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An Efficient Preparation of a Terminal Arylacetylene

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In the past synthetic routes to arylacetylenes *via* cross-coupling reactions of expensive monosubstituted acetylenes, such as trimethylsilylacetylene, using Pd (0) reagents have been the commonly used practice. Due to the high costs of such monosubstituted acetylenes these routes are usually limited to small-scale preparations. An alternative route for the introduction of a protected ethynyl moiety may be *via* the use of 2-hydroxypropan-2-yl by way of the inexpensive reagent 2-methyl-3-butyn-2-ol. Subsequent hydrolysis and deprotection can thus generate the terminal acetylene group. However, the seemingly attractive 2-methyl-3-butyn-2-ol reagent was not so effective as deprotection *via* removal of 2-hydroxypropan-2-yl was more complicated than as first appeared. Thus the traditional method of using trimethylsilyl-acetylene was proved to be the more effective way of introducing a terminal arylacetylene group.

Key Words: Arylacetylenes, Alkynes, Cross-coupling, Hydrolysis.

INTRODUCTION

There has been a great deal of interest in the development of methods introducing ethynyl groups. Numerous routes are available for the synthesis of arylacetylenes[1]. Cross-coupling reactions of organic halides and triflates with monosubstituted acetylenes are among the most commonly used routes[2-9]. This study explores the use of reagent 2-methyl-3-butyn-2-ol (MEBYNOL) as an alternative route to arylacetylenes and compares this procedure with the traditional cross-coupling method, employing the monosubstituted acetylene trimethylsilylacetylene (TMSA) and a Pd (0) reagent. The use of MEBYNOL seemed to be an attractive, economic and a simpler strategy than the later, but investigations herein proved the contrary.

Sonogashira coupling chemistry[9,10] was applied for MEBYNOL with triflates to prepare a protected ethynyl moiety as a MEBYNOL-coupled adduct. The subsequent removal of the protecting group 2-hydroxypropan-

2-yl (2-HP) as acetone would generate the terminal arylacetylene. However, removal of this 2-HP group appeared to be more complicated than originally anticipated. The more traditional synthetic route to these arylacetylenes, involving the Sonogashira coupling reactions of triflates with TMSA, carried out in the presence of Pd(0) as palladium triphenylphosphine complex, proved to be substantially better. Catalytic palladium Pd(0) complex may be generated *in situ*[11], however it is a known fact that palladium complexes as well as being unstable in air, can be difficult to prepare[12,13]. The use of commercially available tetra*kis*(triphenylphosphine)palladium(0) was the better alternative, where subsequent desilylation of the trimethylsilyl (TMS) group would generate the target terminal arylacetylene.

Some groups in the field of polymer chemistry appreciated the application of the TMS group for terminal acetylene protection[14-17], while other groups were not favourable with TMS protection and preferred the MEBYNOL reagent[18-20]. Here are studies using both 2-HP- and TMS-protecting groups derived from MEBYNOL and TMSA, respectively.

EXPERIMENTAL

Commercially available and/or reagent grade solvents and reagents were used without purification unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone-ketyl under a nitrogen atmosphere immediately before use. Methylene chloride (CH_2Cl_2) and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride and pyridine was distilled from potassium hydroxide (KOH) pellets. All non-aqueous reactions were carried out under an atmosphere of nitrogen gas. Glassware was flame-dried under a positive nitrogen flow. Proton NMR spectra were obtained in deuterated chloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm) with tetramethylsilane as an internal standard.

2-Naphthoyl triflate (3): To a solution of 2.20 g (15.26 mmol) of 2-naphthol (**1**) in 8.60 mL pyridine at 0ºC, 2.82 mL (16.79 mmol) of trifluoromethanesulfonic anhydride was slowly added. The resulting mixture was stirred at 0ºC for 5 min, then allowed to warm to room temperature and was stirred at this temperature for 25 h. The resulting mixture was poured into water and extracted with diethyl ether. The ether extract was washed sequentially with water, 10 % aqueous HCl, water and a concentrated sodium chloride solution, dried over $MgSO_4$ and concentrated to yield the crude product. Column chromatography (petroleum ether:ethyl acetate 9:1 v/v) afforded 3.95g (94 %) of the desired product as a yellow waxy solid: m.p. 30-31ºC (lit.[21] 30-31ºC); ^{1}H NMR (300 MHz, $CDCl_3$) 7.39 (d, J=9.1 Hz, 1H), 7.56-7.67 (m, 2H), 7.73 (d, J=7.5 Hz, 1H), 7.80-

7.90 (m, 2H), 7.91 (d, J=8.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 118.4, 119.1, 119.5 (q, J=323.7 Hz), 125.7, 127.4 128.3, 128.9, 130.6, 132.3, 133.1, 146.4; GC/ MS (EI) m/z (relative intensity) 276 (60), 143 (74), 115 (100). The product showed the expected spectral properties[21].

