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Formation of pyridin-4(1*H*)-one versus 1*H*-azepin-4(7*H*)-one by treatment of 4-*tert*-butyldimethylsilyloxy-2-amino-1-aza-bicyclo[4.1.0]hept-3-enes with tetrabutylammonium fluoride

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Abstract—Cycloadducts **3** and **4** were treated with tetrabutylammonium fluoride and rapidly suffer cleavage on the three-membered ring to form either pyridin-4(1*H*)-one or 1*H*-azepin-4(7*H*)-one. When R^1 is an oxycarbonyl or a 2-pyridyl group and R^2 is a negative charge-stabilizing group (cases **3a**,**b** and **4f**) the C–C bond cleaves forming products **5**. However, when R^2=H (case **3c**) the ring expands to seven members. When R^1 is an acyl group the pyridin-4(1*H*)-one formation includes an unexpected shift of the carbonyl group.

1. Introduction

During our work on cycloadditions of 2*H*-azirines with the Danishefsky diene we have been observing the easy formation of azepinones, by treating the cycloadducts with silica.[1] 4-*tert*-Butyldimethylsilyloxy-2-azoyl-1-aza-bicyclo[4.1.0]-hept-3-enes were shown to be less sensitive to silica, but at lower pH the aziridine ring opened after nucleophilic attack to form tetrahydropyridinones.[2] To form a picture of the reactivity of these cycloadducts in basic medium, as we had in acidic medium, we decided to treat them with tetrabutylammonium fluoride as a privileged base. The C–N cleavage of the aziridine moiety forming part of a fused system (five- or six-membered rings) is well documented in the literature.[2,3] Simple aziridines also readily undergo C–N opening to relieve ring strain allowing access to amines,[4] but C–C cleavage to form azomethine ylides occurs at high temperatures. Hudlicky observed the C–C breakage in an aziridine fused to a five-membered ring by heating the sample at 520 °C, ca. 10^{-4} Torr.[5] Takano et al. also observed a similar reaction by thermolysis of aziridines at 200 °C.[6] On the other hand, aziridinyl anions are well known[7] and can be obtained, e.g., by desulfinylation,[8] desilylation[9] or deprotonation[10] of aziridines. An aziridinyllithium species was even stable at −78 °C and could be quenched with a range of electrophiles.[11] We observed now an easy C–C ring opening assisted by the formation of a highly conjugated system; the anion formed can be rapidly neutralized by migration of a proton. When an aroyl group is present at C-6 of 1-aza-bicyclo[4.1.0]hept-3-ene, C–C cleavage of the fused aziridine and development of the anion can be noticed by an unusual carbonyl migration.

2. Results and discussion

Cycloadducts **3** and **4** are formed by Diels–Alder cycloaddition of electrophilic 2*H*-azirines **2** to dienes **I** and **II**. Products **4a**, **4c** and **4f** are known compounds,[2] **4e** was prepared according to the procedure described for the synthesis of the other compounds **4**, products **3a–d** are preferred now, specially for the cost reasons. The starting 3-(*tert*-butyldimethylsilyloxy)-1-(pyrazol-1-yl)-1,3-butadiene **I** is obtained pure in 80% overall yield. Cycloadditions of diene **I** with the 2*H*-azirines **2a–d** are complete within several days at rt in moderate yields (41.5–59%). Also cycloaddition of diene **II** with 2*H*-azirine **2e** to form compound **4e** (yield=50%) occurs in 3 days under similar reaction conditions. In accordance with previous results of Diels–Alder cycloadditions of 2*H*-azirines to 1,3-dienes,[12] cycloadducts are isolated as single isomers and are estimated to have been formed by *endo* approach of reagents (Scheme 1). The main evidence for such selectivity was driven from the chemical shifts of H-7. Values are δ_H=3.94–3.66 ppm for compounds in which R^2=Ar, δ_H=2.10 ppm, when R^2=H, and δ_H ca. 2.50 ppm when R^2=aliphatic. The only exception to the *endo* rule in Diels–Alder reactions involving 2*H*-azirines occur with furan and its derivatives. In those cases,

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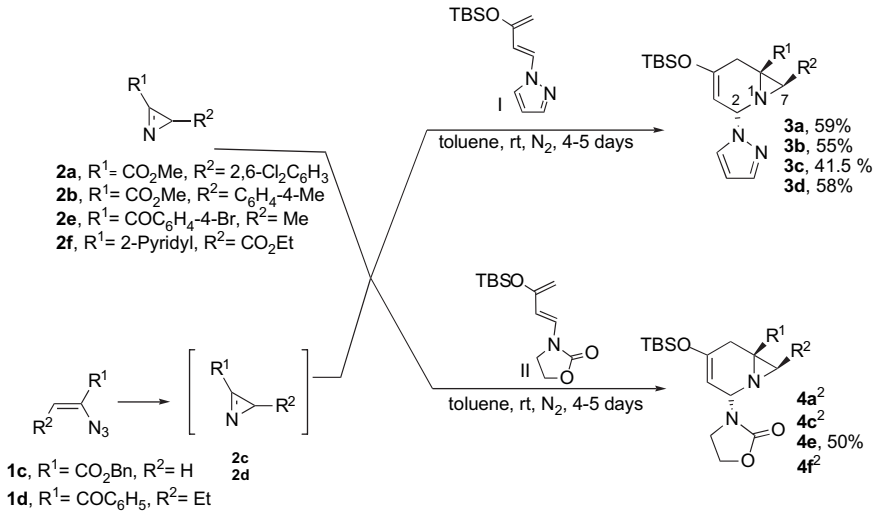
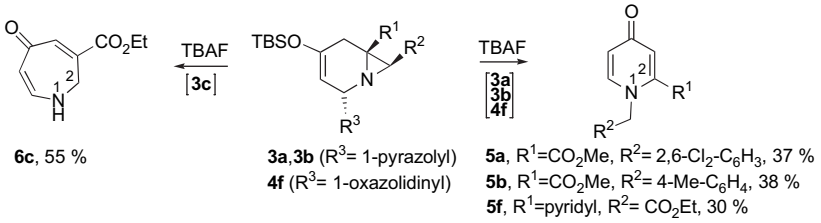


