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Ethynylation of the Ether Derivatives of ω-Haloalkanols with Lithium Acetylide–Ethylenediamide Complex

by M. Karpińska, M. Lewandowska and J. Grodner*

Institute of Industrial Organic Chemistry, Annopol 6, 03-236 Warszawa, Poland
E-mail: grodner@ipo.waw.pl

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A new operationally simple and highly efficient procedure for the ethynylation of ether derivatives of ω-haloalkanols with lithium acetylide–ethylenediamine complex in N,N-dimethylacetamide is described.

Key words: acetylenation, tetrahydropyranyl ethers, terminal alkynes

The ethynylation of the alkyl halides is an important reaction widely used in organic synthesis [1]. It has been traditionally carried out by using alkali metal acetylides, usually obtained *in situ* from acetylene, and a corresponding amide [1] or another base [2]. The best results are obtained by using the lithium acetylide in liquid ammonia with the addition of a small amount of dimethylsulfoxide [3]. Yet, the necessity of applying extremely flammable acetylene and ammonia is a serious drawback of this method. A much safer approach to the synthesis of 1-alkynes consists in utilization of commercially accessible lithium acetylide–ethylenediamine complex (LAEDA) [4]. This reagent permits the use of lithium acetylide as a stable solid (up to 45°C), thus eliminating the need for liquid ammonia.

In the literature many examples of using the lithium acetylide–ethylenediamine complex have been described for the preparation of terminal alkoxysubstituted alkynes, which are particularly useful in the synthesis of insect pheromones [5]. These compounds are prepared from the corresponding chlorides [6] or bromides [7] in dimethyl sulfoxide (DMSO) with an excess of LAEDA complex. The most important parameter of this reaction is the temperature of halide addition, which should be as low as possible, almost bordering the freezing temperature of the reaction mixture (~10°C, [4]). This constitutes a big problem, because even very small exceeding the freezing temperature of the reaction medium causes instant solidification of the solution and thus stops the reaction. Therefore, the use of solvents whose freezing temperature is lower than that of DMSO can considerably facilitate the ethynylation process.

We report herein a study of the reaction with a variety of ether-functionalized ω-halogenoalkanols and LAEDA complex in N,N-dimethylacetamide.

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*Author for correspondence.

RESULTS AND DISCUSSION

To optimize the yield of 10-(tetrahydropyranyloxy)-1-decyne (**3**), the ethynylation reaction has been studied with the use of LAEDA complex and dimethylacetamide (DMA) as a solvent. Under the same conditions of the synthesis different 1-alkynes (**4–6**) were obtained from halides **2**. The results are summarized in Table 1. The ω-halogenoalcohols **2** were obtained from the corresponding α,ω-diols. Half-halogenation of the starting diols was performed with aqueous HCl (9 M) in liquid-liquid extractor for chlorides [8], and with aqueous HBr (48%) in toluene at reflux for bromides [9]. The hydroxyl function of haloalkanols **1a–f** was protected with 2,3-dihydropyrane to obtain tetrahydropyranyl ethers **2a–f**. The acetal **2g** was prepared from bromo alcohol **1f** by oxidation with pyridinium chloroformate [10] followed with protecting the aldehyde function with triethyl orthoformate (Scheme 1).

It was observed that for the optimum conditions of the ethynylation reaction use of chloride **2a** gave a higher yield of product **3** (85%) in comparison with bromide **2d** (76%). Similar results were found for the remaining alkynes **4**–**5** (Table 1). In both cases, for chloride **2a** and bromide **2d**, the main side product of ethynylation was N,N-dimethyl-10-(2-tetrahydropyranyloxy)-decan-amide (**7**). The structure of this compound followed from its spectral data (see experimental part). In ethynylation reaction with participation of bromide, compound **7** was formed in larger quantities than it was in the case of an analogous chloride.

