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A novel method for the synthesis of 5,6-dihydro-4*H*-oxocin-4-ones: 6-*endo*-dig versus 8-*endo*-dig cyclizations

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Abstract—The condensation of substituted α-keto alkynes with *p*-nitrobenzaldehyde in the presence of lithium diisopropylamide (LDA) affords highly substituted 5,6-dihydro-4*H*-oxocin-4-ones in good yields. Surprisingly, no six-membered carbocycles were formed in this 8-*endo*-dig cyclization to the oxocinone system.

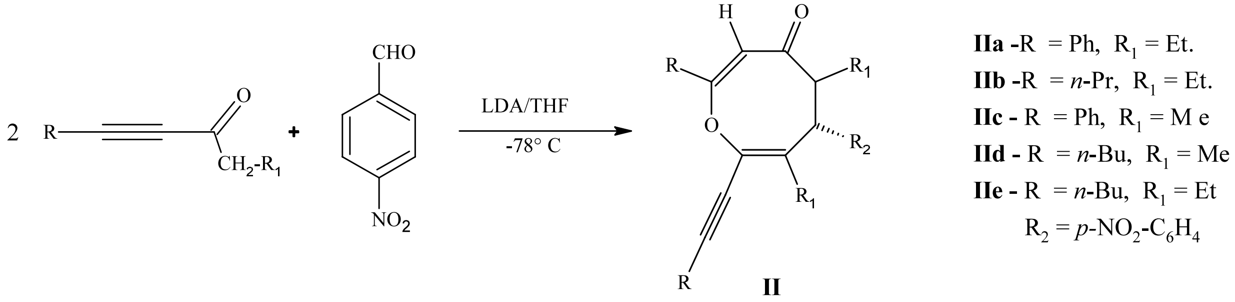
1. Introduction

Five- and six-membered carbocycles and oxygen heterocycles are quite easily synthesized,[1] but the preparation of the corresponding eight membered ring systems represents a more difficult synthetic challenge.[2] Interest in saturated and unsaturated eight-membered oxygen heterocycles are very important due to the presence of this framework in complex natural products possessing interesting biological activities.[3] However the traditional syntheses of these heterocycles involve multi step reactions. In addition there exists very few reports on the synthesis of eight-membered dihydro-oxocinones. The ring expansion of δ-lactones into oxocenones[4] and a rhodium catalyzed cyclization of α,ω-diazo alcohols give oxygen-heterocycles, have been reported.[5] In this communication we wish to report a one-step synthesis of highly substituted 5,6-dihydro-4*H*-oxocin-4-ones.

2. Results and discussion

The synthetic method is very simple and consists of the base (LDA) condensation of two equivalents of α-keto alkyne with *p*-nitrobenzaldehyde, as shown in Scheme 1.

The unsaturated oxocinones **II** obtained were characterized by the usual analytical[6] data (^{1}H and ^{13}C NMR, IR and mass spectrometry) and in the case of Figure 1



Scheme 1.

Keywords: oxocinones; 8-*endo*-dig cyclizations.