Scheme 1.

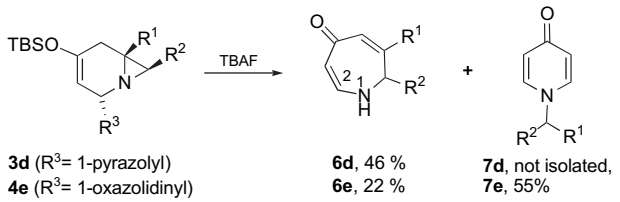


Scheme 2.

the primary cycloadducts are transformed into the thermodynamically more favoured products resulting from the *exo* approach of the reagents.[13]

When adducts **3** and **4** are treated with tetrabutylammonium fluoride they rapidly suffer cleavage of the three-membered ring to form either pyridin-4(1*H*)-one or 1*H*-azepin-4(7*H*)-one. When R^1 is an oxycarbonyl or a 2-pyridyl group and R^2 a negative charge-stabilizing group (cases **3a**,**b** and **4f**), compounds **5** are formed as exclusive products, rendered by the C6–C7 cleavage. But when the negative charge to be formed at the adjacent carbon atom to R^2 cannot be dispersed (case **3c**), the cleavage of C6–N1 occurs, installing the developing charge at the nitrogen atom and thus, the ring expanding to seven members (Scheme 2).

When R^1 is an aroyl group and R^2 is an aliphatic group, 1*H*-azepin-4(7*H*)-one **6** and pyridin-4(1*H*)-one **7** are formed simultaneously (Scheme 3). In one case, product **7** (**7d**) was not isolated, but it was unequivocally identified by ^{1}H NMR spectroscopy in the crude sample of the reaction.

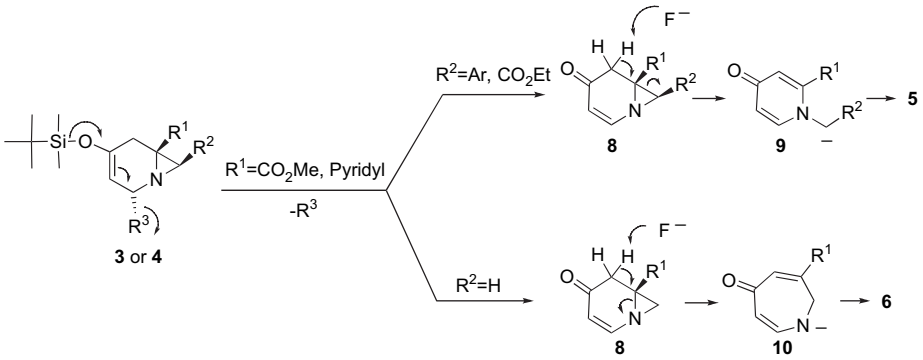


Scheme 3.

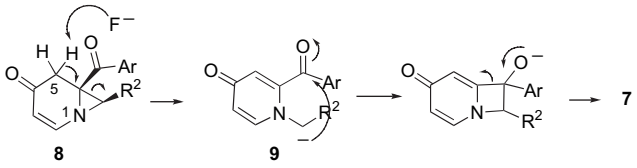
Cleavage of the *tert*-butyldimethylsilyl group in compounds **4** had been observed before in acidic non-nucleophilic medium: a conjugative elimination occurs with breakage of C2–N1 bond or the C2–N-oxazolidone bond. Treatment of compounds **3** and **4** with tetrabutylammonium fluoride solution consistently eliminates the heterocyclic group (oxazolidinyl or pyrazolyl) at C-2. Most probably the major responsibility for silyl group elimination was not the fluoride ion but H_2O present in wet solvents used in the reactions. The amount of fluoride ion seemed not to be critical either in the formation of compounds **5** or **6/7**. Both reactions go to completion with 0.3 equiv of tetrabutylammonium fluoride, which indeed shows that fluoride could not be consumed in the formation of a fluor–silicon bond. The role played by the fluoride ion possibly starts its action as a base, attacking H-5 in the intermediate compound, and continuing by carrying the proton to the developing negative charge with regeneration of the fluoride ion and formation of both products **5** and **6/7** (Scheme 4).

In Scheme 5 a possible mechanism for the formation of compounds **7** is envisaged. The ionic intermediate **9** is proposed to cyclize to a four-membered ring by attack of the carbanion to the nearby ketone group. The ring opening that follows is possibly assisted by the conjugation of the insipient charge with the α,β-unsaturated endocyclic ketone.