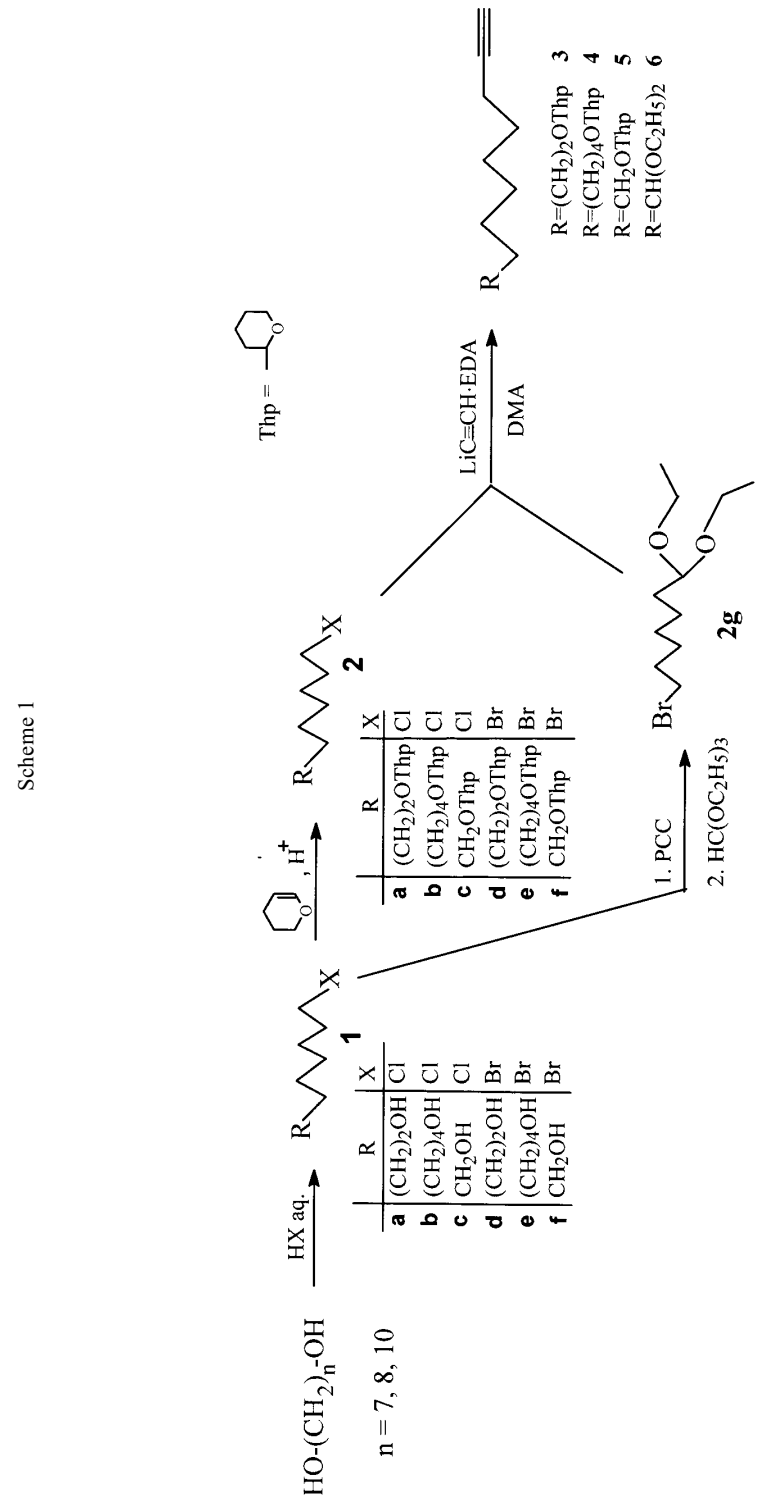
It should be noted that the results for chlorides are comparable with those found in the literature for analogous bromides in DMSO [11]. However, as it was already mentioned earlier the process of ethynylation should be performed at temperatures close to 0°C and this is technically difficult to achieve in the case of DMSO.

Table 1. Ethynylation of the ether derivatives haloalkanols **2**.

Halides **2**		Quant. of LiC≡C EDA[a] [mmol]	Quant. of halide **2** [mmol]	Addition halide **2**		Product	Purity of product[c] [%]	Yield [%]
R	X			time [min]	temp. [°C]			
$(CH_2)_2OThp$	Cl	74	37.5	85	/–5/÷/–2/	**3**	95	85
$(CH_2)_4OThp$	Cl	76	38	80	/–4/÷/–1/	**4**	94	81[d]
CH_2OThp	Cl	69.5	35	80	/–5/÷/–3/	**5**	95	82
$(CH_2)_2OThp$	Br	86	43	120	/–4/÷/–1/	**3**	96	76
$(CH_2)_4OThp$	Br	90	44.5	120	/–2/÷0	**4**	94	73
CH_2OThp	Br	60[b]	30	110	/–4/÷/–1/	**5**	93	74
$CH(C_2H_5)_2$	Br	15[b]	7	105	/–4/÷0	**6**	92	70[d]

[a]Concentration of LAEDA complex in DMA: 1.2 M. [b]Concentration: 2.0 M. [c]Determined by GLC analysis.
[d]Purified by flash chromatography (eluent: hexane-ether, 20:1).

