Convenient synthesis of dodeca-1,3-diynyl ketones by the "diacetylene zipper" reaction*

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Dodeca-1,3-diynyl ketones were synthesized by isomerization of dodeca-5,7-diyne with $H_2N(CH_2)_2NHLi$ and treatment of the *in situ* prepared lithium derivative of dodeca-1,3-diyne with *N*-methoxy-*N*-methylcarboxamides.

Key words: diacetylenes, ketones, *N*-methoxy-*N*-methylcarboxamides, organolithium compounds.

Prototropic migration of an internal triple bond under the action of superbases producing metallated derivatives of terminal acetylenes was named the "acetylene zipper".[1] We have successfully extended this methodology to conjugated disubstituted diacetylenes,[2—4] and accessible lithium 2-aminoethylamide was used as a base. This "diacetylene zipper" reaction turned out to be a convenient method for the synthesis of terminal diynes and, which is especially important, a method for the *in situ* generation of 1-lithio-1,3-diynes. Their subsequent one-pot reactions with electrophilic agents affords functionalized conjugated diacetylenes, excluding steps of isolation and metallation of labile terminal diynes.[2,4] Note that the use of some classical electrophiles does not produce the desired addition products. For example, aldehydes, unlike ketones, react only with excess $H_2N(CH_2)_2NHLi$, no secondary α-diacetylenic alcohols were obtained.[4] Attempts to synthesize diacetylenic ketones by the reaction of 1-lithio-1,3-diynes with benzonitrile were also unsuccessful: under the reaction conditions, the primarily formed imines isomerize to form enediynylamines, which are dimerized and undergo ring closure upon isolation to form 2,3,4,6-tetrasubstituted pyridines.[5]

In the present work, we show that conjugated α-diacetylenic ketones can be synthesized in preparative yields when *N*-methoxy-*N*-methylcarboxamides **1a—c** (the so-called Weinreb amides,[6] Scheme 1) are used as electrophilic agents. The latter react smoothly with only 1 equiv. of organometallic compound **2** yielding stable metal-chelate intermediates **3**, which after quenching of the reaction mixtures form ketones **4a—c** without an admixture of tertiary alcohols. As we have shown,[4] tertiary alcohols are the only products of the reaction of esters with 1-lithio-1,3-diynes. Previously,[7,8] the Weinreb amides were used for the synthesis of monoacetylenic ketones.

Lithium dodeca-1,3-diyne derivative (**2**) was prepared *in situ* by treating the starting diacetylene **5** with 3 equiv. of lithium 2-aminoethylamide. Its subsequent reactions at −15 °C with the Weinreb amides **1a—c** were selective (TLC data). The high yield of the product was achieved when benzamide **1a** was used. In the case of acetamide **1b**, methyl ketone **4b** that formed is unstable and noticeably resinified on isolation and therefore its yield is moderate. The mass spectrum of this product contains the peak of an admixture corresponding to the trimer of compound **4b** (*m/z* 612). The reaction of lithium derivative **2** with *N*-methoxyamides **1a** and **1b** is complete in 20 and 5 min, respectively (TLC data). The reaction of acetylenide **5** with less reactive cinnamamide **1c** is much more slower. Despite extension of the reaction time to 12 h and even the increase in temperature to room temperature, nonconsumed amide **1c** remained in the reaction mixture (TLC data), while the yield of the target product changed insignificantly. Chromatographic separation of the reaction products gave dodeca-1,3-diyne (~10% of the starting disubstituted isomer **5**) along with ketone **4c**.

Thus, we proposed a convenient method for the synthesis of dodeca-1,3-diynyl ketones. Undoubtedly, the method can be extended to other their homologs, because

