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An anionic condensation and fragmentation approach to substituted 3-pyrrolines

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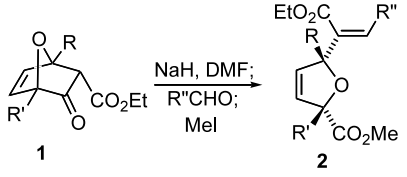
Abstract—We have identified an anionic condensation and fragmentation sequence from the coupling of 7-azabicyclo[2.2.1]heptenones with aldehydes. This reaction leads to the stereoselective formation of disubstituted 3-pyrrolines as are present in a wide array of bioactive molecules.

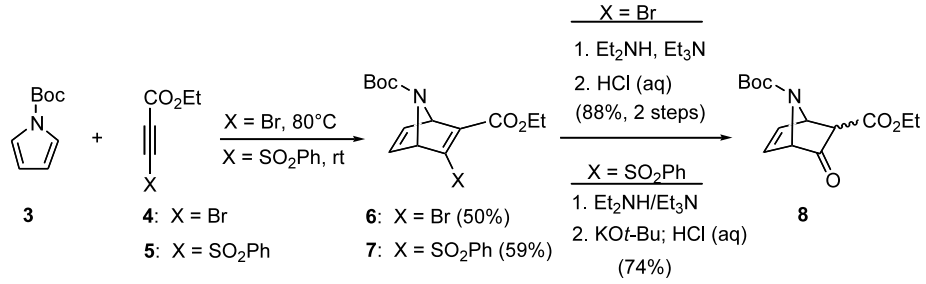
Their presence in a variety of biologically active targets have made substituted pyrroles and pyrrolines popular targets for chemical synthesis.[1] Our interest in these agents came shortly after our discovery that oxabicyclo[2.2.1]heptenones undergo a condensation and fragmentation sequence resulting in the formation of dihydrofurans when subjected to aldehydes and anionic conditions (Eq. (1)).[2]



1 2 (1)

By applying the reaction outlined in Eq. (1) to the analogous nitrogen containing system (i.e. 7-azabicyclo[2.2.1]heptenones), we reasoned that we would be able to access potentially important 3-pyrrolines including pyrroline containing natural products.[3] Described herein is the realization of this goal through the anionic coupling of 7-azabicyclo[2.2.1]heptenone **8** with substituted aldehydes.

In order to examine the aforementioned anionic coupling chemistry, we required ready access to 7-azabicyclo[2.2.1]heptenones and turned to pyrrole Diels–Alder chemistry.[4] In an analogous fashion to our approach to the chemical synthesis of **1**, Boc pyrrole **3** was condensed with bromo-propynoate **4**[5] to give 7-azabicyclo[2.2.1]heptadiene **6**.[6] Hydrolysis of the vinyl bromide then provided coupling precursor **8**. In an effort to avoid the use of **4**,[7] we also carried out the cycloaddition between **3** and alkynyl sulphone **5**[8] to generate **7**. Hydrolysis of the vinyl sulphone was accomplished on large scale by sequentially exposing **7** to Et_2NH/NEt_3, KO*t*-Bu,[9] and acid to give **8** in 74% yield (Scheme 1).



Scheme 1. Synthesis of azabicyclo[2.2.1]heptenone **8**.

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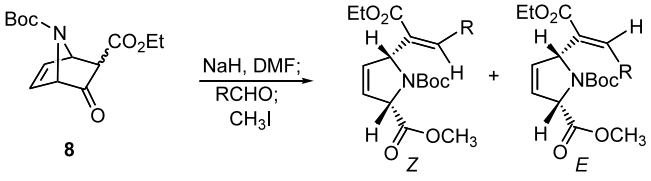
With 7-azabicyclo[2.2.1]heptenone **8** in hand, we examined its anionic condensation chemistry with aldehydes. Our efforts commenced with the anionic condensation of **8** with benzaldehyde in the presence of NaH (Table 1, entry 1). This resulted in the generation of 3-pyrroline **9** in 76% yield as a 2.5:1, *E*:*Z* mixture of olefin isomers.[13] By way of comparison, the anionic coupling of the corresponding 7-oxabicyclo[2.2.1]heptenone gave the dihydrofuran analogous to **9** in 57% yield.[10] We were pleased to find that other aryl substituted aldehydes were also amenable to this transformation. That is, when subjected to **8** and NaH, furfural and anisaldehyde gave 3-pyrrolines **10** and **11** in 87 and 70% yields, respectively (entries 2 and 3). The reaction was not limited to aryl aldehydes; the coupling of **8** with propanal and isobutyraldehyde gave **12** and **13**, respectively (entries 4 and 5). Interestingly, the major olefin isomer was reversed in these latter two reactions.[11] Ethyl glyoxylate was also utilized in the coupling reaction with **8** to give **14**[13] in 83% yield as a 4:1, *Z*:*E* mixture of olefin isomers (entry 6). The transformation of **8** into the corresponding pyrroline appears to be somewhat sensitive to steric inhibition; attempted condensation of **8** with pivaldehyde did not give the expected pyrroline but instead resulted in the formation of alkylated 7-azabicyclo[2.2.1]heptenone upon quenching the anion of **8** with MeI (entry 7).