1-Carbomethoxy-2-naphthoyl triflate (4): The reaction was carried out with 2.20 g (10.88 mmol) of 2-hydroxy-1-methyl naphthoate (**2**) and was worked up in a manner similar to that described above for the synthesis of 2-naphthoyl triflate (**3**). After purification by column chromatography (petroleum ether:ethyl acetate 9:1 v/v) there was obtained 3.52 g (97 %) of the desired product as a yellow waxy solid: m.p. 37-38ºC (lit.[22] 37-38ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (s, 3H), 7.41 (d, J=9.1 Hz, 1H), 7.58-7.68 (m, 2H), 7.91 (d, J=7.6 Hz, 1H), 8.01 (d, J=9.1 Hz, 1H), 8.13 (d, J=8.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 52.9, 116.4, 119.1 (q, J=323.8 Hz), 123.5, 125.6, 127.6, 128.3, 128.7, 130.6, 132.3, 133.0, 144.6, 165.0; GC/ MS (EI) m/z (relative intensity) 334 (75), 303 (22), 201 (65), 173 (42), 145 (100). The product showed the expected spectral properties[22].

2-(3-Methyl-3-hydroxy-1-butynyl)naphthalene (6): To a mixture of 0.041 g (0.16 mmol) of triphenylphosphine, 0.011 g (0.057 mmol) of copper(I) iodide, 1.80 g (6.52 mmol) of 2-naphthoyl triflate (**3**), 1.61 mL (16.57 mmol) of 2-methyl-3-butyn-2-ol (**5**) in 20.00 mL of dry triethylamine under nitrogen, 0.011 g (0.015 mmol) of dichloro*bis*(triphenylphoshine)-palladium was added. The mixture was stirred at 50ºC for 20 min and was then heated at reflux for 20 min. The mixture was cooled to room temperature and 10 mL diethyl ether was added. The mixture was then filtered and the precipitate was washed with 50 mL of diethyl ether. The filtrate was collected and the ether was evapourated *in vacuo* to give a brown viscous residue. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over $MgSO_4$ and concentrated by evaporation *in vacuo* to give the crude product. Column chromatography (petroleum ether:ethyl acetate 4:1 v/v) afforded 0.87 g (64 %) of the desired product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 6H), 2.25 (s, 1H), 7.46-7.57 (m, 2H), 7.73 (d, J=7.4 Hz, 1H), 7.81-7.91 (m, 2H), 7.92 (d, J=8.4 Hz, 1H), 8.50 (d, J=8.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.5, 65.7, 82.4, 94.1, 119.2, 120.0, 126.5, 127.2, 128.0, 128.3, 128.6, 129.0, 130.6, 131.5, 132.8; IR (Nujol) (ν_{max}) 3436, 2366 cm^{-1}; GC/ MS (EI) m/z (relative intensity) 210 (100), 179 (37), 151 (30).

1-Carbomethoxy-2-(3-methyl-3-hydroxy-1-butynyl)naphthalene (7): The reaction was carried out with 1.80 g (5.39 mmol) of 1-carbomethoxy-2-naphthoyl triflate (**4**) and was worked up in a manner similar to that described above for the synthesis of compound **6**. After purification by column chromatography (petroleum ether:ethyl acetate 4:1

v/v) there was obtained 0.98 g (68 %) of the desired product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 6H), 2.20 (s, 1H), 4.09 (s, 3H), 7.50-7.57 (m, 3H), 7.82-7.88 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.3, 52.9, 65.5, 68.1, 80.2, 98.4, 118.7, 125.0, 127.0, 127.6, 128.5, 129.5, 129.8, 132.6, 133.0, 134.4, 168.8; IR (Nujol) (ν_{max}) 3435, 2365 cm^{-1}; GC/ MS (EI) m/z (relative intensity) 268 (26), 221 (100), 179 (31), 151 (29).

