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Oxidative Addition of Azide Anion to Triisopropylsilyl Enol Ethers: Synthesis of α-Azido Ketones and 2-Amino(methoxycarbonyl)alk-2-en-1-ones

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Abstract: Treatment of triisopropylsilyl enol ethers with ceric ammonium nitrate/sodium azide at -20°C in acetonitrile gives α-azido ketones in average to good yields (50-80%). Subsequent conversion of the α-azido ketones into 2-amino(methoxycarbonyl)cycloalk-2-en-1-ones is described.

Introduction

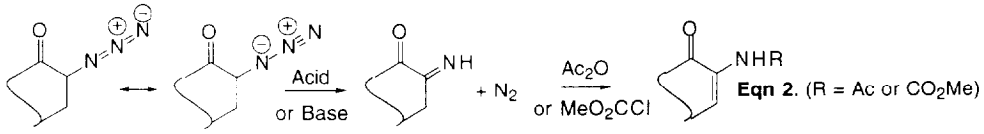
The introduction of nitrogen functionality adjacent to a carbonyl group using electrophilic aminating reagents is a topical area of research, particularly with respect to the synthesis of α-amino acids.[1] We have been examining the reaction of triisopropylsilyl (TIPS) enol ethers with the Sharpless reagent $(TsN)_2Se$,[2] and the reagent combination $PhIO/TMSN_3$.[3] The former reagent results in α-aminotosylation, while the latter leads to unprecendented β-azidonation. While this unusual reaction has revealed a new aspect of enol ether chemistry, we were still interested in electrophilic azidonation reagents that would introduce the azido-functionality into the α-position of a silyl enol ether.

$$2NaN_3 + Ce^{IV} \longrightarrow \left[2N_3^{\bullet} \right] \longrightarrow \left[\underset{?}{N_6} \right] \longrightarrow 3N_2 \qquad \textbf{Eqn 1.}$$

A particularly interesting reaction, first reported in 1915, that has received little attention is the oxidation of sodium azide with ceric ammonium nitrate (CAN) to give dinitrogen (**Eqn 1**).[4] This quantitative determination of azide anion received no attention from organic chemists until 1971 when Trahanovsky and Robbins reported the treatment of olefins with NaN_3/CAN gave α-azido-β-nitrato alkanes.[5] In 1979 Lemieux and Radcliffe described an extension of this azidonitration procedure to enol ethers of carbohydrate substrates (glycals).[6] In 1990 Vogel described a single example of the formation of an α-azido ketone from oxidative azidation [CAN (3 eq)/NaN_3 (1.5 eq)/CH_3CN] of a *t*-butyl dimethylsilyl enol ether.[7] The yield of the α-azido ketone dropped dramatically, to less than 50%, on reaction scales larger than 100 mg, presumably due to hydrolysis of the silyl enol ether. Existing methods for the formation of α-azido ketones are limited to the nucleophilic displacement of halogens by azide, the oxidation of olefins $PhI(OAc)_2/TMSN_3$, and the oxidative azidation of silyl enol ethers.[8] Edwards *et al*,[9] first prepared 2-azido

cyclohexanone in good yield by treating 2-chlorocyclohexanone with sodium azide in dimethylsulphoxide.

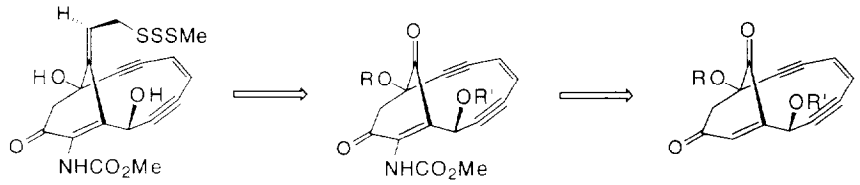
α-Azido ketones are versatile synthetic intermediates; apart from reduction to provide α-amino ketones, they can be induced to undergo tautomerization (acid and base catalyzed) followed by elimination of dinitrogen to give 2-aminoalk-2-en-1-ones (**Eqn 2**).[10]



Eqn 2. (R = Ac or CO_2Me)

