Tracking Zipper reaction using NMR technique

Maged H. Muzael
Science College
Thi-Qar university

Key world: Zipper reaction, Sonogashira reaction, super strong base, triple bond transfer.

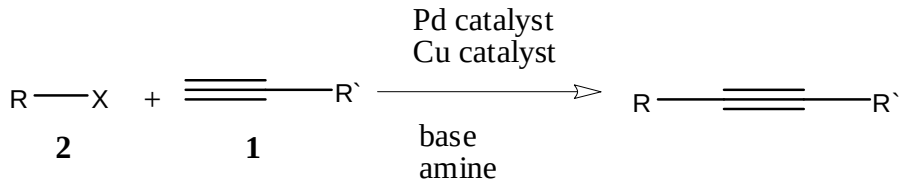
Abstract:

In this study NMR technique was used to track the success of transfer triple bond from the middle of the molecule to the end of the molecule. The first step was coupling reaction (Sonogashira reaction) between propargyl alcohol with 1-Iodododecane using very strong base lithium wire in liquid ammonia. The second step was transfer the triple bond the end of the molecule using the same strong very strong base Lithium in liquid ammonia (Zipper reaction).

Introduction

This study was carried out in two major steps: the first step was Sonogashira reaction and the second was Zipper reaction. Alkynes are a recurring functional group in a wide range of natural products and other bioactive compounds,[1] as well as versatile intermediates in synthesis,[2] the development of methods for incorporating them into organic molecules is an important objective. One widely used process is the Sonogashira reaction, which typically employs a palladium and a copper catalyst to couple a terminal alkyne (**1**) with an aryl or vinyl halide or triflate (**2**) (eq 1). Attractive features of this method include its experimental simplicity and its high atom-

economy and functional-group tolerance (Scheme1).[3]

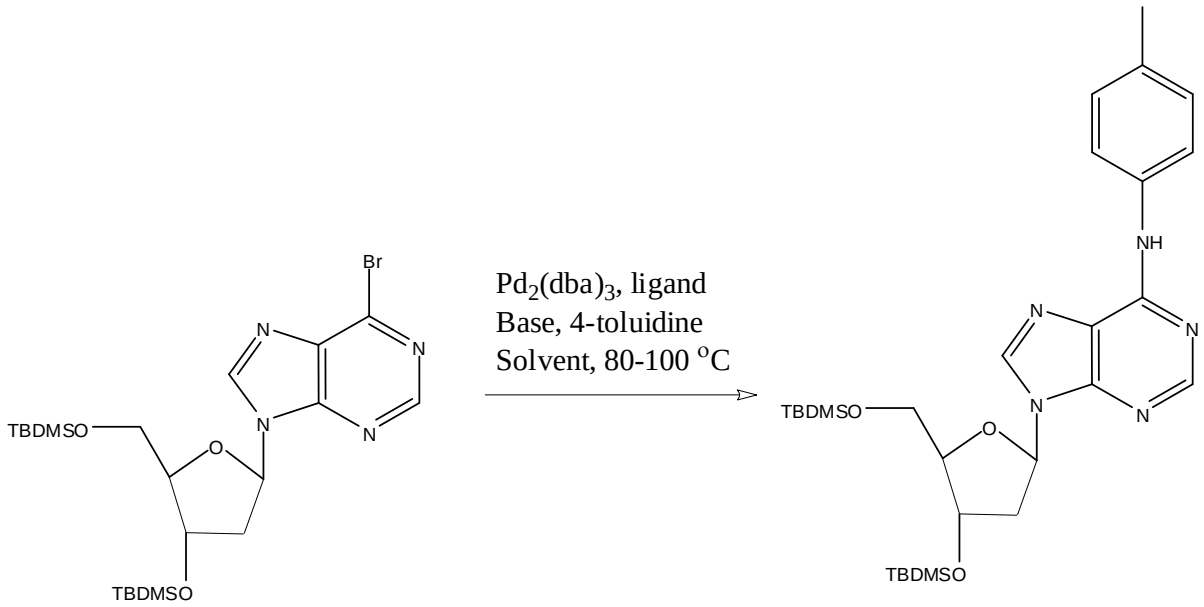


2 **1**

R = vinyl or aryl
R`= Halide

Scheme 1: Typical Sonogashira reaction[3]

