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SELF-CONDENSATION OF ALLYLIC ALCOHOLS MEDIATED BY $TiCl_4$

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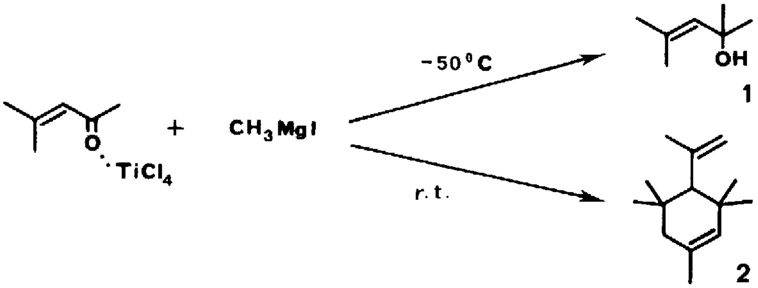
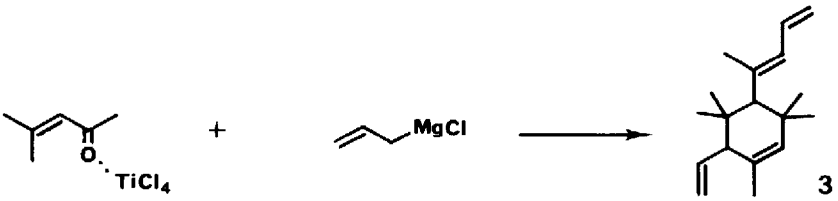
Summary : Addition of Grignard reagents to enones associated with $TiCl_4$ leads to dehydration and Diels-Alder-like reaction giving dimeric hydrocarbons in good yields.

The electrophilic bimolecular addition of a carbo-cation to alkenes mediated by Lewis acid represents a biomimetic synthesis of terpenoids (1, 2). Our work concerns the self-condensation of allylic alcohols in presence of $TiCl_4$ (3). To avoid a strong acidic medium, we add Grignard reagents to enones associated with $TiCl_4$. In these conditions, the products are obtained in high regio- and stereoselectivity.

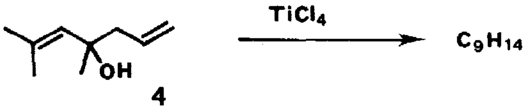
The low temperature addition of methyl magnesium iodide to mesityl oxide associated with $TiCl_4$ affords the expected tertiary alcohol **1** (4). But, when the reaction mixture is allowed to warm up to room temperature, tetramethyl-limonene (3,3,5,5-tetramethyl-p-mentha-1,8-diene) **2** is isolated as the only product (85 % yield)(6,9).



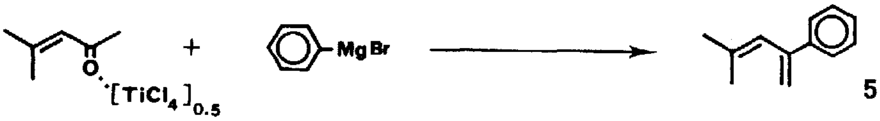
In a similar manner, the addition of the allyl-Grignard reagent to mesityl oxide associated with $TiCl_4$ gives the dimeric hydrocarbon **3** (65 % yield)(10).



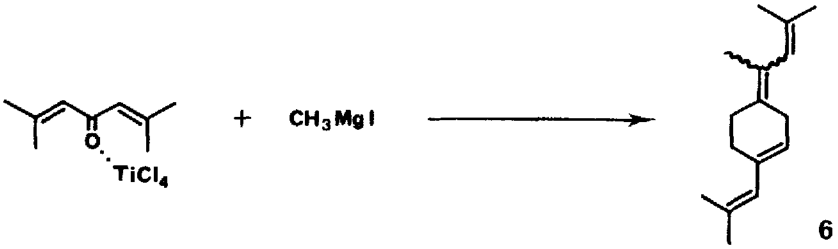
When 2,4-dimethyl-2,6-heptadien-4-ol **4** is treated by $TiCl_4$, only the hydrocarbons (4 isomers) resulting from dehydration are obtained.