Scheme 1


HO-(CH2)n-OH
n = 7, 8, 10
HX aq.
1
a (CH2)2OH Cl
b (CH2)4OH Cl
c CH2OH Cl
d (CH2)2OH Br
e (CH2)4OH Br
f CH2OH Br
Thp =
2
a (CH2)2OThp Cl
b (CH2)4OThp Cl
c CH2OThp Cl
d (CH2)2OThp Br
e (CH2)4OThp Br
f CH2OThp Br
LiC≡CH·EDA
DMA
R=(CH2)2OThp 3
R=(CH2)4OThp 4
R=CH2OThp 5
R=CH(OC2H5)2 6
1. PCC
2. HC(OC2H5)3
2g

In conclusion, the described procedure using the lithium acetylide–ethylenediamine complex and dimethylacetamide as solvent provides an operationally simple and efficient method for direct conversion of ether-functionalized chloro or bromoalkanols to terminal alkynes. The following advantages of this procedure are worth mentioning:

– chlorides were obtained with higher yields than respective bromides,
– application of DMA to avoid the easily freezing DMSO,
– application of chlorides as a starting material lowers the cost of the process.

EXPERIMENTAL

All starting materials were obtained commercially. Lithium acetylide–ethylenediamine complex is available from Aldrich Chemical Company, Inc. Column chromatography was performed on Silica gel 60 (Merck, 0.04–0.063 mm). Thin layer chromatography was performed on Alufolien with Silica gel 60 F_{254} (Merck). IR spectra were measured using a FT/IR-420 „Jasco" instrument (as film). ^{1}H NMR spectra were recorded with a Varian 200 MHz spectrometer for solutions in $CDCl_3$ (internal TMS). Chemical shifts are reported in δ ppm units and coupling constants in Hz units. MS spectra were measured on an API 365 or AMD M-40W spectrometer. Purity of the synthesized compounds was estimated by GC method, using a Varian STAR 3400 CX chromatograph; capillary column: DB1 (30×0.53 mm).

Preparation of ω-chloroalkanols (1a–c).

*8-Chlorooctan-1-o*l (**1a)**. 1,8-Octanediol (23.5 g, 0.16 mol) and aqueous 9N hydrochloric acid (220 ml) were placed in liquid-liquid extractor, heated to 87°C in a water-bath and extracted continuously with a mixture of octane-heptane (1:1) for 20 h. The organic extract was treated with powdered K_2CO_3 and after solvent removal, distillation of the residue through a Vigreux column yielded 20.5 g (78%) of a colorless oil, b.p. 90–92°C/0.6 torr (lit. b.p. 105°C/4 torr [6]), of *ca*. 96% purity. IR: 3340 (OH), 724, 650 (C–Cl); ^{1}H NMR: 1.24–1.86 (m, 13H, 6C**H$_2$** and O**H**), 3.54 (t, 2H, J = 6.8, C**H$_2$**Cl), 3.64 (t, 2H, J = 6.6, C**H$_2$**OH).

10-Chlorodecan-1-ol (**1b)**. The procedure was analogous to that described for chloride **1a**. Yield 72%; b.p. 102–104°C/1 torr (lit. b.p. 100–105°C/0.6 torr [12]); IR: 3325 (OH), 724, 652 (C–Cl); ^{1}H NMR: 1.22–1.86 (m, 17H, 8C**H$_2$** and O**H**), 3.53 (t, 2H, J = 6.7, C**H$_2$**Cl), 3.64 (t, 2H, J = 6.5, C**H$_2$**OH).

7-Chloroheptan-1ol (**1c**). 10.0 g (75.6 mmol) of heptamethylene glycol was refluxed for 2 h with 1.2 g cuprous chloride and 28 ml concentrated hydrochloric acid, and then continuously extracted with toluene for 17 h while the reaction mixture was heated in a water-bath at 87°C. The reaction afforded a crude chlorohydrin. Purification by distillation yielded 9.2 g of a colorless oil, b.p. 118–122°C/14 torr (lit. b.p. 120°C/13 torr [13]). Yield 81%; IR: 3337(OH), 726, 650 (C–Cl); ^{1}H NMR: 1.20–1.86 (m, 11H, 5C**H$_2$** and O**H**), 3.54 (t, 2H, J = 6.7, C**H$_2$**Cl), 3.65 (t, 2H, J = 6.5, CH_2OH).

