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Photoassisted access to complex polyheterocycles containing a β -lactam moiety

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Abstract

Intramolecular cycloadditions of aza-*o*-xylylenes generated via excited state intramolecular proton transfer (ESIPT) to furanacetic acid-based unsaturated pendants was shown to overcome the unfavorable energetics of the azetidinone ring formation, offering rapid access to β -lactams as primary photoproducts. These 2,3- and 3,4-dihydrofuran-containing reactive intermediates are suitable for a broad spectrum of postphotochemical transformations yielding complex polyheterocyclic molecular architectures possessing the β -lactam moiety.

1. Introduction

During the past decade β -lactam chemistry has been enjoying a renaissance (Figure 1):¹ there are on average three new publications containing “ β -lactam” as a keyword appearing daily worldwide, one of which deals with the synthetic approaches to β -lactams. Despite such a remarkable activity in this field² most of the existing synthetic methods including several photochemical ones³ are limited to mono- or bicyclic lactams, and there are relatively few methods applicable to the synthesis of complex polycyclic structures. Very few of such structures are known even though they may be of substantial interest from the medicinal chemistry standpoint.

Previously we have demonstrated that aza-*o*-xylylenes generated via excited state intramolecular proton transfer (ESIPT) in aromatic *o*-aminoketones and aldehydes readily undergo intramolecular [4+4] or [4+2] cycloaddition reactions to tethered unsaturated moieties to yield complex polyheterocyclic structures (Figure 2).⁴ The synthesis of photoprecursors for such cycloadditions is facile and straightforward, and also is congruent with the philosophy of Diversity-Oriented Synthesis.⁵ The photoproducts can be successfully engaged in experimentally simple postphotochemical ground state reactions⁶ resulting in further growth of complexity and generation of novel molecular architectures. We now extend this method to the synthesis of β -lactams.

2. Experimental Section

Common solvents were purchased from Pharmco or Fisher Scientific and used as is, except for THF, which was refluxed over and distilled from sodium benzophenone ketyl prior to

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use. Common reagents were purchased from Aldrich and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz in CDCl₃ (unless noted otherwise). High resolution mass spectra were obtained on the Waters Synapt G2 ESI-MS mass spectrometer from the University of Colorado at Boulder. Flash column chromatography was performed using Teledyne Ultra Pure Silica Gel (230–400 mesh) on a Teledyne Isco Combiflash R_f using Hexanes/EtOAc as an eluent.

Dibromoformaldoxime^{6c}, **N-hydroxy-benzenecarboximidoyl bromide**⁷, **(1E)-N-phenyl-1-pyridin-2-ylmethanimine**⁸, **N-oxide-N-(phenylmethylene)-methanamine**⁹ were prepared according to the published procedures.

N-(2-formylphenyl)-2-(furan-2-yl)acetamide (3). (i) 2-(furan-2-yl)-N-(2-(((trimethylsilyl)oxy)methyl)phenyl)acetamide—1.0 g of 2-furanacetic acid (8.5 mmol, 1 eq) was dissolved in 10 mL of anhyd. DCM along with 1.6 g of CDI (9.8 mmol, 1.15 eq). The reaction was stirred at ambient temperature for 15 min. Upon full consumption of the starting 2-furanacetic acid as monitored by TLC, 1.6 g of **2-(((trimethylsilyl)oxy)methyl)aniline**^{4a} (8.5 mmol, 1 eq) was added and the reaction was stirred for an additional 6 h, before quenching with 20 mL of water. The organic layer was separated, washed with brine, dried over anhyd. Na₂SO₄, filtered, and concentrated *in vacuo* to yield 1.6 g of a 10:1 mixture of crude **2-(furan-2-yl)-N-(2-(((trimethylsilyl)oxy)methyl)phenyl)acetamide**, which was used in the next step without separation or purification.¹⁰ (ii) **N-(2-formylphenyl)-2-(furan-2-yl)acetamide**: 0.49 mL of oxalyl chloride (5.7 mmol, 1.1 eq) dissolved in 6.4 mL of anhyd. DCM (0.9 M solution) was cooled to -78°C before 0.82 mL of dry DMSO (11.5 mmol, 2.2 eq) was slowly added. Upon complete addition, the mixture stirred for 2 min till the evolution of gas stopped. Then, 1.6 g of crude **2-(furan-2-yl)-N-(2-(((trimethylsilyl)oxy)methyl)phenyl)acetamide** (5.2 mmol, 1 eq) dissolved in 10.0 mL of anhydrous DCM (0.5 M solution) was slowly added. Upon complete addition, the mixture was stirred for 15 min, followed by the addition of 3.6 mL of NEt₃ (26.1 mmol, 5 eq). The mixture was then allowed to warm to the ambient temperature at which it was stirred overnight. The reaction was quenched with water and extracted with DCM. The organic layer was separated, washed with brine, dried over anhyd. Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography with hexanes/EtOAc as eluent yielding 1.0 g of **N-(2-formylphenyl)-2-(furan-2-yl)acetamide** (57% over two steps). ¹H NMR (500 MHz, CDCl₃) δ 11.17 (s, 1H), 9.85 (s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 7.64 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.61 (ddd, *J* = 8.5, 7.6, 1.6 Hz, 1H), 7.47 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.23 (td, *J* = 7.5, 1.0 Hz, 1H), 6.45 (dd, *J* = 3.3, 2.0 Hz, 1H), 6.39 (dd, *J* = 3.3, 0.6 Hz, 1H), 3.85 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 195.2, 168.3, 147.5, 142.9, 140.5, 136.1, 135.9, 123.2, 122.0, 120.0, 110.8, 109.4, 38.1.