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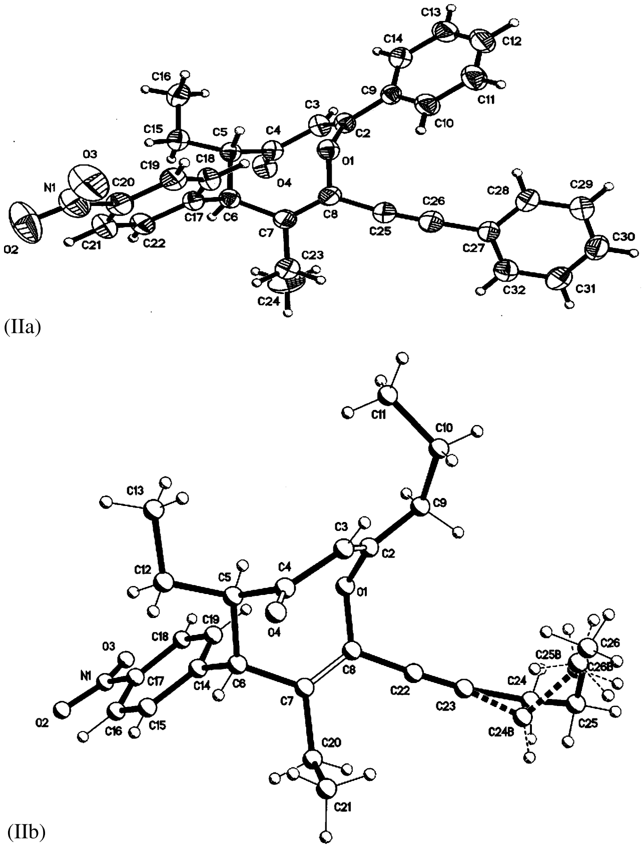
IIa and **IIb** structures were unambiguously established by X-ray crystallography[7] (Fig. 1 **IIa** and **IIb**). A plausible reaction pathway is shown in Scheme 2, which involves an initial aldol condensation to give the intermediate crossed enynone **3**. Michael addition of a second equivalent of the α-keto-alkyne enolate at the double bond of **3** affords **4**, which cyclizes to **II** by conjugate addition of the oxygen enolate.

In this reaction mechanism two points require further comments. First, the second Michael addition of the enynone **3** to α-keto alkyne to give **4** proceeded at the double bond of the crossed enynones in spite of the fact that in these systems the triple bond is more electrophilic.[8] We propose that in intermediate **3** the normal behavior is reversed due to the *p*-nitrophenyl substituent on the double bond, as no reaction was observed when benzaldehyde or *p*-aminobenzaldehyde was used.

Second, the exclusive formation of the eight membered heterocycle rather than the apparently more convenient six-membered carbocycle is intriguing since both cyclizations (8-*endo*-dig and 6-*endo* dig, respectively) are allowed according to Baldwin rules.[9] We suggest that at least two factors contributes to this unexpected regioselective cyclization: (1) In enolate **4** the alkoxide is best aligned than the carbanion for attacking the triple bond[10] and (2) a successful charge stabilization develops in the adduct by formation of the cyclic allenolate[†] **5**. Obviously, the latter is not possible (due to ring strain) if the six-membered carbocycle is being formed.

3. Conclusions

In conclusion, a one-step synthesis of substituted 5,6-dihydro-oxocin-ones was discovered by a regioselective preferential 8-*endo*-dig cyclization instead of 6-*endo*-dig cyclization leading to an eight-membered carbocycle. The cyclization reactions with other types of benzaldehydes containing different electron donating and attracting groups at different positions are under progress in order to extend the scope of this synthetic process.



(IIa)

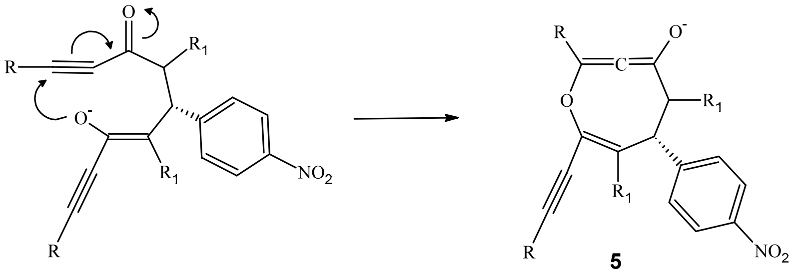
(IIb)

Figure 1.

