Pergamon

Tetrahedron Letters, Vol. 37, No. 8, pp. 1149-1152, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00012-3

Use of a Convertible Isocyanide for Generation of Ugi Reaction Derivatives on Solid Support: Synthesis of α-Acylaminoesters and Pyrroles

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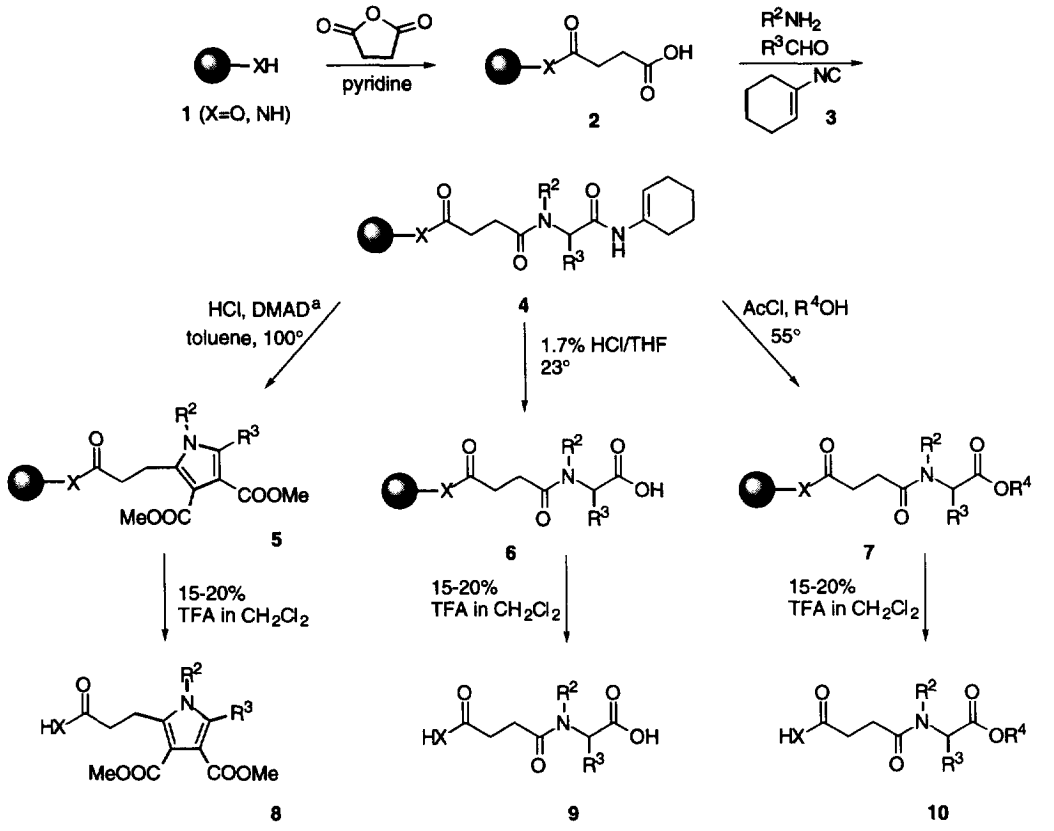
Abstract: The Ugi four component condensation employing 1-isocyanocyclohexene as a convertible isocyanide has been adapted to solid supported synthesis. Using Wang or Rink resin and a linker derived from succinic anhydride, Ugi reactions proceeded smoothly. The products were then converted under acidic alcohol conditions to esters, acids, and to pyrroles via 1,3-dipolar cycloadditions to an acetylene. The intermediate in both transformations is a 1,3-oxazolinium-5-one arising from cycloelimination of the cyclohexenamide from the Ugi product.

Multiple component condensations (MCCs), reactions in which three or more reactants combine in a single reaction event to yield a product displaying features of all inputs, can be a very powerful tool for the generation of combinatorial compound libraries.[1-3] The size of any potential library is inherently limited in two different aspects, the first limitation being the number of available inputs, and the second being the labor and/or time required to execute the synthesis. A multiple component condensation such as the Ugi four component condensation[4] (4CC) is certainly superior to a linear synthesis of the same core structure α-acylaminoamide in terms of required synthetic time and effort, and three of the four components are readily available — a carboxylic acid, an amine, and an aldehyde or ketone. However, the lack of commercially available isocyanides for use as inputs has inspired us to develop a "universal isocyanide" that can be converted, post-condensation, to a variety of new functionalities.[5-7] Such an isocyanide input would free the Ugi reaction from its most serious constraint.

We present here our results on the synthesis of Ugi products employing 1-isocyanocyclohexene as a convertible isocyanide on solid support and subsequent conversions to esters and to pyrroles, both classes of compounds heretofore inaccessible from Ugi 4CC products. We have previously demonstrated solid supported library synthesis of Ugi 4CC products,[8] as well as the conversion of Ugi products to esters and pyrroles in solution.[6] Our corresponding solid supported strategy is shown in Scheme 1.