This transformation was initially reported by Ermoleav,[11] who heated 2-azido cyclohexanone at 110°C in acetic anhydride and acetic acid to give 2-(acetylamino)cyclohex-2-en-1-one. An improvement of this methodology was reported by Effenberger[12] who obtained 2-(acetylamino)alk-2-en-1-ones in good yields using the milder conditions of heating (50°C) an azido ketone in acetic anhydride with catalytic sodium perrhenate (1mol%) and triflic acid (1 mol%) or concentrated hydrochloric acid (1 mol%). Our interest in the latter transformation stems from the need to introduce this functionality into the calicheamicinone precursor **3**, resulting in **2** and eventually calicheamicinone **1**, **Scheme 1**.[13]

Scheme 1



1, Calicheamicinone 2 3

Results and Discussion

When **4** was treated with [CAN (3 eq)/NaN_3 (1.5 eq)/CH_3CN] only moderate yields (30-45%) of the α-azido ketone **5** were obtained. The other products were cyclohexanone (11%), cyclohexenone (10%) and triisopropylsilanol (18%). It should be noted that cyclohexanone is inert to the above reaction conditions. Clearly, even **4** is being competitively hydrolyzed in the acidic (CAN) media. Recently, Evans has reported that TIPS enol ethers are readily dehydrogenated by CAN/DMF/0°C to give α,β-unsaturated ketones.[14] While attempts to buffer the reaction were unsuccessful, we found that increasing the amount of sodium azide (**TABLE 1**, *entry 2*) greatly improved the yield of **5** (67%). Further increases in both NaN_3 and CAN (*entries 3* and *4*) gave **5** in 72 and 83% respectively. The best conditions are those in *entry 3*, since there are less by-products and the α-azido ketone **5** is more readily purified. The separation of the azido ketone **5** from the triisopropylsilanol was troublesome, but when an excess of sodium azide was used the

major reagent derived product is triisopropylsilyl azide, which can more easily be separated from the azido ketone. Trimethylsilyl enol ethers were not suitable substrates for the CAN/NaN_3 reaction due to the ease of hydrolysis to the ketone. The TMS enol ether derived from cyclohexanone gave **5** (38%) and hydrolysis to cyclohexanone.

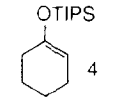
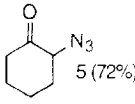
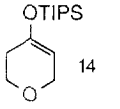
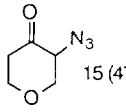
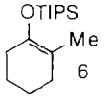
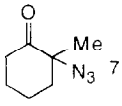
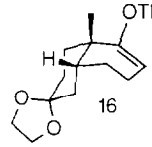
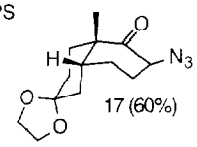
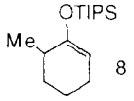
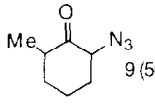
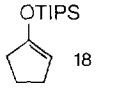
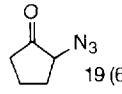
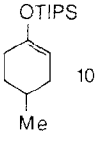
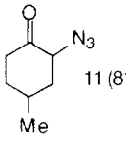
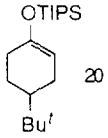
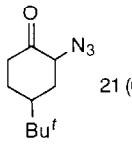
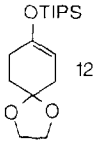
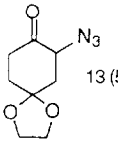
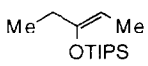
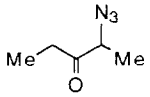
TABLE 1

(Optimization of CAN/NaN_3/CH_3CN/-20°C Reaction Conditions).

Entry	Conditions	Yield of 5 (%)
1	0.25 g (1.5 eq. NaN_3/3.0 eq. CAN)	44
2	0.25 g (3.0 eq. NaN_3/3.0 eq. CAN)	67
3	0.50 g (4.5 eq. NaN_3/3.0 eq. CAN)	72
4	0.25 g (5.0 eq. NaN_3/5.0 eq. CAN)	83[a]
5	0.25 g (2.0 eq. NaN_3/1.5 eq. CAN)	41[b]

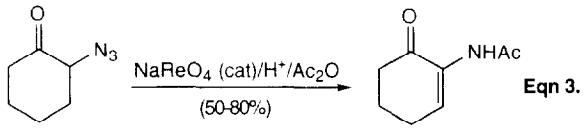
a) Impurities still present after purification. b) Recovered 37% of starting enol ether.