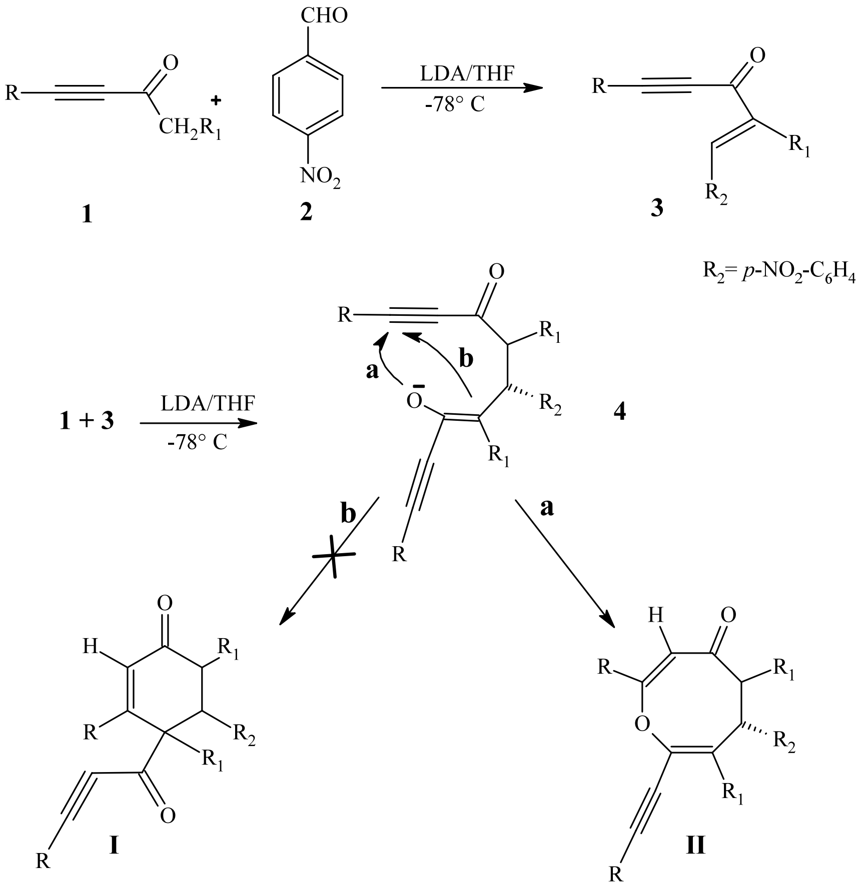
4. Experimental

4.1. Synthesis of substituted 5,6-dihydro-oxocin-ones

General procedure: A typical experiment was performed as follows: To a solution of 2.0 mmol of α-ketoalkyne[11] in 50 mL of dry THF cooled to −78°C under N_2 (1 atm) was added dropwise with vigorous stirring to a solution of 3 mmol of lithium diisopropylamide in THF for 30 min. A solution of the *p*-nitrobenzaldehyde (1 mmol) in THF was added while keeping the temperature at −78°C and the mixture was stirred for 1 h. The progress of the reaction was followed by TLC, the reaction products were quantified by GC in a Hewlett Packard 5890 analyser. After the usual workup, the organic solvent was removed at reduced pressure in a rotary evaporator to give the crude products which were purified by crystallization.



[†] The synthesis of oxocinones by intramolecular alkoxide Michael addition to conjugated ynones was first reported by S. L Schreiber and S. E. Kelly. However, in this case alternate cyclization are not possible.



Scheme 2.

4.2. 5,7-Diethyl-6-(4-nitro-phenyl)-2-phenyl-8-phenylethynyl-5,6-dihydro-oxocin-4-one (IIa)