Succinic anhydride was reacted with either Rink[9] or Wang[10] resin (**1**, X = O or NH) in pyridine to provide a spacer[11] and a free carboxylic acid as the 4CC input. After washing the resin with a 1M acetic acid in CH_2Cl_2 solution, the 4CC reaction was then performed with an amine, and aldehyde, and 1-isocyanocyclohexene (**3**) at 23°. A 1:1 solution of CH_2Cl_2 and methanol was employed to adequately swell the resin. After the reaction was complete and the resin washed again, these cyclohexenamide products **4**

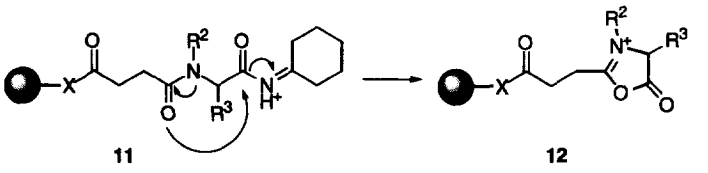


Scheme 1. [a]DMAD = dimethyl acetylenedicarboxylate

could now be converted in three different manners. The products were subjected to 10 equivalents of HCl and 25 equivalents of dimethyl acetylenedicarboxylate (DMAD) in toluene to yield the pyrroles **5**, or to 10 equivalents of acetyl chloride and an alcohol (anhydrous HCl being generated in situ) to produce esters **7**. In addition, a carboxylic acid (product **6**) is produced when cyclohexenamide **4** is treated with a 1.7% conc. HCl in THF solution.

The intermediate in each pathway is münchnone[12] **12** (1,3-oxazolinium-5-one), which results from cycloelimination of the protonated cyclohexenamide moiety **11** (Scheme 2). This labile intermediate can then undergo nucleophilic attack by water or an alcohol to yield acid **6** and esters **7**, respectively. Under similar reaction conditions, loss of a proton from **12** forms a 1,3-dipole (azomethine ylide) which can undergo cycloaddition with an acetylene[13-14] to yield the pyrroles **5** after aromatization and loss of CO_2 from the initial adduct. Standard trifluoroacetic acid cleavage of the products from the resin and purification by preparative TLC for analytical purposes provided the compounds **8-10**, shown in Table 1.

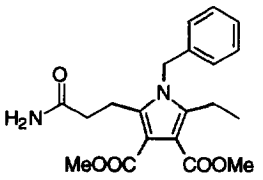
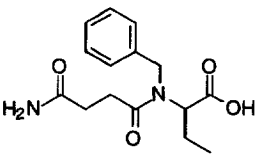
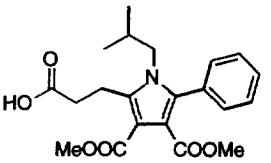
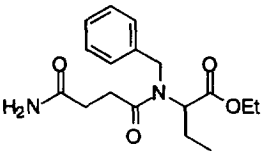
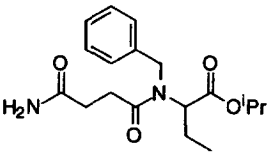
Adaptation of the Ugi reaction and subsequent conversions to solid support represents an important advance in the use of multiple component condensations for library synthesis. While the synthetic advantages



Scheme 2. Formation of münchnone intermediate **12**

of MCCs are evident, a serious drawback is that the products all feature the same core structure. The convertible isocyanide strategy presented here offers two clear advantages: first, only a single isocyanide is needed to yield a variety of products, thus overcoming the paucity of commericially available inputs. Second, products such as pyrroles are accessible, which are entirely unrelated to the α-acylaminoamide which is initially produced. We are presently engaged in improving the yields and expanding the scope of transformations of this kind.

Table 1. Products and Overall Yields of Solid Supported 4CC Product Conversions

Entry	Product[a]	Yield[b]	Entry	Product[a]	Yield[b]
8a		17%	**9**		66%
8b		4%	**10a**		22%
			10b		38%

[a]All products exhibited satisfactory spectral characteristics (^{1}H NMR, FTIR, and HRMS). [b]All yields are of isolated, pure product, and are calculated over four or five steps based on the manufacturer's stated loading level of the resin. (The steps beginning with Rink resin are Fmoc-deprotection, succinic acid attachment, Ugi 4CC, conversion reaction, and TFA cleavage. Beginning with Wang resin eliminates the deprotection step.) Yields are unoptimized, and improvement in these yields is being sought.

Acknowledgment: This work has been supported in part by the Pfizer Undergraduate Fellows Synthetic Organic Chemistry Summer Research Program (A.M.S.), by an Office of Naval Research Graduate Fellowship (T.A.K.), and by funding from the National Institutes of Health (grant GM51095).

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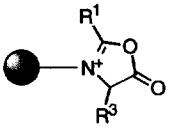
(11) In our initial efforts, deprotected Rink resin was used as the amine input for the Ugi 4CC. While this reaction proceeds smoothly (see reference 8), subsequent conversions of the type presented here failed to result in appreciable yields of expected product. We postulate that the münchnone **13** in this system, bearing a positive charge on nitrogen, cleaves itself off the resin, in much the same manner as protonation by TFA would operate. A mixture of products in the resin washes supports this.



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(14) The results presented here employ only DMAD as the acetylenic dipolarophile in the formation of pyrroles. We have accomplished the corresponding cycloaddition with a variety of other acetylenes in solution (see reference 6), and are working to extend this methodology to solid support.

(*Received in USA* 27 *November* 1995; *revised* 14 *December* 1995; *accepted* 15 *December* 1995)