TABLE 2

ENTRY/SUBSTRATE	PRODUCT (% YIELD)	ENTRY/SUBSTRATE	PRODUCT (% YIELD)
1  4	 5 (72%)	6  14	 15 (47%)
2  6	 7 (49%)	7  16	 17 (60%)
3  8	 9 (56%)	8  18	 19 (65%)
4  10	 11 (81%)	9  20	 21 (65%)
5  12	 13 (59%)	10  22	 23 (30%)

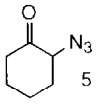
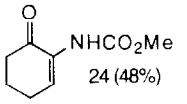
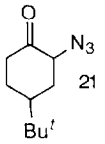
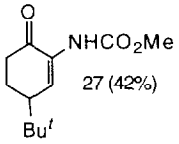
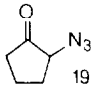
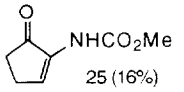
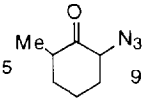
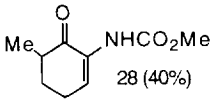
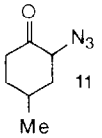
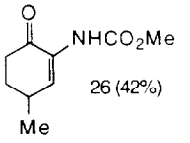
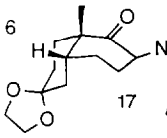
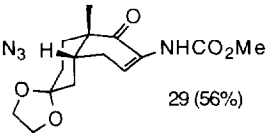
The optimized reaction conditions led to more consistent reactions and were applicable to scale up (0.25-1.0 g). The oxidative azidation was applied to a range of TIPS silyl enol ether derivatives, affording the α-azido ketones in average to good yields (*entries 1-9*), **TABLE 2**. The reaction is not stereospecific as illustrated by the mixtures of diastereomers obtained in *entries 3, 4* and *9*. Introduction of azide at a tertiary center is illustrated by the formation of 2-azido-2-methylcyclohexanone (*entry 2*). This result is interesting as there are few methods available for the introduction of azide at a tertiary carbon adjacent to a carbonyl. 2-Azido-2-methylcyclohexanone **7** has reportedly been obtained *via* S_N2 displacement of the 2-bromo-2-methylcyclohexanone with lithium azide. The article fails to include any experimental data to support the identity of this compound.[9]

Having achieved the initial goal of improving the oxidative azidation of triisopropylsilyl enol ethers, attention was turned to the conversion of the azide to an acyl enamine derivative. As mentioned earlier, 2-(acetylamino)alk-2-en-1-ones have been generated from α-azido ketones by heating the azido ketone in acetic anhydride in the presence of a catalytic amount of triflic acid (1 mol%) or hydrochloric acid (1 mol%) and sodium perrhenate (1 mol%), **Eqn 3**.



Eqn 3.

TABLE 3

ENTRY/SUBSTRATE	PRODUCT (% YIELD)	ENTRY/SUBSTRATE	PRODUCT (% YIELD)
1  5	 24 (48%)	4  21	 27 (42%)
2  19	 25 (16%)	5  9	 28 (40%)
3  11	 26 (42%)	6  17	 29 (56%)

The sodium perrhenate catalyzed azide decompositions can be carried out in the presence of methyl chloroformate, allowing access to the corresponding 2-amino(methoxycarbonyl)cycloalk-2-en-1-ones as depicted in **Table 3**. Acylations of the cyclohexanone derivatives (*entries 1, 3, 4* and *5*) using methyl chloroformate proceeded analogously to those observed with acetic anhydride, in yields close to 45%. *Entry 6* illustrates that the perrhenate catalyzed decomposition of azido ketones can occur in the presence of ketal functionality. Attempts to reduce the extensive polymerization observed in these reactions was unsuccessful.

In conclusion, the oxidative azidation of triisopropysilyl enol ethers provides a direct method for the synthesis of α-azido ketones rather than the normal halogenation followed by displacement with azide anion. While the subsequent tautomerization ($-N_2$) and conversion into 2-amino(methoxycarbonyl)cycloalk-2-en-1-ones proceeds in modest yields, the overall sequence is only two steps.

