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An Azomethine Ylide Approach to Complex Alkaloid-like Heterocycles

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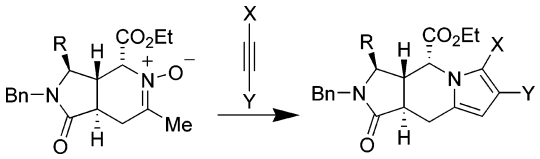
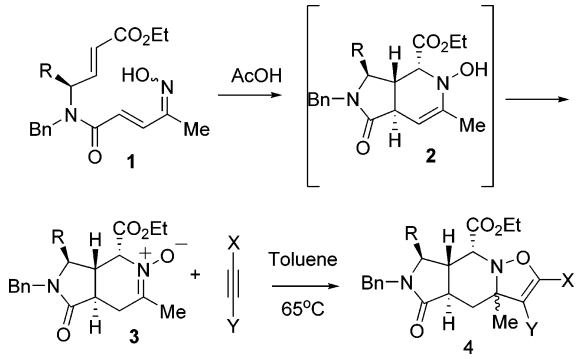


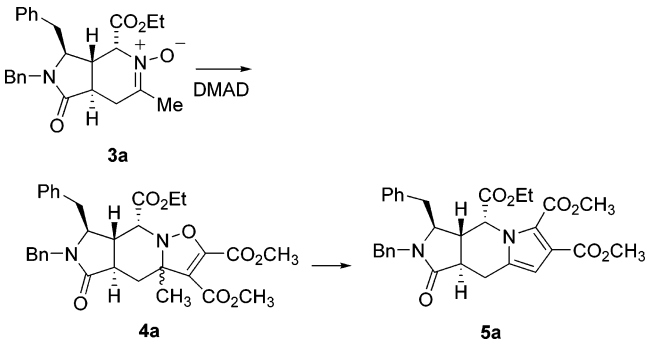
The nitrone above is readily available via the intramolecular aza Diels−Alder reaction of an amino acid derived triene in acetic acid. Subsequent treatment of the nitrone in refluxing toluene with substituted actetylenes produced the pictured pyrrole. At lower temperatures a 2,3-dihydroisoxazole, which is the product of a 3 + 2 dipolar cycloaddition, is produced. Upon heating in refluxing toluene the 2,3-dihydroisoxazole is converted to the pyrrole.

We previously described the synthesis of 2,3-dihydroisoxazoles in our studies on the intramolecular aza Diels−Alder reaction using α,β unsaturated oxime **1** as the diene component (Scheme 1).[1] In these studies we found that the Diels−Alder reaction occurred but was followed by a rearrangement to the nitrone **3**. The rearrangement of *N*-hydroxyenamines to nitrones had been previously reported in other systems but never as a thermodynamic sink for an aza Diels−Alder reaction.[2] We calculated **3** to be 11 kcal more stable than the *N*-hydroxyenamine **2**.[3] In order to chemically verify that it was indeed a nitrone, we allowed it to react with a number of dipolarophiles and isolated a series of 2,3-dihydroisoxazoles **4**. In our initial study, the 3 + 2 cycloadditions were carried out at 60−80 °C in toluene. In a subsequent study, compound **3a** and DMAD were heated at reflux in toluene and gave a pure compound with spectral data inconsistent with the expected structure **4** (Scheme 2). We repeated the reaction at 65 °C, and this afforded a compound with spectra identical to those of a previously isolated sample of **4**. To determine if it was a thermal rearrangement, we then dissolved compound **4** in toluene and heated it to reflux for 2 h. We observed complete conversion to the initially isolated structure. This indicated to us that the isolated product was due to a rearrangement of the 2,3-dihydroisoxazole **4**. After careful spectral analysis including a single-crystal X-ray (Figure 1), we determined the compound to be the fused pyrrole **5**, which was isolated as a single enantiomer.[4,5]

SCHEME 1. 4 + 2, 3 + 2 Approach to Amino Acid Derived Dihydroisoxazoles



SCHEME 2. One-Pot Pyrrole Synthesis



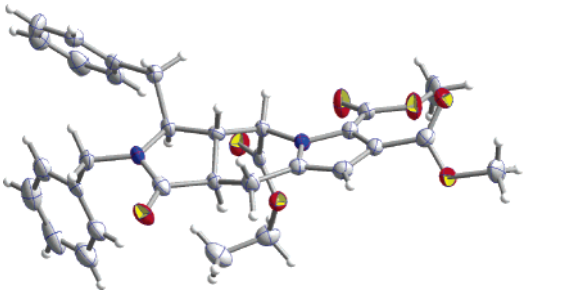


FIGURE 1. ORTEP Diagram of **5a**.