Rearrangements of carbonyl derivatives via enolate anion shift have been described before in the chemistry of the half-cage ketone **11** to the iso-half-cage ketone **13**.[14] The phenomenon starts by homoenolization of proton Ha/Hb,

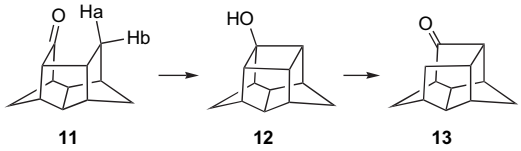


Scheme 4.



Scheme 5.

taken by a base, followed by four-membered ring closure to form the alcohol **12** and finally C–C bond opening to the rearranged half-cage ketone structure **13** (Scheme 6). The process occurs in ^{t}BuOH, in the presence of ^{t}BuOK, 0.9 M, at 175–200 °C. The extremely mild conditions under which the formation of compounds **7** occur are certainly due to the developing negative charge that spontaneously is formed at C-4, after elimination of the H-5 proton from the aminoenone **8** (compare Schemes 5 and 6).



Scheme 6.

The same kind of intermediate **9** was suggested in the synthesis of compounds **5**. In those cases no migration was assigned to the carbonyl group (R^1), which can be understood in view of the poor reactivity of esters compared to ketones.

Major features of compounds **5** in ^{1}H NMR spectra are the expected δ_H for H-5 and H-6, coupling together with J=7.5/7.8 Hz. The chemical shifts take into account the protective effect of the endocyclic nitrogen by conjugation over H-5 (δ_H=6.3–6.5 ppm), and the deprotective effect at β position of the unsaturated ketone moiety H-6 (δ_H=7.1–7.4 ppm). H-3 appears as a doublet with a long range coupling (J=2.7–3.0 Hz) to H-5. In compounds **5a** and **5b** ^{1}H–^{13}C NMR correlation spectra indicate C-5 at δ_C=118.2–119.8 ppm, C-3 at δ_C=120.6–122.5 ppm, C-6 at δ_C=140.0–143.2 ppm and C-2 at δ_C=140.0–140.9 ppm and a higher value for C-2 in compound **5f**, where 2-pyridyl is directly attached to C-2.

Compounds **7** showed H-5 and H-6 at δ_H in the same range of those in compounds **5**, but the signal integrals showed two protons under each signal. The conclusive feature for the assignment of structure **7** was H-1 in the carbon chain attached to the nitrogen pyridinone. Compound **7e** showed H-1 at δ_H=5.57 ppm as a quartet, J=7.2 Hz, coupling with the adjacent methyl group (R^2) and compound **7d** showed H-1 at δ_H=5.18 ppm, as a doublet of doublets, J=5.1 and 10.5 Hz by coupling with the two adjacent protons of the ethyl group (R^2). For compound **7e** ^{13}C signals appeared at the expected δ_C: C-3 and C-5 are coincident at δ_C=118.8 ppm and also C-2 and C-6 at δ_C=139.0 ppm; C-1 is in the aliphatic region (δ_C=63.9 ppm), deshielded both by the nitrogen and the aroyl group.

In compounds **6** the aliphatic proton(s) vicinal to NH appear at δ_H=4.15–4.62 ppm coupling with the mobile proton at the nitrogen atom and other vicinal protons if existing. When R^2=H, no geminal coupling is observed. The NH appeared at δ_H=5.58–6.22 ppm as a broad singlet that disappears after D_2O exchange. In the aminoenone moiety, H-β to the carbonyl showed up at δ_H=6.90–7.06 ppm and H-α at δ_H=5.27–5.29 ppm. The coupling constant between these protons is J=8.4–9.3 Hz. The other H-α to the endocyclic carbonyl shows up as a doublet with a small coupling constant J=2.1–2.4 Hz at δ_H=6.51–7.17 ppm.

3. Conclusion

The main point of this work is the exploitation of the reactivity of 4-*tert*-butyldimethylsilyloxy-2-amino-1-azabicyclo[4.1.0]hept-3-enes in the presence of tetrabutylammonium fluoride and the mechanistic understanding of their reactions. The fused aziridine ring opens in two different ways according to the nature of the R^2 groups attached at C-7: a pyridin-4(1*H*)-one is formed when R^2 is aromatic and 1*H*-azepin-4(7*H*)-one forms as a sole product when R^2 is H. When R^2 is aliphatic two types of compounds are formed simultaneously. An unusual rearrangement of an acyl group at C-6 takes place in the formation of the pyridin-4(1*H*)-one compound.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), doublets of doublets (dd), doublets of doublets of doublets (ddd), doublets of triplets (dt), triplets (t), quartets (q) and multiplets (m). *J* values are in Hertz and δ in parts per million. Infrared spectra were recorded on a Bomem MB 104 or on a Perkin–Elmer spectrophotometer. Samples were run as Nujol mulls and oils as thin films. MS spectra were recorded on a VG Autospec M. spectrometer. Microanalyses were performed in a LECO-CHNS-932 analyser. Melting points (mp) were determined on a Gallenkamp block and are uncorrected. Dry column flash chromatography was carried out using Kieselgel 60 and water pump vacuum. Toluene was dried over sodium followed by distillation. Dichloromethane (DCM) was dried over CaH_2. Acetonitrile (ACN) used was not dried. Petroleum ether 40–60 °C was distilled before use. 2*H*-Azirines **2a**,[14] **b**,[14] **f**,[15] benzyl α-azidoacrylate **1c**[16] and diene **II**[2] were obtained according to the literature. 2*H*-Azirines **2e** and **2d** were obtained by adapting the method of Hemetsberger for the synthesis of carbonyl 2*H*-azirines.[17,18] 4-(1*H*-Pyrazol-1-yl)but-3-en-2-one was obtained by repeating the procedure described in the literature.[19] Diene **I** was obtained by adapting the methodology described for the synthesis of diene **II**.[2] Compounds **4a**, **4c** and **4f** are known compounds and their syntheses were carried out according to the literature.[2] Tetrabutylammonium fluoride was used as 1.0 M solution in tetrahydrofuran (THF), sodium bis-(trimethylsilyl)amide (NaHMDS), 1.0 M in THF and TBDMSCl, and were purchased from Aldrich.