Preparation of ω-bromoalkanols (1d–f). General procedure: To a mixture of diol (0.15 mol) and aqueous 48% HBr (19.5 ml, 0.173 mol) was added toluene (450 ml). The heterogeneous mixture was stirred and kept at gentle reflux (95–97°C) for 72 h. The reaction mixture was allowed to cool to room temp., and the phases were separated. The toluene layer was diluted with ether (700 ml) and washed with 1M NaOH, brine and phosphate buffer (1M, pH 7). Drying ($MgSO_4$) and concentration of the organic solution *in vacuo* gave a yellow oil. The crude product was purified by distillation under reduced pressure with the use of a Büchi B-580 glass oven.

The following compounds were obtained:

8-Bromooctan-1-ol (**1b**). Yield 89%; b.p. 94–100°C/0.2 torr (lit. b.p. 110–119°C/2 torr [14]); IR: 3320 (OH), 645, 560 (C–Br); ^{1}H NMR: 1.20–1.94 (m, 13H, 6C**H$_2$** and O**H**), 3.40 (t, 2H, J = 6.8, C**H$_2$**Br), 3.63 (t, 2H, J = 6.5, C**H$_2$**OH).

10-Bromodecan-1-ol (**1d**). Yield 82%; b.p. 109–114°C/0.4 torr (lit. b.p. 125–127°C/3 torr [14]); IR: 3305 (OH), 640, 561 (C–Br); ^{1}H NMR: 1.20–1.98 (m, 17H, 8C**H$_2$** and O**H**), 3.41 (t, 2H, J = 7.0, C**H$_2$**Br), 3.60 (t, 2H, J = 6.7, C**H$_2$**OH).

7-Bromoheptan-1-ol (**1f**). Yield 87%; b.p. 87–91°C/0.2 torr (lit. b.p. 98–100°C/2 torr [14]); IR: 3345 (OH), 645, 563 (C–Br); ^{1}H NMR: 1.20–1.96 (m, 11H, 5C**H$_2$** and O**H**), 3.40 (t, 2H, J = 6.8, C**H$_2$**Br), 3.62 (t, 2H, J = 6.6, C**H$_2$**OH).

Preparation of 1-tetrahydropyranyloxy-ω-haloalkanes (2a–f). In a typical procedure, a 2,3-dihydropyran (11.8 g, 0.14 mol) was added slowly with stirring and cooling to the haloalcohol **1** (0.1 mol) containing 1–2 drops of conc. hydrochloric acid, so that the temperature did not exceed 20°C. The mixture was stirred at room temp. overnight, and powdered sodium hydroxide (0.4 g) was added. It was then diluted with hexane (150 ml) and added charcoal (1 g). After filtration and elimination of solvent, further purification was proceeded by vacuum distillation – for chlorides, or flash chromatography (eluent: hexane-ether, 20:1) – for bromides to afford pure tetrahydropyranyl ethers.

8-(2-Tetrahydropyranyloxy)-1-chlorooctane (**2a**). Yield 82%; b.p. 118–120°C/0,6 torr (lit. b.p. 124–127°C/3 torr [6]); IR: 1031 (C–O), 722, 650 (C–Cl); ^{1}H NMR: 1.22–1.96 (m, 18 H, 9C**H$_2$**), 3.32–3.96 (m, 4H, 2OC**H$_2$**), 3.53 (t, 2H, J = 6.7, C**H$_2$**Cl), 4.52–4.60 (m, 1H, OC**H**O).

8-(2-Tetrahydropyranyloxy)-1-bromooctane (**2d**). Yield 87%; b.p. 105–107°C/0.1 torr (lit. b.p. 99°C/0.02 torr [15]); IR: 1030 (C–O), 640, 563 (C–Br); ^{1}H NMR: 1.22–1.96 (m, 18H, 9C**H$_2$**), 3.30–3.96 (m, 4H, 2OC**H$_2$**), 3.41 (t, 2H, J = 6.8, C**H$_2$**Br), 4.51–4.62 (m, 1H, OC**H**O).