As these pyrroles were interesting "alkaloid-like" structures, we decided to examine the generality of the preparation. We examined the addition of four different dipolarophiles (DMAD, methylpropynoate, methyl 3-phenylpropynoate, and methyl 3-trifluoromethylpropynoate) to two different nitrones (**2a** and **2b**) that were easily prepared as single diasteriomers by previously described methods.[1] We found that in all cases we could directly access the pyrrole from the nitrone and dipo-

(1) François, D.; Maden, A.; Murray, W. V. *Org. Lett.* **2004**, *6*, 1931−1934.

(2) Alcaide, B.; Almendros, P.; Aly, M. F.; Pardo, C.; Sáez, E.; Torres, M. R. *J. Org. Chem.* **2002**, *67*, 7004−7013.

(3) (a) West, O.; Houk, K. N. *Top. Curr. Chem.* **1996**, 183 (Density Functional Theory IV), 1. (b) CAChe (v 3.8) worksystem, Oxford Molecular, Beaverton, OR.

(4) Lopez-Calle, E.; Eberbach, W. *J. Chem. Soc., Chem. Commun.* **1994**, *3*, 301−2, C.

(5) Schmidt, G.; Stracke, H. U.; Winterfeltd, E. *Chem. Ber.* **1970**, *103*, 3196−3204.

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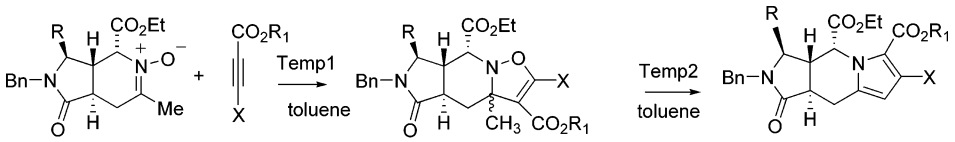
TABLE 1. Pyrrole Synthesis Details



3a-b 4a-e 5a-e

nitrone	R	X	R_1	temp 1/h	yield % (**4**)	temp 2/h	yield % (**5**)
3a	Bn	CO_2Me	CH_3	65 °C/2 h	71 (**4a**)	110 °C/2 h	72 (**5a**)
				110 °C/2 h			59 (**5a**)
3b	iPr	CO_2Me	CH_3	65 °C/2 h	76 (**4b**)	110 °C/2 h	70 (**5b**)
				110 °C/2 h			63 (**5b**)
3b	iPr	H	CH_3	80 °C/2 h	72 (**4c**)	110 °C/2 h	70 (**5c**)
				110 °C/2 h			56 (**5c**)
3b	iPr	Ph	ethyl	75 °C/4 h	78 (**4d**)	110 °C/15 h	58 (**5d**)
				110 °C/15 h			43 (**5d**)
3b	iPr	CF_3	ethyl	80 °C/2 h	83 (**4e**)	110 °C/2 h	58 (**5e**)
				110 °C/2 h			43 (**5e**)

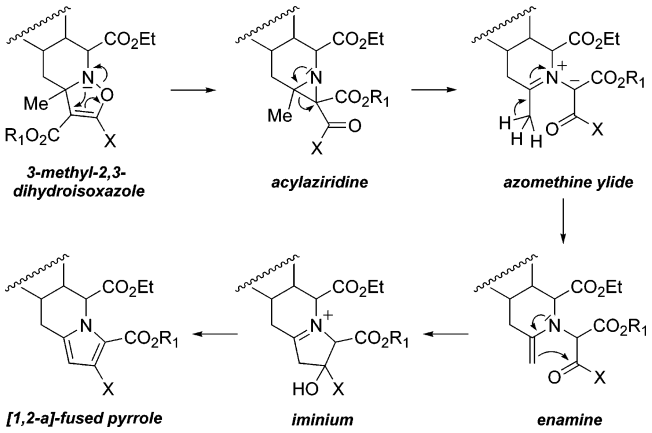


FIGURE 2. Proposed isoxazole rearrangement mechanism.

larophile if the reaction mixture were heated in refluxing toluene. We also found that in each case we could isolate the intermediate 2,3-dihydroisoxazole and convert it to the pyrrole by reflux in toluene. We found no advantage in isolating the intermediate isoxazole **4** with regard to yield or purity profile. The rearrangement proceeded under remarkably similar conditions except in the case where X is phenyl. This is probably due to a less reactive intermediate discussed in the mechanism proposed below. The results of these studies are summarized in Table 1. The structure and stereochemistry of **5a**−**e** has been assigned by NOE and HMBC.

