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DTBB-Catalysed Lithiation of 1,4-Dichloro-2-butyne Under Barbier Conditions: Synthesis of Functionalised Alkynes

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Abstract: The reaction of 1,2-dichloro-2-butyne (**1**) with an excess of lithium powder and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 2.5 mol %) in the presence of an electrophile [Me_3SiCl, Bu^tCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, $(CH_2)_7CO$] in THF at -40°C leads, after hydrolysis with water, to the corresponding disubstituted acetylenes **2** in moderate yields.

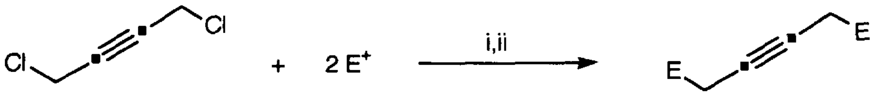
INTRODUCTION

Dilithiated intermediates[1] are interesting organometallic compounds in synthetic organic chemistry due to their possibility of reacting with two electrophilic reagents giving polyfunctionalised molecules in only one reaction step. However, they are in general very reactive and unstable species and the usual methodologies for the preparation of simple organolithium compounds[2] are not always applicable for these type of dianionic[3] reagents. In the case of 1,4-dilithio-2-butyne **I**, its preparation either by deprotonation of 2-butyne[5] or by chlorine/lithium exchange[6] failed. To our best knowledge, the only way to accede to the intermediate **I** is a tin-lithium transmetallation from the corresponding distannyl acetylene[7]. In this paper we apply a combination of an arene-catalysed lithiation[8] with Barbier-type reaction conditions[9] for the use of 1,4-dichloro-2-butyne as adequate precursor of the 1,4-dianion of 2-butyne of the type **I**.

I

RESULTS AND DISCUSSION

The reaction of commercially available 1,4-dichloro-2-butyne (**1**) with an excess of lithium powder (1:14 molar ratio; theoretical 1:4 molar ratio) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB; 1:0.1 molar ratio; 2.5 mol %)[10] in the presence of an electrophile [Me_3SiCl, Bu^tCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, $(CH_2)_7CO$] in THF at -40°C for 1 h[10] led, after hydrolysis with water, to the corresponding reaction products **2** (Scheme 1 and Table 1).



1

2

[E^+=Me_3SiCl, Bu^tCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, $(CH_2)_7CO$]

Scheme 1. *Reagents and conditions*: i, Li powder, DTBB cat. (2.5 mol %), THF, -40°C; ii, H_2O, -40 to 20°C.

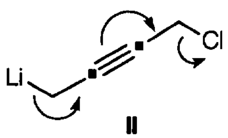
Table 1. Preparation of Compounds **2**

Entry	Electrophile E^+	Product[a]			
		No.	E	Yield (%)[b]	mp (°C)[c]
1	Me_3SiCl	**2a**	Me_3Si	73	-[d]
2	Bu^tCHO	**2b**	Bu^tCHOH	61[e]	-[e]
3	Me_2CO	**2c**	Me_2COH	31	82-83
4	Et_2CO	**2d**	Et_2COH	27[f]	68-70
5	$(CH_2)_4CO$	**2e**	$(CH_2)_4COH$	49	106-107
6	$(CH_2)_5CO$	**2f**	$(CH_2)_5COH$	41	104-105
7	$(CH_2)_7CO$	**2g**	$(CH_2)_7COH$	35	98-99

[a] All products **2** were 95% pure (GLC and 300 MHz ^1H NMR). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**. [c] From chloroform. [d] Oil. [e] 2:1 Mixture of diastereoisomers (^1H NMR). [f] ^1H NMR yield.

The reaction shown in Scheme 1 has to be carried out under the described reaction conditions. Moreover, it is important that the electrophile is present in the lithiation step (Barbier-type reaction): the step-by-step process (tandem lithiation-reaction with the electrophile) failed. Thus, the catalytic lithiation of the starting material **1** as above at temperatures ranging between -90 and -100°C followed by reaction with chlorotrimethylsilane as electrophilic component (compare with Table 1, entry 1) did not give the expected product **2a**: although compound **1** disappeared (GLC) only volatile products were detected. Probably, the first obtained intermediate **II** suffers rapid δ-elimination in absence of the electrophile[6].

Taking in account the last experiment described, and from a mechanistic point of view, two possible pathways can be proposed: (a) after the first lithiation intermediate **II** is formed; in the presence of the electrophile E+ it suffers rapid S_E reaction giving the monosubstituted product **III**, which by a tandem lithiation (**III→IV**) and *in situ* condensation with the electrophile yields finally the corresponding reaction product **2**. The other possiblity (b) involves the dilithiated species **I**, resulting from a second chlorine/lithium exchange from **II**, which by reaction with two molecules of electrophile would afford products **2**. Since the electrophile is present during the lithiation step we think that the more probable route is the (a) one; anyhow, the second way (b) can not be ruled out.



