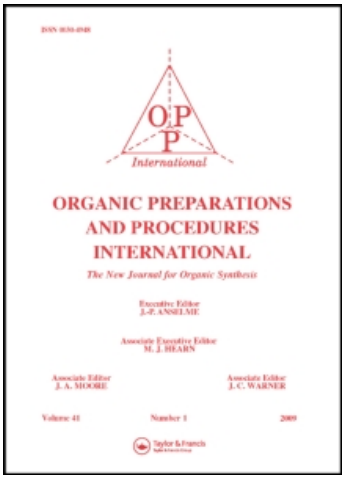


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A LARGE SCALE PREPARATION OF 1-ETHYNYLCYCLOPENTENE AND 1-HEXEN-4-YNE

Enrico Davin[a]; Matteo Giongo[a]; Mario Riocci[a]
[a] Eniricerche Spa, Monterotondo Scab, ITALY

To cite this Article Davin, Enrico , Giongo, Matteo and Riocci, Mario(1995) 'A LARGE SCALE PREPARATION OF 1-ETHYNYLCYCLOPENTENE AND 1-HEXEN-4-YNE', Organic Preparations and Procedures International, 27: 5, 586 — 590
To link to this Article: DOI: 10.1080/00304949509458511
URL: http://dx.doi.org/10.1080/00304949509458511

12. a) R. Bloch and D. Hassan-Gonzales, *Tetrahedron*, **42**, 4975 (1986), ref. 8. b) T. Mandai, J. Gotoh, J. Otera and M. Kawada, *Chemistry Lett.*, 313 (**1980**).

****

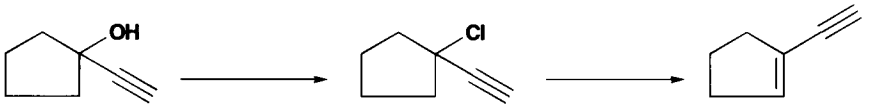
A LARGE SCALE PREPARATION OF 1-ETHYNYLCYCLOPENTENE AND 1-HEXEN-4-YNE

Submitted by (12/07/94) Enrico Davini*, Matteo Giongo* and Mario Riocci*

Eniricerche Spa, Via Ercole Ramarini 32
00016, Monterotondo Scalo, ITALY

Recently we have been interested in a safe and convenient large scale syntheses of 1-ethynylcyclopentene (**3**), 1-hexen-4-yne (**6**) and 1-hexen-3-yne (**9**), to be utilized in long term storage safety tests. A literature search disclosed a synthesis of **3**[1,2] and two procedures of related enyne compounds on a 10-15 g. scale (0.1-0.2 moles),[3,4] no reliable syntheses of **6** and **9** were found. Compounds **3** and **6** have been now efficiently obtained (total yield 70% and 58%, respectively); although the preparation of **9** has been explored by several other routes, it was obtained only as a crude product in 80% yield but always decomposed during attempted workup and isolation.

1-Ethynylcyclopentene (**3**) has been obtained from commercially available 3-ethynyl cyclopentanol **1** *via* **2** (obtained by chlorination with $POCl_3$) followed by dehydrohalogenation. The conversion of **2** to **3** was reported to occur in pyridine at 0° for 15 hours in 56%[2] or at 100° for 15 minutes in "high" yield.[1] Replacement of pyridine by triethylamine resulted in a shorter reaction time (45-60 minutes) at lower temperature. Six runs allowed us to convert a total 670 g. of **1** to 391 g. (70%) of **3** in approximately 95% purity.

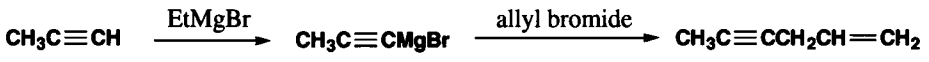


1 **2** **3**

A 10 g. scale synthesis of 1-hexen-4-yne **6** was described[5] (26% yield), through the coupling of allyl iodide with propynylmagnesium bromide **5** (obtained through the exchange from the previously obtained ethylmagnesium bromide). The formation of 1-hepten-4-yne in 61% yield was reported[6] by Cuprous chloride catalyzed[7] coupling of butynylmagnesium bromide with allyl bromide.

