Asian Journal of Chemistry; Vol. 23, No. 8 (2011), 3771-3772

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

NOTE

Solvent Free and Regioselective Hydroboration of Terminal Double Bond for Synthesis of Z-11-Hexadecenol

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(*Received*: 26 November 2010; *Accepted*: 30 April 2011) AJC-9901

Z-11-Hexadecenol was synthesized in high yield by Wittig and hydroboration reactions without solvent. Initially 1,11-hexadecadiene was synthesized as a result of Wittig reaction between *n*-pentyl bromide and C -11 aldehyde. Later hydroboration of the diene formed was carried out by *in situ* generation of borane using sodium borohydride and boron trifluride etherate. The significance of the process lies on the fact that it is solvent free as well as regioselective and the borane:diene ratio was taken as 1:6. The trialkyl borane formed as the result of the above reaction was filtered and the excess diene was recovered. Further oxidation of trialkyl borane resulted in the formation of Z-11-hexadecenol of > 95 % purity. The excess diene recovered from hydroboration reaction showed more purity than its precursor and can be reused again. Thus this method was found to give more atom economy and the process can be scaled up easily without affecting the isomeric purity.

Key Words: Wittig reaction, Sodium borohydride, Boron trifluride etherate, Trialkyl borane, Z-11 Alcohol.

Pheromones are usually obtained in μg to mg quantities which are insufficient for the determination of their absolute configuration as well as for the biological studies to examine practicality in the field. Pheromone synthesis is therefore important in order to establish the structure of a new pheromone and also to provide a plenty of materials to carry out extensive biological studies. Pheromones are usually low molecular weight organic compounds with stereogenic center(s) and/or double bond(s). Hence it is necessary to employ efficient carbon-carbon bond forming reactions and enantioselective reactions to synthesize pheromones. The diene molecules with reactive functional groups at the terminal positions are good synthones for the synthesis of pheromone and related compounds[1]. Synthesis of these molecules in large scale without affecting the stereochemistry is still a challenge. Hydroboration of the diene forming the pheromones are found to yield the required Z-11-hexadecenol alcohol, but the hydroboration should be regioselective towards the terminal double bond. Narasimhan *et al*.[2,3] employed this procedure for the synthesis of the same, but yielded primary alcohol along with secondary. Regioselective hydroboration can be done with sterically hindered boranes like 9-BBN, dicyclohexyl borane, *etc*.[4]. However development of safe, economical hydroborating technique is still important topic in hydroboration research[5-7]. This invention relates to a novel scaling up process of synthesizing Z-11-hexadecenol. The process involves 'green chemistry' without the use of solvents, involving better atom economy. A diene is initially synthesized with an aldehyde having terminal double bond and alkyl halide. This diene is then selectively hydroborated at the terminal position by taking diene six times than that of borane[8-10]. The excess diene can be separated.

All reagents and solvents were purchased from Sigma-Aldrich and were used as supplied. Thin-layer chromatography (TLC) was performed on 0.25 mm pre coated silica gel 60 F_{254} aluminum sheets and column chromatography on silica gel 60 (0.063-0.2 mm) as well as silica gel 60 (< 0.063 mm), products of Merck & Co. (Darmstadt, Germany).

The boiling and melting point were uncorrected. The IR spectra were scanned with a Perkin-Elmer 783 spectrophotometer. The ^{1}H NMR spectra were recorded, with a Bruker (500 MHz) spectrometer, with TMS as internal standard. $CDCl_3$ was used as the solvent. The GLC analyses were carried out on a Shimadzu GC-7A chromatograph fitted with a flame ionization detector and glass packed column for routine analysis and a capillary column for the determination of isomeric compositions. The mass spectra (EI) was recorded at 70 eV with a Shimadzu GC-MS QP-1000A spectrometer. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

Synthesis of pentyl phosphonium bromide: Triphenyl phosphine (27.3 g, 100 mmol) was taken in a dried round bottom flask with side arm adaptor and septum. The flask was purged three times with nitrogen and subsequently immersed into an oil bath (90 ºC). 100 mL of benzene was added followed by 250 mL of acetonitrile and *n*-bromo pentane (16.6 g, 110 mmol) was added dropwise into the reaction vessel and stirred for 72 h. The reaction was monitored by TLC. After the completion of the reaction, the solvents were distilled out and the product obtained as crystalline solid. The melting point was determined to be 166-168 ºC.