4.2. Synthesis of 1-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)-1*H*-pyrazole I

To a solution of 4-(1*H*-pyrazol-1-yl)but-3-en-2-one (0.69 g; 5.07 mmol) in recently dried THF (40 mL) was slowly added a diluted solution of NaHMDS (1.0 M in THF; 5.58 mL; 1.1 equiv) in dry THF (12 mL) under magnetic stirring at −78 °C for 1 h. After 1 h a solution of TBDMSCl (0.84 g; 5.07 mmol) in dry THF (5 mL) was added, and the reaction mixture was left to stir for 1 h at rt. The reaction mixture was poured into diethyl ether (40 mL), passed through a pad of Celite and the filtrate evaporated to give a brown oil that proved to be virtually pure 3-(*tert*-butyldimethylsilyloxy)-1-(pyrazol-1-yl)-1,3-butadiene **I** (1.25 g; 5.00 mmol; 98.6%) by ^{1}H NMR, which was used for further reactions without purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=0.24 (s, 6H, 2×Me), 1.02 (s, 9H, 3×Me), 4.38 (s, 1H, H-4), 4.42 (s, 1H, H-4), 6.37 (t, *J*=2.4 Hz, 1H, Py), 6.56 (d, *J*=13.5 Hz, 1H, H-2), 7.28 (d, *J*=13.5 Hz, 1H, H-1), 7.58 (d, *J*=2.4 Hz, 1H, Py), 7.63 (s, 1H, Py). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=−4.6 (Me), 18.3 (C), 25.8 (Me), 96.1 (C-4), 107.3 (CH, Py), 115.2 (C-2), 127.1 (C-1), 128.1 (CH), 128.2 (CH), 141.2 (CH, Py), 153.1 (CH, Py). IR (neat) ν_{max} (cm^{-1}) 2956, 2930, 2886, 2859, 1658, 1598. HRMS (ESI) calcd 251.1580 [M+1]; found 251.1578.

4.3. Synthesis of cycloadducts 3

4.3.1. Methyl 4-(*tert*-butyldimethylsilyloxy)-7-(2,6-dichorophenyl)-2-(1*H*-pyrazol-1-yl)-1-aza-bicyclo[4.1.0]-hept-3-ene-6-carboxylate 3a. To a solution of diene **I** (0.85 g; 0.00316 mol) in toluene (15 mL) was added 2*H*-azirine **2a** (0.63 g; 0.00316 mol) and the resulting mixture was stirred at rt for 5 days under nitrogen. The solvent was removed to afford a yellow oil, which was subjected to dry flash chromatography (silica; pet. ether/diethyl ether; polarity gradient) giving the title adduct **3a** as an oil (0.82 g; 1.86 mmol; 59%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=0.23 (s, 3H, Me), 0.25 (s, 3H, Me), 0.96 (s, 9H, 3×Me), 2.97 (dt, *J*=18.6, 2.4 Hz, 1H, H-5), 3.12 (d, *J*=18.6 Hz, 1H, H-5), 3.40 (s, 3H, OMe), 3.94 (s, 1H, H-7), 4.88 (t, *J*=2.1 Hz, 1H, H-3), 6.29–6.31 (m, 2H, H-2, 1H, Py), 7.01 (m, 1H, Ar), 7.14 (d, *J*=7.5 Hz, 2H, Ar), 7.55 (d, *J*=1.5 Hz, 1H, Py), 7.73 (d, *J*=2.1, 1H, Py). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=−4.5 (Me), −4.4 (Me), 17.9 (C), 25.5 (Me), 27.6 (C-5), 42.1 (C-7), 45.7 (C-6), 52.3 (Me), 72.3 (C-2), 98.2 (C-3), 105.7 (CH, Py), 128.1 (CH, Ph), 130.1 (CH, Ph), 131.1 (CH, Py), 135.6 (C, Ph), 140.1 (CH, Py), 149.5 (C-4), 170.0 (CO). IR (neat) ν_{max} (cm^{-1}) 3007, 1749, 1726, 1679, 1582, 1561, 1504. HRMS (ESI) calcd 516.1253 [M+Na]; found 516.1247.