10-(2-Tetrahydropyranyloxy)-1-chlorodecane (**2b**). Yield 79%; b.p. 125–129°C/0.4 torr (lit. b.p. 142–147°C/1 torr [12]); IR: 1033 (C–O), 724, 652 (C–Cl); ^{1}H NMR: 1.20–1.94 (m, 22 H, 11C**H$_2$**) 3.28–3.96 (m, 4H, 2OC**H$_2$**), 3.51 (t, 2H, J = 6.8, C**H$_2$**Cl), 4.54–4.62 (m, 1H, OC**H**O).

10-(2-Tetrahydropyranyloxy)-1-bromodecane (**2e**). Yield 86%; b.p. 147–150°C/0.1 torr (lit. b.p. 132°C/0.01 torr [16]); IR: 1033 (C–O), 642, 560 (C–Br); ^{1}H NMR: 1.20–1.96 (m, 22H, 11C**H$_2$**), 3.30–3.96 (m, 4H, 2OC**H$_2$**), 3.41 (t, 2H, J = 6.8, C**H$_2$**Br), 4.50–4.62 (m, 1H, OC**H**O).

7-(2-Tetrahydropyranyloxy)-1-chloroheptane (**2c**). To a stirred solution of haloalkanol **1e** (6.6 g, 0.045 mol) in CH_2Cl_2 (8 ml) and one drop of conc. hydrochloric acid was added dropwise dihydropyran (6 ml, 0.065 mol) at 5°C. After stirring overnight at room temperature, the mixture was neutralized with powdered potassium bicarbonate (anhydrous) and diluted with hexane (50 ml). The organic solution was filtered, and the solvent removed. Distillation of the crude product yielded 8.7 g (85%) colorless oil, b.p. 132–134°C/4 torr (lit. b.p. 112–114°C/0.2 torr [17]); IR: 1033 (C–O), 724, 652 (C–Cl); ^{1}H NMR: 1.20–1.98 (m, 16 H, 8C**H$_2$**), 3.32–3.96 (m, 4H, 2OC**H$_2$**), 3.53 (t, 2H, J = 6.8, C**H$_2$**Cl), 4.54–4.60 (m, 1H, OC**H**O).

7-(2-Tetrahydropyranyloxy)-1-bromoheptane (**2f**). The procedure was analogous to that described for chloride **2c**. Yield 89%; b.p. 103–105°C/0.2 torr (lit. b.p. 102–103°C/0.08 torr [15]); IR: 1032 (C–O), 645, 558 (C–Br); ^{1}H NMR: 1.20–1.98 (m, 16 H, 8C**H$_2$**), 3.30–3.94 (m, 4H, 2OC**H$_2$**), 3.41 (t, 2H, J = 6.8, C**H$_2$**Br), 4.55–4.61 (m, 1H, OC**H**O).

Preparation of 7-bromoheptanal diethyl acetal (2g). To a suspension of pyridinium chlorochromate (5 g, 23 mmol) in dry dichloromethane (30 ml) under argon, a solution of 7-bromoheptanol ((3 g, 15 mmol) in dry dichloromethane (3 ml) was added and the mixture was stirred for 1.5 h at room temperature. Anhydrous diethyl ether (30 ml) was added to the reaction mixture, and the supernatant was decanted from the black gum. The insoluble residue was washed twice with anhydrous ether (15 ml) and the combined organic solution was filtered through a short column of silica gel and concentrated *in vacuo*. The crude aldehyde was added to a mixture of triethyl orthoformate (2.2 g, 2.4 ml) and a catalytic amount of ammonium chloride (80 mg) in anhydrous ethanol (30 ml). The mixture was heated at reflux for 7 h, then cooled, diluted with water and extracted with ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated to yield the crude product as a pale yellow oil. Purification by flash chromatography (eluent: hexane-ether, 10:1) yielded a colorless oil (1.7 g, 48% from two stages). IR: 1728 ($C(OC_2H_5)_2$), 645, 562 (C–Br); ^{1}H NMR: 1.18–1.97 (m, 10H, 5C**H$_2$**), 1.24 (t, 6H, J = 6.8, 2C**H$_3$**), 3.40–3.78 (m, 4H, 2OC**H$_2$**), 3.44 (t, 2H, J = 6.9, C**H$_2$**Br), 4.51 (t, 1H, J = 5.7, OC**H**O).

