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Complexity-Enhancing Acid-Promoted Rearrangement of Tricyclic Products of Tandem Ugi 4CC/Intramolecular Diels−Alder Reaction

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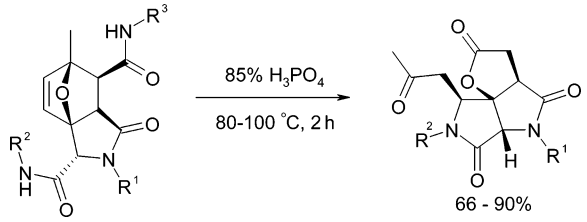

The unexpected rearrangement of 2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1-one products of the tandem Ugi 4CC/intramolecular Diels−Alder reaction in 85% H_3PO_4 was discovered to provide diastereomerically pure tricyclic bis-lactam lactone-containing natural product-like products in high yield. Mechanistic rationale for the observed rearrangement was proposed and has been tentatively confirmed by additional experiments.

Judiciously designed tandem processes have been widely used to access skeletally diverse and complex molecular scaffolds in the worldwide effort to probe into unexplored regions of chemical space via diversity-oriented synthesis.[1] Tricyclic adducts such as **1**, resulting from the Ugi four-component condensation (Ugi 4CC) of a furfural, a monoderivatized maleic acid, a primary amine, and an isonitrile followed by intramolecular Diels−Alder reaction (IMDA), were first described by Paulvannan[2] and subsequently used by Schreiber and co-workers[3] as rigid and densely functionalized templates for a number of diversity-oriented synthetic transformations.

In our continuing research program directed toward development of novel medicinally relevant compound libraries based on isoindol-1-ones and analogues thereof,[4] we became interested in H_3PO_4-promoted dehydrative aromatization of the tricyclic adducts **1** into isoindol-1-ones **2** in analogy to the aromatization reaction described for similar 2,3,7,7a-tetrahydro-3a,6-epoxy-isoindol-1-ones (lacking the carboxamide side chain at C-3, compared to **1**).[5] To that end, we prepared a series of Ugi 4CC/IMDA bisamide adducts using the published procedure.[2] To our delight, all products were obtained in diastereomerically pure form after crystallization from methanol. The relative stereochemistry (3-α, 7-*exo*, 7a-*exo*) of the products was confirmed by a single-crystal X-ray analysis of a representative compound (**1d**; see Supporting Information).

When adducts **1** were treated with 85% H_3PO_4 at 80−100 °C for 2 h, full conversion of the starting material into a single product was achieved. However, ^1H and ^{13}C NMR analyses showed the products obtained to be drastically different from the expected isoindol-1-ones **2** (the presence of a single set of signals in the NMR spectra indicated diastereomeric purity of the compounds examined). Single-crystal X-ray analysis of a representative product of the H_3PO_4 reaction (**3d**; see Supporting Information) confirmed both identity and relative stereochemistry of the compounds obtained (**3a**−**f**, Scheme 1), all of which were isolated in good to excellent yields (Table 1). The compounds obviously lack the maleic monoamide (R^3) residue and clearly resulted from a skeletal rearrangement of the epoxyisoindol-1-ones **1** rather than the initially anticipated dehydration process.

To account for the exclusive formation of the diastereomerically pure natural product-like lactones **3**, we proposed a *tentative* mechanism (Scheme 2) that rationalizes the observed behavior of the tricyclic compounds **1** in 85% H_3PO_4 at elevated temperatures in contrast to the simple dehydrative aromatization of the similar (albeit nonsubstituted at C-3) molecular systems reported by Varlamov and co-workers.[5] We believe that the secondary C_3-carboxamide side chain assists the heterolytic disruption of the C_6-C_7 bond, which leads to the formation of the new lactam ring and the hydrolytically prone cyclic enol ether moiety in transient species **4**. Acid-promoted opening of the cyclic enol ether (to liberate the 2-oxopropyl side chain) then generates the C-3a tertiary carbocation (**5**) which is intercepted by the proximal C-7a β-oriented carboxamide side chain. Finally, hydrolysis of the protonated iminolactam **6** leads to the loss of the R^3NH_2 and the formation of the lactone **3** isolated from the reaction mixture after workup.

To test the viability of the proposed mechanism, we prepared an analogous object for H_3PO_4-promoted rearrangement using monofumarate (**7**). We reasoned that, according to the outlined mechanism, the outcome of the rearrangement would not depend on the nature of the acid residue, and the C-7a ester side chain in the ester analogue of the intermediate **5** should be, as well, capable of intercepting the cationic center. Further, the stereochemical outcome of the rearrangement should not depend on the configuration at C-7 (which is different in **7** and **1e**[2] derived from fumaric monoester and maleic monoamide, respectively) but only on that at C-7a (which is the same in both compounds[2]).

