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A Short Synthesis of Conjugated Unsaturated Alcohols

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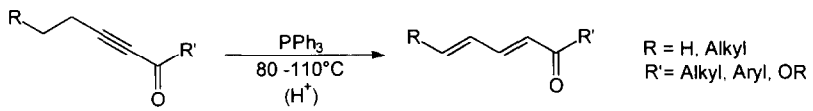
Abstract: Isomerization of acetylenic pentafluorophenyl esters in the presence of phosphines gives rise to activated dienoic esters, which can be reduced directly in a simple one pot procedure to the corresponding conjugated unsaturated alcohols **6-10**. The higher reactivity of the pentafluorophenyl esters in comparison to alkyl esters allows their selective isomerization.

Conjugated unsaturated alcohols are an interesting class of compounds, not only because of their occurrence in nature,[1] but also from a synthetical point of view. They are important intermediates for the synthesis of complex molecules,[2] a variety of them based on Diels-Alder reactions using the diene moiety of 2,4 dienols.[3] On the other hand, selective functionalizations of one or the other double bond are also possible. For example epoxidations[4] and cyclopropanations[5] preferentially occur at the double bond adjacent to the hydroxy group, while asymmetric dihydroxylations prefer the second, more electron rich double bond.[6] Most syntheses, especially for the *all-trans* configurated unsaturated alcohols, are using the Wittig and Horner-Emmons reaction, giving rise to the corresponding unsaturated esters, followed by a reduction step.[3] Besides theses well established approaches, organometallic transformations, such as cross coupling reactions[7] or metal-catalyzed isomerizations of acetylenes to dienes,[8] are also becoming more and more important.

Recently we described a new isomerization of acetylenic carbonyl compounds in the presence of triphenylphosphine.[9] While acetylenic ketones can easily be isomerized in the presence of 5-10% of triphenylphosphine at 80-100°C, the corresponding less reactive esters react only in the presence of weak acids (e.g. acetic acid). This procedure gives easy and cheap access to conjugated unsaturated esters and ketones, although problems may arise during the isomerization process with acid or thermo labile compounds.



Much milder conditions can be used if the reaction is carried out with activated esters. Especially pentafluorophenol (PFP) esters are suitable for this purpose. These esters are easily obtained from the corresponding acids using the Steglich procedure (DCC/DMAP),[10] and can be used without further purification. The isomerization of these esters proceeds under much milder conditions because of the strong electron withdrawing effect of the fluorine atoms and the resulting activation of the triple bond.[11]

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Using 10 mol% of triphenylphosphine the isomerization can be carried out at room temperature and under neutral conditions, which is important for the application of this procedure to sensitive substrates. In general, the isomerization is complete after stirring the reaction mixture overnight. If the esters tolerate higher temperatures, the amount of phosphine can be reduced (<1%). The higher temperatures are necessary for acceptable turnovers. From a synthetical point of view, it is convenient to carry out the isomerization with 5% of phosphine at 40-50°C, because under these conditions most reactions are complete after 4-5 hours. After cooling the reaction mixture to 0°C and addition of a slight excess of Dibal solution, the conjugated unsaturated alcohols can be directly obtained in a convenient one pot procedure. Various acetylenic esters were investigated so far (table 1). In general, the yields obtained are high, and the (*E*,*E*)-dienes are formed preferentially (> 92%).

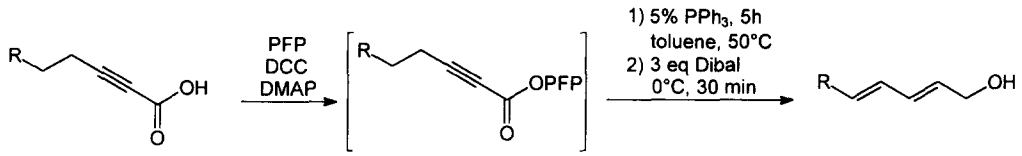
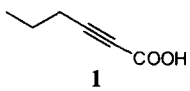
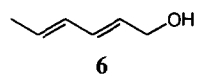
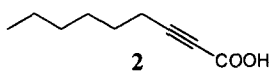
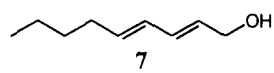
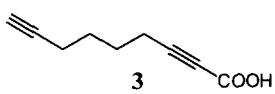
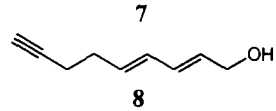
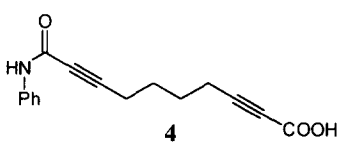
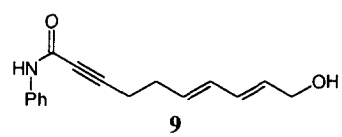
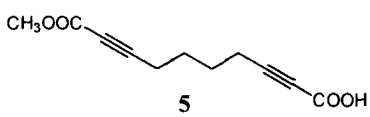
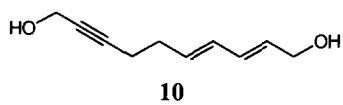
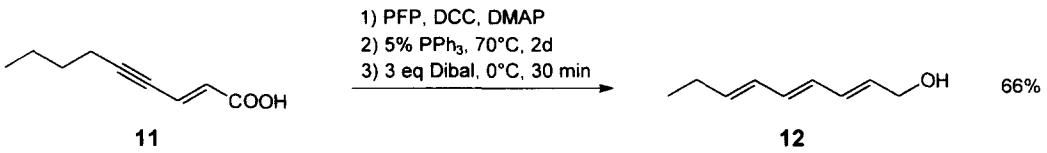