Synthesis of 1,11-hexadecadiene: Pentyl phosphonium bromide (42.4 g, 100 mmol) was taken in a dried round bottom flask with side arm adaptor and septum. The flask was purged with nitrogen and connected to a mercury bubbler and 400 mL of dry THF was added to the flask. Sodium amide was added through the side arm, using a solid addition funnel. The stirred and allowed to react at room temperature till the appearance of tomato red colour. The reaction mixture was cooled to -15 ºC and added undecenyl aldehyde dropwise. The reaction was followed by TLC and after the completion, reaction quenched with aqueous NH_4Cl solution. The organic layer separated and the aqueous layer extracted two times with ethyl acetate. The organic portions combined and dried with anhydrous sodium sulphate. The product concentrated by rotary evaporator and chilled, added *n*-hexane. The phosphine oxide thus precipitated filtered out. The crude product thus obtained showed 85 % purity in GC and used as such for the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.29 (t, *J* = 5.4Hz, 2H) 2.41 (m, 2H) 2.05-2.04 (m, 4H) 1.29-1.65 (m, 12H) 0.87-0.91 (m, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 129.8, 44.2, 32.4, 32.0, 30.1, 29.7, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 14.5. MS (EI) M^+ = 221.8, b.p. 297 ºC.

Synthesis of Z-11-hexadecen-1-ol: Sodium borohydride (400 mg, 10 mmol) was taken in a dried round bottom flask with side arm adaptor and septum. The flask was purged with nitrogen and connected to a mercury bubbler. The synthesized 1,11-hexadecadiene (13.3 g, 60 mmol) was added through the side arm. The reaction mixture was stirred well and the temperature brought down to -20 ºC. Boron trifluride etherate solution (1.6 mL, 11 mmol) added dropwise by using a syringe. The reaction was maintained at -20 ºC for 0.5 h and slowly brought to room temperature. The reaction was allowed to stir at room temperature for 2 h and then warmed the mixture to 60 ºC for 1 h. The trialkyl borane thus precipitated filtered from the diene and washed with *n*-hexane. The recovered diene washed with 3M NaOH solution and finally with brine. The trialkyl borane taken in another round bottom flask, containing 10 mL 3M NaOH solution and 5 mL 30 % H_2O_2 and stirred for 2 h. After the oxidation been completed, the reaction was quenched with dil. HCl and the organic layer separated. The aqueous layer extracted two times with ethyl acetate and the organic layers combined. The organic portion dried over anhydrous sodium sulphate and concentrated by rotary evaporator. The crude product showed > 95 % isomeric purity.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.37 (t, *J* = 5.4Hz, 2H) 3.59 (s, 1H) 2.44 (m, 2H) 2.05-2.04 (m, 4H) 1.29-1.65 (m, 12H) 0.88-0.91 (m, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 129.9, 64.8, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 14.5. MS (EI) M^+ = 237.3, b.p. 309 ºC.

Wittig reaction was performed with *n*-pentyl bromide and C-11 aldehyde which resulted in the formation of 1,11-hexadecadiene of mearly 85 % purity. This yielded diene was exclusively Z isomer. The diene thus obtained was used as such without any purification in the next step. Then hydroboration reaction carried out regioselectively on the terminal double bond by taking diene six times excess than that of borane. Borane was generated *in situ* by the reaction between sodium borohydride and boron trifluride etherate. As the result of the reaction trialkyl borane was formed filtered and washed with *n*-hexane. Also excess diene was recovered and it washed with aqueous NaOH to remove traces of trialkyl borane. The diene thus obtained showed more purity (90 %) than the diene formed as a result of Wittig reaction. Later trialkyl borane was oxidized and Z-11-hexadecenol was synthesized with *ca.* 95 % isomeric purity. Thus this method proves to be a cost effective method for synthesizing pheromones of the type, Z-11-hexadecenol, Z-11-hexadecenal, Z-11-hexadecenyl acetate, where more number of purification steps were eliminated and found to provide better atom economy.

REFERENCES

1. S. Narasimhan, S. Madhavan, G.K. Prasad, *J. Org. Chem.*, **60**, 5314 (1995).
2. S. Narasimhan, G.K. Prasad and S. Madhavan, *Tetrahedron Lett.*, **36**, 1141 (1995).
3. S. Narasimhan and G.K. Prasad, *Org. Prep. Proced. Int.*, **25**, 108 (1993).
4. H.C. Brown and S. Narasimhan, *Organometallics*, **1**, 762 (1982).
5. P. Karrer, W. Karrer, H. Thomann, F. Horlacher and W. Mader, *Helv. Chim. Acta*, **4**, 76 (1921).
6. P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).
7. H. Seki, K. Koga, H. Matsuo, S. Ohiki, I. Mutsuo and S. Yamada, *Chem. Pharm. Bull.*, **13**, 995 (1965).
8. D.A. Dickman, A.I. Meyers, G.A. Smith and R.E. Gawley, In ed.: J.P. Freeman, In Organic Syntheses; Wiley: New York, Coll. Vol. 7, p. 530 (1990).
9. G.A. Smith and R.E. Gawley, *Org. Synth.*, **63**, 136 (1985).
10. A. Giannis and K. Sandhoff, *Angew. Chem. Int. Ed.*, **28**, 218 (1989).