A Practical Synthesis of (Z)- and (E)-8-Dodecene-1-yl Acetate, Components of Lepidoptera Insect Sex Pheromones

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New and practical synthesis of (Z)-8-dodecene-1-yl acetate and (E)-8-dodecene-1-yl acetate were developed. The synthesis were based on a C₃+C₆=C₉ and C₉+C₃=C₁₂ coupling scheme, the starting material being 2-propyn-1-ol and 1,6-hexadiol. The routes involve, as the key step, the use of the same mercury derivative of the terminal-alkyne ω-functionalised as intermediate. The first coupling reaction took place between methoxyallene and Grignard reagent of 1-tert-butoxy-6-bromo-hexan obtaining 1-tert-butoxy-non-8-yne, which is transformed in di[1-tert-butoxy-non-8-ynyl]mercury, the common intermediate in the synthesis of the two pheromones. In order to obtain (Z)-8-dodecene-1-yl acetate and (E)-8-dodecene-1-yl acetate, the mercury derivative was directly lithiated and then alkylated with 1-bromo-propan obtaining 1-tert-butoxy-dodec-8-yne. After acetylation of 1-tert-butoxy-dodec-8-yne and stereoselective reduction in the presence of NiP-2 catalyst gave (Z)-8-dodecene-1-yl acetate with 85 % isomeric purity. After reduction with lithium aluminium hydride of 1-tert-butoxy-dodec-8-yne and acetylation was obtained (E)-8-dodecene-1-yl acetate with 90% isomeric purity.

Keywords: (Z)-8-dodecene-1-yl acetate, (E)-8-dodecene-1-yl acetate, Lepidoptera, sex pheromone

(Ω) (Z)-8-dodecene-1-yl acetate and (E)-8-dodecene-1-yl acetate are components for a lot of Lepidoptera insect sex pheromones [1]. In our country some important economic pest insects are: Grapholita molesta (oriental fruit moth), Grapholita funebrana (plum fruit moth), Hedya nubiferana (green budworm moth). The synthesis of (Z)-8-dodecene-1-yl acetate and (E)-8-dodecene-1-yl acetate are well known in the literature [2-5]. The paper [6] describes synthesis of the (11Z, 13Z)-hexadecadiene-1-yl acetate, using cross-coupling reactions for the stereospecific introduction of double bonds. The paper describes new and practical synthesis of (Z)-8-dodecene-1-yl acetate and (E)-8-dodecene-1-yl acetate based on the C-alkylation reaction, using the same mercury derivative of the terminal alkyne ω-functionalized.

Experimental part

GS-MS analysis were performed on a GS-MS spectrometer Agilent 7890A GC&5975 GS/MS. ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) spectra were recorded at rt in CDCl₃, on a Bruker 300 MHz spectrometer, using TMS line as reference. A Perkin Elmer Spectrometer Model 700 was used for IR spectra.

Methyl propargyl ether (4)

To a mixture of 86.36 g (1.540 moles) of distilled 2-propyn-1-ol (3) and 22 mL of water was added with cooling a solution of 89g (2.225 moles) of NaOH in 141 mL H₂O. After the addition is complete was added dropwise 84 mL of NH₄Cl, finally dried over anhydrous MgSO₄. The mixture was refluxed for 2.5 h and after that was distilled in vacuum of 2-3 mm Hg. It was obtained 67g (957 mmoles) of methoxyallene (5) with 90% isomeric purity.

Keywords: (Z)-8-dodecene-1-yl acetate, (E)-8-dodecene-1-yl acetate, Lepidoptera, sex pheromone

Methoxyallene (5)

Potassium tert-butoxide was prepared by refluxing 40g (1.850 moles) of dry tert-butanol with 4.3g (110 mmoles) of metal potassium up to the total consumption of the metal. Excess of alcohol was removed by distillation from rotavapor and finally to vacuum at 2-3 mm Hg. Bath water temperature was maximum 50°C. It was obtained 14.4g (128 mmoles) of potassium tert-butoxide. Yield: 80%.

Over 14.4g (128 mmoles) of previously prepared potassium tert-butoxide was added 77g (1.1 moles) of methyl propargyl ether (4) in a 500 mL benzene and then was added 47% of metal potassium up to the total consumption of the metal. Excess of alcohol was removed by distillation from rotavapor and finally to vacuum at 2-3 mm Hg. The collection flask was cooled externally up to 70°C. It was obtained 67g (957 mmoles) of methoxyallene (5). Yield: 87%.