Experimental

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer or a 881 grating spectrophotometer either neat or in $CHCl_3$ as indicated. Proton NMR spectra were recorded on a General Electric QE-300 300 MHz spectrometer in the indicated solvent, and are reported in ppm downfield from TMS. Carbon-13 NMR spectra were recorded on a General Electric QE-300 spectrometer at 75 MHz in the solvent indicated. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard; (e) or (o) indicate even or odd numbers of hydrogens carried by the carbon. Low resolution chemical ionization (CI) mass spectra were obtained on a TSQ 70 instrument, and the exact mass determinations were obtained on a VG analytical ZAB2-E instrument.

Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. Preparative layer chromatography was performed using Merck 60 F_{254} silica gel, glass supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F_{254} silica gel. Air and moisture sensitive reactions were performed under usual inert atmosphere techniques (i.e. in glassware dried by a Bunsen flame or in an oven at 140°C, then cooled under argon, and performed under a blanket of argon). Solvents and commercial reagents were dried and purified before use: Et_2O and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2, benzene, and CH_3CN were distilled from calcium hydride under argon. Methyl chloroformate was distilled under argon at reduced pressure.

General preparation of triisopropylsilyl enol ethers. To a solution of the ketone (20 mmol) in CH_2Cl_2 (40 mL) under argon or nitrogen atmosphere at 0°C, triethylamine (40 mmol) was slowly added followed by dropwise addition of triisopropylsilyl triflate (21 mmol). When the reaction was complete (by tlc) the mixture was partitioned between CH_2Cl_2 and H_2O. The layers were

separated, the organic layer washed once with H_2O, dried (Na_2SO_4), filtered and concentrated *in vacuo*. All silyl enol ethers were prepared using this general procedure, unless otherwise stated. The TIPS enol ethers **4**, **6**, **8** and **10** have been described previously.[2]

4-Ethyleneketal-1-triisopropylsilyl(oxy)-cyclohexene 12. Colorless oil, purified *via* flash column chromatography (SiO_2; 20% Et_2O/80% hexanes). 99% yield. IR (film) 2946, 2866, 1673, 1464, 1434 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (1H, t, J = 3.3 Hz), 3.95 (4H, s), 2.23 (4H, m), 1.75 (2H, t, J = 6.5 Hz), 1.10-0.95 (21H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 150.0 (s), 107.7 (s), 100.2 (d), 64.3 (t), 33.9 (t), 31.2 (t), 28.5 (t), 17.9 (q), 12.5 (d). HRMS m/e calcd for $C_{17}H_{32}O_3Si$ 312.212. Found 312.212.

4-Triisopropylsilyl(oxy)-pyran-3-ene 14. Colorless oil, purified *via* flash column chromatography (SiO_2; 20% EtOAc/80% hexanes), 91% yield. IR (film) 2943, 2892, 2867, 1673 , 1464 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (1H, m), 4.08 (2H, m), 3.75 (2H, t, J = 5.8 Hz), 2.12 (2H, td, J's = 5.8, 0.9 Hz), 1.20-0.90 (21H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 148.0 (s), 101.4 (d), 64.7 (t), 64.6 (t), 30.6 (t), 17.8 (q), 12.5 (d). HRMS (M^+ + 1) m/e calcd for $C_{14}H_{29}O_2Si$ 257.194. Found 257.194.

***cis*-8-Ethyleneketal-1-methyl-2-triisopropylsilyl(oxy)-bicyclo[4.4.0]dodec-2-ene 16**. White waxy solid, purified *via* flash column chromatography (SiO_2; 10% EtOAc/90% hexanes), 87% yield. IR ($CHCl_3$) 2947, 2891, 2868, 1658, 1464 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.57-4.55 (1H, t, J = 3.6 Hz), 3.94 (4H, s), 2.22-1.74 (6H, m), 1.58-1.44 (3H, m), 1.35-1.22 (2H, m), 1.14 (3H, s), 1.08-1.05 (21H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 153.3 (s), 109.8 (s), 99.1 (d), 64.2 (t), 64.1 (t), 39.4 (q), 38.2 (s), 35.8 (d), 32.3 (t), 31.9 (t), 28.1 (t), 23.4 (t), 21.0 (t), 18.2 (q), 13.0 (d). HRMS calcd for $C_{22}H_{40}O_3Si$ 380.275. Found 380.274.