It's applications include pharmaceuticals, natural products, organic materials, and nanomaterials.[4] Specific examples N6-modified adenine nucleosides is by displacement reactions of a leaving group from an electrophilic nucleoside analog by an amine. and this approach has been effectively used to synthesize various classes of compounds. Typically, the electrophilic nucleosides are 6-halo-9[2-deoxy-b-D-erythro-pentofuranosyl]purines (halogen-/Cl, Br, I) (**3**). If exceptional reactivity is sought in the substitution reaction, then 6-fluoro-9[2-deoxy-b-D-erythro-pentofuranosyl]purine (**4**) (Scheme 2).[6]



3 **4**

Scheme 2: synthesis nucleoside derivative using Sonogashira reation

In order to transfer the triple bond from internal position to the terminal position Zipper reaction was employed. Potassium 3-aminopropylamide, KAPA, is well-known as an efficient reagent in isomerizing internal acetylenes to the terminal position.[7] KAPA has been used in the synthesis of pheromones and fatty acids. The reagent was first prepared by C. A. Brown, from 1,3-propanediamine and potassium hydride. The main disadvantages of using potassium hydride are that it is hazardous; is expensive, and has short shelf stability. *An* alternative route was developed by Brandsma who reacted potassium amide made in liquid ammonia with 1,3-propanediamine at 80°C. Since we frequently employ KAPA for synthesis of pheromone analogues, it was essential to develop an alternative route Figure 1.[8]

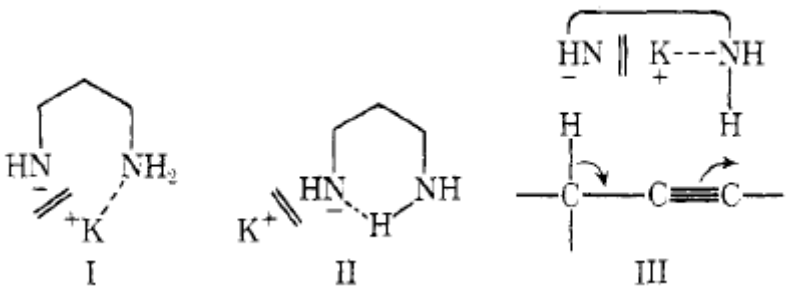
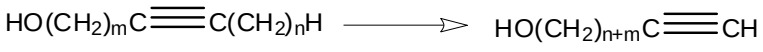


Figure 1: KAPA catalyst effect in zipper reaction

The "acetylenic zipper" reaction offers a unique method for effecting the functionalization of the end of a long hydrocarbon chain. The reaction, which involves the base-mediated isomerization of an alkyne with an internal triple bond to the terminal alkyne (**5**), has been performed on both unsubstituted alkynes and alkyn-1-01s. The latter give ω-hydroxy alkynes (**6**) (Scheme 3):[9]