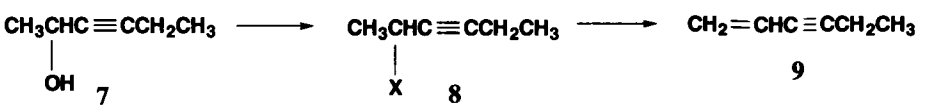
We therefore attempted to couple **5** with allyl bromide using CuCl as catalyst; some problems arose from the low solubility of **5** and the high volatility of propyne, but these were overcome by the use of suitable equipment.[8b] The isolation of **6** from the solvent (tetrahydrofuran) was very trouble-

some despite the reasonable 20° difference in the bps of the two compounds. Only the utilization of a high efficiency fractionating column allowed us to obtain a pure product. The average yield of **6** in four runs was 58%, twice as much as was previously reported.[5]



4 **5** **6**

The attempted synthesis of pure 1-hexen-3-yne (**9**) met with several problems, initially in the selection of a reliable procedure and secondly in the isolation of the pure product. Two potentially interesting syntheses[9,10] suffer from low yields (about 30%) and the utilization of two reactants listed as carcinogenics. In fact, the syntheses of **9** require either the homologation of sodium vinylacetylide with diethyl sulfate[9] or the potassium hydroxide promoted cleavage of ethyl-2-hexynyl ether, obtained from sodium pentynide and chloromethyl ethyl ether.[10] In addition, a large volume of liquid ammonia (about 1.5 liter for 100 gram of starting material) is necessary for the formation of the sodium alkyne salt.



a) X = Cl b) X = OAc c) X = OTos

Several experiments starting from commercially available 3-hexyn-2-ol (**7**) were made in order to obtain **9**. Reaction of **7** with $POCl_3$ in the presence of pyridine or triethylamine gave only the 2-chloro-3-hexyne (**8a**). The dehydration of **7** with acetic anhydride catalyzed by *p*-toluenesulfonic acid[11] readily gave 2-acetoxy 3-hexyne **8b**, but no further elimination was observed. However, attempted elimination of toluenesulfonic acid from the tosyl derivative **8c**,[12] with potassium hydroxide[13] led only to impure **9** (about 80% yield, GLC). This reaction had been reported to be successfully applied[13] in the synthesis of pent-2-en-4-yne from 4-pentyn-2-ol. Compound **9** was unstable to isolation, in particular when ethyl ether (even if freshly distilled) was used. A violent decomposition with formation of a black residue was observed under all distillation conditions, even in the presence of a polymerization inhibitor. Analogous explosive decomposition was reported[12] for the isolation of the isomeric compound 3-hexen-1-yne. The substitution of a mixture of *n*-pentane-ethyl ether as solvent, allowed us to concentrate the crude product until about 50% of the solvent was removed; however, successive distillation (also under vacuum) invariably led to decomposition of the product. It is interesting to note that **9** is reported to distill at 680 mm (bp. 80-81°[10]) and, like other enynes[12], at 84-85° at atmospheric pressure.[9]

The scale-up procedures usually reported on a small scale in the literature, always exhibited some problems on a larger scale: conversion, efficient methods of isolation, small (safe) solvent utilization. Thus a number of the methods which seemed attractive at first become impractical when applied on a larger scale.

EXPERIMENTAL SECTION

3-Ethynyl cyclopentanol (**1**) and 3-hexyn-2-ol (**7**) were purchased from Lancaster (UK), propyne from Ucar-SIO (Italy). All other reagents were obtained from Fluka and were used as received. Gas-chromatographic analyses were performed on a Hewlett-Packard 5890 using an DB-1 (30m) column, equipped with a FID detector. All syntheses were performed under N_2 atmosphere using a 3 L round-bottomed, four necked flask, equipped with a dropping funnel-gas inlet, a thermometer, a mechanical stirrer and a reflux condenser, unless stated othervise. ^{1}H NMR spectra were recorded at 400 MHz on a Varian XL 400 spectrometer and data are reported as p.p.m. (δ) downfield from TMS with multiplicities, assignments and J values (Hz) in parentheses.