1-Triisopropylsilyl(oxy)-cyclopentene 18. Colorless oil, purified *via* flash column chromatography (SiO_2; pentanes), 94% yield. IR ($CHCl_3$) 2946, 2868, 1644, 1464 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.64-4.62 (1H, m), 2.34-2.30 (4H, m), 1.87-1.82 (2H, m), 1.20-1.06 (21H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 155.5 (s), 102.1 (d), 33.6 (t), 28.7 (t), 21.5 (t), 17.9 (q), 12.5 (d). HRMS (M^+ + 1) m/e calcd for $C_{14}H_{29}OSi$ 241.199. Found 241.198.

4-*t*-butyl-1-triisopropylsilyl(oxy)-cyclohexene 20. Colorless oil, purified *via* flash column chromatography (SiO_2; hexanes), 94% yield. b.p. 124°C at 1.5 mmHg. IR (film) 2944, 2665, 1673, 1463 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.87-4.85 (1H, m), 2.15-1.97 (3H, m), 1.85-1.77 (2H, m), 1.28-1.14 (2H, m), 1.10-1.01 (21H, m), 0.88 (9H, s). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 150.6 (s), 103.3 (d), 44.1 (d), 32.1 (s), 31.0 (t), 27.4 (q), 25.2 (t), 24.5 (t), 18.0 (q), 12.7 (d). HRMS calcd for $C_{19}H_{38}OSi$ 310.269. Found 310.268.

Z-3-Triisopropylsilyl(oxy)-pent-2-ene 22. Colorless oil, purified *via* flash column chromatography (SiO_2; pentanes), 81% yield. IR (film) 2967, 2945, 2894, 1678, 1464 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (1H, q, J = 6.6 Hz), 2.15-2.00 (2H, q, J = 7.3 Hz), 1.60-1.52 (3H, d, J = 6.6 Hz), 1.20-1.05 (21H, m), 1.05-0.98 (3H, t, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, APT) δ 153.2 (s), 99.3 (d), 29.4 (t), 18.1 (q), 13.3 (q), 11.7 (q), 10.7 (d). HRMS m/e calcd for $C_{14}H_{30}OSi$ 242.207. Found 242.207.

General Procedure for the Preparation of α-Azido Ketones. To a 0.4M mixture of the triisopropylsilyl enol ether (1.99 mmol) in distilled CH_3CN at -20 °C under argon or nitrogen atmosphere was added sodium azide (8.86 mmol, 4.5 eq), followed by dropwise addition of a 0.4M solution of ceric ammonium nitrate (CAN) (5.90 mmol, 3 eq.) in CH_3CN. The progress of the reaction was monitored by tlc, when the reaction was complete, the mixture was quenched by the addition of ice-cold water. The aqueous mixture was extracted with ice-cold Et_2O, the layers were separated and the organic layer was washed once with ice-cold water. The aqueous layers were extracted once with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. In general the crude products were purified *via* flash column chromatography using silica gel, eluting with ether/pentanes, the relative ratios vary depending on the compound. All of the azido-ketones were prepared using this general procedure, unless otherwise stated.

2-Azido-cyclohexan-1-one 5. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 25% Et_2O/75% hexanes), 72% yield. IR (film) 2944, 2866, 2103, 1721 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (1H, dd, J = 11.3, 6.0 Hz), 2.47-2.42 (1H, m), 2.34-2.20 (2H, m), 2.02-1.96 (1H, m), 1.90-1.86 (1H, m), 1.69-1.54 (3H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 205.5 (s), 66.2 (d), 40.5 (t), 33.3 (t), 26.8 (t), 23.5 (t). HRMS m/e calcd for $C_6H_{10}N_3O$ (M^++1) 140.082. Found 140.082.

2-Azido-2-methyl-cyclohexan-1-one 7. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 25% Et_2O/75% pentanes), 49% yield. IR ($CHCl_3$) 2949, 2868, 2102, 1722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.61-2.51 (1H, m), 2.37-2.28 (1H, m), 1.91-1.56 (6H, m), 1.35 (3H, s). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 207.7 (s), 67.9 (s), 39.1 (t), 38.2 (t), 26.9 (t), 21.1 (t), 20.4 (q). HRMS m/e calcd for $C_7H_{11}N_3O$ 153.090. Found 153.090.