4.3.2. Synthesis of methyl 4-(*tert*-butyldimethylsilyloxy)-7-(*p*-tolyl)-2-(1*H*-pyrazol-1-yl)-1-aza-bicyclo[4.1.0]hept-3-ene-6-carboxylate 3b. A solution of azirine **2b** (0.83 g; 4.44 mmol) in dry DCM (35 mL) was added to diene **I** (1.21 g; 4.84 mmol). The reaction mixture was stirred under nitrogen for 17 h at rt. The solvent was removed and the crude oil subjected to dry flash chromatography (silica; pet. ether/diethyl ether; polarity gradient) to give the product as a yellow solid (1.06 g; 2.42 mmol; 55%); mp 99.8–103.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=0.22 (s, 3H, Me), 0.25 (s, 3H, Me), 0.97 (s, 9H, 3×Me), 2.24 (s, 3H, Me), 2.69 (dt, *J*=18.6, 2.1 Hz, 1H, H-5), 3.07 (d, *J*=18.6 Hz, 1H, H-5), 3.42 (s, 3H, OMe), 3.66 (s, 1H, H-7), 5.02 (t, *J*=1.8 Hz, 1H, H-3), 6.25 (t, *J*=2.1 Hz, 1H, Py), 6.31 (br s, 1H, H-2), 6.89 (d, *J*=8.1 Hz, 2H, Ar), 6.96 (d, *J*=8.1 Hz, 2H, Ar), 7.51 (d, *J*=1.5 Hz, 1H, Py), 7.70 (d, *J*=2.1 Hz, 1H, Py). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=−4.6 (Me), −4.4 (Me), 17.9 (C), 21.0 (Me), 25.5 (Me), 28.2 (C-5), 42.4 (C-7), 47.8 (C-6), 51.9 (Me), 72.0 (C-2), 98.3 (C-3), 105.9 (CH, Py), 127.1 (CH, Ph), 128.4 (CH, Ph), 128.6 (CH, Ph), 131.8 (CH, Py), 136.6 (C, Ph), 140.0 (CH, Py), 148.8 (C-4), 169.8 (CO). IR (Nujol mull) ν_{max} (cm^{-1}) 3132, 3114, 1740, 1688, 1410. Anal. Calcd for $C_{24}H_{33}N_3O_3Si$: C, 65.57; H, 7.57; N, 9.56. Found: C, 5.54; H, 7.58; N, 9.36.

4.3.3. Synthesis of benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(1*H*-pyrazol-1-yl)-1-aza-bicyclo[4.1.0]hept-3-ene-6-carboxylate 3c. A solution of benzyl α-azido acrylate **1c** (1.20 g; 5.91 mmol) in dry toluene (180 mL) was heated under reflux for 5 h. The reaction mixture was cooled, the diene **I** (1.20 g; 5.91 mmol) added and the mixture stirred at rt for 8 days. The volume was reduced to half and a new portion of freshly prepared azirine, obtained from benzyl α-azido acrylate (1.20 g; 5.91 mmol) in toluene (180 mL), was added after being cooled. The reaction was continued for another 24 h and the solvent removed to give a dark oil that was

subjected to dry flash chromatography [pet. ether (3)/ether (1)] giving an yellow oil (1.04 g; 2.45 mmol; 41.5%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=0.19 (s, 3H, Me), 0.20 (s, 3H, Me), 0.94 (s, 9H, 3×Me), 2.10 (s, 1H, H-7), 2.41 (s, 1H, H-7), 2.68 (dd, *J*=0.9, 18.0 Hz, 1H, H-5), 2.94 (dm, *J*=18.0 Hz, 1H, H-5), 4.85 (t, *J*=2.1 Hz, 1H, H-3), 5.10 (d, *J*=12.3 Hz, 1H, CH_2Ph), 5.29 (d, *J*=12.3 Hz, 1H, CH_2Ph), 6.10 (br s, 1H, H-2), 6.30 (dd, *J*=1.8, 2.4 Hz, 1H, Py), 7.35 (s, 5H), 7.59 (d, *J*=2.1 Hz, 1H, Py), 7.62 (d, *J*=2.1 Hz, 1H, Py). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=−4.6 (Me), −4.4 (Me), 17.9 (C), 25.5 (Me), 27.1 (C-5), 30.0 (C-7), 39.4 (C-6), 65.8 (*C*H_2Ph), 72.2 (C-2), 97.6 (C-3), 105.9 (CH, Py), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 135.5 (C), 140.1 (CH, Py), 149.2 (C-4), 171.1 (CO). IR (neat) ν_{max} (cm^{-1}) 3054, 2986, 1739. HRMS (ESI) calcd 448.2032 [M+Na]; found 448.2027.