The product was obtained as a yellow solid in a 70% yield as described in the general procedure; mp 150–152°C. Mass spectrum EI: $m/z=477$; IR (selected cm^{-1}) 1686 (C=O), 2212 (C≡C), 1599 (C=C), 1461 and 1380 (N=O); ^{1}H NMR δ_H (300 MHz; CDCl$_3$; TMS ppm): 8.2 (d, 2Ha^2, $J=8.7$ Hz), 7.8 (d, 2Hb^2, $J=8.7$ Hz), 7.5 and 7.2 (m, 10H, 2 phenyl), 6.5 (s, 1H, CH), 3.9 (t, 1H, CH, $J=2.4$ Hz), 3.3 (d, 1H, CH, $J=11.1$ Hz), 2.4 (m, 2H, CH$_2$), 1.9 (m, 2H, CH$_2$), 0.97 (t, 3H, CH$_3$, $J=7.5$ Hz), 0.73 (t, 3H, CH$_3$, $J=7.5$ Hz); ^{13}C NMR δ_C: 204.6 (C$_4$), 169.5 (C$_2$), 149.7 (C$_{20}$), 147.2 (C$_{17}$), 140.1 (C$_9$), 137.8 (C$_8$), 133.5 (C$_7$), 131.4 (C$_{28}$, C$_{32}$), 131.3 (C$_{22}$, C$_{18}$), 129.9 (C$_{11}$, C$_{13}$), 129.0 (C$_{30}$), 128.7 (C$_{29}$, C$_{31}$), 128.4 (C$_{12}$), 127.3 (C$_{10}$, C$_{14}$), 124.0 (C$_{19}$, C$_{21}$), 121.9 (C$_{27}$), 116.0 (C$_3$), 95.3 (C$_{26}$), 83.0 (C$_{25}$), 57.0 (C$_5$), 52.7 (C$_6$), 27.1 (C$_{15}$), 24.2 (C$_{23}$), 12.2 (C$_{16}$), 12.2 (C$_{24}$).

4.3. 5,7-Diethyl-6-(4-nitro-phenyl)-8-pent-1-ynyl-2-propyl-5,6-dihydro-oxocin-4-one (IIb)

Yield 72%; white solid; mp 102–104°C. Mass spectrum EI: $m/z=409$; IR (selected cm^{-1}) 1700 (C=O), 2220(C≡C), 1610 (C=C), 1465 and 1380 (N=O); ^{1}H NMR δ_H; (300 MHz; CDCl$_3$; TMS ppm): 8.2 (d, 2Ha^2, $J=8.7$ Hz), 7.5 (d, 2Hb^2, $J=8.7$ Hz), 6.5 (s, 1H, CH), 3.8 (t, 1H, CH, $J=2.4$ Hz), 3.2 (d, 1H, CH, $J=8.1$ Hz), 2.8 (m, 2H, CH$_2$), 2.5 (t, 2H, CH$_2$, $J=7.4$ Hz), 2.3 (t, 2H, CH$_2$, $J=6.9$ Hz), 2.2 (m, 2H, CH$_2$), 1.8 (m, 2H, CH$_2$), 1.6 (m, 2H, CH$_2$), 1.2 (m, 3H, CH$_3$), 1.0 (m, 3H, CH$_3$), 0.83 (t, 3H, CH$_3$, $J=7.5$ Hz), 0.66 (t, 3H, CH$_3$, $J=7.5$ Hz); ^{13}C NMR δ_C: 205.1 (C$_4$), 175.0 (C$_2$), 150.1 (C$_{17}$), 147.1 (C$_{14}$), 137.9 (C$_8$), 137.3 (C$_7$), 129.6 (C$_{15}$, C$_{19}$), 123.9 (C$_{16}$, C$_{18}$), 118.0 (C$_3$), 95.6 (C$_{23}$), 76.0 (C$_{22}$), 57.2 (C$_5$), 52.1 (C$_6$), 37.6 (C$_9$), 26.6 (C$_{24}$), 24.2 (C$_{25}$), 21.9 (C$_{12}$), 21.3 (C$_{20}$), 19.1 (C$_{10}$), 13.8 (C$_{11}$), 13.5 (C$_{26}$), 12.1 (C$_{13}$), 12.0 (C$_{21}$).