5 **6**

Scheme 3: Transfer triple bond from internal position to the terminal position

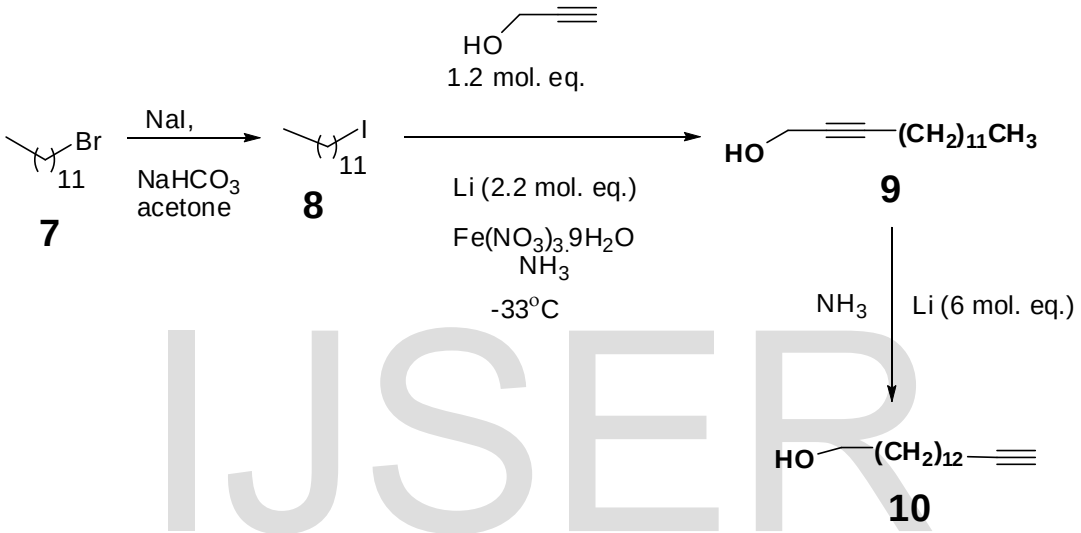
The mechanism is thought to involve a random-walk process in which a series of allene-alkyne interconversions take place along the carbon chain until the terminal acetylide salt is formed.[10] The reaction is particularly useful in the synthesis of pheromones and of long-chain fatty acid derivatives. For instance, Pabon *et a1.*[6] have obtained the 22-carbon acetylenic alcohol 21-docosyn-1-01 from 11-docosyn-1-01 in 87% yield-a transformation that involves a *minimum* of ten intermediate alkyn-1-01s. [11]

The reaction requires a strong base. The base used by Brown and Yamashita was potassium 1,3-diaminopropanide, generated *in situ* by adding potassium hydride to the solvent 1,3-diaminopropane.[7] Alternative approaches have been investigated due to the expensive and hazardous nature of potassium hydride; ethylenediamine has been found to be an unsuitable replacement for 1,3-diaminopropane. As an example, for the synthesis of 9-decyn-1-ol from 2-decyn-1-ol, the lithium salt of 1,3-diaminopropane in the presence of potassium tert-butoxide affords yields of approximately 85%.[10]

Discussion

In order to synthesis a C-15 carbon chain with bifunctional groups at 1 and 15-positions, (**10**), (Scheme (**4**)). To prepare it, 1-bromododecane (**7**) was first stirred with sodium iodide (**8**) in acetone in the presence of sodium bicarbonate to produce the corresponding iodide. Proton NMR was used to confirm the formation of the (**8**) which gave a triplet at 3.2 ppm for the CH_2 group adjacent to iodine. The 1-iododododecane (**8**) produced (80.2 mmol) was reacted with the dianion of prop-2-yn-

1-ol (89.19 mmol), following a modification of a method reported by Vaughn *et al.*[12] The reaction initially started with the preparation of the very strong base; lithium wire was added in portions to liquid ammonia. A deep blue colour was observed, and ferric nitrate (0.2 g) was added and left to stir for 30 minutes, to prepare lithium amide. Prop-2-yn-1-ol (5 g, 89.19 mmol) in dry ether (Scheme (**4**)); it was necessary to add 2 mol.eq. of the base or more since the terminal proton of the alkyne is less acidic (pKa = 25)[13] than the alcohol proton (pKa = 13.6).[14] Addition of the iodide led to reaction at the softer acetylide carbon rather than the alkoxide oxygen.



Scheme 4: Preparation of the bifunctional C-15 chain

The formation of the product (**9**) was verified by the proton NMR spectrum which gave a triplet for $(CH_2)_a$ adjacent to the hydroxyl group at 4.25 ppm (J = 2.25 Hz), and a triplet of triplets for $(CH_2)_b$ adjacent to the triple bond at 2.21 ppm (J = 7.25, 1.9 Hz) due to the adjacent to $(CH_2)_c$, and the other $(CH_2)_a$ across the triple bond (Figure (**3-4**)). The carbon NMR gave a signal at 86.69 ppm and at 51.44 ppm for the alkyne carbon and the carbon next to the oxygen, respectively. The terminal methyl group showed a triplet at 0.88 ppm (J = 6.95 Hz).