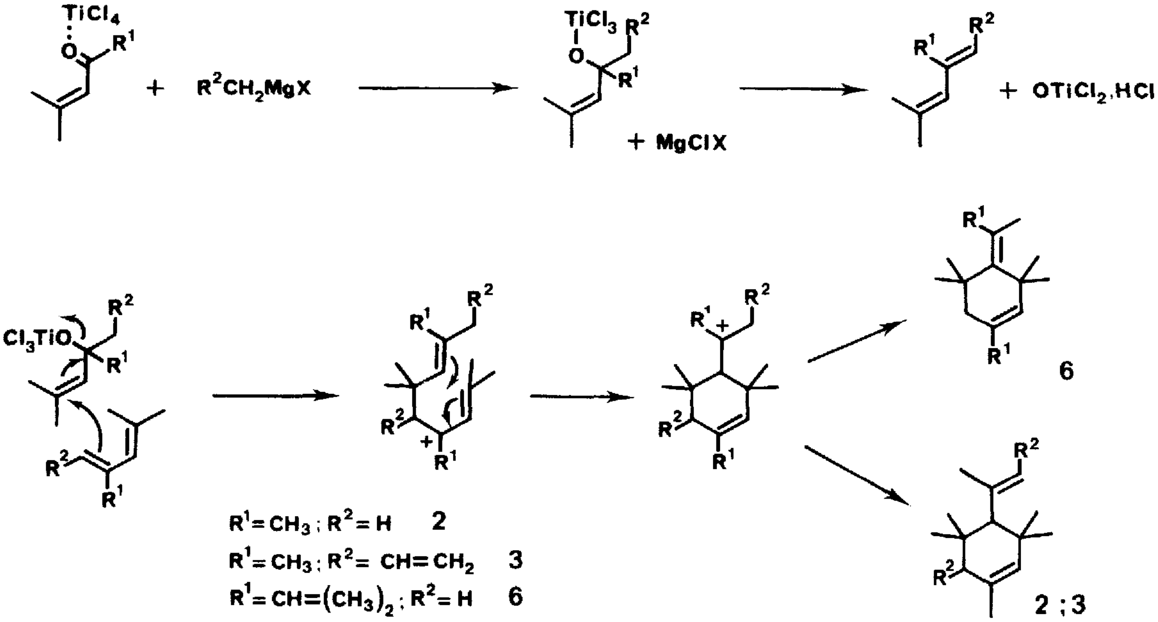
In contrast, the addition of phenyl magnesium bromide to mesityl oxide associated with 0.5 equi. of $TiCl_4$, gives only one diene **5** (11, 12).



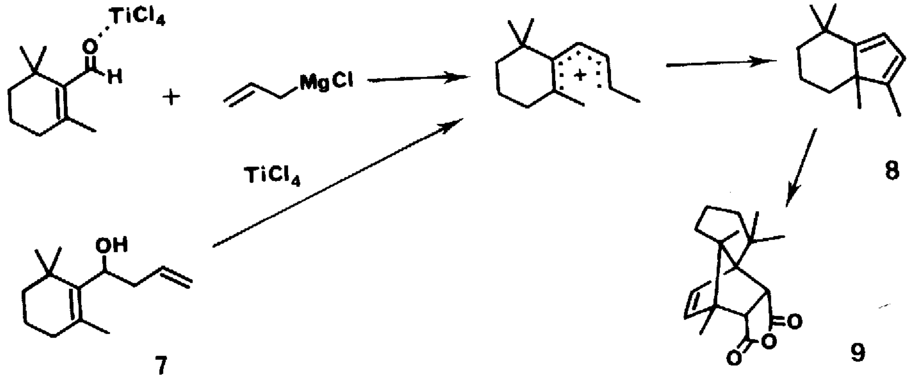
The addition of methyl magnesium iodide to phorone leads to a main product **6** (the stereochemistry of the exocyclic double bond is not determined)(13).



These Diels-Alder-like reactions are consistent with a protic acid catalyzed process (14). The following unifying mechanism can be proposed :



Hydrocarbon **8** can be obtained either by addition of allyl magnesium chloride to cyclocitral associated with $TiCl_4$ or directly from dienic alcohol **7** (15, 16). No product coming from a dimerization of the dienic precursor is obtained. Cyclopentadiene **8** results from a cyclization of the pentadienyl cation.