6-Bromo-hexane-1-ol (7)

To a solution 118 g (1 mole) of 1,6-hexan-diol (6) solved in 500 mL benzene was added 81g (1 mole) of hydrobromic acid 47%. The reaction mixture was refluxed for 3h. The organic layer was separated and washed with brine, saturated NaHCO₃ solutions and dried over anhydrous MgSO₄. After removal of the solvent the product was purified by liquid – liquid distribution (petroleum ether: aqueous methanol) obtaining 83.48 g (0.458 moles) of 6-bromo-hexane-1-ol (7). Yield: 65%; GC purity: 95%.

Mass spectrum (m/z, %): 164(<1); 162(1.47); 149(<1); 135(12.74); 133(13.72); 121(<1); 108(3.92); 106(4.41); 96(1.96); 94(1.96); 92(3.92); 83(57.84); 82(16.17); 81(4.9); 80(<1); 79(1.96); 69(15.68); 68(2.45); 67(13.72); 57(6.86); 56(8.82); 55(100); 54(11.76); 53(8.82); 51(1.96); 50(<1); 49(2.94); 44(4.41); 43(19.6); 42(28.43); 41(80.39); 40(7.35); 39(41.17); 38(2.94); 37(2.45); 28(9.8);

1-tert-Butoxy-6-bromo-hexane (8)

To a solution 75.45 g (410 mmoles) of 6-bromo-hexan-1-ol (7) and 452 mL tert-butyl-methyl-ether (MTBE) [7] was
added dropwise 27.33 mL concentrated sulfuric acid under cooling. The reaction mixture was maintained at 40°C. The reaction was checked by TLC on silica gel (benzene:ether 2:1, detection with H2SO4, d=1.25). The reaction mixture was diluted with water. After removal of the tert-butyl-methanol under reduced pressure, the mixture was extracted with ethyl ether (3x50 mL). The combined ethereal extracts were washed with saturated NaHCO3 solution up to basic and dried over Na2SO4. After removal of the solvent, 62.54 (263 mmoles) g of 1-tert-butoxy-6-bromo-hexane (8) was obtained in yield of 74%, GC purity: 85%.

**8-Dodecynyl-1-yl acetate (13)**

2.3 g (9.66 mmoles) of 1-tert-butoxy-dodec-8-yne (12) was dissolved in 9.66 mL of 1:10 mixture of acetyl chloride : acetic acid and was refluxed for 4.5 h. The reaction development was checked up by TLC on silica gel G (benzene:ether, 15:1, detection with H2SO4, d=1.25). The reaction mixture was extracted with petroleum ether, washed with brine and with aqueous NaHCO3, till neutral pH of the washings. After drying over MgSO4 and removal of the solvent was obtained 2 g (8.9 mmoles) of 8-dodecyn-1-yl acetate (13). Yield: 80%, GC purity: 85%.

**8-Dodecenc-1-yl acetate (13a)**

8-Dodecynyl-1-yl acetate (13) was hydrogenated at (Z)-8-dodecyn-1-yl acetate (13) in the presence of the NiP-2/ EDCA catalyst, prepared in situ according to the standard procedure [10]. (Z)-8-Dodecenc-1-yl acetate (13a) was obtained in yield of 74%, GC purity: 85%.

**Di[1-tert-butoxy-non-8-ynie]mercury (11)**

4.39 g (260 mmoles) of potassium iodide dissolved in 43.19 mL water were added 17.49 (64 mmoles) g mercury (II) chloride and the mixture was stirred till the mercury salt was dissolved. To the mixture were added 33.12 mL of 10% sodium hydroxide solution [9]. After external cooling of reaction mixture with ice, were added dropwise 10.4 g (53 mmoles) of 1-tert-butoxy-non-8-ynie (10) dissolved in 220 mL cooled ethyl alcohol. The obtained precipitate was filtrated and washed on the filter with cooled aqueous ethyl alcohol 50%. After drying were obtained 21.94 g (37 mmoles) of di(1-tert-butoxy-non-8-ynie) mercury (11). Yield: 70%, m.p.=100°C.

**1-tert-Butoxy-dodec-8-yne (12)**

All operations were performed in an inert gas atmosphere and under stirring.

7 g (12 mmoles) of compound 11 in 33 mL diglyme was treated with 0.168 g lithium (24 mmoles) at 110°C for 3 h.