Irradiation of N-(2-formylphenyl)-2-(furan-2-yl)acetamide—A solution with ca. 3.0 mM of **N-(2-formylphenyl)-2-(furan-2-yl)acetamide** in 3:1 ethanol/H₂O was degassed and irradiated in a Pyrex or borosilicate glass reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300–400 nm UV source with peak emission at 350 nm)

until the reaction was complete, as determined by ^1H NMR. The solution was concentrated and the mixture was purified by flash chromatography.

11-hydroxy-15-oxa-4-azatetracyclo[10.2.1.0^{1,4}.0^{5,10}]pentadeca-5,7,9,13-tetraen-3-one (5)—From 1.0 g of **3** was obtained 0.39 g (39%) of the title compound and 0.41 g (41%) of **4**. ^1H NMR (500 MHz, CDCl_3) δ 7.79 (dd, J = 8.0, 1.3 Hz, 1H), 7.76 (dt, J = 8.0, 1.2 Hz, 1H), 7.32 (td, J = 7.6, 1.6 Hz, 1H), 7.20 (td, J = 7.7, 1.3 Hz, 1H), 6.71 (dd, J = 5.8, 1.9 Hz, 1H), 6.10 (dd, J = 5.8, 0.9 Hz, 1H), 5.26 (t, J = 4.7 Hz, 1H), 4.99 (dt, J = 3.9, 1.4 Hz, 1H), 3.51 (d, J = 15.5 Hz, 1H), 3.46 (d, J = 15.5 Hz, 1H), 2.33 (d, J = 7.0 Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 160.6, 135.0, 131.2, 129.9, 128.6, 128.4, 128.3, 124.9, 121.3, 94.0, 84.4, 76.2, 45.7. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_3$ + (MH) $^+$ 230.0817 found 230.0816.

10-hydroxy-6-oxa-2-azatetracyclo[9.4.0.0^{2,5}.0^{5,9}]pentadeca-1(15),7,11,13-tetraen-3-one (4)—From 1.0 g of **3** was obtained 0.41 g (41%) of the title compound and 0.39 g (39%) of **5**. ^1H NMR (500 MHz, CDCl_3) δ 7.53 (m, 1H), 7.32 (m, 3H), 6.39 (t, J = 2.8 Hz, 1H), 5.03 (dd, J = 3.0, 2.4 Hz, 1H), 4.95 (d, J = 6.4 Hz, 1H), 4.22 (dt, J = 6.4, 2.4 Hz, 1H), 3.61 (d, J = 15.7 Hz, 1H), 3.46 (d, J = 15.7 Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 164.7, 147.3, 132.4, 132.3, 128.1, 127.2, 124.9, 122.7, 99.3, 91.5, 67.6, 52.0, 50.3. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_3$ + (MH) $^+$ 230.0817 found 230.0821.