Our current working hypothesis for the azabicyclo[2.2.1]heptenone to pyrroline transformation is outlined in Scheme 2 for the condensation with benzaldehyde. We believe that the initial aldolate undergoes a cyclization reaction onto the pendant ketone to give oxetane intermediate **15**. Anionic fragmentation relieves the ring strain present in **15** and leads to the corresponding 3-pyrroline **16**.[12]

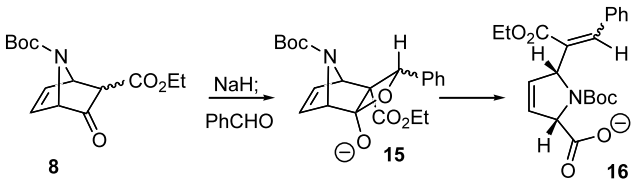
To conclude, we have identified a novel anion mediated condensation and fragmentation reaction of azabicyclo[2.2.1]heptene ring systems. Our current efforts are focused on further evaluating the scope of this reaction as well as its use in the synthesis of pyrroline containing natural products.

Table 1. Azabicyclo[2.2.1]heptenone–aldehyde condensations



Entry	R	Pyrroline	Yield (%)	*E*:*Z*
1	Ph	**9**	76	2.5:1[a]
2	2-Furyl	**10**	87	2:1[a]
3	*p*-OMePh	**11**	70	4:1[a]
4	Et	**12**	84	1:4[a]
5	*i*-Pr	**13**	60	1:18[a]
6	CO_2Et	**14**	83	1:4[b]
7	*t*-Bu	–	–[c]	

[a] From ^1H NMR integration of the vinyl signals.
[b] From ^1H NMR integration of the methyl ester signals.
[c] Product was methylated **8**.



Scheme 2. Working hypothesis for the condensation of azabicyclo[2.2.1]heptenones with aldehydes.

Acknowledgements

We are grateful to the National Science Foundation (CHE-9983715) for support of this work. Support of the NMR facility in the Department of Chemistry at the University of Arizona by the National Science Foundation under Grant No. 9729350 is also gratefully acknowledged. We are indebted to Dr. Neil Jacobsen and Dr. Arpad Somagyi for help with NMR and mass spectra experiments, respectively.

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4. For a review on the synthesis of 7-azabicyclo[2.2.1]heptenes which includes Diels–Alder approaches see: Chen, Z.; Trudell, M. L. *Chem. Rev*. **1996**, *96*, 1179.
5. (a) Heaton, C. D.; Noller, C. R. *J. Am. Chem. Soc*. **1949**, *71*, 2948; (b) Chamberlain, P.; Rooney, A. E. *Tetrahedron Lett*. **1979**, *20*, 383; (c) Leroy, J. *Tetrahedron Lett*. **1992**, *33*, 2969.
6. Zhang, C.; Trudell, M. L. *J. Org. Chem*. **1996**, *61*, 7189.
7. WARNING: Bromoalkyne **4** is a known lachrymator. In addition, the use of **4** has led to painful skin rashes in spite of the use of protective gear and a well ventilated, high flow fume hood.

