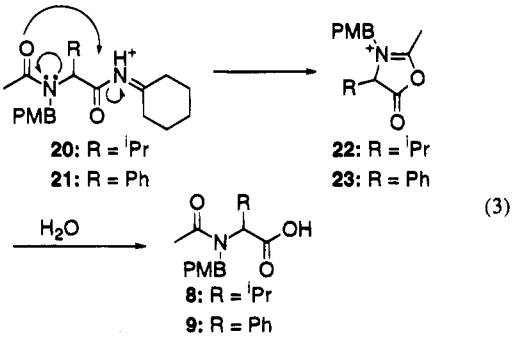
Table 1. Results of Four-Component Condensations and Subsequent Cleavage of Cyclohexenamides

Condensation Product[a]	Nu:	Cond.[b]/ Yield[c]	Product
 **5**	H_2O	A/56%	 **8**
 **6**	H_2O	A/83%	 **9**
 **6**	MeOH	B/100%	 **10**
 **6**	EtOH	B/57%	 **11**
 **6**	BnOH	C/75%	 **12**
 **5**	EtSH	D/68%	 **13**
 **7**	^{t}BuOH	E/64%	 **14**

[a] PMB, *p*-methoxybenzyl. [b] Reaction conditions: (A) 1.7% HCl in THF, room temperature, overnight; (B) indicated alcohol as solvent, 5 equiv of AcCl, 55 °C, 3 h; (C) 5 equiv of AcCl, 10 equiv of BnOH in THF, 55 °C, 3 h; (D) EtSH as solvent, 10 equiv of AcCl, room temperature, overnight; (E) 5 equiv of AcCl, 10 equiv of ^{t}BuOH in THF, 55 °C, 48 h. [c] All yields are for isolated, purified product.

Scheme 2



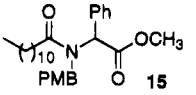
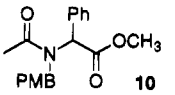
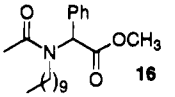
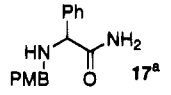
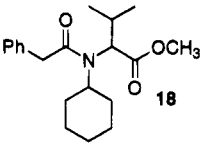
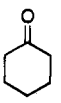
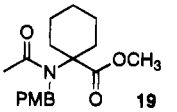
(3)

functional groups can be easily transformed into any amide by standard DCC coupling methods (acid) or aluminum amidation (methyl esters).[16] Finally, extension of Ugi products as a variety of esters represents a compound class not available from the standard 4CC.

Table 2 details the results of one-pot conversions of Ugi reaction products to methyl esters. The 4CCs were carried out as before in methanol at room temperature. After the reactions were monitored by thin-layer chromatography (TLC) and judged complete, 10 equiv of acetyl chloride was introduced into the methanolic solution as a means of generating HCl anhydrously,

(16) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171–4174.

Table 2. Results of *in Situ* Acidic Methanolyses of Four-Component Condensation Products

R^1COOH	R^2NH_2	R^3CHO	Product	Isol. Yld.
1-undecyl-	PMB-	Ph-	 **15**	65%
CH_3-	PMB-	Ph-	 **10**	79%
CH_3-	1-decyl	Ph-	 **16**	99%
H-	PMB-	Ph-	 **17**[a]	45%
$PhCH_2$-	C_6H_{11}-	^{i}Pr-	 **18**	67%
CH_3-	PMB-		 **19**	55%

[a] We believe isolation of **17** results from rapid cleavage of the *N*-formyl group and the resulting inability to form an intermediate of type **22**. Hydrolysis of the *N*-acyliminium group by adventitious water or during workup follows.[17]

and the reaction warmed to 55 °C for 3 h. Methyl ester was the only isolable product after workup (see Table 2 footnote and ref 17 regarding **17**), thus representing an extension of the Ugi reaction to a "four plus one"-component condensation, the cyclohexenamide functionality having been switched *in situ* to a methyl ester. *The structural contribution of the isocyanide component has thus been reduced to a single carbon atom.*

We have presented here studies on freeing the Ugi 4CC from the restraints of its isocyanide input by developing a convertible isocyanide that can give rise to a variety of functional groups rapidly and simply. We believe that these new functionalities remarkably extend both the usefulness of the Ugi reaction and its potential for generating arrays of diverse compounds. The scope of further transformations of this type is being investigated, and the results will be reported in due course.

Acknowledgment. This work was supported in part by a graduate fellowship from the Office of Naval Research (T.A.K.) and a gift from Ontogen Corp., Carlsbad, CA.

Supporting Information Available: Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **5**–**19**, as well as lists of IR absorbances and results of mass spectrometric analysis (36 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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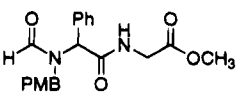
(17) We have also found that acidic methanolysis conditions as detailed in the footnote to Table 1 rapidly deformylated **24** (30 min). In addition, isolation of the 4CC precursor of **17** and treatment with acidic methanolysis conditions as per Table 1 led to **17**.

 **24**