II

III

IV

In conclusion, we present here a reasonable alternative to the tin route[7] for the synthon **I**, which is simple and rapid to be carried out and starts from commercially available material **1**.

EXPERIMENTAL PART

General.- For general information, see reference 9f.

Preparation of Compounds **2**. *General Procedure*.- To a blue suspension of lithium powder (*ca.* 100 mg,14 mmol) and DTBB (26 mg, 0.1 mmol) in THF (3 ml) at -40°C was added a solution of 1,4-dichloro-2-butyne (1 mmol) and the corresponding electrophile (2 mmol) in THF (3 ml) during *ca.* 1h. Then, the reaction mixture was hydrolysed with water (10 ml) and extracted with diethyl ether (2x10 ml) and ethyl acetate (2x10 ml). The organic layer was dried over Na_2SO_4 and evaporated (15 Torr) to give a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate) to give the title compounds **2**. Yields and mp's are given in Table 1; other physical, analytical and spectroscopic data, as well as the corresponding literature references for known compounds, follow.

1,4-Bis(trimethylsilyl)-2-butyne (**2a**)[8b]: R_f 0.45 (hexane); ν_{max} (film) 1250 and 850 cm^{-1} [$Si(CH_3)_3$]; δ_H 0.08 [18H, s, 2xSi(CH_3)] and 1.42 (4H, s, 2x$CH_2C{\equiv}C$); δ_C -2.05 [6C, 2xSi(CH_3)$_3$], 7.15 (2C, 2x*C*$H_2C{\equiv}C$) and 75.6 (2C, $C{\equiv}C$); *m/z* 200 (M^++2, 4%), 199 (M^++1, 9), 198 (M^+, 36), 183 (27), 155 (10), 110 (47), 109 (12), 95 (17), 83 (13), 75 (12), 74 (27), 73 (100), 59 (16), 58 (11), 55 (12), 45 (68), 44 (14) and 43 (45).

2,2,9,9-Tetramethyl-5-decyne-3,8-diol (**2b**): R_f 0.63 (hexane/ethyl acetate: 3/2); ν_{max} (film) 3360 (OH) and 1070 cm^{-1} (CO); δ_H 0.90, 0.91 [36H, 2s, 4x(CH_3)$_3$C], 2.21 (4H, m, 2xC*H*HC$\equiv$CC*H*H), 2.39 (4H, m, 2xCH*H*C$\equiv$CCH*H*), 2.67 (2H, deformed d, 2xOH), 2.93 (2H, deformed d, 2xOH) and 3.40 (4H, m, 4xC*H*OH); δ_C 22.60 (2C), 22.65 (2C) (4xCH_2), 25.6 [12C, 4x(*C*H_3)$_3$C], 34.5 [4C, 4x(CH_3)$_3$*C*], 77.7 (2C), 77.75 (2C) (4xCHOH) and 80.25 (4C, 2x$C{\equiv}C$); *m/z* 193 (M^+-H_2O-CH_3, 1%), 123 (13), 122 (11), 109 (19), 107 (100), 93 (19), 87 (72), 83 (12), 81 (16), 79 (12), 71 (20), 70 (89), 69 (43), 57 (83), 55 (19), 53 (15), 45 (23), 43 (37), and 41 (70) (Found: C, 74.0; H, 11.6. $C_{14}H_{26}O_2$ requires C, 74.29; H, 11.58).

2,7-Dimethyl-4-octyne-2,7-diol (**2c**)[11]: R_f 0.27 (hexane/ethyl acetate: 3/2); mp 82-83°C; ν_{max} (Nujol) 3260 (OH) and 1160 cm^{-1} (CO); δ_H 1.30 (12H, s, 4xCH_3), 2.35 (4H, s, 2x$CH_2C{\equiv}C$) and 2.45 (2H, br s, 2xOH); δ_C 28.6 (4C, 4xCH_3), 34.35 (2C, 2x$CH_2C{\equiv}C$), 70.0 (2C, 2xCO) and 79.6 (2C, $C{\equiv}C$); *m/z* 137 (M^+-H_2O-CH_3, 3%), 94 (29), 79 (48), 77 (15), 59 (100), 43 (68) and 41 (15) (Found: C, 69.9; H, 10.5. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66).