Table 1. Synthesis of conjugated unsaturated alcohols

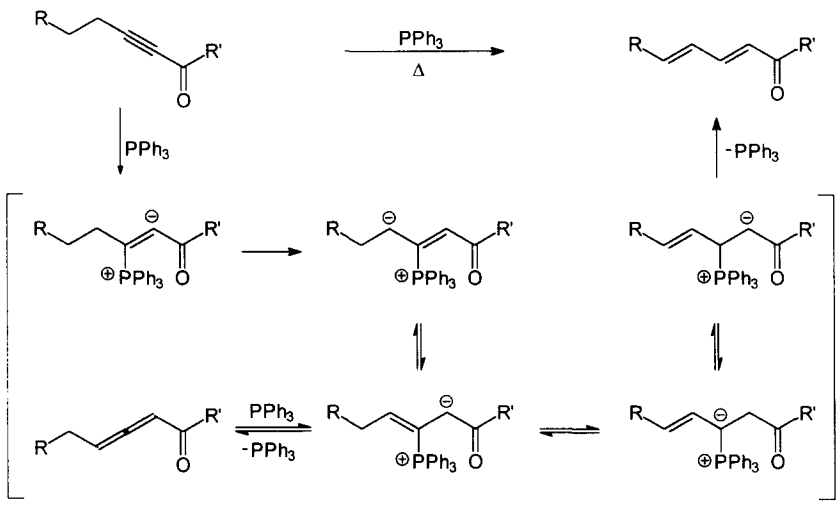
Entry	Substrate	Product	Yield [%]
1	 **1**	 **6**	88
2	 **2**	 **7**	96
3	 **3**	 **8**	76
4	 **4**	 **9**	73
5	 **5**	 **10**	68

The isomerization only occurs on activated double bonds, while terminal acetylenes (entry 3) and acetylenic amides (entry 4) are not affected under the reaction conditions used. The increased reactivity of the pentafluorophenyl esters in comparison to alkyl esters allows their selective isomerization (entry 5). Subsequent reduction of both ester functionality's[12] results in the formation of the corresponding unsaturated diol. The isomerization can also be applied to conjugated activated enyne esters,[13] giving rise to conjugated trienols. In this case, prolonged reaction times and slightly higher temperatures are necessary.



11 12

The isomerization of activated double bonds only occurs in the presence of phosphines. No reaction was observed in the presence of tertiary amines, as determined by GC analysis, which is especially well suited to monitor the reaction progress. A possible mechanism for the isomerization is shown below. The reaction probably starts with a nucleophilic addition of the phosphine on the activated triple bond, followed by a set of proton transfer steps. This mechanism seems reasonable because several of the intermediates shown here can be trapped and used for further reactions, e. g. Michael additions.[14]



In summary, the described one pot procedure allows the straightforward synthesis of *all-trans* configurated conjugated unsaturated alcohols in good yields.

EXPERIMENTAL

General. All reactions were carried out in oven-dried glassware (100°C) under an atmosphere of argon. The products were purified by flash chromatography on silica gel (32 - 63 μm). Mixtures of ethyl acetate and hexanes were used as eluants. TLC was performed on commercially precoated Polygram© SIL-G/UV 254 plates (Macherey-Nagel). Visualization was accomplished with iodine and potassium permanganate solution. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WH-200 and a Bruker AC-300 spectrometer. Chemical shifts were reported in δ relative to $CHCl_3$ as an internal reference. GC analyses were performed on a Hewlett-Packard 5890 Series II instrument equipped with HP-225 column (25% Cyanopropylphenyl-dimethylpolysiloxan, 15m × 0.53 mm). Melting points were determined on a Tottoli melting point apparatus and are uncorrected. Most of the required unsaturated acids were prepared according to the literature.