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SCHEME 1. Tandem Ugi 4CC/IMDA Reaction Products and Their Acid-Promoted Transformation

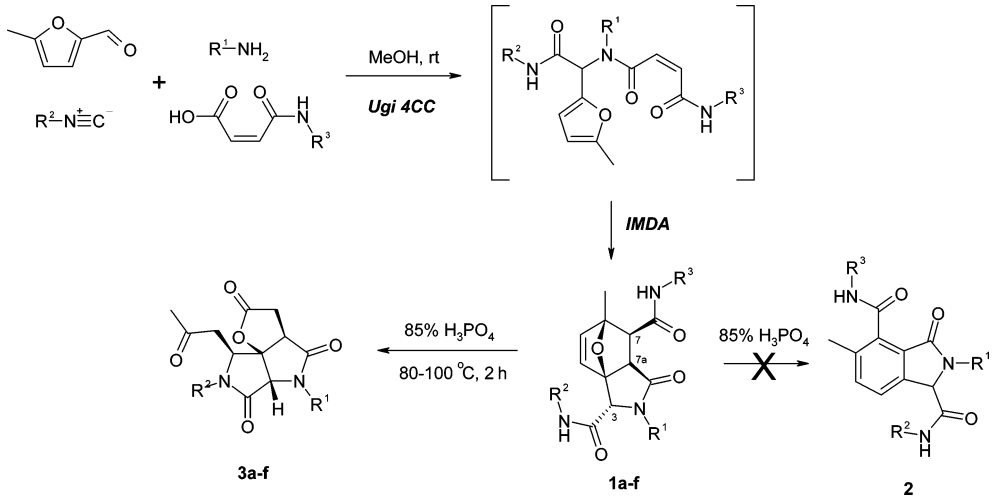
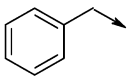
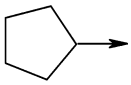
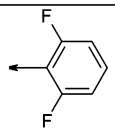
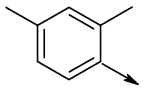
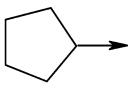
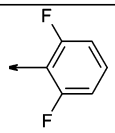
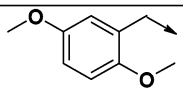
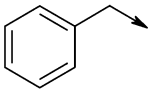
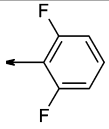
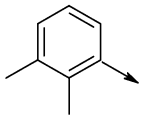
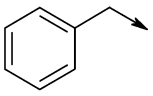
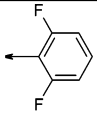
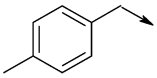
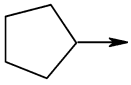
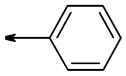
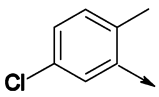
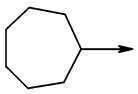
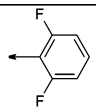


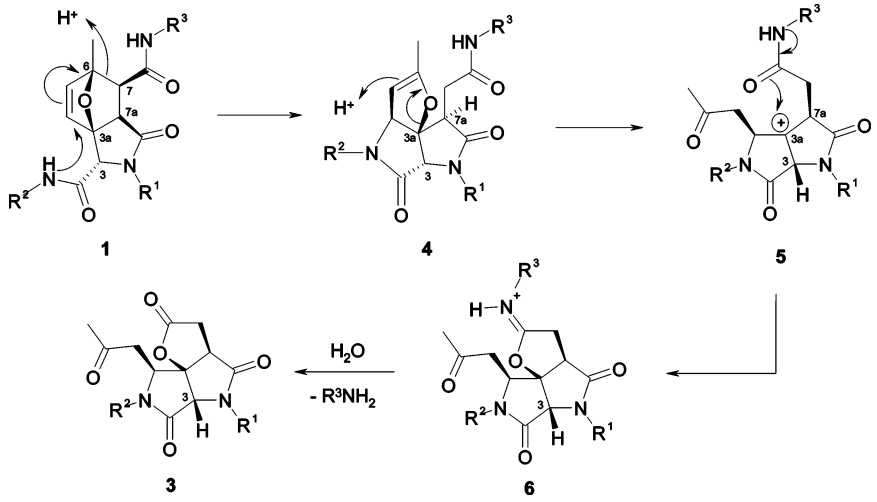
TABLE 1. Tricyclic Ugi 4CC/IMDA Compounds (1) Prepared in This Work and Products of Their Rearrangement in 85% H_3PO_4 (3)

compound	R^1	R^2	R^3	yield of **1**, %	yield of **3**, %
1(3)a				92	66
1(3)b				89	75
1(3)c				78	90
1(3)d				79	74
1(3)e				68	88
1(3)f				79	87