Preparation of 10-(2-tetrahydropyranyloxy)-1-decyne (3); typical procedure: To a cooled (–5°C) 1.2 M suspension of lithium acetylide–ethylenediamide complex (6.8 g, 74 mmol) in dry DMA (62 ml) under argon was added dropwise of 8-(2-tetrahydropyranyl-oxy)-1-chlorooctane (**2a**; 9.3 g, 37.5 mmol) for 85 minutes. After stirring for 16 h at room temperature, the resulting mixture was hydrolyzed by the careful addition of ice/water (100 ml) and extracted with petroleum ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product **3**, which was contaminated with *ca*. 4 % of N,N-dimethyl-10-(2-tetrahydropyranyl-

oxy)-decan-amide (**7**) by GC was purified by distillation with a Büchi B-580 glass oven; yield 7.55 g (85%); b.p. 120–126°C/0.4 torr (lit. b.p. 168–173°C/5.5 torr [6]).

Spectral data of 10-(2-tetrahydropyranyloxy)-1-decyne (**3**): IR: 3340 and 2130 (C≡CH), 1033 (C–O); ^{1}H NMR: 1.22–1.94 (m, 18H, 9C**H$_2$**), 1.91 (t, 1H, J = 2.8, C≡C**H**), 2.02–2.21 (m, 2H, C**H$_2$**C≡C), 3.28–3.94 (m, 4H, 2OC**H$_2$**), 4.50–4.52 (m, 1H, OC**H**O); HRMS (ESI): $[M + Na]^+$ m/e 261.1830, calcd. for $C_{15}H_{26}O_2Na$ 261.1825.

Spectral data of N,N-dimethyl-10-(2-tetrahydropyranyloxy)-decan-amide (**7**): IR: 1650 (C=O), 1032 (C–O); ^{1}H NMR: 1.22–1.88 (m, 20H, 10C**H$_2$**), 2.30 (t, 2H, J = 8.0, C**H$_2$**C=O), 2.94 (s, 3H, NC**H$_3$**), 3.00 (s, 3H, NC**H$_3$**), 3.68–3.92 (m, 4H, 2C**H$_2$**O), 4.58 (dd, 1H, J = 3.0, 4.5, OC**H**O); MS (EI): $[M]^+$ m/e 299. Above procedure was followed for synthesis of terminal alkynes 4–6 (see Table 1).

12-(2-Tetrahydropyranyloxy)-1-dodecyne (**4**). B.p. 137–144°C/0.2 torr (lit. b.p. 118°C/0.05 torr [16]); IR: 3340 and 2130 (C≡CH), 1033 (C–O); ^{1}H NMR: 1.20–1.96 (m, 22H, 11C**H$_2$**), 1.94 (t, 1H, J = 2.6, C≡C**H**), 2.18 (dt, 2H, J = 2.6, 6.8, C**H$_2$**C≡ C), 3.28–3.96 (m, 4H, 2OC**H$_2$**), 4.52–4.62 (m, 1H, OC**H**O); HRMS (ESI): $[M + Na]^+$ m/e 289.2150, calcd. for $C_{17}H_{30}O_2Na$ 289.2138.

9-(2-Tetrahydropyranyloxy)-1-nonyne (**5**). B.p. 112–116°C/0.2 torr (lit. 107–110°C/0.2 torr [17]); IR: 3308 and 2120 (C≡ CH), 1030 (C–O); ^{1}H NMR: 1.20–1.98 (m, 16H, 8C**H$_2$**), 1.94 (t, 1H, J = 2.8, C≡C**H**), 2.10–2.26 (m, 2H, C**H$_2$**C≡C), 3.30–3.96 (m, 4H, 2C**H$_2$**O), 4.50–4.62 (m, 1H, OC**H**O); MS (ESI): $[M + Na]^+$ m/e 247.2.

9,9′-Diethoxy-1-nonyne (**6**). IR: 3310, 2120 (C≡CH), 1727 (C(OC$_2$H$_5$)$_2$), 1062 (C–O); ^{1}H NMR: 1.20 (t, 6H, J = 7.0, 2C**H$_3$**), 1.26–1.70 (m, 10H, 5C**H$_2$**), 1.94 (t, 1H, J = 2.6, C≡C**H**), 2.18 (dt, 2H, J = 2.6, 6.8, C**H$_2$**C≡ C), 3.40–3.74 (m, 4H, 2OC**H$_2$**), 4.48 (t, 1H, J = 5.8, OC**H**O); HRMS (ESI): $[M + Na]^+$ m/e 235.1656, calcd. for $C_{13}H_{24}O_2Na$ 235.1669.

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