***Deca-2,8-diynedioic acid mono anilide* (4).** 5 mL (7.5 mmol) of BuLi (1.5N in hexanes) were added to a solution of 1 mL (7.5 mmol) 1,7-octadiyne in 50 mL dry THF at -60°C. The mixture was stirred for 30 min at this temperature, before a solution of 890 mg (7.5 mmol) of phenyl isocyanate in 3 mL THF was added. After removing the cooling bath and stirring at room temperature for further 30 min, the reaction mixture was cooled again to -60°C. 5 mL (7.5 mmol) of BuLi (1.5N in hexanes) were added, and after 10 min the reaction mixture was quenched by addition of dry ice. The mixture was warmed to room temperature, before water was added. After separation of the phases, the organic layer was extracted twice with 1N NaOH solution. The combined aqueous solutions were washed with ether and acidified by addition of 1N $KHSO_4$ solution. The product was extracted with CH_2Cl_2. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (EtOAc/hexanes 8/2). Yield: 1.13 g (4.2 mmol, 56%) **4** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.02 (s_{br}, 1H), 8.57 (s_{br}, 1H), 7.53 (d, *J* = 7.7 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 2.29 (m, 4H), 1.67 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.16, 151.67, 137.17, 128.77, 124.70, 119.96, 90.17, 88.43, 76.03, 73.43, 26.31, 26.14, 18.03, 17.97. HRMS calc. for $C_{16}H_{15}NO_3$: 269.1048; found: 269.1045. MS (EI) (m/e, %): 269 (M+, 0.7), 267 (7.9), 225 (54), 224 (100), 210 (17), 196 (16).

***Deca-2,8-diynedioic acid monomethyl ester* (5).** 11 mL (16.5 mmol) of BuLi (1.5N in hexanes) were added to a solution of 1 mL (7.5 mmol) 1,7-octadiyne in 50 mL dry THF at -60°C. After stirring for 30 min at this temperature dry ice was added. The mixture was warmed to room temperature, before water was added. After separation of the phases, the organic layer was extracted twice with 1N NaOH solution. The combined aqueous solutions were washed with ether and acidified by addition of 1N $KHSO_4$ solution. The product was extracted with CH_2Cl_2. A solution of diazomethane was added, until TLC indicated a significant amount of the mono ester. Evaporation of the solvent gave rise to 1.3 g of a pale yellow solid. The pure mono ester **5** was obtained by flash chromatography on silica gel (EtOAc/hexanes 6/4). Yield: 655 mg (3.15 mmol, 42%) **5** as a colorless wax. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s_{br}, 1H), 3.73 (s, 3H), 2.37 (m, 4H), 1.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.11, 154.01, 90.75, 88.49, 73.15, 72.93, 52.42, 26.18, 26.10, 18.02, 17.91. HRMS calc. for $C_{11}H_{12}O_4$: 208.0732; found: 208.0712. MS (EI) (m/e, %): 208 (M^+, 0.7), 207 (5), 193 (4), 191 (2), 177 (11), 105 (100), 103 (73).

General procedure for the preparation of pentafluorophenyl esters and their isomerization/reduction

1 mmol alkynoic acid **1-5** and pentafluorophenol were dissolved in 5 ml CH_2Cl_2 and after addition of 0.1 mmol of DMAP the solution was cooled to -20°C. A solution of 1 mmol DCC in 1 ml CH_2Cl_2 was added and the mixture was allowed to warm to room temperature overnight.[10] After filtration and evaporation of the solvent the residue was dissolved in 5 ml of toluene. 0.05 mmol of triphenylphosphine was added and the solution was warmed to 50°C for 5 hours. After cooling in an ice bath, 3 mmol of 1M Dibal solution were added and the mixture was stirred at 0°C for 30 min. After slow addition of 10 ml of 1N HCl solution the aqueous layer was extracted twice with ethyl acetate. Evaporation of the solvent and subsequent flash chromatography yielded the expected unsaturated alcohols. To avoid an oxidation, these compounds should be stored under argon, preferentially in a fridge.