Postphotochemical Transformations

Addition of nitrile oxide, general procedure I^{6d}—1 eq of photoproduct was dissolved in EtOAc. To this was added 3 eq of N-hydroxy-benzenecarboximidoyl bromide or dibromoformaldoxime and 6 eq of KHCO_3 . An additional 3 eq of N-hydroxy-benzenecarboximidoyl bromide or dibromoformaldoxime and 6 eq of KHCO_3 were added after stirring for 12 h. The reaction was monitored by NMR until the starting photoproduct was consumed. The resulting mixture was diluted with water, extracted with 3 $\times$ 20 mL of EtOAc, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The mixture was then purified by flash chromatography.

Nitrone Cycloaddition—1 eq of photoproduct was dissolved in 1 mL of anhyd. toluene along with 4 eq of nitrone. The reaction was sealed in a high pressure reaction vessel and heated to completion as shown by ^1H NMR. The toluene was removed *in vacuo* and the residue purified by flash chromatography.

Povarov Cycloaddition:¹¹—A solution was prepared with 2 eq of the corresponding imine and 1 eq of corresponding photoproduct in 1.5 mL of 2,2,2-trifluoroethanol. This was warmed to 40°C until the reaction was complete as observed by ^1H NMR. The resulting mixture was concentrated *in vacuo* and purified by flash chromatography.

Hetero Diels-Alder Cycloaddition:¹²—1 eq of photoproduct and 1 eq of 1,3-dicarbonyl compound were dissolved in 0.7 mL of dry acetonitrile. To this was added 0.08 eq of L-proline and 1.3 eq of 37% aq. formaldehyde solution. The reaction stirred at ambient temperature until full consumption of the photoproduct, as determined by ^1H NMR. The

reaction was diluted with water and extracted with EtOAc. The organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The mixture was then purified by flash chromatography.

14-bromo-11-hydroxy-16,18-dioxo-4,15-

diazapentacyclo[10.6.0.0^{1,4}.0^{5,10}.0^{13,17}]octadeca-5,7,9,14-tetraen-3-one (6)—

From 0.14 g of **4**, 0.37 g of dibromoformaldoxime, and 0.36 g of KHCO₃, was obtained 85 mg (40%) of the title compound. ¹H NMR (500 MHz, DMSO) δ 7.44 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.37 (m, 2H), 7.20 (ddd, *J* = 7.8, 6.7, 1.9 Hz, 1H), 6.04 (d, *J* = 6.0 Hz, 1H), 5.81 (d, *J* = 5.8 Hz, 1H), 4.82 (t, *J* = 5.4 Hz, 1H), 4.39 (dd, *J* = 5.9, 0.5 Hz, 1H), 3.28 (d, *J* = 15.5 Hz, 1H), 3.27 (d, *J* = 4.9, 1H), 3.14 (d, *J* = 15.5 Hz, 1H). ¹³C NMR (126 MHz, DMSO) δ 165.5, 142.4, 131.8, 131.0, 129.2, 127.6, 124.9, 118.5, 107.5, 88.5, 63.8, 59.0, 51.9, 43.9. HRMS (ESI) calcd for C₁₄H₁₂BrN₂O₄⁺ (MH)⁺ 350.9980 and 352.9960 found 350.9981 and 352.9962

11-hydroxy-14-phenyl-16,18-dioxo-4,15-

diazapentacyclo[10.6.0.0^{1,4}.0^{5,10}.0^{13,17}]octadeca-5,7,9,14-tetraen-3-one (7)—

From 150 mg of **4** (0.7 mmol) was obtained 0.11 g (47%) of the title compound. ¹H NMR (500 MHz, CDCl₃) δ 7.75 (m, 2H), 7.56 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.49 (m, 4H), 7.42 (td, *J* = 7.7, 1.4 Hz, 1H), 7.22 (td, *J* = 7.6, 1.2 Hz, 1H), 6.36 (d, *J* = 6.3 Hz, 1H), 4.97 (dd, *J* = 8.9, 5.1 Hz, 1H), 4.69 (d, *J* = 6.3 Hz, 1H), 3.49 (d, *J* = 16.0 Hz, 1H), 2.96 (d, *J* = 16.0 Hz, 1H), 2.85 (d, *J* = 5.2 Hz, 1H), 1.83 (d, *J* = 8.9 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 164.5, 157.5, 131.3, 131.0, 130.5, 130.3, 129.4, 126.9, 125.1, 124.5, 123.3, 119.2, 107.7, 87.8, 66.0, 53.8, 52.2, 45.2. HRMS (ESI) calcd for C₂₀H₁₆N₂O₄⁺ (MH)⁺ 349.1183 found 349.1179

