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Cs_2CO_3 Promoted coupling reactions for the preparation of skipped diynes

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Dedicated to the memory of Professor G. Sodano

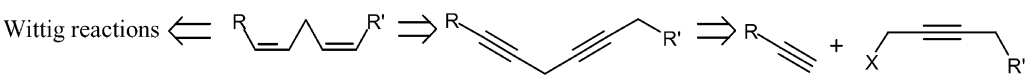
Abstract—An improved methodology for the preparation of copper(I) alkynides has been developed using cesium carbonate as base. In the presence of cesium carbonate and CuI various 1-alkynes were converted smoothly to the corresponding copper alkynides which in situ reacted with propargylic halides in order to synthesize skipped diynes.

1. Introduction

The (*Z*)-homoconjugated polyene moiety is present in a large number of biologically important natural products such as polyunsaturated fatty acids, pheromones and allomones. The interesting biological activities of these compounds have stimulated their total synthesis or the preparation of labelled analogues for biosynthetic studies. Two traditional methods for the formation of the all (*Z*) homoconjugated polyene include the sequential olefin preparation by Wittig reaction[1] or the selective partial reduction of a polyyne (Scheme 1).[2]

In this latter methodology generally the polyyne is prepared by metal mediated coupling of 1-alkynes and propargylic halides. However, when a group I alkynide is used, in a coupling with a propargylic or allylic halide, side reactions, such as multiple alkylation, isomerization and polymerization are reported.[3] On the other hand, copper(I) alkynides proved to be more useful reagents giving better results in these reactions and several methodologies have been proposed in which a copper(I) alkynide is generated by action of a base in the presence of copper salts.[4] A methodology based on copper(I) alkynide was described by Jeffery et al. In this route propargylic halides were treated with 1-alkynes in the presence of copper iodide, sodium carbonate and tetra-*n*-butylammonium chloride.[5] Pivnitsky and co-workers proposed a similar approach in which a copper alkynide was prepared by action of K_2CO_3 as base in the presence of CuI and NaI; the formation of the skipped diyne was then obtained by reaction of this in situ formed alkynide with a propargylic tosylate or halide.[6] In a further study, a French group showed that the first methodology gave unsatisfactory results in some applications and investigated the influence of temperature, solvent and copper salts on the second described procedure. The results obtained showed that the use of CuI, DMF at room temperature gave good yields in many cases although the coupling of methyl decynoate (**1d**) was reported to be not completely satisfactory even in these conditions.[7]

Recently in the course of our work devoted to the synthesis[8] of the bioactive marine macrolides aplyolides, e.g. **4**–**6**,[9] we planned a synthetic strategy based on consecutive couplings between terminal alkynes and propargylic halides. However, during the development of this total synthesis we found that some planned coupling reactions gave unsatisfactory results using both the described methodologies. In fact, we decided to change the alkali metal cation present in the carbonate used as base, passing from potassium to cesium. This change gave good results and solved our synthetic problem. In this paper we describe this approach



Scheme 1.

Keywords: alkynes; copper alkynides; cesium effect; skipped diynes; natural products synthesis.
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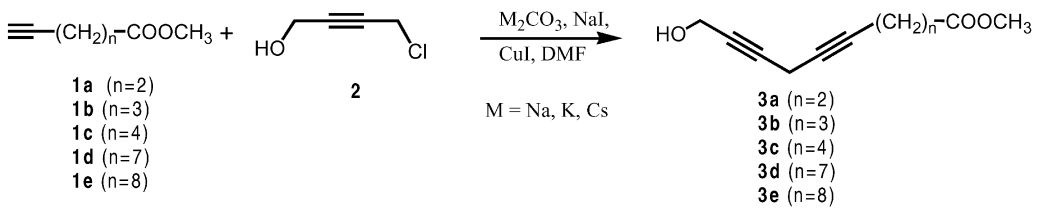
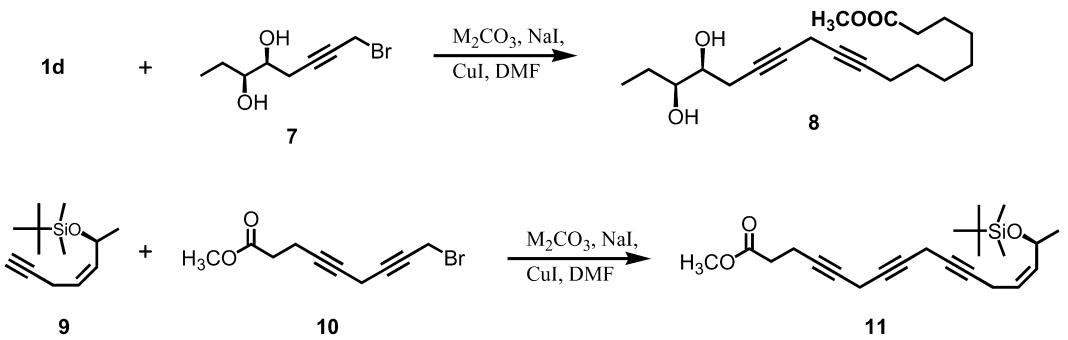


Scheme 2.