1-Ethynylcyclopentene (3). - To a warm (45°) solution of 3-ethynylcyclopentanol (**1**, 111.6 g, 1 mole) in 800 mL (584 g, 5.78 moles) of triethylamine under N_2, was added dropwise (30 min) 75 mL of $POCl_3$ (154 g, 0.82 mole). The temperature rose to about 75° and this temperature was maintained for an additional hour. After cooling to RT, the mixture was added to 1.2 Kg of crushed ice and stirred vigorously. The layers were separated and the aqueous phase was extracted with Et_2O:*n*-pentane (1:1, 5 x 150 mL). The combined organic phases were then washed with 3 x 250 mL of HCl 2.5 N to remove triethylamine, with saturated $NaHCO_3$ solution and with water. The organic layer was dried overnight over $MgSO_4$. The solvent was distilled off through a 40 cm. Vigreux column at atmospheric pressure (max. temp. 80°) and under vacuum (112 mmHg) at RT. At the same pressure (112 mmHg) at 80°, two fractions of **3** were obtained, the first (13 g) with 50% purity, the second (56.5 g) with >95% purity. GC conditions isotherm 70° for 2 min, ramp rate 30°/min until 150°; r.t.: **1** 2.6 min, **3** 1.7 min. ^{1}H NMR ($CDCl_3$): δ 6.13 (t, 1H, C=C-H), 2.95 (s, 1H,CC-H), 2.52-2.35 (m, 4H, CH_2-3 and CH_2-5), 1.9 (m, 2H, CH_2-4). This procedure was repeated five times, using a total of 670 g (6 moles) of **1**. In the six runs, a total of 391 g (purity > 95%) of **3**, bp 80°/112 mmHg, lit.[1,2] bp ca. 55°/120 mmHg and 60-62°/100 Tor, was produced.

1-Hexen-4-yne (6).- Ethylmagnesium bromide was prepared under standard conditions,[8a] starting from Mg turnings (44 g, 1.83 moles) and 220 g (2 moles) of EtBr in 700 mL of Et_2O. The exothermic reaction was kept at reflux temperature, until the end of the ethyl bromide addition. The suspension was stirred overnight at RT and diluted with 800 mL of distilled THF. The water-cooled reflux condenser was replaced with a Dry Ice-acetone condenser (-80°) and a lecture bottle of propyne was connected to the flask with a Tygon tube that was attached to a needle. The suspension of ethylmagnesium bromide was warmed to 40° and propyne (**4**, 100 g, 2.8 moles) was bubbled in for about 2.5 hrs (the amount of **4** used was determined by weighing the lecture bottle before and after the addition).[8b] Progressively a grayish white precipitate, probably the partially insoluble propynylmagnesium bromide (**5**), was formed. After the addition, the reaction mixture was stirred at 40° for an additional 2 hrs; after cooling to RT, CuCl (3.2 g) was added with stirring for 20 min. Then a solution of allyl bromide (200 g, 1.64 mole) in 200 mL of THF was added, dropwise, over about 1 hr since the reaction is exothermic. The mixture was kept at 40° overnight; slowly a yellow-green precipitate was formed. After cooling, the mixture was hydrolyzed with 2.5 N HCl, with the formation of two phases.

The aqueous layer was extracted 3 times with 100 mL of Et_2O. The combined organic solutions were washed with water (four times the volume of organic phase) to remove HCl and THF, and finally dried over $MgSO_4$. The solution was distilled initially through a 80 cm Vigreux column to eliminate Et_2O and EtBr (bp. < 40°) and THF at 65-67°. The first fraction (69-86°) consisted of mixture of THF and **6** (1:1). Finally about 24 g. of pure **6** distilled, bp. 86-88°, lit.[5] bp. 86-88°. Some **6** remained in the residue. GC conditions isotherm 45° for 6 min: **6** 1.9 min. ^1H NMR ($CDCl_3$): δ 5.8 (m, 1H, $\underline{H}$-CCH_2), 5.3 and 5.1 (AB, 2H, H_2C=C), 2.9 (m, 2H, CH_2), 1.8 (s, 3H, CH_3). The reaction was repeated 3 times. For a more convenient isolation of the products, the fractions containing THF and **6** from all the 4 reactions (about 1 liter) were collected, toluene (300 mL) was added as an alternative, higher bp. solvent, and 1% hydroquinone monomethylether, a polymerization inhibitor, was added. The solution was distilled through a fractionating, adiabatic column of Normschliff Geratebau (length 1 m, internal diameter 15 mm, packed with glass Wilson helices of 3 mm diameter). The following four reflux ratios (R) and distillation flask temperatures (T) were adopted and maintained through the control unit: 1) T = 60°, R = 1:4; 2) T = 85°, R = 1:4; 3) T = 90-110°, R = 1:20; 4) T = 110°, R = 1:5. The resulting fractions were obtained: fraction 1: bp. 35-40° (Et_2O and EtBr); fraction 2, bp. 65-67° (THF), fraction 3, bp. 69-86° (THF and **6**); fraction 4, bp. 87-90° pure **6**. In the four runs, a total of 295.6 g of **7**, total yield 58.5%, was obtained.