3.69 g (30 mmoles) of 1-bromo-propan dissolved in 10 mL diglyme was added dropwise at 90°C afterwards the temperature was raised to 120-125°C under stirring for 4.5 h. The mixture was poured out over 100 g of crushed ice. The reaction mixture was extracted with petroleum ether. The ethereal solution was washed successively with 10% HCl, water and brine till neutral pH of the washings. After drying over MgSO4, the solvent was removed and 2.3 g (9.6 mmoles) of 1-tert-butoxy-dodec-8-ynie (12) was obtained. Yield: 81%, GC purity: 80%.

**Di[1-tert-butoxy-non-8-ynie]mercury (11)**

41.30 mL diglyme was added dropwise at 90°C afterwards the temperature was raised to 120-125°C under stirring for 4.5 h. The mixture was poured out over 100 g of crushed ice. The reaction mixture was extracted with petroleum ether. The ethereal solution was washed successively with 10% HCl, water and brine till neutral pH of the washings. After drying over MgSO4, the solvent was removed and 2.3 g (9.6 mmoles) of 1-tert-butoxy-dodec-8-ynie (12) was obtained. Yield: 81%, GC purity: 80%.

**Di[1-tert-butoxy-non-8-ynie]mercury (11)**

41.30 mL diglyme was added dropwise at 90°C afterwards the temperature was raised to 120-125°C under stirring for 4.5 h. The mixture was poured out over 100 g of crushed ice. The reaction mixture was extracted with petroleum ether. The ethereal solution was washed successively with 10% HCl, water and brine till neutral pH of the washings. After drying over MgSO4, the solvent was removed and 2.3 g (9.6 mmoles) of 1-tert-butoxy-dodec-8-ynie (12) was obtained. Yield: 81%, GC purity: 80%.
was obtained 2.5 g (10.5 mmoles) of 1-tert-butoxy-E-8-dodecene (14). GC purity: 93%. Yield: 83%.

Mass spectrum (m/z, %): 240(1.12), 225(2.24), 184(<1); 166(4.49); 138(<1); 111(10.11); 97(19.10); 83(15.73); 71(24.71); 41(32.58); 29(13.48)

(E)-8-Dodecene-1-yl acetate (2)

2.5 g (10.5 mmoles) of 1-tert-butoxy-dodec-8-ene (14) was dissolved in 10.5 mL of 1:10 mixture of acetyl chloride:acetic acid and was refluxed for 4-5 h. The reaction development was checked up by TLC on silica gel G (hexane:ether, 15:1, detection with H2SO4 d=1.25). The solution was poured on crushed ice, extracted with petroleum ether, washed with brine and with aqueous NaHCO3 till neutral pH of the washings. After drying over MgSO4 and removal of the solvent the product was purified by distillation (70-80°C/2-3 mmHg) obtaining 2 g (8.84 mmoles) of E-8-dodecene-1-yl acetate (2). Yield: 80%, GC purity: 90%.

Mass spectrum (m/z, %): 240(1.12); 225(2.24); 184(<1); 166(8.03); 123(5.3); 109 (10.6); 95(26.5); 81(46); 67(58.4); 55(55.7); 41(57.5); 29(15.0)

Results and discussions

For the synthesis of (Z)-8-dodecene-1yl acetate (1) and (E)-8-dodecen-1-yl acetate (2) we explored the pathway outlined in scheme 1. The synthesis were based on C6+C3=C9 and C9+C3=C12 coupling schemes, the routes involving the use of the same mercury derivative of the terminal alkyne ω-functionalised as intermediate.

The first coupling reaction took place between methoxylallene (5) and Grignard reagent of 1-tert-butoxy-6-bromo-hexan (9) obtaining 1-tert-butoxy-non-8-yne (10), which is transformed in di[1-tert-butoxy-non-8-yne]mercury (11), the common intermediate in the synthesis of the two pheromones.

2-Propyn-1-ol (3) with dimethyl sulfate was transformed in methyl propargyl ether (4) which under action of potassium tert-butoxyd gave methoxylallene (5).

Use has been made of methyl-t-butyl-ether [6] in acid catalysis in order to protect the -OH function of the 6-bromo-hexane-1-ol (7).

1-tert-Butoxy-non-8-yne (10) was checked by means of IR spectrum (film, cm–1: 895 m, 1110 vs, 1220 vs, 2160 w -C a" C-, 3280 s a"CH), which presents the vibration of
terminal triple bond and the mass spectrum characteristic to a tert-butyl ether (fig. 1).