14-hydroxy-11-(phenyl)-2-oxo-10,21-

diazahexacyclo[11.10.0.0^{1,21}.0^{3,12}.0^{4,9}.0^{15,20}]tricoso-4(9),5,7,15,17,19-

hexaen-22-one (9)—From 0.10 g of **4** (0.43 mmol) was obtained 55 mg (56%) of the title compound. ¹H NMR (500 MHz, CDCl₃) δ 7.64 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.46 (td, *J* = 7.8, 1.4 Hz, 1H), 7.43 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.19 (td, *J* = 7.6, 1.1 Hz, 1H), 5.49 (s, 1H), 5.04 (d, *J* = 2.2 Hz, 1H), 3.36 (d, *J* = 15.7 Hz, 1H), 3.32 (d, *J* = 15.7 Hz, 1H), 2.73 (q, *J* = 1.8 Hz, 1H), 2.27 (dt, *J* = 10.0, 1.0 Hz, 1H), 2.23 (dt, *J* = 10.0, 1.0 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 162.2, 131.3, 130.7, 130.5, 124.3, 122.2, 118.2, 98.7, 86.0, 74.2, 49.4, 38.2, 37.5. HRMS (ESI) calcd for C₁₃H₁₁NO₃Na⁺ (MNa)⁺ 252.0638 found 252.0637.

14-hydroxy-6,8-dimethyl-2,4-dioxo-6,8,21-

triazahexacyclo[11.10.0.0^{1,21}.0^{3,12}.0^{5,10}.0^{15,20}]tricoso- 5(10),15,17,19-

tetraene-7,9,22-trione (8)—From 100.0 mg of **4** (0.42 mmol) and 65 mg of 1,3-dimethyl barbituric acid (0.42 mmol) was obtained 55 mg (33%) of the title compound. ¹H NMR (500 MHz, DMSO) δ 7.65 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.40 (td, *J* = 7.5, 1.3 Hz, 1H), 7.36 (tdd, *J* = 7.5, 1.7, 0.80 Hz, 1H), 7.19 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.14 (d, *J* = 5.3 Hz, 1H), 5.80 (d, *J* = 4.0 Hz, 1H), 4.93 (t, *J* = 5.8 Hz, 1H), 3.74 (d, *J* = 15.8 Hz, 1H), 3.42 (d, *J* = 15.8 Hz, 1H), 3.24 (s, 3H), 3.20 (dd, *J* = 10.6, 6.3, 1H), 3.18 (s, 3H), 2.97 (d, *J* = 15.9 Hz, 1H), 2.40 (dd, *J* = 15.9, 6.3 Hz, 1H), 2.34 (m, 1H). ¹³C NMR (126 MHz, DMSO) δ 165.5, 162.7, 154.4,

151.0, 134.7, 132.2, 128.2, 127.6, 126.5, 123.1, 103.6, 93.2, 82.9, 66.7, 51.2, 46.8, 38.3, 28.8, 28.0, 19.5. HRMS (ESI) calcd for $C_{20}H_{20}N_3O_6^+ (MH)^+$ 398.1347 found 398.1342.

14-bromo-11-hydroxy-16,18-dioxo-4,15-diazapentacyclo[10.5.1.0^{1,4}.0^{5,10}.0^{13,17}]octadeca-5,7,9,14-tetraen-3-one (10) and 16-bromo-11-hydroxy-14,18-dioxo-4,15-diazapentacyclo[10.5.1.0^{1,4}.0^{5,10}.0^{13,17}]octadeca-5,7,9,14-tetraen-3-one (10')—