3,8-Diethyl-5-decyne-3,8-diol (**2d**): R_f 0.46 (hexane/ethyl acetate: 3/2); mp 68-70°C; ν_{max} (film) 3400 (OH) and

1135 cm^{-1} (CO); δ_H 0.88 (12H, t, J= 7.3, 4xCH_3), 1.56 (8H, m, 4xCH_2CH_3), 1.75 (2H, br s, 2xOH) and 2.33 (4H, s, 2x$CH_2C\equiv C$); δ_C 7.9 (4C, 4xCH_3), 29.6 (2C, 2x$CH_2C\equiv C$), 30.75 (4 C, 4xCH_2CH_3), 73.95 (2C, 2xCO) and 79.2 (2C, $C\equiv C$); m/z 179 (M^+-H_2O-C_2H_5, 6%), 122 (30), 107 (22), 93 (32), 91 (10), 87 (65), 79 (15), 70 (16), 57 (100), 55 (12), 53 (10), 45 (71), 43 (23) and 41 (30) (Found: C, 73.9; H, 11.6. $C_{14}H_{26}O_2$ requires C, 74.29; H, 11.58).

1,4-Bis-(1-hydroxycyclopentyl)-2-butyne (**2e**)[12]: R_f0.31 (hexane/ethyl acetate: 3/2); mp 106-107°C; ν_{max} (film) 3290 (OH) and 1190 cm^{-1} (CO); δ_H 1.57-1.88 (16H, m, 8xring CH_2), 2.20 (2H, br s, 2xOH) and 2.46 (4H, s, 2x$CH_2C\equiv C$); δ_C 24.1 (4C), 39.2 (4C) (8xring CH_2), 31.8 (2C, 2x$CH_2C\equiv C$), 79.2 (2C, $C\equiv C$) and 81.1 (2C, 2xCO); m/z 204 (M^+-H_2O, 2%), 121 (10), 120 (100), 119 (11), 105 (45), 103 (14), 92 (55), 91 (43), 85 (95), 79 (14), 67 (48), 57 (11), 55 (24), and 41 (17) (Found: C, 74.8; H, 9.9. $C_{14}H_{22}O_2\cdot 0.1H_2O$ requires C, 75.03; H, 9.98).

1,4-Bis-(1-hydroxycyclohexyl)-2-butyne (**2f**): R_f 0.41 (hexane/ethyl acetate: 3/2); mp 104-105°C; ν_{max} (film) 3300 (OH) and 1150 cm^{-1} (CO); δ_H 1.40-1.70 (20H, m, 10xring CH_2), 2.08 (2H, br s, 2xOH) and 2.35 (4H, s, 2x$CH_2C\equiv C$); δ_C 22.15 (4C), 25.6 (2C), 36.85 (4C) (10xring CH_2), 33.15 (2C, 2x$CH_2C\equiv C$), 70.55 (2C, 2xCO) and 79.4 (2C, $C\equiv C$); m/z 233 (M^+-OH, 1%), 232 (M^+-H_2O, 3), 134 (65), 119 (18), 106 (11), 105 (11), 99 (100), 92 (12), 91 (20), 81 (52), 79 (14), 55 (23), 43 (10) and 41 (14) (Found: C, 75.9; H, 10.4. $C_{16}H_{26}O_2\cdot 0.1H_2O$ requires C, 76.21; H, 10.47).

1,4-Bis-(1-hydroxycyclooctyl)-2-butyne (**2g**): R_f0.47 (hexane/ethyl acetate: 3/2); mp 98-99°C; ν_{max} (film) 3360 (OH) and 1065 cm^{-1} (CO); δ_H 1.45, 1.64, 1.83 (28H, 3m, 14xring CH_2), 2.23 (2H, br s, 2xOH) and 2.35 (4H, s, 2x$CH_2C\equiv C$); δ_C 22.2 (4C), 24.7 (2C), 28.1 (4C), 35.6 (4C) (14xring CH_2), 32.75 (2C, 2x$CH_2C\equiv C$), 73.85 (2C, 2xCO) and 79.6 (2C, $C\equiv C$) ; m/z 127 (M^+-$C_{12}H_{19}O$, 81%), 109 (28), 98 (49), 97 (17), 95 (13), 93 (11), 84 (19), 83 (44), 82 (21), 81 (25), 79 (18), 77 (13), 71 (10), 70 (20), 69 (29), 68 (11), 67 (68), 57 (18), 56 (24), 55 (100), 54 (20), 53 (28), 51 (15), 44 (15), 43 (60), 42 (50) and 41 (90). (Found: C, 77.4; H, 11.0. $C_{20}H_{34}O_2\cdot 0.2H_2O$ requires C, 77.46; H, 11.18)[13].

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