4.3.4. Synthesis of (4-(*tert*-butyldimethylsilyloxy)-7-ethyl-2-(1*H*-pyrazol-1-yl)-1-aza-bicyclo[4.1.0]hept-3-en-6-yl)(phenyl)methanone 3d. α-Azido acrylate **1d** (0.54 g; 2.69 mmol) was solubilized in dry toluene (20 mL) and heated under reflux for 3 h. The solution was concentrated to half of its volume and diene **I** (0.53 g; 2.12 mmol) was added. The reaction mixture was stirred for 4 days at rt. The solvent was removed and the crude oil was subjected to dry flash chromatography (silica; pet. ether/ether; polarity gradient) to give the product as a yellow oil. Yield (0.52 g; 1.23 mmol; 58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=0.18 (s, 3H, Me), 0.22 (s, 3H, Me), 0.38 (t, 3H, Me), 0.67–0.80 (m, 1H, CH_2Me), 0.93 (s, 9H, 3×Me), 1.41–1.56 (m, 1H, CH_2Me), 2.47 (dt, *J*=2.4, 17.7 Hz, 1H, H-5), 2.50–2.56 (m, 1H, H-7), 2.90 (d, *J*=17.7 Hz, 1H, H-5), 5.06 (t, *J*=2.1 Hz, 1H, H-3), 6.30 (dd, *J*=1.8, 2.1 Hz, 1H, Py), 6.35 (br s, 1H, H-2), 7.48 (t, *J*=8.1 Hz, 2H, Ar), 7.53–7.60 (m, 2H, Py+Ar), 8.02 (d, *J*=8.1 Hz, 1H, Py). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=−4.5 (Me), −4.3 (Me), 10.5 (Me), 17.9 (C), 23.9 (CH_2), 25.5 (Me), 29.2 (C-5), 42.1 (C-7), 50.3 (C-6), 72.0 (C-2), 98.8 (C-3), 106.0 (CH, Py), 128.6 (CH), 128.8 (CH), 129.5 (CH), 133.4 (CH, Py), 135.2 (C), 139.9 (CH, Py), 148.8 (C-4), 197.1 (CO). IR (neat) ν_{max} (cm^{-1}) 3062, 2960, 2931, 2886, 2859, 1677, 1580, 1579, 1514. HRMS (ESI) calcd 446.2240 [M+Na]; found 446.2234.

4.3.5. Synthesis of 3-(6-(4-bromobenzoyl)-4-(*tert*-butyldimethylsilyloxy)-7-methyl-1-aza-bicyclo[4.1.0]hept-3-en-2-yl)oxazolidin-2-one 4e. To a solution of diene **II** (0.27 g; 1.0 mmol) in toluene (15 mL) was added azirine **2e** (0.28 g; 1.0 mmol) and the resulting mixture was stirred at rt for 3 days under nitrogen. The solvent was removed to give a crude oil, which was subjected to dry flash chromatography (silica; pet. ether/diethyl ether; polarity gradient) to afford the adduct as a yellow solid (0.25 g; 0.50 mmol; 50%); mp 135–137 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=0.16 (s, 3H, Me), 0.18 (s, 3H, Me), 0.91 (s, 9H, 3×Me), 1.09 (d, *J*=6.0 Hz, 3H, Me), 2.41 (dm, *J*=17.7 Hz, 1H, H-5), 2.50 (q, *J*=6.0 Hz, 1H, H-7), 2.82 (d, *J*=17.7 Hz, 1H, H-5), 3.62 (t, *J*=7.8 Hz, 2H, CH_2ox), 4.38 (m, 2H, CH_2ox), 4.62 (t, *J*=1.8 Hz, 1H, H-3), 5.86 (br s, 1H, H-2), 7.63 (d, *J*=7.8 Hz, 2H, Ar), 7.94 (d, *J*=7.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=−4.6 (Me), −4.4 (Me), 15.1 (Me), 17.9 (C), 25.5 (Me), 29.2 (C-5), 34.6 (C-7), 41.4 (CH_2ox), 47.2 (C-6), 62.1 (CH_2ox), 65.6 (C-2), 98.1 (C-3), 128.8 (Ar), 131.1 (Ar), 131.9 (Ar), 134.2 (Ar), 149.5 (C-4), 157.4 (CO-ox), 196.9 (CO). IR (Nujol mull) ν_{max} (cm^{-1}) 3062, 2962, 2887, 1753, 1664, 1584. HRMS (ESI) calcd 507.1315 [M+1]; found 507.131.

4.4. Treatment of the cycloadducts 3 and 4 with tetrabutylammonium fluoride

4.4.1. Synthesis of pyridines 5.

4.4.1.1. Synthesis of methyl 1-(2,6-dichlorobenzyl)-4-oxo-1,4-dihydro-pyridine-2-carboxylate 5a. To a solution of cycloadduct **3a** (233 mg; 0.46 mmol) in ACN (5 mL) was added $Bu_4N^+F^-$ in THF (1 M, 146 μL, 0.15 mmol; 0.32 equiv) at 0 °C. The reaction mixture was stirred for 2 h at rt. The solvent was evaporated, DCM (10 mL) was added and then a multiple washing with water (3×15 mL) was carried out. The organic layers were combined and dried over $MgSO_4$. The solvent was removed to afford a yellow oil that spontaneously crystallize (54 mg; 0.17 mmol; 37%); mp 119–121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=3.98 (s, 3H, Me), 5.64 (s, 2H, CH_2), 6.33 (dd, *J*=3.0, 7.8 Hz, 1H, H-5), 6.94 (d, *J*=3.0 Hz, 1H, H-3), 7.11 (d, *J*=7.8 Hz, 1H, H-6), 7.31 (dd, *J*=6.6, 9.3 Hz, 1H, Ar), 7.43–7.40 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=51.1 (CH_2), 53.5 (Me), 119.8 (CH, C-5), 122.0 (CH, C-3), 129.1 (CH, Ar), 131.3 (CH, Ar), 136.8 (C), 140.5 (C-6), 140.9 (C-2), 163.3 (CO), 178.5 (CO, C-4). IR (Nujol mull) ν_{max} (cm^{-1}) 1748, 1625, 1558, 1537. HRMS (ESI) calcd 312.0194 [M+1]; found 312.0192.