From 0.10 g of **5** (0.5 mmol) was obtained 0.12 g (68%) of a 1.2 : 1 mixture of regioisomers **10** and **10'** that were inseparable by chromatography. HRMS (ESI) calcd for $C_{14}H_{12}BrN_2O_4^+ (MH)^+$ 350.9980 and 352.9960 found 350.9969 and 352.9967 1H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.0, 1.3 Hz, **10'**, 1H), 7.80 (d, J = 7.9 Hz, **10**, 1H), 7.77 (m, **10**, 1H), 7.25–7.42 (m, **10**, 2H and **10'**, 3H), 5.10 (d, J = 8.8 Hz, **10**, 1H), 4.97 (m, **10'**, 1H), 4.90 (m, **10**, 1H), 4.88 (d, J = 8.5 Hz, **10'**, 1H), 4.77 (d, J = 3.0 Hz, **10**, 1H), 4.71 (d, J = 3.0 Hz, **10'**, 1H), 4.14 (d, J = 15.8 Hz, **10**, 1H), 3.73 (dd, J = 8.6, 1.0 Hz, **10'**, 1H), 3.69 (d, J = 8.7 Hz, **10**, 1H), 3.61 (d, J = 15.9 Hz, **10'**, 1H), 3.51 (d, J = 15.8 Hz, **10**, 1H), 3.49 (d, J = 15.8 Hz, **10'**, 1H), 2.53 (d, J = 5.7 Hz, **10'**, 1H), 2.49 (d, J = 5.6 Hz, **10**, 1H).

11-hydroxy-14-phenyl-16,18-dioxo-4,15-diazapentacyclo[10.5.1.0^{1,4}.0^{5,10}.0^{13,17}]octadeca-5,7,9,14-tetraen-3-one (11)—

From 200 mg of **5** (1.0 mmol) was obtained 91 mg (31%) of the title compound. 1H NMR (500 MHz, $CDCl_3$) δ 7.89 (m, 3H), 7.86 (dt, J = 8.0, 1.4 Hz, 1H), 7.47 (m, 3H), 7.39 (td, J = 7.4, 1.4 Hz, 1H), 7.31 (td, J = 7.9, 1.3 Hz, 1H), 4.99 (m, 1H), 4.94 (d, J = 8.5 Hz, 1H), 4.73 (dd, J = 3.0, 0.8 Hz, 1H), 4.09 (dd, J = 8.6, 1.0 Hz, 1H), 3.68 (d, J = 15.7 Hz, 1H), 3.52 (d, J = 15.7 Hz, 1H), 2.73 (d, J = 5.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 157.0, 132.2, 130.6, 129.5, 129.0, 128.9, 128.0, 127.6, 127.2, 125.6, 120.9, 94.1, 87.2, 85.1, 73.8, 53.9, 44.0. HRMS (ESI) calcd for $C_{20}H_{16}N_2O_4^+ (MH)^+$ 349.1183 found 349.1183

anti-11-hydroxy-15-methyl-14-phenyl-16,18-dioxo-4,15-diazapentacyclo[10.5.1.0^{1,4}.0^{5,10}.0^{13,17}]octadeca-5,7,9-trien-3-one (12)—From 100 mg of **5** (0.44 mmol) was obtained 51 mg (32%) of the title compound. 1H NMR (500 MHz, $CDCl_3$) δ 7.80 (dt, J = 7.8, 1.4 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.39 (m, 3H), 7.33 (m, 3H), 7.26 (td, J = 7.6, 1.4 Hz, 1H), 4.92 (dd, J = 5.5, 3.5 Hz, 1H), 4.65 (d, J = 7.0 Hz, 1H), 4.52 (d, J = 3.2 Hz, 1H), 3.44 (d, J = 15.3 Hz, 1H), 3.30 (d, J = 8.5 Hz, 1H), 3.23 (d, J = 15.3 Hz, 1H), 3.03 (t, J = 7.7 Hz, 1H), 2.51 (s, 3H), 2.40 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 136.3, 131.6, 131.0, 129.3, 129.0, 128.6, 128.5, 127.7, 125.6, 121.3, 93.1, 84.9, 81.5, 77.5, 72.4, 61.9, 43.3, 42.3. HRMS (ESI) calcd for $C_{21}H_{21}N_2O_4^+ (MH)^+$ 365.1496 found 365.1501

3. Results and Discussion

Photoprecursors **3** are easily accessible through the amide coupling of commercially available *o*-aminobenzyl alcohol and 2-furanacetic acid, with subsequent oxidation of the alcohol moiety to aldehyde. The photoprecursors were dissolved in 75% aqueous methanol, degassed by an argon purge, and irradiated in a Rayonet photoreactor equipped with 16W RPR-3500 UV lamps (broadband 300–400 nm UV source with peak emission at 350 nm) until the reaction was complete, as monitored by 1H NMR. This resulted in the formation of