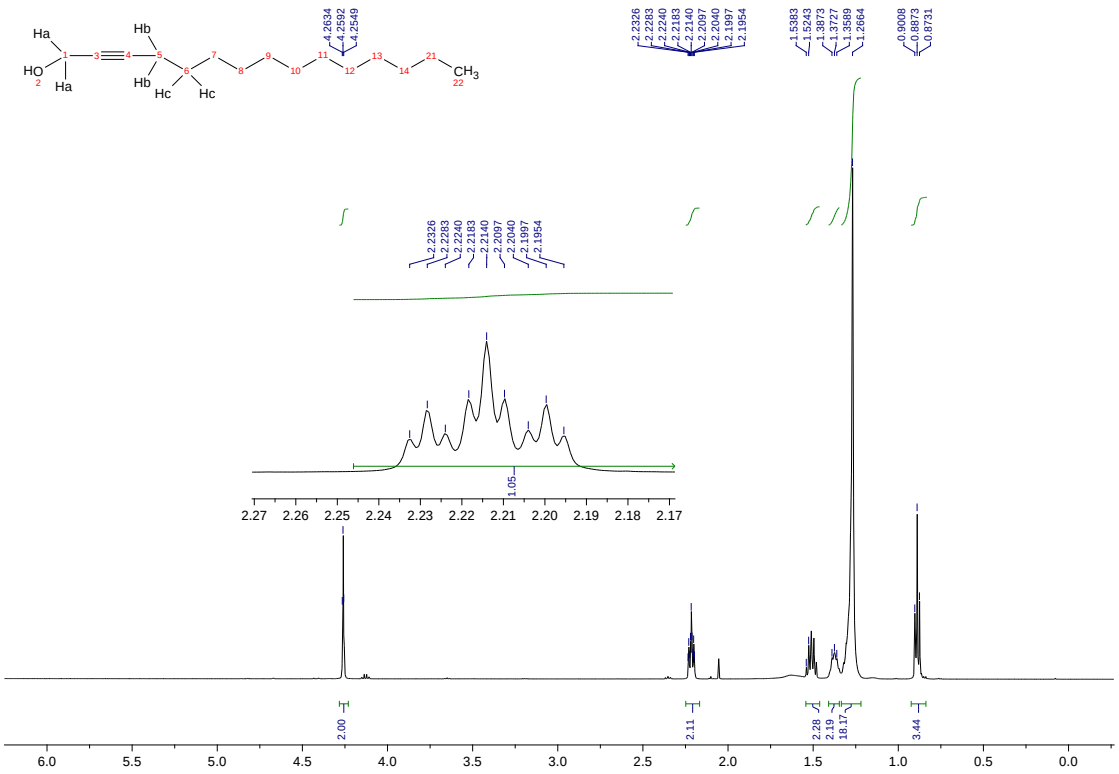


Figure (2): Proton NMR spectrum for compound (9)

The final step was the transfer of the triple bond to the end of the chain using a 'zipper reaction', which required the use of a very strong base.[14, 15] This reaction was first reported as an effective method for the transfer of a triple bond along a hydrocarbon chain.[16] The initial step of this reaction was the preparation of the strong base, since it is required to transfer the triple bond from one end of the chain to the other. The preparation of this base using sodium hydride and 1,3-diaminopropane has been reported; one disadvantage of this procedure is the use of lithium hydride which is hazardous and has a short shelf life.[17] An alternative method developed for the preparation of the base was the treatment of potassium amide in liquid ammonia with 1,3-propanediamine at 80 ^{o}C.[18] In this study, the base was prepared by treating 1,3-diaminopropane with lithium wire and heating the solution to 70 ^{o}C until a blue colour was discharged. This was followed by adding potassium-*tert*-butoxide (6.25 g, 55 mmol) and pentadec-2-yn-1-ol (3.13 g, 139.6 mmol). The reaction was quenched by pouring into ice water.[17]

The successful formation of the product (**10**) was confirmed by proton NMR which showed a triplet for the CH_2 group adjacent to oxygen at 3.54 ppm (J = 6.65 Hz). The alkyne proton showed a triplet at 1.88 ppm (J = 2.5 Hz) and the CH_2 group adjacent to the alkyne group gave a triplet of doublets at 2.11 ppm (J = 7.25, 2.5 Hz)

demonstrating the lack of a terminal methyl group (Figure **2**). The carbon NMR gave signals at 84.54 ppm and at 67.94 ppm for the alkyne carbons and at 62.57 ppm for the carbon next to the oxygen.