2-Azido-6-methyl-cyclohexan-1-one 9. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 10% Et_2O/90% pentanes), 56% yield, (1:1.5 *trans*:*cis*). IR ($CHCl_3$) 3012, 2944, 2839, 2867, 2104, 1723 cm^{-1}. For *trans*- ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (1H, t, J = 5.3 Hz), 2.87-2.75 (1H, m), 2.0-1.9 (2H, m), 1.88-1.69 (2H, m), 1.55-1.42 (2H, m), 1.10 (3H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 209.0 (s), 65.5 (d), 42.3 (d), 34.7 (t), 33.0 (t), 19.5 (t), 14.9 (q). For *cis*- ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (1H, dd, J = 12.5, 6.2 Hz), 2.44-2.36 (1H, m), 2.32-2.25 (1H, m), 2.08-2.01 (1H, m), 1.90-1.80 (1H. m), 1.78-1.70 (1H, m), 1.66-1.56 (1H, m), 1.37-1.29

(1H, m), 1.01 (3H, d, J = 6.4 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 207.0 (s), 66.3 (d), 44.6 (d), 35.9 (t), 34.1 (t), 23.5 (t), 13.9 (q). HRMS m/e calcd for $C_7H_{11}N_3O$ 153.090. Found 153.091.

2-Azido-4-methyl-cyclohexan-1-one 11. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 25% Et_2O/75% pentanes), 81% yield, (1:3 *trans*:*cis*). IR ($CHCl_3$) 2963, 2953, 2114, 1727 cm^{-1}. For *cis* ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (1H, dd, J = 13.0, 6.1 Hz), 2.47-2.30 (2H, m), 2.26-2.18 (1H, m), 2.05-1.94 (2H, m), 1.44-1.32 (2H, m), 1.00 (3H, d, J = 6.4 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 205.6 (s), 65.3 (d), 41.1 (t), 39.8 (t), 34.8 (t), 30.9 (d), 20.7 (q). For *trans* ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (1H, dd, J = 7.8, 5.3 Hz), 2.55-2.45 (2H, m), 2.40-2.31 (1H, m), 2.16-2.09 (1H, m), 1.94-1.83 (2H, m), 1.82-1.75 (1H, m), 1.58-1.52 (1H, m), 1.04 (3H, d, J = 7.0 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 206.3 (s), 64.2 (d), 39.3 (t), 36.6 (t), 33.2 (t), 26.3 (d), 18.8 (q). HRMS (M^+ + 1) m/e calcd for $C_7H_{12}N_3O$ 154.098. Found 154.098.

2-Azido-4-ethyleneketal-cyclohexan-1-one 13. Pale yellow waxy solid, purified *via* flash column chromatography (SiO_2; 40% Et_2O/60% pentanes), 59% yield. IR ($CHCl_3$) 2966, 2893, 2115, 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (1H, dd, J = 13.2, 6.3 Hz), 4.04-3.92 (4H, m), 2.67-2.55 (1H, m), 2.43-2.36 (1H, m), 2.26-2.18 (1H, m), 2.02-1.85 (3H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 204.4 (s), 106.5 (s), 64.8 (t), 64.6 (t), 62.8 (d), 40.2 (t), 36.1 (t), 34.0 (t). HRMS (M^+ + 1) m/e calcd for $C_8H_{12}N_3O_3$ 198.088. Found 198.088.

3-Azido-tetrahydro-4H-pyran-4-one 15. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 50% Et_2O/50% pentanes), 47% yield. IR ($CHCl_3$) 2926, 2868, 2115, 1728 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.28-4.19 (2H, m), 4.10-4.04 (1H, ABX, J_{AB} = 10.5, J_{AX} = 10.4 Hz), 3.66 (1H, ddd, J = 14.6, 11.5, 3.1, Hz), 3.41 (1H, t, J = 10.7 Hz), 2.75-2.64 (1H, m), 2.55 (1H, dt, J = 14.5, 2.5 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 201.7 (s), 70.9 (t), 68.1 (t), 64.13 (d), 41.8 (t). HRMS m/e calcd for $C_5H_8N_3O_2$ (M^++1) 142.062. Found 142.062.