2-(Trimethylsilylethynyl)naphthalene (10): A flask filled with 1.80 g (6.52 mmol) of 2-naphthoyl triflate (**3**) and 12.0 mL of DMF was efficiently stirred and alternately evacuated and flushed with nitrogen at ambient temperature to deoxygenate the solution. The solution was cooled in ice and 1.57 mL (11.09 mmol) of (trimethylsilyl)acetylene and 1.93 mL (11.09 mmol) of *N*,*N*-diisopropylethylamine was added in sequence. The resulting pale yellow solution was deoxygenated as before. Then 0.25 g (1.30 mmol) of copper(I) iodide and 0.38 g (0.33 mmol) tetra*kis*(triphenylphosphine)palladium(0) was added, followed by a third deoxygenation cycle. The brown mixture was maintained at 0ºC, while the progress of the reaction was monitored by TLC. An aliquot of the reaction mixture was withdrawn with a nitrogen flushed syringe and injected into a small test tube containing diethyl ether and water. After the biphasic mixture was swirled briefly, the ethereal layer was allowed to separate and was analyzed by TLC (hexanes:diethyl ether 4:1 v/v). The TLC analysis indicated consumption of the starting triflate after 22 h at 0ºC upon which the reaction mixture was poured into a separatory funnel containing 100 mL of water and 50 mL of saturated aqueous ammonium chloride solution. The resulting brown suspension was extracted with 50 % ethyl acetate-hexanes. The organic layers were combined and washed with water, dried ($MgSO_4$) and concentrated by evapouration *in vacuo*. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 9:1 v/v) to yield 1.34 g (92%) of the desired product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.30 (s, 9H), 7.42 (d, J=8.0 Hz, 1H), 7.44-7.54 (m, 2H), 7.68 (d, J=8.3 Hz, 1H), 7.72-7.81 (m, 2H), 7.88 (d, J=8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 0.0, 54.1, 100.0, 110.2, 119.3, 120.5, 125.2, 128.2, 129.1, 129.8, 133.0, 133.9, 135.3; GC/ MS (EI) m/z (relative intensity) 224 (26), 209 (61), 194 (100), 179 (30); HRMS Calcd for $C_{15}H_{16}Si$: 224.1021; Found: 224.1027 m/z.

1-Carbomethoxy-2-(trimethylsilylethynyl)naphthalene (11): The reaction was carried out with 1.80 g (5.39 mmol) of 1-carbomethoxy-2-naphthoyl triflate (**4**) and was worked up in a manner similar to that described above for the synthesis of 2-(trimethylsilylethynyl)naphthalene (**10**). After purification by column chromatography (petroleum ether:ethyl acetate 9:1 v/v) there was obtained 1.44 g (95 %) of the desired product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.31 (s, 9H), 4.06 (s, 3H), 7.45-7.55 (m, 3H), 7.76-7.80 (m, 2H), 7.91 (d, J=8.2 Hz, 1H); ^{13}C NMR (75.5

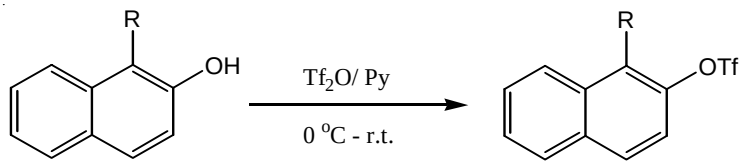
MHz, $CDCl_3$) δ 0.0, 52.3, 99.2, 102.7, 118.9, 124.9, 127.0, 127.5, 128.0, 128.1, 129.3, 129.6, 132.6, 134.8, 168.5; GC/ MS (EI) m/z (relative intensity) 282 (36), 267 (61), 251 (10), 237 (100); HRMS Calcd for $C_{17}H_{18}O_2Si$: 282.1076; Found: 282.1076 m/z.

2-Ethynylnaphthalene (8): To a solution of 0.75 g (3.35 mmol) of 2-(trimethylsilylethynyl)naphthalene (**10**) in 28.0 mL of THF, 4.02 mL of tetrabutylammonium fluoride (1 M solution in THF, 4.02 mmol) was added dropwise over 5 min. The reaction was stirred for 1 h, the progress of which was monitored by TLC (petroleum ether:ethyl acetate 9:1 v/v). Water was added to quench the reaction and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated by evaporation *in vacuo* to give the crude product. Column chromatography (petroleum ether:ethyl acetate 9:1 v/v) and recrystallization (ethanol/water) afforded 0.47 g (92 %) of product as a yellow solid: m.p. 98-100ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 1H), 7.70 (d, J=7.4 Hz, 1H), 7.72-7.78 (m, 2H), 7.80-7.90 (m, 2H), 7.91 (d, J=8.3 Hz, 1H), 8.50 (d, J=8.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.7, 77.0, 77.4, 126.3, 127.2, 127.8, 128.0, 129.0, 130.0, 131.5, 132.0, 132.7; GC/ MS (EI) m/z (relative intensity) 152 (100), 139 (26), 125 (10), 111, (4), 98 (13), 86 (8), 75 (31). Anal. (%) Calcd for $C_{12}H_8$: C, 94.70; H, 5.30; Found: C, 94.81; H, 5.35.