Winterfeldt previously studied the mechanism of the thermal rearrangement and proposed two potential pathways.[5] Recent reports support an azomethine ylide intermediate in the isoxazole to pyrrole conversion.[6] The proposed mechanism is outlined in Figure 2. The initial step is the formation of the acylaziridine through N−O bond cleavage and followed by bond reorganization. The acylaziridine ring opens to give the azomethine ylide. Tautomerization and protonation generates an enamine intermediate which cyclizes to an iminium which then dehydrates and isomerizes to the pyrrole. This mechanism would also explain the slower formation of **5d** because the phenyl ketone is the least reactive carbonyl in the enamine addition step.

(6) (a) Zhao, B-X.; Yu, Y.; Eguchi, S. *Tetrahedron* **1996**, *52* (37), 12049−12060. (b) Lopez-Calle, E.; Keller, M.; Eberbach, W. *Eur. J. Org. Chem.* **2003**, *8*, 1438−1453.

We believe that, with the ease of preparation of amino acid derived nitrones of structure **3** and the facile stereospecific production of the densely functionalized pyrroles of structure **5**, this approach provides a ready entry into potentially valuable biological templates.

Experimental Section

General Procedure A. A solution of nitrone **3a**[1] or **3b** (1 mmol) and alkyne (mmol) in toluene was heated at 65−80 °C for 2−4 h. The solvent was then evaporated, and the residue was subjected to column chromatography to afford pure products **4a**−**e** (71−83% yield).

Conversion of the Nitrones or Isoxazoles into [1,2-*a*]-Fused Pyrroles. General Procedure B. A solution of isoxazole (1 mmol) in toluene was heated at reflux for 2 h. The solvent was then evaporated, and the residue was subjected to column chromatography to afford pure products **5a**−**e** (58% to 72% yield).

General Procedure C. A solution of nitrone **3a** or **3b** (1 mmol) and alkyne (mmol) in toluene was heated at reflux for 2 h. The solvent was then evaporated, and the residue was subjected to column chromatography to afford pure products **5a**−**e** (43−63% yield).

2,3-Dibenzyl-1-oxo-2,3,3a,4,8,8a-hexahydro-1*H*-2,4a-diaza-*s*-indacine-4,5,6-tricarboxylic Acid 4-Ethyl Ester 5,6-Dimethyl Ester (3*S*, 3a*R*, 4*R*, 8a*R*) 5a. Isolated as white needles, mp 135−138 °C (acetone). R_f = 0.49 (silica, CH_2Cl_2/MeOH 95:5). $[\alpha]_D^{20}$ −92 (*c* 1, $CHCl_3$). IR (thin film, cm^{-1}) ν_{max} 2985, 2952, 2906, 2851, 1739, 1702, 1496, 1455, 1441, 1417, 1294, 1267, 1255, 1216, 1200, 1078. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 1.04 (t, J = 7.1 Hz, 3 H), 2.77−2.82 (m, 2 H), 2.91−2.96 (m, 1 H), 3.27 (dd, J = 5.3 Hz, 13.8 Hz, 1 H), 3.56 (d, J = 9.5 Hz, 1H), 3.67 (s, 3 H), 3.77 (s, 3 H), 3.77−3.83 (m, 1 H), 4.02 (m, 2 H), 4.17 (d, J = 15.3, 1 H), 4.72 (d, J = 5.3 Hz, 1 H), 5.03 (d, J = 15.3 Hz, 1H), 5.32 (d, J = 9.8 Hz, 1H), 6.58 (s, 1H), 7.09−7.23 (m, 5H), 7.23−7.33 (m, 5H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ ppm 14.2, 29.1, 38.5, 39.2, 44.5, 44.8, 52.6, 58.0, 59.3, 60.1, 62.0, 111.1, 122.7, 123.1, 127.5, 128.6, 129.1, 129.7, 130.3, 135.1, 135.6, 135.7, 161.1, 165.0, 168.1, 171.3. HRMS (FAB+) *m*/*z* calcd for $C_{31}H_{32}N_2O_7$ $(M + H)^+$, 545.2288; found, 545.2275. Anal. Calcd for $C_{31}H_{32}N_2O_7$: C, 68.37; H, 5.92; N, 5.14. Found: C, 68.57; H, 6.08; N, 5.12.