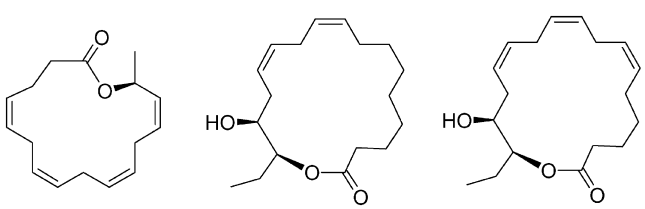


Scheme 3.

Table 1. Skipped diyne formation by coupling reactions between copper(I) alkynides and propargylic halides

Entry	Alkyne	Propargyl halide	Skipped diyne	Yields (%)		
				Na_2CO_3	K_2CO_3	Cs_2CO_3
1	**1a**	**2**	**3a**	65	85	95
2	**1b**	**2**	**3b**	60	85	94
3	**1c**	**2**	**3c**	56	76	90
4	**1d**	**2**	**3d**	39	56	79
5	**1e**	**2**	**3e**	36	59	71
6	**1d**	**7**	**8**	35	51	80
7	**9**	**10**	**11**	34	42	70

extending the application to different substrates with the aim to furnish an improved general method for the preparation of skipped polyynes.



Aplyolide A (4) Aplyolide B (5) Aplyolide C (6)

2. Results and discussion

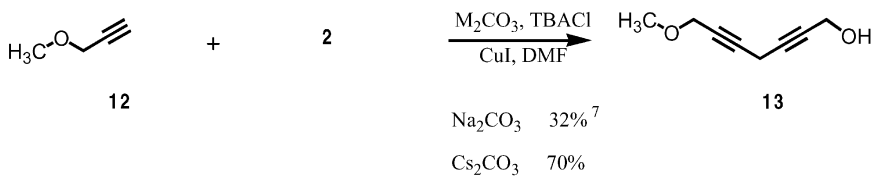
Coupling of terminal alkynes **1** with chlorobutynol (**2**) was chosen as a model reaction. We developed our investigation by screening different carbonates (Na_2CO_3, K_2CO_3, Cs_2CO_3) for efficient coupling conditions using various substrates (Scheme 2).

The results obtained (Table 1; entries 1–5) showed that a clear trend of increasing yields of the skipped diyne is seen progressing from Na_2CO_3 to K_2CO_3 to Cs_2CO_3. Furthermore, reactions with the latter carbonate were also by far the cleanest with only a very minor amount of side products. Propargylic halides containing a larger chain were then considered in order to apply the present procedure to more complex substrates. Also in these cases the reactions were conducted in the presence of different carbonates (Scheme 3).

As shown in Table 1 cesium carbonate was found once again to be the most effective base in these reactions to give skipped polyynes **8** and **11** in 80 and 70%, respectively (entries 6 and 7).

With these results in hand, we turned back to the procedure proposed by Jeffery and co-workers. In fact, we considered that this procedure probably failed to give excellent results in certain cases because of the kind of carbonate (Na_2CO_3) chosen. Therefore, we decided to carry out a reaction under phase transfer conditions but in the presence of cesium carbonate (Scheme 4).

In this case the change of carbonate caused a dramatic effect. In fact, the yields of skipped diynes where good when the reaction was performed in the presence of cesium carbonate.



Scheme 4.

These results show a prominent ability of cesium to enhance this substitution reaction. An explanation of this 'cesium effect' is not known although comparatively high solubility in DMF, appropriate basicity and good stability have been invoked to explain this behaviour.[10]

3. Conclusion

In conclusion, we have shown in this study that the use of cesium carbonate enhances the coupling between alkynes and propargylic halides and this methodology is believed to offer a general synthetic method to skipped diynes for a variety of applications.