[4+2] and [4+4] cycloadducts with excellent diastereoselectivity: only *anti*-[4+4] and *syn*-[4+2] primary photoproducts were obtained, where *syn*- and *anti*- refers to the respective arrangement of the benzylic hydroxy-group in the quinolinol or benzoazacane ring, and furan's oxygen. Compounds **4** and **5** represent an unprecedented topology for a polyheterocyclic scaffold possessing a β -lactam ring in which the lactam is fused to benzoquinoline and azacane rings which, in turn, are fused with reactive 4,5 or 2,5-dihydrofuran moieties.

The structure of the products was determined by comparing the experimental spin-spin coupling constants with those calculated using the *relativistic force field* (*rff*) approach developed in our laboratory (Figure 3).¹³ In the case of [4+2] cycloadduct the spin-spin coupling constant (SSCC) of benzylic proton on the neighboring CH served to distinguish between *syn*- and *anti*-diastereomers. For the *syn*-cycloadduct this SSCC is calculated at 6.4 Hz, whereas for *anti*-product SSCC the value is 9.2 Hz – almost a 3 Hz difference. In calculations of the proton spin-spin coupling constants, the *rff DU8* method was shown to achieve ~0.3Hz accuracy (rmsd), so the 3 Hz difference is conclusive.

The experimentally observed SSCC is 6.4 Hz, unambiguously pointing to the *syn*-arrangement of benzylic hydroxyl-group and dihydrofuran moiety. This conclusion is further confirmed by NOE data: excitation of one of the methylene protons at 3.61 ppm produced a 4.9% NOE enhancement on the benzylic proton. The proof of the structure of [4+4] cycloadduct was somewhat more challenging, because of the similarity in the calculated values of the CH(OH)-CH SSCC for *syn*- and *anti*-diastereomers. It was found, however, that the relative position of the hydroxy-group has a significant effect on the chemical shift and the SSCC of the adjacent aromatic proton in the *ortho*-position: for the *anti*-adduct it was calculated to be 8.1 Hz, whereas for *syn* – 7.6 Hz. The experimental value of 8.0 Hz provides support for the *anti*-arrangement of the hydroxy-group and the oxa-bridge.

It is peculiar that the diastereoselectivity in this reaction is opposite to the one observed for the reaction of furan *propanamide* photoprecursor in Figure 2, which results in the formation of *syn*-[4+4] *anti*-[4+2] cycloadducts.

Both [4+2] and [4+4] adducts can be further introduced in postphotochemical cycloaddition reactions, which substantially increase the complexity of the frameworks formed. Expectedly, 2,3-dihydrofuran-containing [4+2] cycloadduct **4** proved to be more reactive than the [4+4] azacane **5**. It reacted under the 1,3-dipolar or hetero-Diels-Alder conditions with bromonitrile oxide generated *in situ* from dibromoformaldoxime,¹⁴ N-benzylideneaniline¹¹ and oxabutadiene formed from dimethylbarbiturate and formaldehyde.¹² It is instructive that despite the known high reactivity of the β -lactam moiety we have not observed any significant degradation or side reactions and the yields of the products formed ranged from moderate to good. Cycloadditions to the [4+2] primary photoproduct (**4**), which possesses a 2,3-dihydrofuran moiety, are both stereo- and regioselective, Scheme 2. 1,3-Dipolar cycloaddition of bromonitrile oxide to **4** occurs from the *exo*-face and results in single diastereomer **6**. Similar outcome was observed with another 1,3-dipole, benzonitrile oxide, generated from bromohydroxamic acid. The *oxa*-Diels-Alder reaction of the [4+2] cycloadduct with the barbiturate-derived oxadiene also

resulted in the formation of **8** as the single product of *exo*-attack. In all the cases the reactions seem to proceed via charge-controlled transition state and yield only one cycloadduct. The structure of the products was confirmed by the calculation of the SSCC, Figure 4.

Under the conditions of Povarov reaction,¹¹ instead of isolation of the expected [4+2] cycloaddition product, we observed the formation of acetal **9**. The structure of the product was elucidated using the *rff* calculations, Figure 3.