4.4.1.2. Synthesis of methyl 1-(4-methylbenzyl)-4-oxo-1,4-dihydro-pyridine-2-carboxylate 5b. To a solution of cycloadduct **3b** (0.24 g; 0.55 mmol) in ACN (13 mL) was added $Bu_4N^+F^-$ in THF (1 M; 550 μL; 0.55 mmol) at 0 °C. The reaction mixture was stirred for 1 h at rt. The solvent was evaporated, DCM (15 mL) was added and then a multiple washing with water (3×15 mL) was carried out. The organic layers were combined and dried over $MgSO_4$. The solvent was removed and a yellow oil was obtained (54 mg; 0.21 mmol; 38%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=2.33 (s, 3H, Me), 3.80 (s, 1H, Me), 5.30 (s, 2H, CH_2), 6.44 (dd, *J*=3.0, 7.5 Hz, 1H, H-5), 6.91 (d, *J*=3.0 Hz, 1H, H-3), 6.99 (d, *J*=7.8 Hz, 2H, Ar), 7.15 (d, *J*=7.8 Hz, 2H, Ar), 7.43 (d, *J*=7.8 Hz, 2H, H-6). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=21.1 (Me), 53.3 (Me), 57.4 (CH_2), 119.4 (CH, C-5), 122.5 (CH, C-3), 127.1 (CH, Ph), 129.7 (CH, Ph), 132.3 (C, Ph), 138.5 (C, Ph), 140.0 (C-2), 143.2 (C-6), 162.9 (CO), 178.8 (CO, C-4). IR (neat) ν_{max} (cm^{-1}) 3395, 3028, 2955, 2925, 1738, 1632, 1567, 1515. HRMS (ESI) calcd 258.1130 [M+1]; found 258.1126.

4.4.1.3. Synthesis of ethyl 2-(4-oxo-2-(pyridin-2-yl)-pyridin-1(4*H*)-yl)acetate 5f. To a solution of adduct **4f** (0.16 g; 0.36 mmol) in ACN (5 mL) was added $Bu_4N^+F^-$ in THF (1.0 M, 124 μL; 0.32 equiv) at 0 °C. The resulting mixture was stirred at rt for 2 h. DCM (20 mL) was added, the organic phase washed with H_2O (3×15 mL), dried with $MgSO_4$ and solvent removed to afford an oil contaminated with the reagent ammonium salt. The crude was dissolved in Et_2O (20 mL) and washed with H_2O (20 mL). The aqueous phase was extracted with DCM (3×10 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated to give the pure title pyrimidone **5f** as a yellow

oil (28 mg; 0.108 mmol; 30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=1.20 (t, J=7.2 Hz, 3H, Me), 4.15 (q, J=7.2 Hz, 2H, CH_2), 4.72 (s, 2H, CH_2), 6.45 (dd, J=2.7, 7.5 Hz, H-5), 6.55 (d, J=2.7 Hz, 1H, H-3), 7.33 (d, J=7.5 Hz, 1H, H-6), 7.37–7.41 (m, 1H, Py), 7.58 (dm, J=7.8 Hz, 1H, Py), 7.85 (td, J=1.5, 8.7 Hz, 1H, Py), 8.62–8.65 (m, 1H, Py). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=14.0 (Me), 55.0 (CH_2), 61.9 (CH_2), 118.2 (CH, C-5), 120.6 (CH, C-3), 124.2 (CH, Py), 124.7 (CH, Py), 137.8 (CH, Py), 143.2 (C-6), 148.8 (CH, Py), 149.0 (C-Py or C-2), 152.6 (C-2 or C-Py), 167.5 (CO), 179.3 (CO, C-4). IR (neat) ν_{max} (cm^{-1}) 2963, 1747, 1633, 1572. HRMS (ESI) 259.1082 [M+1]; found 259.1110.

4.4.2. Synthesis of azepines 6 and pyridines 7.

4.4.2.1. Synthesis of benzyl 5-oxo-2,5-dihydro-1*H*-azepine-3-carboxylate 6c. To a solution of adduct **3c** (0.26 g; 0.58 mmol) in ACN (5 mL) was added $Bu_4N^+F^-$ in THF (1.0 M; 185 μL; 0.32 equiv) at 0 °C. The resulting mixture was stirred at rt for 2 h. DCM (15 mL) was added, the organic phase washed with H_2O (3×15 mL), dried with $MgSO_4$ and the solvent was removed to afford a crude oil, which was subjected to dry flash chromatography (silica; pet. ether/diethyl ether; polarity gradient). A yellow oil was obtained (0.08 g; 0.32 mmol; 55%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=4.15 (d, J=5.1 Hz, 2H, CH_2, H-2),[†] 5.24 (s, 2H, CH_2), 5.29 (dt, J=2.4, 8.4 Hz, 1H, H-6), 6.22 (br s, 1H, NH), 7.06 (dd, J=5.7, 8.4 Hz, 1H, H-7), 7.17 (d, J=2.4 Hz, 1H, H-4), 7.36 (s, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=42.4 (CH_2, C-2), 67.4 (CH_2), 103.7 (CH, C-6), 128.1 (CH, Ar), 128.5 (CH, Ar), 129.2 (C), 135.1 (C), 149.3 (CH, C-7), 142.1 (CH, C-4), 165.2 (CO), 189.2 (CO, C-5). IR (neat) ν_{max} (cm^{-1}) 3180, 1701, 1635, 1590, 1561, 1505. HRMS (ESI) calcd 244.097 [M+1]; found 244.0974.