3-Azido-8-ethyleneketal-1-methyl-bicyclo[4.4.0]dodecan-1-one 17. Pale yellow waxy solid, purified *via* flash column chromatography (SiO_2; 25% Et_2O/75% pentanes), 60% yield, (2:1 eq:ax). IR ($CHCl_3$) 3017, 2958, 2888, 2106, 1716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.22 (1H, dd, J = 12.8, 6.8 Hz), 3.95-3.86 (4H, m), 2.32-2.14 (4H, m), 1.89-1.64 (3H, m), 1.57-1.37 (4H, m), 1.25 (3H, s). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 208.7 (s), 108.9 (s), 64.3 (t), 64.1 (t), 63.0 (d), 48.7 (s), 42.5 (q), 37.1 (t), 32.2 (t), 31.5 (t), 29.0 (t), 26.2 (t), 24.6 (t). HRMS m/e calcd for $C_{13}H_{19}O_3N_3$ 265.143. Found 265.143.

2-Azido-cyclopentan-1-one 19. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 25% Et_2O/75% pentanes), 65% yield. IR (film) 2947, 2888, 2104, 1718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (1H, t, J = 9 Hz), 2.40-2.24 (3H, m), 2.09-1.99 (1H, m), 1.98-1.66 (2H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 213.4 (s), 64.0 (d), 35.4 (t), 28.9 (t), 18.1 (t). CIMS m/e 126 (parent), 96 (base). HRMS m/e calcd for $C_5H_7N_3O$ 125.059. Found 125.058.

2-Azido-4-*t*-butyl-cyclohexan-1-one 21. Colorless oil, purified *via* flash column chromatography (SiO_2; 30% Et_2O/70% pentanes), 65% yield, (2:1 eq:ax, inseparable). IR ($CHCl_3$) 2962, 2868, 2111, 1726 cm^{-1}. Inseparable mixture of *cis*- and *trans*- azide isomers. ^1H NMR (300 MHz, $CDCl_3$) δ 3.93-3.87 (2H, m), 2.56-2.42 (2H, m), 2.33-2.22 (4H, m), 2.06-1.95 (2H, m), 1.66-1.54 (2H, m), 1.45-1.37 (4H, m), 0.861 (9H, s), 0.835 (9H, s). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 207.3 (e), 205.8 (e), 65.9 (o), 65.5 (o), 45.8 (o), 41.0 (e), 40.7 (o), 39.7 (e), 37.3 (s), 34.6 (e), 32.2 (e), 32.0 (e), 27.8 (e), 27.3 (o), 27.1 (o), 26.4 (e). HRMS m/e calcd for $C_{10}H_{17}N_3O$ 195.137. Found 195.138.

2-Azido-3-pentanone 23. Pale yellow oil; purified *via* flash column chromatography (SiO_2; 30% Et_2O/70% pentanes), 30% yield. IR ($CHCl_3$) 2943, 2894, 2868, 2101, 1723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (1H, q, J = 14.1, 7.0 Hz), 2.54 (2H, q, J = 7.2, 14.3 Hz), 1.41 (3H, d, J = 7.1 Hz), 1.00 (3H, t, J = 7.0 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 208.3 (s), 62.9 (d), 32.3 (t), 15.7 (q), 17.3 (q). HRMS m/e calcd for $C_5H_9N_3O$ 127.075. Found 127.075.

General Preparation of 2-amino(methoxycarbonyl)alk-2-en-1-ones. To a 0.7M solution of azido-ketone in methyl chloroformate was added $NaReO_4$ (1 mol %), followed by TFA (1 mol %), the mixture was placed under argon or nitrogen atmosphere and heated to 55°C. The progress of the reaction was monitored by infrared spectroscopy for the disappearance of the N_3 band (2110 cm^{-1}). When the reaction was complete, the mixture was concentrated *in vacuo*, the dark oily residue was taken up in ether, filtered, and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (SiO_2). This general procedure was used for the following compounds unless otherwise stated.

2-Amino(methoxycarbonyl)cyclohex-2-en-1-one 24. White crystals, recrystallized from hexanes, 48% yield. M. p. 39-40°C. IR ($CHCl_3$) 3394, 3021, 2954, 2894, 2874, 1731, 1677, 1643, 1529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, t, J = 4.4 Hz) 7.20 (1H, bs, -NH), 3.59 (3H, s), 2.42-2.34 (4H, m), 1.92-1.84 (2H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 193.3 (s), 153.7 (s), 132.0 (s), 127.5 (d), 51.8 (q), 36.8 (t), 24.3 (t), 22.2 (t). HRMS m/e calcd for $C_8H_{12}NO_3$ (M+ +1) 170.082. Found 170.081.