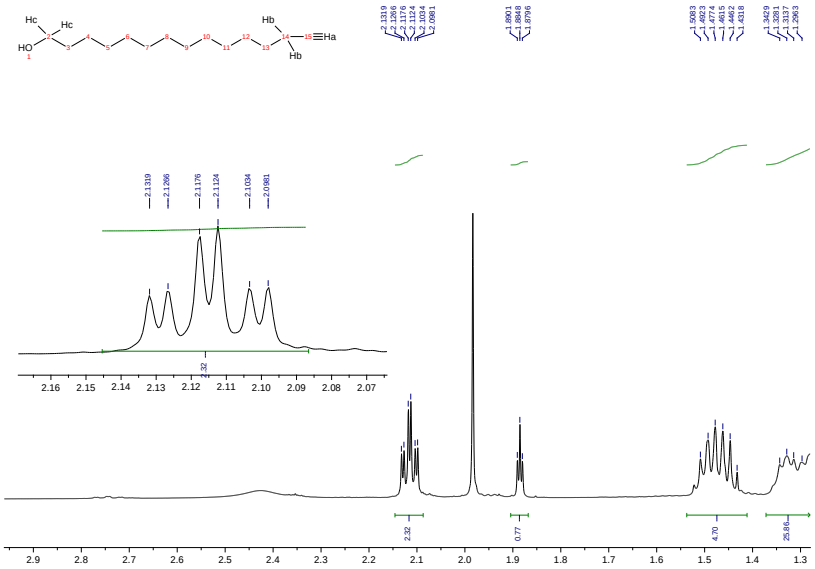


Figure (2): Proton NMR for compound (10)

Experimental

Experiment 1: 1-Iodododecane (8)

1-Bromododecane (15 g, 60.18 mmol), sodium iodide (27.05 g, 180.54 mmol) and sodium hydrogen carbonate (20.22 g, 240.73 mmol, 99%) were dissolved in acetone (500 ml) and refluxed for 3 hours and left overnight. The solvent was evaporated and the product was extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and the product was purified by column chromatography, eluting with petrol to yield 1-iodododecane (17.74 g, 59.88 mmol, 99 %). This showed δ_H (500MHz, $CDCl_3$): 3.19 (2H, t, J = 5 Hz), 1.84 (2H, q, J = 5 Hz), 1.40 (2H, pent., J = 10 Hz), 1.38 (16H, br s), 0.90 (3H, t, J = 5 Hz); δ_C: 33.65, 31.97, 30.59, br 29.69, 29.62, 29.50, 29.41, 28.62, 22.74, 14.17, 6.96; ν_{max}/cm^{-1}: 2924, 2853, 1609, 1493, 1465, 1426, 1182, 1203, 1166, 824, 720 cm^{-1}.

Experiment 2: Pentadec-2-yn-1-ol 9)

Liquid ammonia (200 ml) was decanted into a 3 neck (500 ml) round-bottomed flask surrounded with cotton wool and fitted with a liquid nitrogen/IMS condenser, protected with a soda lime tube. Lithium wire (1.36 g, 0.196 mol) was washed with petrol and added in 1 cm portions over 30 min, with a deep blue colour being observed. Ferric nitrate (0.2