2-Benzyl-3-isopropyl-1-oxo-2,3,3a,4,8,8a-hexahydro-1*H*-2,4a-diaza-*s*-indacine-4,5,6-tricarboxylic Acid 4-Ethyl Ester 5,6-Dimethyl Ester (3*S*, 3a*R*,4*R*, 8a*R*) 5b. Isolated as a yellow oil, R_f = 0.56 (silica, CH_2Cl_2/MeOH 95:5). $[\alpha]_D^{20}$ −82 (*c* 1, $CHCl_3$). IR (thin film, cm^{-1}) ν_{max} 2955, 1738, 1700, 1492, 1440, 1422, 1323,

1293, 1260, 1223, 1199, 1167. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.90 (d, J = 7.1 Hz, 3 H), 1.05 (t, J = 7.1 Hz, 3 H), 1.12 (d, J = 7.4 Hz, 3 H), 1.60 (m, 1 H), 2.34 (m, 1 H), 2.80 (m, 1 H), 3.47 (dd, J = 4.0 Hz, 11.5 Hz, 1 H), 3.56 (d, J = 9.5 Hz, 1H), 3.74 (d, J = 15.2 Hz, 1 H), 3.80 (s, 3 H), 3.77−3.83 (m, 1 H), 3.85 (s, 3 H), 4.11 (m, 1 H), 4.17 (m, 1 H), 5.26 (d, J = 15.2, 1 H), 5.32 (s, 1 H), 5.60 (d, J = 5.3 Hz, 1 H), 6.38 (s, 1H); 7.17 (d, J = 7.4 Hz, 2 H), 7.28 (s, 1 H), 7.33 (m, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ ppm 14.1, 15.3, 19.2, 25.3, 27.0, 29.4, 37.8, 38.2, 44.4, 52.5, 60.0, 60.3, 62.7, 109.0, 121.2, 123.0, 128.1, 128.9, 133.6, 136.9, 161.8, 165.1, 168.3, 173.0. HRMS (FAB+) *m*/*z* calcd for $C_{27}H_{32}N_2O_7$ $(M + H)^+$, 497.2288; found, 497.2282. Anal. Calcd for $C_{27}H_{32}N_2O_7$: C, 65.31; H, 6.50; N, 5.64. Found: C, 65.17; H, 6.70; N, 5.39.

2-Benzyl-3-isopropyl-1-oxo-2,3,3a,4,8,8a-hexahydro-1*H*-2,4a-diaza-*s*-indacine-4,5-dicarboxylic Acid 4-Ethyl Ester 5-Methyl Ester (3*S*, 3a*R*, 4*R*, 8a*R*) 5c. Isolated as a yellow oil, R_f = 0.45 (silica, CH_2Cl_2/MeOH 98:2). $[\alpha]_D^{20}$ −88 (*c* 1, $CHCl_3$). IR (thin film, cm^{-1}) ν_{max} 2967, 1743, 1700, 1481, 1438, 1424, 1393, 1372, 1338, 1325, 1269, 1235, 1198, 1159, 1106, 1095, 1079, 1057. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.90 (d, J = 7.1 Hz, 3 H), 1.03 (t, J = 7.2 Hz, 3 H), 1.14 (d, J = 7.1 Hz, 3 H), 2.30 (m, 1 H), 2.37 (m, 1 H), 2.78 (m, 1H), 2.84 (m, 1H), 3.47 (dd, J = 4.8 Hz, 16.2 Hz, 1 H), 3.56 (d, J = 9.7 Hz, 1 H), 3.76 (s, 3 H), 4.11 (m, 1 H), 4.17 (m, 1 H), 5.26 (d, J = 15.2, 1 H), 5.76 (d, J = 5.4 Hz, 1 H), 6.09 (d, J = 4.0 Hz, 1 H), 7.01 (s, 1 H), 7.17 (d, J = 7.4 Hz, 2 H), 7.28 (s, 1 H), 7.33 (m, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ ppm 14.2, 15.3, 19.1, 25.3, 27.0, 29.4, 37.7, 38.2, 44.1, 51.5, 60.0, 61.3, 107.6, 118.2, 121.0, 126.1, 127.0, 135.6, 161.2, 168.4, 173.6. HRMS (FAB+) *m*/*z* calcd for $C_{25}H_{30}N_2O_5$ $(M + H)^+$, 439.2233; found, 439.2234. Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.21; H, 7.02; N, 6.30.