4.4. 5,7-Dimethyl-6-(4-nitro-phenyl)-2-phenyl-8-phenylethynyl-5,6-dihydro-oxacin-4-one (IIc)

Yield 75%; yellow solid; mp 135–137°C. Mass spectrum EI: $m/z=449$; IR (selected cm^{-1}) 1690 (C=O), 2215 (C≡C), 1589 (C=C), 1460 and 1385 (N=O); ^{1}H NMR δ_H (300 MHz; CDCl$_3$; TMS ppm): 8.2 (d, 2Ha^2, $J=8.7$ Hz), 7.6 (d, 2Hb^2, $J=8.7$ Hz), 7.5 and 7.2 (m, 10 H, 2 phenyl), 6.4 (s, 1H, CH), 4.2 (t, 1H, CH, $J=2.4$ Hz), 3.2 (d, 1H, CH, $J=9.0$ Hz), 1.8 (s, 3H, CH$_3$), 0.97 (d, 3H, CH$_3$, $J=7.3$ Hz); ^{13}C NMR δ_C 204.6 (C$_4$), 169.3 (C$_2$), 149.1 (C$_{19}$), 147.3 (C$_{16}$), 137.5 (C$_9$), 134.5 (C$_8$), 133.4 (C$_7$), 131.4 (C$_{26}$, C$_{30}$), 131.2 (C$_{17}$, C$_{21}$), 129.7 (C$_{11}$, C$_{13}$), 129.0 (C$_{28}$), 128.7 (C$_{27}$, C$_{29}$), 128.4 (C$_{12}$), 127.4 (C$_{10}$, C$_{14}$), 124.0 (C$_{18}$, C$_{20}$), 121.8 (C$_{25}$), 115.2 (C$_3$), 95.6 (C$_{24}$), 83.2 (C$_{23}$), 56.0 (C$_5$), 48.7 (C$_6$), 20.3 (C$_{15}$), 16.0 (C$_{22}$).

4.5. 5,7-Dimethyl-6-(4-nitro-phenyl)-8-hex-1-ynyl-2-butyl-5,6-dihydro-oxocin-4-one (IId)

Yield 70%; yellow solid; mp 97–99°C. Mass spectrum EI: $m/z = 409$; IR (selected cm^{-1}) 1667 (C=O), 2213 (C≡C), 1520 (C=C), 1450 and 1343 (N = O); selected); ^{1}H NMR δ_H (300 MHz; CDCl$_3$; TMS ppm): 8.2 (d, 2Ha^2, $J = 8.7$ Hz), 7.5 (d, 2Hb^2, $J = 8.7$ Hz), 5.6 (s, 1H, CH), 3.9 (s, 1H, CH), 3.1 (d, 1H, CH, $J = 2.4$ Hz), 2.4 (t, 2H, CH$_2$, $J = 7.4$ Hz), 2.3 (t, 2H, CH$_2$, $J = 6.9$ Hz), 1.6 (s, 3H, CH$_3$), 1.5 (m, 6H, CH$_2$), 1.1 (m, 3H, CH$_3$), 0.9 (m, 6H, CH$_3$); ^{13}C NMR δc: 204.9 (C$_4$), 172.4 (C$_2$), 150.0 (C$_{17}$), 147.1 (C$_{14}$), 137.0 (C$_8$), 133.0 (C$_7$), 129.6 (C$_{15}$, C$_{19}$), 123.9 (C$_{16}$, C$_{18}$), 117.0 (C$_3$), 96.1 (C$_{22}$), 81.0 (C$_{21}$), 55.0 (C$_5$), 49.0 (C$_6$), 35.4 (C$_9$), 29.7 (C$_{23}$), 22.3 (C$_{24}$), 22.0 (C$_{10}$), 19.0 (C$_{11}$), 18.4 (C$_{25}$), 17.8 (C$_{12}$), 13.5 (C$_{13}$), 12.8 (C$_{20}$).