4. Experimental

All reactions were carried out under argon. Reagents were purchased from Fluka or Aldrich chemical companies. Flash chromatography was performed over Merck silica gel 60 (230–400 mesh). Infra-red absorption spectra were recorded on a Bruker Vector 22 instrument, as thin films. Both ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin DRX instrument at 400.135 and 100.03 MHz, respectively. Mass spectra were measured on Thermoquest Finnigan MS (EI, 70 eV) instruments.

4.1. General procedure for the synthesis of skipped diynes

M_2CO_3 (10 mmol), NaI (10 mmol) and CuI (10 mmol), each finely ground and anhydrous, were suspended in dry DMF (20 ml) with stirring. Subsequently, terminal alkyne (10 mmol) was added all at once and kept stirring for 20 min. Propargylic halide (10 mmol) was added dropwise and the suspension was stirred at rt under argon for 20 h, then quenched with sat. aq. NH_4Cl and extracted with Et_2O. After drying (Na_2SO_4) and concentration, the products were purified by flash chromatography.

4.1.1. 9-Hydroxy-nona-4,7-diynoic acid methyl ester (3a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (2H, t, J=2.0 Hz), 3.68 (3H, s), 3.16 (2H, t, J=2.0 Hz), 2.53 (4H, m), 2.00 (1H, bs); ^{13}C NMR δ (100 MHz, $CDCl_3$): 172.4 (s); 79.6 (s); 78.6 (s); 78.5 (s); 74.3 (s); 51.6 (q); 50.5 (t); 33.1 (t); 14.3 (t); 9.5 (t); IR: ν_{max} 3418 (br), 2250, 1737 cm^{-1}; EIMS: (relative intensity) m/z 180 [M]$^+$ (33), 163 (17), 149 (22), 134 (96), 119 (91), 91 (100). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.58; H, 6.65.

4.1.2. 10-Hydroxy-deca-5,8-diynoic acid methyl ester (3b). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (2H, t, J=2.1 Hz), 3.64 (3H, s), 3.14 (2H, tt, J=2.1, 2.1 Hz), 2.40 (2H, t, J=7.3 Hz), 2.24 (2H, tt, J=7.0, 2.1 Hz), 1.81 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (s), 78.6 (s), 78.5 (s), 74.0 (s), 73.9 (s), 50.7 (q), 49.5 (t), 31.9 (t), 23.0 (t), 17.2 (t), 8.9 (t); IR: ν_{max} 3400 (br), 2244, 1732, 1024 cm^{-1}; EIMS: (relative intensity) m/z 194 [M]$^+$ (4), 179 (6), 146 (19), 132 (48), 118 (67), 104 (28), 90 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.09; H, 7.32.

4.1.3. 11-Hydroxy-undeca-6,9-diynoic acid methyl ester (3c). Dark yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (2H, t, J=2.1 Hz), 3.67 (s, $-OCH_3$), 3.17 (2H, tt, J=2.1, 2.4 Hz), 2.34 (2H, t, J=7.5 Hz), 2.19 (2H, tt, J=7.0, 2.4 Hz), 1.75 (2H, m), 1.56 (2H, m); ^{13}C NMR ($CDCl_3$): δ 174.1 (s), 80.2 (s), 78.8 (s), 78.5 (s), 73.9 (s), 51.5 (q), 50.8 (t), 33.4 (t), 27.8 (t), 23.9 (t), 18.2 (t), 9.7 (t); IR: ν_{max} 3400 (br), 2244, 1740, 1022 cm^{-1}; EIMS: (relative intensity) m/z 208 [M]$^+$ (2); 147 (8); 131 (23); 129 (50); 115 (100); 91 (85); 77 (24). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.12; H, 7.68.

4.1.4. 14-Hydroxy-tetradeca-9,12-diynoic acid methyl ester (3d). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (2H, t, J=2.1 Hz), 3.66 (3H, s), 3.17 (2H, tt, J=2.2, 2.1 Hz), 2.30 (2H, t, J=7.5 Hz), 2.15 (2H, tt, J=6.9, 2.2 Hz), 1.62 (2H, m), 1.52 (2H, m), 1.40 (2H, m), 1.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0 (s), 80.4 (s), 78.2 (s, 2C), 73.1 (s), 51.0 (q), 50.4 (t), 33.6 (t), 28.8 (t), 28.5 (t), 28.3 (t), 28.1 (t), 24.4 (t), 18.1 (t), 9.3 (t); IR: ν_{max} 3400 (br), 2243, 1732, 1022 cm^{-1}; EIMS: (relative intensity) m/z 250 [M]$^+$ (22), 218 (6), 160 (10), 146 (18), 132 (48), 118 (64), 104 (28), 90 (100). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.89; H, 8.81.