The molecular peak of 1-tert-butoxy-non-8-yne (10) was not identified, the mass spectrum presenting only characteristic fragmentations (m/z 57, m/z=59). It is necessary to mention the base peak in the spectrum (m/z=59), the peak m/z 57 which is generated by the very stable tertiary carbocation +C(CH₃)₃, the peak corresponding to the cleavage of a methyl group from the branch part (m/z=181) and of a neutral molecule of isobutylene (m/z=140).

1-tert-Butoxy-non-8-yne (10) with mercuric chloride in an aqueous solution containing potassium iodide and sodium hydroxide (Nessler's reagent) [9] was precipitated as di[1-tert-butoxy-non-8-yne]mercury (11), the common intermediate in the synthesis of the two sex pheromones.

The key step in our acetylenic route consisted in transmetallation of compound 11, which was directly lithiated by treating with metal lithium in diglyme and then alkylated with 1-bromo-propan obtaining 1-tert-butoxy-dodec-8-yne (12).

In order to obtain (Z)-8-dodecen-1-yl acetate (1), the tert-butyl ether 12 was converted into the acetate 13 with acetic anhydride. 8-Dodecyn-1-yl acetate (13) was hydrogenated using Ni-P2/EDA catalyst [9], obtaining (Z)-8-dodecen-1-yl acetate (1) with 85% isomeric purity.

In order to obtain (E)-8-dodecene-1-yl acetate (2), 1-tert-butoxy-dodec-8-yne (12) was reduced with lithium aluminium hydride and then acetylated.

The mass spectrum of (Z)-8-dodecen-1-yl acetate (1) and (E)-8-dodecene-1-yl acetate (2) are identical, characteristic to alkenol acetates, by mass spectrometry the geometry of double bond can not be established (fig. 2).

Are present: m/z 166 resulted from the cleavage of acetic acid from the molecular ion, m/z 61 as ion of double transposition (CH₃COOH⁺) and m/z 43 (CH₃CO⁺).

The chemical structure of the compounds 1 and 2 was confirmed by ¹H-NMR and ¹³C-NMR spectrum.

¹H-NMR spectrum (fig. 3) of (Z)-8-dodecene-1-yl acetate (1) includes the following signals: triplet at δ=0.96 ppm corresponding to the protons of the methyl group from position 12 (3H, J=7.5Hz), multiplet (δ=1.31-1.42 ppm) for metthylene protons from positions 3,4,5,6 and 11 (10H), multiplet at δ=1.60 ppm (2H), for methylene protons from position 2, triplet (δ=1.96-2.01ppm) for methylene protons from position 7 and 10 (4H), triplet at δ=4.04 ppm corresponding to the protons of the methylene group from position 1 (2H), singlet at δ=2.03 ppm for methyl group protons from position 1' (3H) and multiplet δ=5.35 ppm for the olefinic group protons (2H, J=10.8Hz).

¹³C-NMR spectrum, confirms the existence of Z-configuration, the chemical shifts of allylic carbons (C₆ and C₇) according with data obtained from a series of related
compounds with 12 C-atoms in the molecule [11, 12], values of the chemical shifts δ = 27.3 ppm for C7 and 29.4 ppm for C10. The acetoxy group from compound 1 was confirmed by δ = 171.1 ppm for C2' and δ = 20.4 ppm for C1' (fig. 4).

The 1H-NMR spectrum of E-(8)-dodecene-1-yl acetate (2) shows a triplet at δ = 3.98 ppm, assigned of the methylene group protons bearing of acetoxy group, a multiplets at δ = 5.30 ppm showing presence of olefinic bond with trans geometry. The singlet at δ = 2.01 ppm corresponding of the methyl group protons from acetoxy group and the multiplets (δ = 1.25 -1.35 ppm) for methylene protons from the center of the molecule (fig. 5).

13C-NMR spectrum, confirms the existence of E-configuration, the chemical shifts of allylic carbons (C7 and C10) according with data obtained from a series of related compounds with 12 C-atoms in the molecule [11, 12], values of the chemical shifts being δ = 32.3 ppm for C7 and 34.7 ppm for C10 (fig. 6).
Conclusions

It was presented new synthesis of (Z)-8-dodecene-1-yl acetate and (E)-8-dodecene-1-yl acetate, components of Lepidoptera insects sex pheromones, using the same intermediate, di[tert-butoxy-non-8-yne] mercury, which is directly lithiated and then alkylated with 1-bromo-propan.

References

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