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Application of the Cleavable Isocyanide in Efficient Approach to Pyroglutamic Acid Analogues with Potential Biological Activity

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Abstract—Two efficient procedures have been developed for the synthesis of pyroglutamic acid analogues **28**, **29**, and **34**. According to the first method the Ugi (4C3C) reaction is followed by a post-transformation reaction, and the second method involves the Michael addition reaction. The present methodologies demonstrate the applicability of 1-(2,2-dimethoxyethyl)-2-isocyanobenzene (**15**) as a cleavable isocyanide in the Ugi/ post-transformation reaction and a strong nucleophile in the Michael addition reaction. The framework of pyroglutamic acid analogues has been constructed by the selective cleavage of the *C*-terminal amide bond and nucleophilic addition to the activated α,β-unsaturated carbonyl group.

Keywords: cleavable isocyanide, Ugi (4C3C) reaction, Michael addition, pyroglutamic acid analogues

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Pyroglutamic acid is a core-structure of many bioactive compounds [1]. Examples of biological activities of pyroglutamic acid analogues include antibiotics such as omuralide **1** which shows an inhibitory effect toward 20*S* proteasome in bacterial cells [2, 3]. Lactacystin **2**, salinosporamide A **3** [4, 5], and dysibetaine **4** are currently used in treatment of human cancer. In addition, (–)-Pramanicin **5** and (+)-epolactaene **6** can induce apoptosis in a human leukemia B-cell line [6] (see the figure).

Multicomponent reactions (MCRs) are characterized by the unique ability to generate highly complex molecular structures from various starting materials in one-pot processes [7]. A combination of reactions with other strategies (such as Ugi–post-transformations) has been extensively used in synthesis of biologically active products [8, 9] and structures of multitude functionality [10, 11].

Isocyanide-based multicomponent reactions (IMCRs) have attracted close attention due to their applicability to generate biologically active molecules in a single step. Although isocyanides have demonstrated the utility in multicomponent reactions, they have not been demonstrated as "cleavable" in cleavage of α-acyloxyamide derivatives [12]. Therefore, the design and synthesis of cleavable isocyanides are required to provide an efficient access to biologically active molecules. Among the cleavable isocyanides are (β-isocyanoethyl) ethyl carbonate **7** [13], 1-cyclohexenylisonitrile **8** [14–16], *tert*-butylisonitrile **9** [17], *p*-methoxy phenyl isocyanide **10** [18, 19], diphenyl methyl isocyanide **11** [20], 1-isocyanomethyl benzotriazoles **12** [21], 4-isocyanopermethyl-butane-1,1,3-triol **13** [22], 2-nitrophenyl isocyanide **14** [23], and 1-(2,2-dimethoxyethyl)-2-isocyanobenzene **15** [24].

Although it has not been possible to cleave the hindered *C*-terminal amides of some α -acyloxyamide derivatives generated from multicomponent products, 1-(2,2-dimethoxyethyl)-2-isocyanobenzene (**15**) has been synthesized for a selective cleavage of the resultant *C*-terminal amide bond as well as it's applicability in the stereocontrolled synthesis [25–27]. In our ongoing approach to efficient methods of synthesis of biologically active pyroglutamic acid analogues, we have synthesized isocyanide **15** and studied its application in Ugi–post-transformation and Michael addition reaction in the synthesis of new pyroglutamic acid analogues **28**, **29**, **34** (Scheme 1).

RESULTS AND DISCUSSION

In Ugi–post-transformations, the Ugi products were used efficiently in the approach to structurally complex molecules [28, 29]. The key objective for synthesis of