g) was then added and the solution stirred with a mechanical stirrer for 30 mins, then prop-2-yn-1-ol (5 g, 89.19 mmol) in dry ether (10 ml) was added over 30 min. The resultant mixture was then stirred for 1 hour, and then 1-iodo-octadecane (**8**) (23.77 g, 80.2 mmol) in dry ether (10 ml) was added over 30 mins. The reaction was stirred for 3 hours, keeping the condensers temperature maintained. The reaction was then left without stirring for 18 hours to allow the ammonia to evaporate. The reaction mixture was then diluted with ethyl acetate (250 ml) and the mixture quenched with 10 % sulfuric acid (50 ml). The aqueous layer was re-extracted with ethyl acetate (3x100 ml), the combined organic extracts were dried over $MgSO_4$ and the solvent evaporated to give a crude dark brown oil, which was purified via column chromatography eluting with petrol/ethyl acetate (10:1) to give a yellow oil, pentadec-2-yn-1-ol (**9**) (3.13 g, 13.9 mmol, 38 %). This showed δ_H (500 MHz, $CDCl_3$): 4.25 (2H, t, J = 2.25 Hz), 2.21 (2H, tt, J = 7.25, 1.9 Hz), 1.50 (2H, q, J = 6.95 Hz), 1.37 (2H, q, J = 6.95 Hz), 1.26 (17H, s), 0.88 (3H, t, J = 6.95 Hz); δ_C: 86.69, 51.44, 31.89, 29.64, 29.61, 29.50, 29.33, 29.12, 28.86, 28.59, 22.67, 18.71, 14.09; ν_{max}/cm^{-1}: 3017, 2954, 2916, 2851, 1470, 1216, 1136, 1019, 758, 717.

Experiment 3: Pentadec-14-yn-1-ol (10)

Lithium wire (0.58 g, 83.76 mmol) was added in (1 cm) portion to dry 1, 3-diamino-propane (70 ml, 0.838 mol) under a nitrogen atmosphere and stirred for 30 min. The mixture was heated to 70 ^oC until the blue colour discharged. The mixture was cooled to 25 ^oC and potassium-*tert*-butoxide (6.25 g, 55 mmol) was added and the mixture was left to stir for 20 min at room temperature, then pentadec-2-yn-1-ol (**9**) (3.13 g, 139.6 mmol) was added dropwise over 30 min. The mixture was stirred for 45 min. then poured into ice water (300 ml). The product was extracted with ethyl acetate (3x70ml), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography eluting with petrol/ethyl acetate (5:1) to yield the title compound (2.11 g, 68 %). This showed δ_H (500MHz, $CDCl_3$): 3.54 (2H, t, J = 6.65 Hz), 2.11 (2H, td, J = 7.25, 2.5 Hz), 1.88 (1H, t, J = 2.5 Hz), 1.47 (4H, q, J = 8.2 Hz), 1.32 (2H, q, J = 7.25 Hz), 1.21 (17H, s); δ_C: 84.54, 67.94, 62.57, 32.63, 31.77, 29.48, 29.45, 29.39, 29.36, 29.33, 29.21, 28.96, 28.61, 28.34, 25.66, 22.53, 18.22, 13.94; ν_{max}/cm^{-1}: 3282, 2918, 2850, 1470, 1215, 1058, 757, 628.

References:

1 Journal of the American Chemistry Society, 2003, 125, 13642-13643.

2 Coordination Chemistry Reviews, Volume 257, Issues 15–16, August 2013, Pages 2143-2191

3 Journal of Organometallic Chemistry, Volume 755, 1 April 2014, Pages 78-85

4 Journal of Organometallic Chemistry 653 (2002) 46–49

5 Journal of Organometallic Chemistry, Volume 653, Issues 1–2, 1 July 2002, Pages 234-251

6 Journal of Organometallic Chemistry 653 (2002) 234_/251

7 Journal American Chemistry Society. 1975, 97, 891

8 Journal of the American Chemical Society / 97.4 / February 19, I975

9 Journal . Chemistry . Society., Chemistry . Communication 959 (1976)

10 Journal Organic . Chemistry . 1980,45, 735-737

11 Tetrahe dron Letter., 2565 (1976

12 Journal Organic Chemistry., 1937, 02, 1-22.

13 J. Clayden, N. Greeves, S. Warren and J. Wothers, *Organic Chemistry*,Oxford University Press, 2004.

14 Journal of the American Chemistry Society, 1994, 116, 3177-3179.

14 proceedings of the National Academy of science of the United States of America, 2001, 98, 2194-2198.

15 Journal of the American Chemistry Society, 1991, 113, 701-703.

16 Journal of the American Chemistry Society, 1975, 97, 891-892.

17 Journal Organic Chemistry, 1980, 45, 734-735.

18 Journal Organic Chemistry, 1984, 49, 2494-2496

19 C. D. Blue and D. J. Nelson, *J. Org. Chem.*, 1983, 48, 4538-4542.