1-Carbomethoxy-2-ethynylnaphthalene (9): The reaction was carried out with 0.75 g (2.66 mmol) of 1-carbomethoxy-2-(trimethylsilylethynyl)naphthalene (**11**) and was worked up in a manner similar to that described above for the synthesis of 2-ethynylnaphthalene (**8**). After purification by column chromatography (petroleum ether:ethyl acetate 9:1 v/v) and recrystallization (ethanol/water) there was obtained 0.50 g (90 %) of product as a yellow solid: m.p. 101-103ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 1H), 4.07 (s, 3H), 7.49-7.58 (m, 3H), 7.81-7.91 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 52.6, 81.5, 81.6, 118.0, 125.1, 127.2, 127.7, 128.1, 128.4, 129.4, 129.8, 132.8, 135.1, 168.5; GC/ MS (EI) m/z (relative intensity) 210 (84), 179 (62), 151 (100), 139 (20), 125 (8), 111, (4), 98 (14), 86 (8), 75 (33); Anal. (%) Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79; Found: C, 80.08; H, 4.83.

RESULTS AND DISCUSSION

Respective triflates of 2-naphthol (**1**) and 2-hydroxy-1-methylnaphthoate (**2**) were prepared using the method of Echavarren[23] (Fig. 1), where compound **1** and subsequently **2**, in separate reactions, was reacted with trifluoromethanesulfonic anhydride (triflic anhydride) in pyridine at 0°C. After warming to room temperature the reaction mixtures were stirred for 25 h.

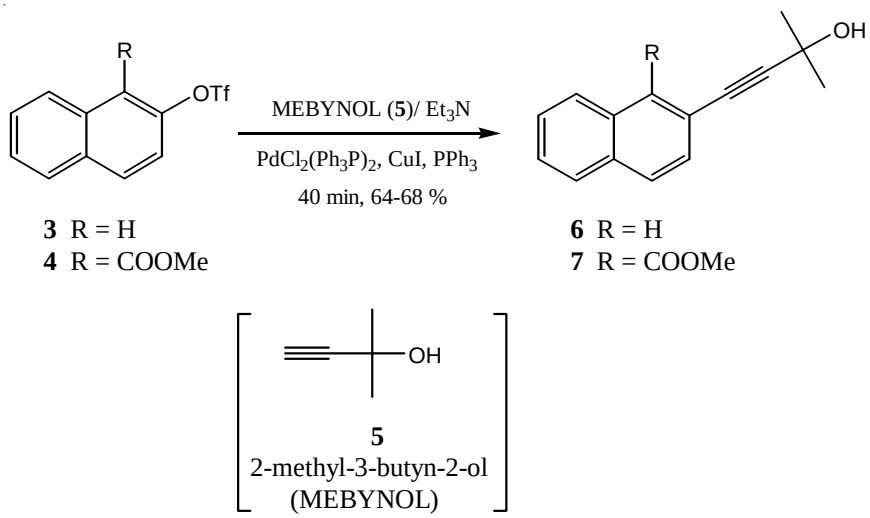


1 R = H
2 R = COOMe

3 R = H
4 R = COOMe

Fig. 1. Conversion of **1** and **2** into **3** and **4**, respectively

The MEBYNOL (**5**) reagent was then employed in a Sonogashira coupling with triflates **3** and **4** to prepare protected ethynyl moieties (**6** and **7**). The MEBYNOL-coupled adducts **6** and **7**, prepared by a modified literature procedure[20], involved the coupling of **3** and **4** with MEBYNOL (**5**), under refluxing conditions in dry Et_3N, using Pd(II)/Cu(I) catalysis (Fig. 2). The NMR and GC/MS spectral data revealed the desired products (**6** and **7**) in fair yields.