4.6. 5,7-Diethyl-6-(4-nitro-phenyl)-8-hex-1-ynyl-2-butyl-5,6-dihydro-oxocin-4-one (IIe)

Yield 71%; yellow solid; mp 135–137°C. Mass spectrum EI: $m/z = 437$; IR (selected cm^{-1}) 1672 (C=O), 2221(C≡C), 1524 (C=C), 1458 and 1346 (N=O); ^{1}H NMR δ_H (300 MHz; CDCl$_3$; TMS ppm): 8.1 (d, 2Ha^2, $J = 8.7$ Hz), 7.5 (d, 2Hb^2, $J = 8.7$ Hz), 6.5 (s, 1H, CH), 3.7 (t, 1H, CH, $J = 2.4$ Hz), 3.2 (d, 1H, CH, $J = 14$ Hz), 2.8 (m, 2H, CH$_2$), 2.5 (m, 2H, CH$_2$), 2.3 (t, 2H, CH$_2$, $J = 6.9$ Hz), 2.2 (m, 2H, CH$_2$), 1.8 (m, 6H, CH$_2$), 1.2 (m, 2H, CH$_2$), 0.96 (m, 3H, CH$_3$), 0.67 (t, 9H, CH$_3$, $J = 7.5$ Hz); ^{13}C NMR δ_C: 205.4 (C$_4$), 172.4 (C$_2$), 151.0 (C$_{18}$), 147.1 (C$_{15}$), 137.9 (C$_8$), 137.1 (C$_7$), 129.8 (C$_{16}$, C$_{20}$), 123.8 (C$_{17}$, C$_{19}$), 115.6 (C$_3$), 95.7 (C$_{24}$), 84.0 (C$_{23}$), 56.9 (C$_5$), 52.5 (C$_6$), 35.4 (C$_9$), 30.4 (C$_{25}$), 22.0 (C$_{26}$), 21.9 (C$_{13}$), 21.7 (C$_{21}$), 19.3 (C$_{10}$), 19.0 (C$_{11}$), 18.4 (C$_{27}$), 15.0 (C$_{12}$),13.5 (C$_{28}$), 12.1 (C$_{14}$), 11.9 (C$_{22}$).

5. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre CCDC Nos. 203659 and 203660.

Acknowledgements

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6. α-Ketoalkynes were prepared according to a published method,[10] *p*-nitrobenzaldehyde was used as received from the supplier. IR spectra were recorded in CHCl$_3$ or KBr on a Nicolet FT 5SX spectrometer. NMR spectra were recorded on a JEOL GX300 instrument at 300 MHz for ^{1}H and 75 MHz for ^{13}C using (CH$_3$)$_4$Si as an internal reference and CDCl$_3$ as solvent at 25°C. The mass spectra were obtained using a JEOL JMS-AX505 HA spectrometer.
7. Crystal structure determination of compound **IIa**. Crystal data: $C_{31}H_{27}NO_4$, $M = 477.54$, orthorhombic, $a = 21.624(1)$, $b = 8.875(1)$, $c = 26.745(2)$ Å, $U = 5132.7(6)$ Å^3, $T = 293$°K, space group *Pbca*, $Z = 8$, μ(Mo–Kα) = 0.082 mm^{-1}, 39691 reflections measured, 4527 unique ($R_{int} = 0.1061$) which were used in all calculations. The final $wR(F^2)$ was 0.0650 (all data). Crystal structure of compound **IIb**. Crystal data: $C_{25}H_{31}NO_4$, $M = 409.51$, orthorhombic, $a = 8.726(1)$, $b = 14.021(1)$, $c = 19.071(1)$ Å, $U = 2333.3(3)$ Å^3, $T = 293$ °K, space group $P2_12_12_1$, $Z = 4$, μ(Mo–Kα) = 0.078 mm^{-1}, 19152 reflections measured, 4107 unique ($R_{int} = 0.0803$) which were used in all calculations. The final $wR(F^2)$ was 0.0693.
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