REFERENCES

1. R. Carlson and W. Cox, *J. Org. Chem.*, **42**, 2384 (1977).
2. L. Brandsma, *"Preparative Acetylenic Chemistry"*, 2nd ed., p. 204, Elsevier, Amsterdam, 1988.
3. L. Brandsma and H. D. Vekrujsse, *"Synthesis of Acetylenes, Allenes and Cumulenes. A Laboratory Manual"*, p. 1-276, Elsevier, Amsterdam, 1981.
4. Ref. 2, p. 1-321.
5. P. A. Pinke and R. G. Miller, *J. Am. Chem. Soc.*, **96**, 4221 (1974).
6. M. Winter and F. Gautschi, *Helv. Chim. Acta*, **45**, 2567 (1962).
7. For a review, see J. F. Normant, *Synthesis*, 63 (**1972**).
8. a) *Org. Synth., Coll. Vol. 4*, p. 792; b) *ibid., Coll. Vol. 7*, p. 456.
9. R. Jacobson and W. H. Carothers, *J. Chem. Soc.*, **55**, 1622 (1933).
10. G. M. Mkryan, N. A. Papazyan, A. V. Arutyunyan and S. M. Gasparyn, *J. Org. Chem. URSS*, **5**, 1524 (1969).
11. Ref. 2, p. 203.

12. Ref 2, p. 205.

13. G. Eglington and M. C. Whiting, *J. Chem. Soc.*, 3650 (**1950**).

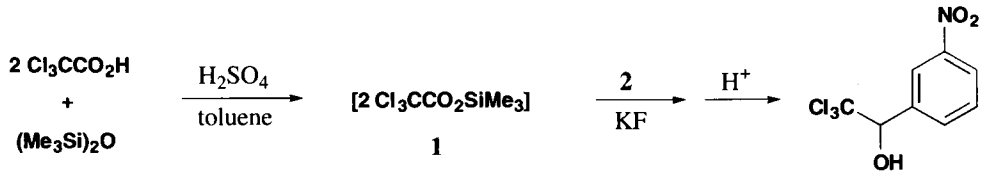
****

TRIMETHYLSILYL TRICHLOROACETATE AS A CHLOROFORM ALTERNATIVE FOR THE SYNTHESIS OF α-(TRICHOLOROMETHYL)-3-NITROBENZYL ALCOHOL

Submitted by Steven A. Weissman
(01/24/95)

Merck Manufacturing Division, Merck & Co., Inc.
P. O. Box 2000, Rahway, NJ 07065

The desire to eliminate halogenated solvents and/or reagents such as chloroform, methylene chloride and carbon tetrachloride from the manufacture of pharmaceuticals has become an industry-wide goal, owing to the health and environmental concerns raised by their use.[1] We sought to develop a chloroform-free synthesis of α-(trichloromethyl)-3-nitrobenzyl alcohol (**3**), a precursor in the synthesis of clorsulon, a compound used in the treatment of liver flukes in animals.[2]



3

Traditionally, aromatic α-(trichloromethyl)carbinols are prepared by condensing the corresponding aldehyde or ketone with trichloromethide anion, generated by the action of base (such as KOH)[3] on chloroform (usually in >100% excess) or by the decomposition of trichloroacetic acid (or its sodium salt) in DMSO.[4] The presence of strong base in the former method often promotes the competing Cannizzaro reaction.[3] These methods have been employed for the synthesis of **3** in 98%[5] and 60% yield,[4a] respectively. Recently, trimethylsilyl trichloroacetate (**1**) (TMS-TCA), conveniently prepared *via* the sulfuric acid-catalyzed reaction between trichloroacetic acid and hexamethyldisiloxane[6] has been employed as an alternative trichloromethide synthon.[7] Herein, the utility of this reagent is described for the one-pot synthesis of **3** in excellent yield.

TMS-TCA (**1**) was generated and reacted with *m*-nitrobenzaldehyde (**2**) in the presence of a catalytic amount of potassium carbonate and 18-crown-6[7a] in the absence of solvent for 5 hrs at 70°.[8]