4.4.2.2. Synthesis of 6-benzoyl-7-ethyl-1*H*-azepin-4(7*H*)-one 6d. To a solution of the adduct **3d** (0.34 g; 0.80 mmol) in ACN (10 mL) was added $Bu_4N^+F^-$ in THF (1 M; 260 μL; 0.26 mmol; 0.32 equiv) at 0 °C. The resulting solution was stirred at rt for 1 h. The solvent was evaporated, and the crude material[‡] dissolved in ether (20 mL), washed with water (2×20 mL), dried over $MgSO_4$ and evaporated to give a yellow oil, pure product **6d**. Yield (0.09 g; 0.37 mmol; 46%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=0.95 (t, J=7.5 Hz, 3H, Me), 1.85 (m, 1H, CH_2Me), 2.05–2.20 (m, 1H, CH_2Me), 4.45 (dt, J=6.3, 9.3 Hz, 1H, H-7), 5.29 (ddd, J=1.8, 2.4, 9.3 Hz, 1H, H-3), 5.58 (br s, 1H, NH), 6.62 (d, J=2.4 Hz, 1H, H-5), 6.91 (dd, J=7.2, 9.3 Hz, 1H, H-2), 7.30 (t, J=7.5 Hz, 2H, Ar), 7.60 (t, J=6.3 Hz, 1H, Ar), 7.80 (d, J=6.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=10.7 (Me), 22.0 (CH_2), 55.4 (C-7), 102.8 (C-3), 128.5 (CH, Ar), 129.6 (CH, Ar), 132.9 (CH, Ar), 136.6 (C), 141.4 (C-5), 141.7 (C-6), 145.6 (C-2), 189.1 (CO), 197.0 (CO). R (DCM) ν_{max} (cm^{-1}) 3252, 3054, 1653, 1576, 1519. HRMS (ESI) 264.1000 [M+Na]; found 264.0996.

4.4.2.3. Synthesis of 6-(4-bromobenzoyl)-7-methyl-1*H*-azepin-4(7*H*)-one 6e and 1-(1-(4-bromophenyl)-1-oxopropan-2-yl)pyridin-4(1*H*)-one 7e. To a solution of adduct **4e** (0.15 g; 0.296 mmol) in ACN (5 mL) was added $Bu_4N^+F^-$ in THF (1.0 M; 93 μL; 0.095 mmol; 0.32 equiv) at 0 °C. The mixture was stirred at rt for 2 h. DCM (15 mL) was added, the organic phase washed with H_2O (3×15 mL), dried over $MgSO_4$ and solvent was removed to afford an oil, that spontaneously crystallizes to give the title pyridinone **7e** (50 mg; 0.163 mmol; 55%); mp 120–123 °C. The mother liquid was also recovered and the solvent evaporated to afford azepinone compound **6e** (20 mg; 0.065 mmol; 22%). Compound **7e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=1.75 (d, J=7.2 Hz, 3H, Me), 5.57 (q, J=7.2 Hz, 1H, CH), 6.41 (d, J=7.5 Hz, 2H), 7.67 (d, J=7.5 Hz, 2H), 7.82 (d, J=8.7 Hz, 2H), 7.82 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=18.7 (Me), 63.9 (C-1′), 118.8 (C-3+C-5), 130.0 (Ar), 132.7 (Ar), 139.0 (C-2+C-6), 178.9 (CO), 193.9 (CO). R (Nujol mull) ν_{max} (cm^{-1}) 2918, 2850, 1692, 1638, 1584, 1564. HRMS (ESI) calcd 306.0130 [M+1]; found 306.0135.

*Compound **6e***: ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H=1.57 (d, J=7.2 Hz, Me), 4.62 (quint, J=6.6 Hz, 1H, H-7), 5.27 (ddd, J=1.5, 2.1, 8.7 Hz, 1H, H-3), 6.15 (br s, 1H, NH), 6.51 (d, J=2.1 Hz, 1H, H-5), 6.90 (dd, J=6.9, 8.7 Hz, 1H, H-2), 7.61 (d, J=8.7 Hz, 2H), 7.65 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C=15.3 (Me), 58.4 (C-7), 102.1 (C-3), 128.3 (C), 131.0 (CH, Ar), 131.7 (CH, Ar), 134.8 (C), 140.0 (C-5), 141.7 (C-6), 147.2 (C-2), 188.2 (CO), 195.4 (CO). R (DCM) ν_{max} (cm^{-1}) 3230, 2962, 1653, 1584, 1534. HRMS (ESI) 3056.0129 [M+1]; found 306.012.

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[†] After D_2O exchange collapses to a singlet.

[‡] Some absorptions in the ^{1}H NMR spectrum of the crude material were attributed to the pyridinone **7d**: 5.18 (dd, J=5.1, 10.5 Hz, 1H, H-1), 6.42 (d, J=7.5 Hz, 2H), 7.43 (d, J=7.5 Hz, 2H).

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