In conclusion, the condensation of Grignard reagents with enones asociated with $TiCl_4$ can be a practical method for the obtention of Diels-Alder-like products in high selectivity.

References and Notes

(1) (a) Banthorpe, D.V.; Charlwood, B.V.; Francis, M.J.O., Chem. Rev., **1972**, 72, 115. (b) Cordell, G.A. ibid., **1975**, 75, 425. (c) Poulter, C.D.; Satterwhite, D.M.; Rilling, H.C. J. Am. Chem. Soc., **1976**, 98, 3376. (d) Poulter, C.D.; Wiggins, P.L.; Le, A.T. ibid. **1981**, 103, 3926. (e) Mash, E.A.; Gurria, G.M.; Poulter, C.D., ibid. **1981**, 103, 3927.

(2) Julia M.; Schmitz, C. Bull. Soc. Chim. Fr. **1986**, 630.

(3) El Idrissi, M.; Santelli, M. Tetrahedron Lett. **1987**, 28, 2583.

(4) Unlike alkyl-zinc (5), Grignard reagents do not substitute chlorine atom of $TiCl_4$.

(5) Reetz, M.T.; Steinbach, J.; Westermann, J.; Peter, R. Ang. Chem. Int. Ed. Eng., **1980**, 19, 1011.

(6) The dimerization of **1** giving **2** could be accomplished using tris (p-bromophenyl)-aminium hexachloroantimonate (7) or protic acid (8).

(7) (a) Bellville, D.J.; Bauld, N.L. J. Am. Chem. Soc., **1982**, 104, 2665. (b) Gassman, P.G.; Singleton, D.A. ibid. **1984**, 106, 7993.

(8) (a) Escher, A.; Ubersax, B.; Neuenschwander, M. Chimia, **1981**, 35, 251. (b) Hoffmann, H.M.R.; Vathke-Ernst, H. Chem. Ber. **1981**, 114, 1182. (c) Giguere, R.J.; von Ilsemann, G.; Hoffmann, H.M.R. J. Org. Chem. **1982**, 47, 4948.

(9) To a $TiCl_4$ (1.89 g, 10 mmol) solution in ether (30 mL) and methylene chloride (20 mL) stirred at -50 °C was slowly added 0.98 g (10 mmol) of mesityl oxide. Then, an ethereal solution of methyl magnesium iodide (12 mmol) was slowly added. The reaction mixture was warmed up to room temperature over 3 h. and was stirred for 12 h. The reaction mixture was poured into ice. After usual work-up, the organic layer were dried ($MgSO_4$), then the solvent removed with a rotatory evaporator and the resulting crude oil was distillated, affording **2** (85 % yield): bp 65 ° (4 torr); IR (film) : 3100, 3070, 1645, 1630, 900 cm^{-1}; ^1H NMR (CCl_4) δ 5.13 (1, s. br.), 5.00 (1, s. br.), 4.77 (1, s. br.), 1.97 (2, s), 1.87 (3, s), 1.67 (3, s), 1.1 (3, s), 1.03 (3, s), 0.97 (6, s); mass spectrum m/e 192 (43)(HRMS calcd for $C_{14}H_{24}$ 192.1878, found 192.1874), 177 (4), 149 (6), 135 (50), 96 (100).

(10) The same procedure described for the preparation of **2** has been used with allyl-magnesium chloride (12 mmol). The reaction mixture was stirred at room temperature for 60 h and then poured into ice. After usual work-up the resulting crude oil was chromatographed on silica gel (pentane) giving **3** (65 % yield). IR (film) 3095, 1645, 925 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.08-5.27 (3, m), 5.27-4.63 (4, m), 5.00 (1, s br.), 2.65 (1, d J = 6.4 Hz), 1.70 (6, s br.), 1.07 (12, s); ^{13}C NMR δ 137.58 (d), 136.90 (d), 133.90 (d), 131.57 (s), 131.01, 130.72 (d), 115.72 (t), 115.38 (t), 47.34 (s), 42.53 (s), 29.13 (q)(2C), 25.17 (d), 24.18 (q)(2C), 21.6 (d), 19.24 (q), 17.36 (q); mass spectrum m/e 244 (11)(HRMS calcd for $C_{18}H_{28}$ 244.2190, found 244.2187), 229 (10), 201 (8), 187 (8), 173 (8), 123 (100), 121 (20), 91 (16), 81 (53).