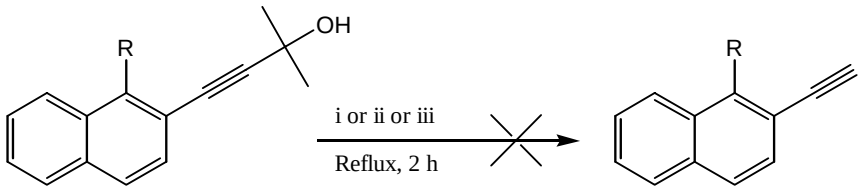


3 R = H
4 R = COOMe

6 R = H
7 R = COOMe

Fig. 2. Reaction of **3** and **4** with MEBYNOL (**5**)

Deprotections of the 2-HP group from the MEBYNOL coupled products were then attempted to give the terminal arylacetylenes (**8** and **9**). Hydrolyses and deprotections of **6** and **7** were attempted in several ways using various solvent/base mixtures as depicted in Fig. 3[18-20]. The reactions were heated at reflux for 2 h, but removal of the 2-HP group as acetone appeared to be more complicated than originally anticipated. These reaction conditions seemed to be too severe as the reaction mixtures were difficult to characterize.



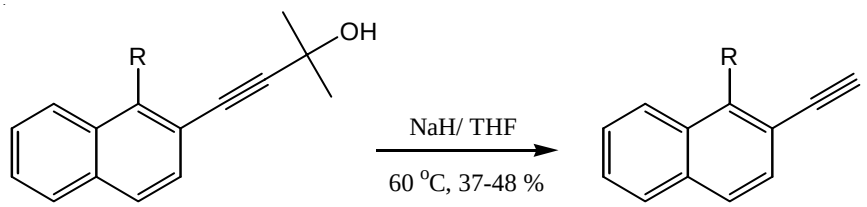
6 R = H
7 R = COOMe

8 R = H
9 R = COOMe

i, ^{t}BuOK, THF; ii, KOH, Toluene; iii, KOH, *i*-PrOH

Fig. 3. Attempted deprotections of **6** and **7** using various solvent/base mixtures

Milder reaction conditions were then attempted, where compound **6** and subsequently compound **7**, in separate reactions, were dissolved in THF and stirred with sodium hydride at 60ºC (Fig. 4). The desired alkynes (**8** and **9**) were obtained, *albeit* in low yields.

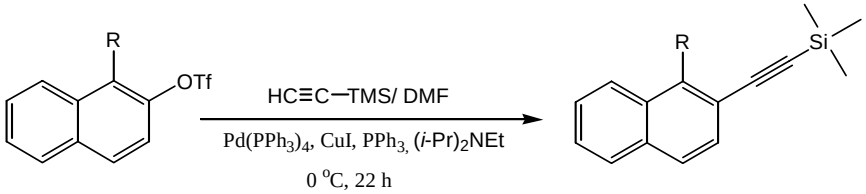


6 R = H
7 R = COOMe

8 R = H
9 R = COOMe

Fig. 4. Deprotections of MEBYNOL-coupled compounds **6** and **7** using NaH

Deprotections of the 2-HP group did not proceed in preferred yields. Sonogashira coupling reaction of TMSA with triflates **3** and **4** for TMS-protection was then considered and were carried out in the presence of Pd(0)/Cu(I) using the method of Myers and co-workers[24] (Fig. 5). The reaction mixtures were stirred at 0ºC for 22 h, the progress of the reactions being monitored by thin-layer chromatography (TLC). The desired coupling products were isolated in excellent yields (≥ 92 %).

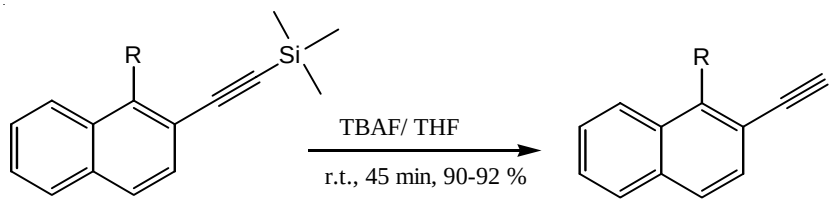


3 R = H
4 R = COOMe

10 R = H
11 R = COOMe

Fig. 5. Coupling reaction of **3** and **4** with TMSA

TMS-protected compounds were treated with TBAF in THF, under typical reaction conditions, to afford the desired terminal alkynes (**8** and **9**) in high yields (≥ 90 %) (Fig. 6).



10 R = H
11 R = COOMe

8 R = H
9 R = COOMe

Fig. 6. Deprotections of **10** and **11** using TBAF

Conclusions

In conclusion, the traditional synthetic route to arylacetylenes using TMSA was the most reliable procedure and remains a useful and attractive strategy for introducing terminal acetylene functions. Some workers preferred MEBYNOL protection to the ultimate terminal acetylene, while others preferred to work with TMSA, demonstrating that reaction strategy is compound specific. The class of compounds herein showed that the TMSA reagent was the reagent of choice for the target compounds.

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