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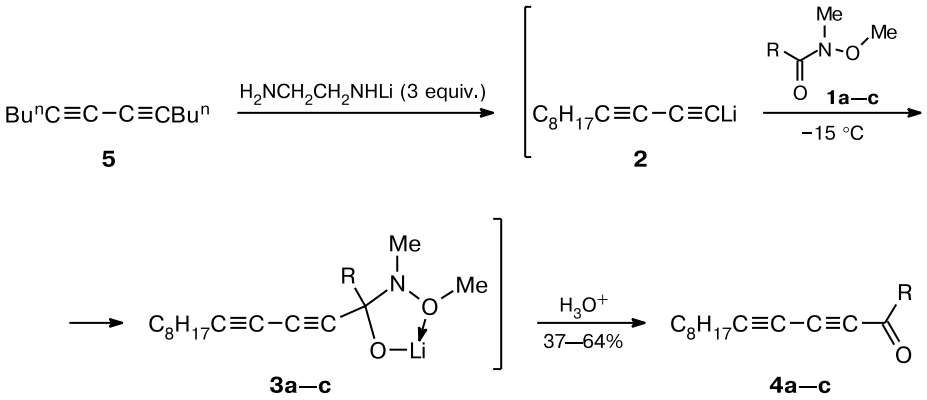
Scheme 1



1, 3, 4: R = Ph (**a**), Me (**b**), PhCH=CH (**c**)

the methodology of "diacetylene zipper" was tested on the related series of internal diynes in combination with other electrophiles.[2—4] It should be noted that the earlier described methods for syntheses of aliphatic conjugated diynones were based on considerably less available terminal diynes[9,10] or their organoelement derivatives.[11,12]

Experimental

The starting dodeca-5,7-diyne was synthesized by a known method from 1-hexyne.[13] *N*-Methoxy-*N*-methylamides **1a—c** were prepared by the reaction of the corresponding acyl chlorides with *N,O*-dimethylhydroxylamine hydrochloride (Acros) according to a known procedure.[6] IR spectra were recorded on a Specord IR-75 spectrometer (2% solutions in CCl_4). ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX-300 instrument (working frequencies 300.13 and 75.5 MHz, respectively) for solutions in $CDCl_3$. Mass spectra (EI, 70 eV) were recorded on an INCOS 50 Finnigan instrument. Benzene, hexane, and THF (reagent grade, Vekton) were dried by refluxing over, and distillation from, sodium in the presence of sodium benzophenone ketyl under argon. Ethylenediamine (99%, Aldrich) was refluxed over, and distilled first from KOH and then from, metallic sodium. Chromatography was carried out on silica gel L 40/60 (Chemapol). TLC analysis was carried out on aluminum plates with Kieselgel 60 F_{254} (Merck, 1.05554) in a hexane—ether (2 : 1) solvent mixture.

Synthesis of α-diacetylenic ketones (general procedure). Lithium (0.21 g, 0.03 mol) was introduced by small portion in an argon flow into a solution of ethylenediamine (2.4 mL, 0.03 mol) in anhydrous THF (7.2 mL). After the exothermic formation of lithium 2-aminoethylamide completed, dry benzene (7.2 mL) and hexane (7.2 mL) were added to the suspension, the mixture was cooled to 16—18 °C, and dodeca-5,7-diyne (1.62 g, 0.01 mol) was poured in one portion. The color of the reaction mixture changed from yellowish-gray to dark brown, indicating the formation of acetylenide. Fifteen min after the addition of the diyne, the reaction mixture was diluted with dry THF (10 mL) and cooled to −15 °C, and a solution of the corresponding *N*-methoxy-*N*-methylamide **1a—c** (0.01 mol) in THF (5 mL) was added dropwise. The course of the reaction was monitored by TLC. After the end of the reaction, the mixture was poured into water, and the aqueous layer was extracted with ether (3×15 mL). The combined ethereal extracts were washed with a saturated solution of ammonium chloride to the neutral pH of the aqueous phase and dried with $MgSO_4$. The solvent was removed *in vacuo*, and the products were purified by chromatography (eluent petroleum ether—CH_2Cl_2, gradient 6 : 1 → 1 : 1).