2-Benzyl-3-isopropyl-1-oxo-6 phenyl-2,3,3a,4,8,8a-hexahydro-1*H*-2,4a-diaza-*s*-indacine-4,5-dicarboxylic Acid Diethyl Ester (3*S*, 3a*R*, 4*R*, 8a*R*) 5d. Isolated as a yellow oil, R_f = 0.22 (silica, CH_2Cl_2/MeOH 99:1). $[\alpha]_D^{20}$ −96 (*c* 1, $CHCl_3$). IR (thin film, cm^{-1}) ν_{max} 2975, 2938, 1745, 1694, 1467, 1455, 1446, 1429, 1325, 1293, 1264, 1248, 1226, 1196, 1161, 1108, 1095, 1078, 1026. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.92 (d, J = 6.9 Hz, 3 H), 1.04 (t, J = 7.1 Hz, 3 H), 1.08 (t, J = 7.1 Hz, 3 H), 1.16 (d, J = 7.0 Hz, 3 H), 2.34 (m, 1 H), 2.44 (m, 1 H), 2.78 (m, 1H), 2.87 (dd, J = 13.2, 16.1, 1 H) 3.47 (dd, J = 4.9 Hz, 16.1 Hz, 1 H), 3.61 (d, J = 9.7 Hz, 1 H), 3.86 (d, J = 15.2 Hz, 1 H), 4.06−4.23 (m, 4 H), 5.2(d, J = 15.3, 1 H), 5.77 (d, J = 5.4 Hz, 1 H), 6.16 (s, 1 H), 7.21 (d, J = 7.4 Hz, 2 H), 7.32−7.40 (m, 8 H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ ppm 13.3, 13.5, 14.2, 18.1, 25.3, 26.1, 37.2, 37.8, 43.2, 59.0, 59.2, 59.4, 60.6, 108.2, 117.1, 126.2, 126.5, 126.6, 127.1, 127.6, 134.2, 135.2, 161.0, 168.7, 172.5. HRMS (FAB+) *m*/*z* calcd for $C_{32}H_{36}N_2O_5$ $(M + H)^+$, 529.2702; found, 529.2702. Anal. Calcd for $C_{32}H_{36}N_2O_5$: C, 72.70; H, 6.86; N, 5.30. Found: C, 72.42; H, 6.99; N, 5.11.

2-Benzyl-3-isopropyl-1-oxo-5-trifluoromethyl-2,3,3a,4,8,8a-hexahydro-1*H*-2,4a-diaza-*s*-indacine-4,6-dicarboxylic Acid Diethyl Ester (3*S*, 3a*R*, 4*R*, 8a*R*) 5e. Isolated as a yellow oil, R_f = 0.63 (silica, CH_2Cl_2/MeOH 98:2). $[\alpha]_D^{20}$ −98 (*c* 1, $CHCl_3$). IR (thin film, cm^{-1}) ν_{max} 2973, 2939, 2908, 2879, 1744, 1702, 1698, 1686, 1496, 1466, 1458, 1439, 1421, 1398, 1381, 1357, 1324, 1296, 1268, 1220, 1200, 1135, 1079, 1026. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.85 (d, J = 7.0 Hz, 3 H), 1.03 (t, J = 7.1 Hz, 3 H), 1.10 (d, J = 7.1 Hz, 3 H), 1.29 (t, J = 7.0 Hz, 3 H), 2.29−2.34 (m, 2 H), 2.44 (m, 1 H), 2.78 (m, 1H), 2.87 (dd, J = 12.3, 16.3, 1H), 3.43 (dd, J = 5.1 Hz, 16.6 Hz, 1 H), 3.57 (d, J = 9.7 Hz, 1 H), 3.81 (d, J = 15.2 Hz, 1 H), 4.05−4.2 (m, 4 H), 5.15 (d, J = 15.1, 1 H), 5.72 (d, J = 5.3 Hz, 1 H), 6.16 (s, 1 H), 7.17 (d, J = 7.4 Hz, 2 H), 7.32−7.40 (m, 3 H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ ppm 13.1, 13.3, 14.2, 18.2, 25.3, 26.5, 28.1, 37.3, 37.8, 43.2, 60.0, 60.2, 59.4, 60.5, 107.3, 128.2, 128.5, 133.8, 135,4, 159.0, 168.1, 172.0. HRMS (FAB+) *m*/*z* calcd for $C_{27}H_{31}F_3N_2O_5$ $(M + H)^+$, 521.2263; found, 521.2270. Anal. Calcd for $C_{27}H_{31}F_3N_2O_5$: C, 62.30; H, 6.00; N, 5.38. Found: C, 62.07; H, 6.22; N, 5.09.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra and analyzed NOE data for compounds **5a**−**e**. X-ray data for compound **5a** is included as well. Calculations on the aza Diels−Alder reaction are also presented. This material is available free of charge via the Internet at http://pubs.acs.org.

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