Two pairs of methylene protons were observed in the ¹H NMR spectrum of acetal **9**: one, at 3.36 and 3.32 ppm with the germinal SSCC of 15.7 Hz, belongs to the azetidinone ring, whereas the other, at 2.23 and 2.27 ppm with the germinal SSCC of 10.0 Hz – to the bridge methylene of the 2,6-dioxabicyclo[2.2.1]heptane moiety. The formation of the acetal results in the significant changes in the value of SSCC for the benzylic proton, which is now 2.2 Hz (compare with 6.4 Hz in the open form of **4**) and its neighboring tetrahydrofuran proton (2.73 ppm). We previously reported¹⁵ a similar acetalization in the case of *p*-methoxy substituted benzoidal aromatics. The example reported here, however, is the first one involving furan moiety. Remarkably, this strained acetal moiety is forming in the structure, already strained by the β-lactam moiety installed during the photochemical step.

Expectedly, [4+4] cycloadduct **5** was somewhat less reactive than dihydrofuran **4**. However, we were able to engage it in dipolar cycloadditions with the two nitrile oxides and the nitron, N-benzylidenemethanamine oxide, derived from benzaldehyde and methylhydroxylamine.⁹ It should be noted that the [4+2] photoproduct does not tolerate the conditions required for the reaction with the nitron. In contrast to the postphotochemical transformations of [4+2] cycloadduct, the reactions of [4+4] result in the formation of the mixture of regio- (compounds **10** and **11**) and stereoisomers (compounds **12** and **12'**). Interestingly, the substitution on formaldoximes influenced considerably the ratio of the regioisomers: **10** and **10'** are formed in a 1.5:1 ratio, whereas the ratio for **11** and **11'** was 6:1. The structures of the products were determined using (i) NOE experiments, (ii) the calculated and experimental SSCCs and (iii) the analogy with the previously studied examples.

The structures of the products were determined using comparison of the calculated and experimental SSCCs and by analogy with the previously studied examples. Elucidation of the structure of compound **12** required additional NOE experiments to ascertain the stereochemistry of the phenyl group. For this purpose the CHN proton at 3.30 ppm was irradiated, and NOE of 4% on the CHON proton at 4.65 ppm was observed, implying respective *syn* position of these two protons.

In conclusion, we developed a method for photoassisted access to fused polyheterocyclic molecular architectures containing the β-lactam moiety. The primary photoproducts are amenable to postphotochemical transformations preserving the β-lactam moiety, while offering considerable increase of molecular complexity as a result of experimentally simple single step reactions. The resulting polyheterocyclic β-lactams possess a minimal number of rotatable bonds, and a high Lovering's fsp3 factor.¹⁶