1-Phenyltrideca-2,4-diyn-1-one (4a). The yield was 60—64%, viscous yellowish oil.* ^{1}H NMR, δ: 0.89 (t, 3 H, C(13)H$_3$, J = 7.3 Hz); 1.23—1.53 (m, 10 H); 1.59 (m, 2 H, C(7)H$_2$); 2.41 (t, 2 H, C(6)H$_2$, J = 6.5 Hz); 7.48 (t, 1 H, p-CH$_{arom}$, J = 7.6 Hz); 7.62 (t, 2 H, m-CH$_{arom}$, J = 7.6 Hz); 8.12 (d, 2 H, o-CH$_{arom}$, J = 7.6 Hz). ^{13}C NMR, δ: 14.48, 20.13, 23.03, 28.20, 29.26, 29.39, 29.50, 32.19, 64.51, 71.87, 78.94, 91.35, 129.01, 129.99, 134.68, 137.08, 177.55. IR, ν/cm^{-1}: 3080 (w), 2875 (s), 2940 (s), 2245 (s), 2150 (s), 1650 (s), 1600 (m), 1580 (m), 1470 (m), 1455 (s), 1320 (s), 1270 (s), 1170 (s), 990 (m), 700 (s), 660 (m). Mass spectrum, m/z (I_{rel} (%)): 266 [M]$^+$ (2), 265 [M − 1]$^+$ (3), 237 (11), 223 (10), 210 (20), 209 (18), 195 (10), 181 (17), 170 (26), 165 (21), 152 (13), 139 (83), 115 (11), 105 (100), 91 (16), 77 (43), 55 (24), 43 (23), 41 (36).

Tetradeca-3,5-diyn-2-one (4b). The yield was 45—52%, viscous yellowish oil.* ^{1}H NMR, δ: 0.88 (t, 3 H, C(14)H$_3$, J = 7.3 Hz); 1.23—1.48 (m, 10 H); 1.56 (m, 2 H, C(8)H$_2$); 2.35 (t, 2 H, C(7)H$_2$, J = 7.3 Hz); 2.38 (s, 3 H, C(1)H$_3$). ^{13}C NMR, δ: 14.47, 20.05, 23.03, 28.15, 29.21, 29.36, 29.48, 32.17, 33.02, 64.13, 72.92, 76.78, 91.47, 184.08. IR, ν/cm^{-1}: 2940 (s), 2870 (s), 2240 (s), 2150 (m), 1680 (s), 1470 (m), 1430 (m), 1365 (s), 1265 (s), 1140 (s), 1020 (w), 970 (m), 620 (m), 570 (w). Mass spectrum, m/z (I_{rel} (%)): 204 [M]$^+$ (1), 203 [M − 1]$^+$ (3), 189 (17), 175 (9), 161 (10), 147 (13), 133 (13), 118 (10), 81 (16), 77 (12), 55 (32), 43 (100), 41 (64).

(*E*)-1-Phenylpentadec-1-ene-4,6-diyn-3-one (4c). The yield was 37—45%, m.p. 30—31 °C. Found (%): C, 86.22; H, 8.46. $C_{21}H_{24}O$. Calculated (%): C, 86.26; H, 8.27. ^{1}H NMR, δ: 0.89 (t, 3 H, C(15)H$_3$, J = 7.3 Hz); 1.18—1.48 (m, 10 H); 1.60

* Ketones **4a,b** are rather rapidly oxidized in air, thus preventing to obtain satisfactory elemental analysis data.

(quint, 2 H, $H_2C(9)$, J = 7.3 Hz); 2.40 (t, 2 H, $H_2C(8)$, J = 7.3 Hz); 6.79 (d, 1 H, =CH, J = 16 Hz); 7.42 (m, 3 H); 7.58 (d, 2 H, o-CH_{arom}, J = 7.0 Hz); 7.80 (d, 1 H, =CH, J = 16 Hz). ^{13}C NMR, δ: 14.50, 20.10, 23.05, 28.23, 29.27, 29.40, 29.51, 32.2, 64.47, 71.50, 77.37, 90.68, 128.83, 129.12, 129.49, 131.71, 134.37, 149.38, 177.69. IR, ν/cm^{-1}: 3050 (w), 2950 (s), 2875 (s), 2245 (s), 2150 (m), 1630 (s), 1605 (s), 1455 (m), 1335 (m), 1300 (s), 1280 (s), 1155 (s), 1090 (m), 980 (m), 700 (m), 680 (m). Mass spectrum, m/z (I_{rel} (%)): 292 $[M]^+$ (21), 291 $[M - 1]^+$ (8), 235 (10), 207 (40), 194 (31), 178 (33), 165 (83), 152 (23), 139 (17), 131 (44), 115 (38), 103 (60), 91 (56), 77 (100), 67 (42), 63 (46), 55 (81), 39 (67).

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