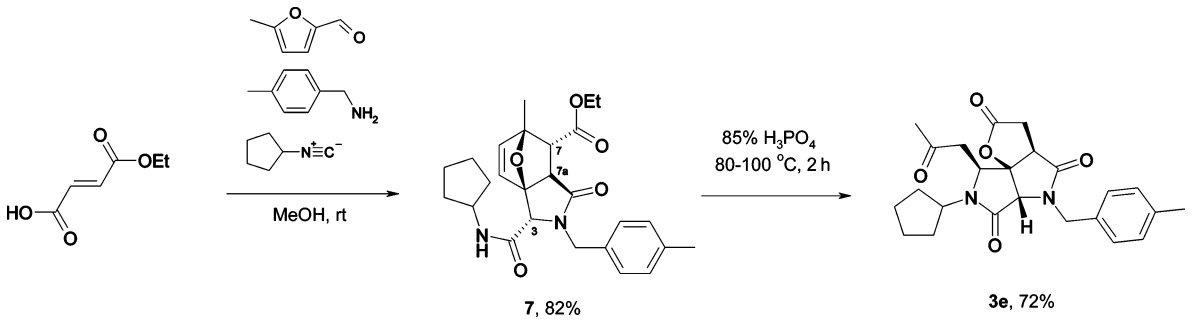
Indeed, when exposed to 80−100 °C 85% H_3PO_4 for 2 h, **7** rearranged into the same product **3e** as was previously obtained via rearrangement of **1e** (the identity of the products isolated in excellent yield from both reactions was established by comparison of their ^1H and ^{13}C NMR spectra).

Finally, from the proposed mechanism, we predicted that, if the Ugi 4CC/IMDA products **1** are exposed to the treatment with a catalytic amount of a Lewis acid in *nonpolar medium*, the rearrangement-triggering heterolysis of the C_6-C_7 bond in **1** would not be favored and the dehydrative aromatization

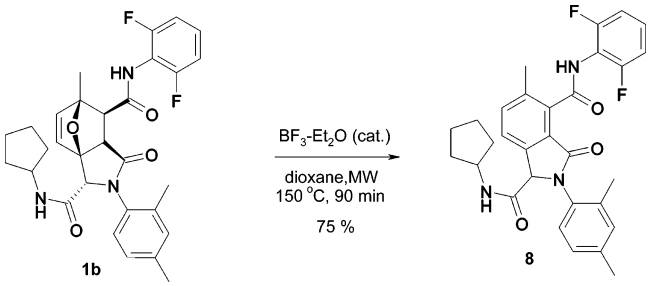
SCHEME 2. Proposed Mechanism for the H_3PO_4-Promoted Rearrangement of the Epoxyisoindol-1-ones 1 into Tricyclic Lactams 3



SCHEME 3. Preparation of a Tricyclic Ugi 4CC/IMDA Product Using Ethyl Monofumarate and its Rearrangement in 85% H_3PO_4



SCHEME 4. Dehydrative Aromatization of an Ugi 4CC/IMDA Product



(which was our initial goal) could be the major outcome. As shown in the Scheme 4, effective aromatization was indeed achieved upon microwave irradiation of the dioxane solution of a representative Ugi 4CC/IMDA adduct (**1b**) at 150 °C for 90 min in the presence of BF_3 etherate (0.2 equiv) to lead to a good isolated yield of the isoindol-1-one **8**. Notably, in this case, no rearrangement product (**3b**) was detected in the reaction mixture by LCMS analysis.

In conclusion, we have discovered a novel high-yielding rearrangement of the previously described Ugi 4CC/IMDA products **1** into the diastereomerically pure tricyclic lactones of hitherto unknown, unique, natural product-like structure (**3**). Alternatively, it was shown that exposure of **1** to a catalytic amount of BF_3 etherate in dioxane under microwave irradiation leads to the initially expected isoindol-1-ones (**8**). Due to the technical simplicity and high yield, both processes can be viewed as promising chemotype-differentiating tools in diversity-oriented synthesis of novel compound libraries for biological screening. Further efforts in our laboratories are focused on assessment of the generality and synthetic utility of the newly discovered rearrangement (**1→3**). The results of these studies will be reported in due course.