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References

1. Kamath A, Ojima I. Tetrahedron. 2012; 68:10640. [PubMed: 23264702]
2. (a) Brandi A, Cicchi S, Cordero FM. Chem Rev. 2008; 108:3988. [PubMed: 18781723] (b) Pitts CR, Lecktkat T. Chem Rev. 2014; 114:7930. [PubMed: 24555548]
3. (a) Bella AF, Jackson LV, Walton JC. Org Biomol Chem. 2004; 2:421. [PubMed: 14747872] (b) Scanlan EM, Slawin AMZ, Walton JC. Org Biomol Chem. 2004; 2:716. [PubMed: 14985812] (c) Scheffer JR, Wang K. Synthesis. 2001:1253.(d) Natarajan A, Wang K, Ramamurthy V, Scheffer JR, Patrick B. Org Lett. 2002; 4:1443. [PubMed: 11975599] (e) Kaanumalle LS, Sivaguru J, Arunkumar N, Karthikeyan S, Ramamurthy V. Chem Commun. 2003:116.(f) Natarajan A, Mague JT, Ramamurthy V. J Am Chem Soc. 2005; 127:3568. [PubMed: 15755178] (g) Ohba S, Hosomi H, Tanaka K, Miyamoto H, Toda F. Bull Chem Soc Jpn. 2000; 73:2075.(h) Wang R, Chen C, Duesler E, Mariano PS, Yoon UC. J Org Chem. 2004; 69:1215. [PubMed: 14961673] (i) Toda F, Miyamoto H, Inoue M, Yasaka S, Matijasic I. J Org Chem. 2000; 65:2728. [PubMed: 10808447]
4. (a) Mukhina OA, Kumar NNB, Arisco TM, Valiulin RA, Metzel GA, Kutateladze AG. Angew Chem, Int Ed. 2011; 50:9423.(b) Kumar NNB, Mukhina OA, Kutateladze AG. J Am Chem Soc. 2013; 135:9608. [PubMed: 23789841] (c) Mukhina OA, Kumar NNB, Cowger TM, Kutateladze AG. J Org Chem. 2014; 79:10956. [PubMed: 25370821] (d) Kumar NNB, Kuznetsov DM, Kutateladze AG. Org Lett. 2015; 17:438. [PubMed: 25587772] (e) Mukhina OA, Kuznetsov DM, Cowger TM, Kutateladze AG. Angew Chem Int Ed. 2015; 54:11516.(f) Mukhina OA, Kutateladze AG. J Am Chem Soc. 2016; 138:2110. [PubMed: 26866604] (g) Kumar NNB, Kutateladze AG. Org Lett. 2016; 18:460. [PubMed: 26760049]
5. (a) Schreiber SL, Burke MD. Angew Chem Int Ed. 2004; 43:46.(b) Galloway WRJD, Isidro-Llobet A, Spring DR. Nat Commun. 2010; 1:80. [PubMed: 20865796]
6. (a) Nandurkar NS, Kumar NNB, Mukhina OA, Kutateladze AG. ACS Comb Sci. 2013; 15:73. [PubMed: 23157463] (b) Cronk WC, Mukhina OA, Kutateladze AG. J Org Chem. 2014; 79:1235. [PubMed: 24397435] (c) Umstead WJ, Mukhina OA, Kutateladze AG. Eur J Org Chem. 2015:2205. (d) Umstead WJ, Mukhina OA, Kumar NNB, Kutateladze AG. Aust J Chem. 2015:1672.
7. Liu, Ying. TIANJIN INST PHARM RESEARCH, assignee. Oxime Derivatives Containing Thienopyridine, Preparation Method and Application Thereof. Patent. CN101402641. Apr 8. 2009 Print
8. Borriore E, Prato M, Scorrano G, Stivanello M, Lucchini V. J Heterocyclic Chem. 1988; 25:1831.
9. Canterbury DP, Herrick IR, Um J, Houk KN, Frontier AJ. Tetrahedron. 2009; 65:3165. [PubMed: 20161228]
10. Padwa A, Reger Can TS. J Chem. 2000; 78:749.
11. Spanedda MV, Hoang VD, Croisse B, Bonnet-Delpon D, Bégué J-P. Tetrahedron Lett. 2003; 44:217.
12. Stevenson R. Heterocycles. 1988; 27:1929.
13. (a) Kutateladze AG, Mukhina OA. J Org Chem. 2015; 80:5218. [PubMed: 25885091] (b) Kutateladze AG, Mukhina OA. J Org Chem. 2014; 79:8397. [PubMed: 25158224] (c) Kutateladze AG, Mukhina OA. J Org Chem. 2015; 80:10838. [PubMed: 26414291]
14. Vyas DM, Chiang Y, Doyle TW. Tetrahedron Lett. 1984; 25:487.
15. Kuznetsov DM, Mukhina OA, Kutateladze AG. Angew Chem. 2016; 55:6988. [PubMed: 27097759]
16. Lovering F, Bikker H, Humblet C. J Med Chem. 2009; 52:6752. [PubMed: 19827778]

Figure 1.
Number of publications (A) mentioning "β-lactam" according to Scifinder database statistics
(B) referring to the synthesis of β-lactams

Figure 2.

Photoassisted access to polyheterocycles via the azaxylylene strategy

Figure 3.
Experimental (and calculated) SSCCs in β -lactams **4**, **5** and **9**

Figure 4.
Comparison of experimental and calculated SSICC for products of postphotochemical transformations **6–8**

Figure 5. Comparison of experimental and calculated SSCC for compounds **10–12**

Scheme 1.

Synthesis of the photoprecursor, and the photoinduced cyclization.

Scheme 2.

Postphotochemical transformations of [4+2] photoproduct

Scheme 3.

Formation of acetal **9** under the conditions of Povarov reaction.

Scheme 4.

Postphotochemical transformations of [4+4] photoproduct **5**. Compounds **10** and **10'** were isolated as a mixture of regioisomers; minor regioisomer **11'** and diastereomer **12'** were observed by NMR but not isolated