2-Amino(methoxycarbonyl)cyclopent-2-en-1-one 25. Pale yellow solid, purified *via* SiO_2 preparative tlc (40% Et_2O/60% pentanes), 16% yield. IR ($CHCl_3$) 3401, 3027, 3020, 3016, 2927, 2867, 1737, 1707, 1644 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (1H, bs, -NH), 6.91 (1H, bs), 3.74 (3H, s), 2.63-2.61 (2H, m), 2.41-2.39 (2H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 203.0 (s), 153.9 (s), 137.4 (d), 137.1 (s), 52.6 (q), 32.4 (t), 24.6 (t). HRMS m/e calcd for $C_7H_{10}NO_3$ (M+ +1) 156.066. Found 156.067.

2-Amino(methoxycarbonyl)-4-methyl-cyclohex-2-en-1-one 26. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 10% Et_2O/90% pentanes), 42% yield. IR ($CHCl_3$) 3393, 3029, 1728, 1679, 1645, 1524 cm^{-1}. ^1H NMR (300 MHz, d_6 DMSO) δ 7.55 (1H, bs), 7.03 (1H, dd, J = 0.7, 3.2 Hz), 3.62 (3H, s), 2.74-2.66 (1H, m), 2.28-2.12 (2H, m), 2.08-2.02 (1H, m), 1.62-1.54 (1H, m), 1.13 (3H, d, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 153.9, 131.1, 126.7, 52.0, 44.8, 30.3, 21.1, 16.9. HRMS (M+·+1) m/e calcd for $C_9H_{14}NO_3$ 184.097. Found 184.098.

2-Amino(methoxycarbonyl)-4-*t*-butyl-cyclohex-2-en-1-one 27. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 40% Et_2O/60% pentanes), 42% yield. IR ($CHCl_3$) 3393, 3028, 3013, 2964, 2872, 1728, 1673, 1634 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (1H, s), 7.22 (1H, s), 3.67 (3H, s), 2.62-2.54 (1H, m), 2.39-2.25 (2H, m), 2.07-1.99 (1H, m), 1.70-1.57 (1H, m), 0.95 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7 (s), 154.1 (s), 132.2 (s), 130.7 (d), 52.0 (d), 46.2 (q), 36.5 (t), 33.2 (s), 27.2 (q), 23.7 (t). HRMS m/e calcd for $C_{12}H_{20}NO_3$ (M+·+1) 226.144. Found 226.145.

2-Amino(methoxycarbonyl)-6-methyl-cyclohex-2-en-1-one 28. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 10% Et_2O/90% pentanes), 40% yield. IR ($CHCl_3$) 3395, 3024, 3020, 3013, 2938, 2865, 1732, 1673, 1645 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.30 (1H, t, J = 3.9 Hz), 7.27 (1H, bs, -NH), 3.65 (3H, s), 2.46-2.36 (3H, m), 2.04-1.95 (1H, m), 1.74-1.61 (1H, m), 1.12 (3H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 196.4 (s), 154.0 (s), 131.5 (s), 126.9 (d), 52.0 (d), 40.7 (q), 30.4 (t), 23.6 (t), 15.1 (q). HRMS (M+·+1) m/e calcd for $C_9H_{14}NO_3$ 184.097. Found 184.097.

3-Amino(methoxycarbonyl)-8-ethyleneketal-1-methyl-[4.4.0]dodec-3-en-2-one 29. Pale yellow oil, purified *via* flash column chromatography (SiO_2; 40% Et_2O/60% pentanes), 56% yield. IR ($CHCl_3$) 3394, 3026, 3020, 3014, 2954, 2888, 1726, 1666, 1648 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (1H, bs, -NH), 7.14-7.12 (1H, m), 3.87 (4H, s), 3.70 (3H, s), 2.90-2.81 (1H, m), 2.3-2.1 (3H, m), 1.70 (1H, t, J = 13 Hz), 1.58-1.34 (4H, m) 1.14 (3H, s). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 197.2 (s), 154.1 (s), 129.7 (s), 122.6 (d), 108.7 (s), 64.2 (t), 64.1 (t), 52.1 (q), 45.1 (s), 39.4 (d), 37.4 (t), 31.9 (t), 31.5 (t), 27.2 (t), 24.3 (q). HRMS m/e calcd for $C_{15}H_{22}NO_5$ (M+·+1) 296.150. Found 296.150.

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