8. Shen, M.; Schultz, A. G. *Tetrahedron Lett*. **1981**, *22*, 3347.
9. While the KO*t*-Bu step was not needed on small scale (0.07 mmol), the yield of **8** was much lower (10–25%) on larger scale when the KO*t*-Bu step was omitted. Presumably, KO*t*-Bu serves to eliminate the sulphone from the amino sulphone intermediate that was generated from the reaction of **7** with NEt_3 and $HNEt_2$.
10. When exposed to the condensation reaction with aldehydes, oxabicyclo[2.2.1]heptenones having substitution at the bridgehead gave much higher yields of dihydrofurans than those lacking substitution. See Ref. 2.
11. The olefin geometry was determined spectroscopically from the presence (*Z*-isomer) or lack (*E*-isomer) of NOEs between the exocyclic vinyl hydrogen and the ethyl ester hydrogens.
12. As indirect evidence of this mechanism, we have found that **1** undergoes a two-carbon ring expansion reaction when exposed to unsaturated ketones and esters. See Ref. 2b and: Rainier, J. D.; Xu, Q. *Org. Lett*. **1999**, *1*, 1161.
13. Representative characterization data: **9** (*Z*-isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.26 (m, 6H), 6.09 (m, 0.3H), 6.04 (m, 0.7H), 5.84 (m, 0.7H), 5.79 (m, 0.3H), 5.36 (d, $J=1.6$ H, 0.7 Hz), 5.18 (d, $J=2.4$ Hz, 0.7H), 5.12 (d, $J=2.3$ Hz, 0.3H), 4.16 (q, $J=7.1$ Hz, 2H), 3.80 (s, 2H), 3.79 (s, 1H), 1.46 (s, 3H), 1.45 (s, 6H), 1.14–1.10 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.2, 168.1, 168.0, 153.6, 152.9, 136.0, 135.5, 132.8, 132.7, 132.5, 131.5, 128.7, 128.4, 128.3, 128.0, 128.0, 127.9, 127.8, 123.5, 123.4, 80.8, 80.7, 67.4, 67.2, 67.0, 66.5, 60.7, 52.4, 52.2, 28.3, 28.2, 13.7; IR (CCl_4) 2957, 2369, 1721, 1387 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{28}NO_7$ (MH^+) 402.1917, found 402.1917. **9** (*E*-isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.27 (m, 6H), 6.04 (s, 0.7H), 5.96–5.88 (m, 1.3H), 5.72 (s, 0.3H), 5.70 (s, 0.7H), 5.12 (s, 0.7H), 5.03 (s, 0.3H), 4.32–4.25 (m, 1H), 4.12–4.07 (m, 1H), 3.75 (s, 3H), 1.44–1.35 (m, 3H), 1.27 (s, 7.8 H), 1.25 (s, 1.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.1, 167.1, 154.4, 153.7, 138.4, 137.3, 134.9, 134.6, 133.4, 132.7, 131.0, 130.7, 129.4, 129.4, 128.4, 128.3,128.1, 127.5, 126.9, 125.5, 124.8, 80.6, 80.2, 66.9, 66.8, 62.9, 62.7, 62.7, 60.6, 52.0, 51.8, 28.1, 14.0; IR (CCl_4) 2974, 1797, 1729, 1400 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{28}NO_7$ (MH^+) 402.1917, found 402.1915. **14**: (*E*-isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38–6.36 (m, 1H), 6.25 (s, 1H), 5.93–5.82 (m, 2H), 5.08–5.07 (m, 0.66H), 5.00 (s, 0.33H), 4.27–4.09 (m, 4H), 3.70 (s, 2H), 3.69 (m, 1H), 1.39 (s, 6H), 1.37 (s, 3H), 1.29–1.21 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 169.0, 166.0, 165.2, 154.1, 149.6, 149.1, 130.8, 130.4, 130.0, 125.2, 125.1, 123.2, 123.1, 80.8, 80.6, 66.8, 66.7, 63.0, 62.8, 61.6, 61.4, 60.9, 52.1, 52.0, 28.1, 28.0, 14.1, 14.0, 14.0, 13.9; IR (CCl_4) 2981, 1709, 1387, 1178,1060 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{28}NO_8$ (MH^+) 398.1815, found 398.1803. **14** (*Z*-isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, $J=0.7$ Hz, 0.6H), 6.53 (s, 0.4H), 6.01–5.96 (m, 1H), 5.84–5.79 (m, 1H), 5.31 (s, 0.4H), 5.24 (s, 0.6H), 5.14 (dd, $J=4.8$, 2.4 Hz, 0.6H), 5.08 (d, $J=2.4$ Hz, 0.4H), 4.32–4.28 (m, 2H), 4.24–4.17 (m, 2H), 3.79 (s, 1.8 H), 3.78 (s, 1.2H), 1.46 (s, 5H), 1.45 (s, 4H), 1.32–1.26 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 170.0,166.3, 165.8, 165.4, 153.2, 144.9, 144.6, 130.8, 124.6, 124.5, 123.8, 122.4, 81.3, 81.1, 66.9, 66.5, 66.4, 66.3, 61.5, 60.8, 60.8, 52.4, 52.3, 28.1, 28.1, 14.0, 13.9; IR (CCl_4) 2999, 1710,1385 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{28}O_8N$ (MH^+) 398.1815, found 398.1805.