4.1.5. 15-Hydroxy-pentadeca-10,13-diynoic acid methyl ester (3e). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (2H, t, J=2.1 Hz), 3.65 (3H, s), 3.16 (2H, tt, J=2.1, 2.1 Hz), 2.29 (2H, t, J=7.5 Hz), 2.14 (2H, tt, J=7.0, 2.1 Hz), 1.61 (2H, m), 1.52 (2H, m), 1.38 (2H, m), 1.30 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 (s), 84.9 (s), 80.2 (s), 78.3 (s), 73.1 (s), 50.9 (q), 50.0 (t), 33.4 (t), 28.6 (t), 28.5 (t), 28.4 (t), 28.2 (t), 28.1 (t), 24.3 (t), 18.1 (t), 9.2 (t); IR: ν_{max} 3405 (br), 2244, 1738, 1023 cm^{-1}; EIMS: (relative intensity) m/z 264 [M]$^+$ (20), 232 (7), 204 (10), 146 (23), 132 (45), 118 (48), 104 (28), 90 (81), 75 (100). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.61; H, 9.08.

4.1.6. 15,16-Dihydroxy-octadeca-9,12-diynoic acid methyl ester (8). Yellow oil; ^{1}H NMR δ ($CDCl_3$): 3.65 (3H, s), 3.60 (1H, ddd, J=6.4, 5.3, 4.3 Hz), 3.50 (1H, ddd, J=8.0, 4.6, 4.3 Hz), 3.12 (2H, tt, J=2.3, 2.2 Hz), 2.46 (1H, ddt, J=16.7, 5.3, 2.3 Hz), 2.41 (1H, ddt, J=16.7, 6.4, 2.3 Hz), 2.29 (2H, t, J=7.5 Hz), 2.13 (2H, tt, J=7.0, 2.3 Hz), 1.62 (2H, m), 1.55 (2H, m),1.47 (2H, m), 1.40–1.24 (6H, m), 0.98 (3H, t, J=7.4 Hz); ^{13}C NMR ($CDCl_3$): δ 174.3; 80.7; 77.6; 76.2; 74.5; 74.0; 71.9; 51.4; 34.0; 29.0; 28.7; 28.6; 28.5; 26.4; 24.8; 24.4; 18.6; 10.0; 9.8. IR: ν_{max} 3400

(br), 2220, 1739 cm^{-1}; EIMS: (relative intensity) *m/z* 322 $[M]^+$(25), 291 (6), 263 (47), 235 (8), 221 (13), 231 (100), 207 (13). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.65; H, 9.26.

4.1.7. 15-(*tert*-Butyl-dimethyl-silanyloxy)-hexadec-13-ene-4,7,10-triynoic acid methyl ester (11). Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (1H, bdd, J=10.9, 7.5 Hz), 5.32 (1H, dt, J=10.9, 7.0 Hz), 4.58 (1H, dq, J=7.5, 6.2 Hz), 3.70 (3H, s), 3.11 (4H, m), 2.92 (2H, bd, J=7.0 Hz), 2.50 (4H, m), 1.19 (3H, d, J=6.2 Hz), 0.91 (9H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (s), 136.7 (d), 122.3 (d), 78.6 (s), 78.4 (s), 74.7 (s, 2C), 74.6 (s), 74.0 (s), 64.9 (d), 51.7 (q), 33.3 (t), 25.8 (q, 3C), 24.5 (q), 18.1 (s), 17.4 (t), 14.7 (t), 9.7 (t, 2C), −5.0 (q), −5.2 (q); IR: ν_{max} 1734 cm^{-1}; EIMS: (relative intensity) *m/z* 386 $[M]^+$ (3.8), 329 (5), 255 (4), 226 (9.5), 159 (67), 131 (83), 115 (100). Anal. Calcd for $C_{23}H_{34}O_3Si$: C, 71.46; H, 8.86. Found: C, 71.34; H, 8.68.

4.1.8. 7-Methoxy-hepta-2,5-diyn-1-ol (13). Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (2H, t, J=2.1 Hz), 4.05 (2H, t, J=2.1 Hz), 3.34 (3H, s), 3.23 (2H, tt, J=2.1, 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.2 (s), 79.1 (s), 79.0 (s), 76.3 (s), 59.9 (t), 57.5 (q), 50.9 (t), 9.8 (t); IR: ν_{max} 3400 (br), 2245 cm^{-1}; EIMS: (relative intensity) *m/z* 138 $[M]^+$ (8), 121 (6), 107 (18), 90 (99), 76 (100). Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.47; H, 7.24.

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