***(E,E)-2,4-Hexadienol* (6).**[15] Following the general procedure **6** was obtained from sorbic acid (**1**) in 88% yield after flash chromatography on silica gel (EtOAc/hexanes 3/7) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16 (dd, *J* = 15.1, 10.3 Hz, 1H), 6.03 (ddd, *J* = 14.8, 10.3, 1.4 Hz, 1H), 5.68 (dt, *J* = 14.9, 6.2 Hz, 1H), 5.63 (dq, *J* = 14.6, 6.6 Hz, 1H), 4.08 (d, *J* = 6.2 Hz, 2H), 1.88 (s_{br}, 1H), 1.71 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.63, 130.51, 129.73, 128.93, 63.15, 13.89.

***(E,E)-2,4-Nonadienol* (7).**[16] Following the general procedure **7** was obtained from 2-nonynoic acid (**2**)[17] in 96% yield after flash chromatography on silica gel (EtOAc/hexanes 2/8) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.17 (dd, *J* = 14.8, 10.4 Hz, 1H), 6.00 (dd, *J* = 14.8, 10.4 Hz, 1H), 5.67 (dt, *J* = 14.8, 6.7 Hz, 2H), 4.13 (d, *J* = 6.7 Hz, 2H), 2.05 (q, *J* = 6.7 Hz, 2H), 1.33 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.74, 132.24, 129.02, 128.63, 63.33, 32.04, 32.00, 21.97, 13.63.

***(E,E)-8-Nonyne-2,4-dienol* (8).** Following the general procedure **8** was obtained from 2,8-nonadiynoic acid (**3**)[18] in 76% yield after flash chromatography on silica gel (EtOAc/hexanes 2/8) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.19 (dd, *J* = 15.0, 10.4 Hz, 1H), 6.08 (dd, *J* = 14.7, 10.4 Hz, 1H), 5.71 (m, 2H), 4.12 (d, *J* = 6.0 Hz, 2H), 2.26 (m, 4H), 2.13 (s_{br}, 1H), 1.94 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.51, 131.33, 130.41, 130.10, 83.45, 68.54, 63.10, 31.27, 18.27. Anal. calc. for $C_9H_{12}O$: C 79.37, H 8.88; found: C 79.25, H 8.79.

***(E,E)-10-Hydroxy-2-decyne-6,8dienoic acid anilide* (9).** Following the general procedure **9** was obtained from deca-2,8-diynedioic acid mono anilide (**4**) in 73% yield after flash chromatography on silica gel (EtOAc/hexanes 1/1) as a pale yellow solid, mp. 98 - 100°C. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.53 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.19 (m, 2H), 5.75 (m, 2H), 4.87 (acidic H's), 4.06 (d, *J* = 5.4 Hz, 2H), 2.47 (m, 2H), 2.37 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ = 153.93, 139.84, 133.07, 132.96, 132.88, 132.22, 130.27, 126.05, 121.65, 89.32, 77.56, 63.71, 32.32, 19.99. Anal. calc. for $C_{16}H_{17}NO_2$: C 75.27, H 6.71; found: C 75.50, H 6.66.

***(E,E)-2,4-Decadien-8-yne-1,10-diol* (10).** Following the general procedure **10** was obtained from deca-2,8-diynedioic acid monomethyl ester (**5**) in 68% yield after flash chromatography on silica gel (EtOAc/hexanes 1/1) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.20 (dd, *J* = 14.9, 10.4 Hz, 1H), 6.08 (dd, *J* = 14.8, 10.4 Hz, 1H), 5.75 (m, 2H), 4.21 (s, 2H), 4.14 (d, *J* = 6.0 Hz, 2H), 2.27 (s_{br}, 4H), 1.80 (s_{br}, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.67, 131.22, 130.48, 85.31, 78.77, 63.13, 51.09, 31.41, 18.64. Anal. calc. for $C_{10}H_{14}O_2$: C 72.26, H 8.49; found: C 71.85, H 8.53.

***(E,E,E)-2,4,6-Nonatrienol* (12).** Following the general procedure (longer reaction time: 2d at 70°C) **12** was obtained from 2-nonen-4-ynoic acid (**11**)[19] in 66% yield after flash chromatography on silica gel (EtOAc/hexanes 2/8) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.14 (m, 4H), 5.76 (m, 2H), 4.16 (d, *J* = 5.7 Hz, 2H), 2.12 (dq, *J* = 7.4, 6.5 Hz, 2H), 1.68 (s_{br}, 1H), 1.00 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.42, 133.66, 132.05, 130.23, 129.13, 128.91, 63.32, 25.70, 13.17. Anal. calc. for $C_9H_{14}O$: C 78.78, H 10.28; found: C 78.28, H 10.21.

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