Experimental Section

Typical Procedure 1: Tandem Ugi 4CC/Intramolecular Diels−Alder Reaction: 5-Methylfurfural (1 equiv), a primary amine (1 equiv), an isonitrile (1.1 equiv), and a maleic acid monoamide (1.0 equiv, prepared from maleic anhydride and a respective aniline according to the literature procedure[6]) were combined in ethanol (3−5 mL/mmol) and heated at 50 °C for 1−2 h and then stirred at rt for 8 h. The product precipitated from the ethanolic solution was filtered off, washed with 10% ethanol in ether to remove excess isonitrile, and air-dried. Further crystallization from ethanol−water (1:1 in all cases) provided analytically pure material.

1a: White solid, mp = 129−131 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.65 (s, 1H), 8.47 (d, J = 6.7 Hz, 1H), 7.20 − 7.36 (m, 6H), 7.15 (t, J = 8.5 Hz, 2H), 6.35 (AB, J = 5.5 Hz, 2H), 4.79 (d, J = 15.9 Hz, 1H), 4.21 (s, 1H), 4.04 (m, 1H), 3.70 (d, J = 15.9 Hz, 1H), 2.86 (AB, J = 8.5 Hz, 2H), 1.82 (m, 2H), 1.61 (m, 2H), 1.60 (s, 3H), 1.51 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 167.3, 166.5, 157.7 (dd, J = 247.3, 5.6 Hz), 139.9, 136.4, 135.8, 128.2, 127.5 (t, J = 9.1 Hz), 127.2, 126.9,

(6) Moore, M. L.; Miller, C. S.; Miller, E. *J. Am. Chem. Soc.* **1940**, *62*, 2097−2099.

114.6 (t, J = 16.9 Hz), 111.6 (d, J = 23.2 Hz), 89.1 (d, J = 20.0 Hz), 61.3, 52.7, 50.6, 47.6, 44.2, 32.3, 31.9, 23.3, 15.4; LCMS m/z 522 (M + H); HRMS calcd for $C_{29}H_{30}O_4N_3F_2$ (M + H) 522.2199, found 522.2198.

Typical Procedure 2: Rearrangement of the Products of Tandem Ugi 4CC/Intramolecular Diels−Alder Reaction in 85% H_3PO_4: An Ugi 4CC/Diels−Alder adduct (**1a**−**f** or **7**) was dissolved in 85% H_3PO_4 (3 mL/1 mmol), and the reaction temperature was raised to 80−100 °C and was maintained for a period of 1−2 h. After cooling to rt, the reaction mixtures were poured into rt water (100 mL), and the resulting mixture was extracted with methylene chloride (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and water, dried over anhydrous MgSO4, filtered, and diluted with equal volume of ether. Massive precipitation occurred, and the precipitate was collected by filtration. Crystallization from water−ethanol (1:1) provided analytically pure material.

3a: White solid, mp = 167−168 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35 (t, J = 6.7 Hz, 2H), 7.30 (t, J = 6.7 Hz, 1H), 7.16 (d, J = 7.3 Hz, 2H), 4.96 (d, J = 14.9 Hz, 1H), 4.40 (d, J = 14.9 Hz, 1H), 4.30 (d, J = 8.6 Hz, 1H), 4.24 (s, 1H), 3.78 (dd, J = 8.6, 16.5 Hz, 1H), 3.68 (d, J = 10.4 Hz, 1H), 2.97−3.10 (m, 2H), 2.88 (d, J = 16.5 Hz, 1H), 2.66 (d, J = 18.3 Hz, 1H), 2.06 (s, 3H), 1.62−1.90 (m, 6H), 1.48 (br s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 206.7, 173.6, 171.3, 167.2, 135.5, 128.7, 127.6, 84.9, 62.1, 58.3, 54.8, 46.3, 44.3, 42.5, 29.9, 29.2, 28.1, 23.6, 23.5; LCMS m/z 411 (M + H); HRMS calcd for $C_{23}H_{27}O_5N_2$ (M + H) 411.1914, found 411.1901.

Acknowledgment. We would like to thank Caroline Williams of ChemDiv, Inc., for her help in obtaining and analyzing compound characterization data.

Supporting Information Available: Experimental procedures and characterization data for the newly synthesized compounds (**1a**−**f**, **3a**−**f**, **7**, and **8**) and X-ray crystallographic files (CIF) for compounds **1d** and **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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