(11) Protic catalyzed elimination on 4-methyl-2-phenyl-3-penten-2-ol leads to a mixture of hydrocarbons; see : Jacobs, T.L.; Meyers, R.A. J. Am. Chem. Soc. **1964**, 86, 5244.

(12) To a $TiCl_4$ (0.945 g, 5 mmol) solution in ether (30 mL) and methylene chloride (20 mL) stirred at -50 °C was slowly added 0.98 g (10 mmol) of mesityl oxide followed by the addition of an ethereal solution of phenyl magnesium bromide (15 mmol). The reaction mixture was slowly warmed up to room temperature over 12 h. After usual work-up, diene **5** (85 % yield) and biphenyl (12 % yield) were isolated by chromatographic separation. **5** : IR (film) 1610, 1600, 895, 720 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.22 (5, s br.), 5.87 (1, s br.), 5.40 (1, d J = 2.0 Hz), 4.97 (1, d J = 1.8 Hz), 1.85 (3, d J = 1.0 Hz), 1.68 (3, d J = 1.0 Hz); mass spectrum m/e 158 (37), 143 (100), 128 (52), 115 (17), 91 (7).

(13) The same procedure described for the preparation of **2** was used with phorone (1.38 g, 10 mmol) and methyl magnesium iodide (12 mmol). The reaction mixture was stirred at room temperature for 2 h. Work-up afforded a crude oil which was chromatographed on silica gel (pentane) and preparative GLC. **6** : IR (film) 3085, 1640-1610, 905-890 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.67 (1, s br.), 5.42 (1, s br.), 5.12 (1, s br.), 1.83 (6 s br.), 1.73 (9, s br.), 1.73 (2, s), 1.04 (12, s); ^{13}C NMR δ 145.72 (s), 136.20 (d), 132.51 (s), 132.44 (s), 130.80 (s), 46.62 (s), 46.48 (s), 32.72 (q), 30.66 (q), 26.75 (q), 26.68 (q), 26.01 (q), 23.01 (q), 23.86 (q), 19.50 (q); mass spectrum m/e 272 (8), 257 (2), 201 (2), 190 (2), 175 (2), 136 (20), 121 (100), 105 (18), 91 (16), 79 (16), 77 (13).

(14) The aminium cation radical catalyzed Diels-Alder reaction of the 2,4-dimethyl-1,3-pentadiene leads to an another adduct different from **2** (see, 7b).

(15) Ohloff, G.; Uhde, G. Helv. Chim. Acta **1970**, 53, 531.

(16) 1.54 g (10 mmol) of β-cyclocitral was added to an ethereal solution of allyl magnesium chloride stirred at -30 °C. The reaction mixture was slowly warmed up to room temperature over 12 h. Usual work-up gave **7**. To a $TiCl_4$ (1.89 g, 10 mmol) suspension in ether (30 mL) stirred at -50 °C was slowly added **7**. The reaction mixture was warmed up to room temperature and stirred for 30 h. Work up afforded a crude oil which was purified by chromatography on silica gel (pentane). **8** (80 % yield): IR (film) 3040, 825 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.82 (2, s br.), 1.82 (3, s), 1.18 (3, s), 1.07 (6, s); mass spectrum m/e 176 (33)(HRMS calcd for $C_{13}H_{20}$ 176.1565, found 176.1568), 162 (10), 161 (100), 133 (20), 119 (24), 107 (32), 105 (28), 91 (24).

8 (440 mg, 2.5 mmol) and maleic anhydride (250 mg) were refluxed in toluene (2 mL) for 6 h. After removing of the solvent, the crude adduct was chromatographed on silica gel (pentane-ether 4/1). **9** : mp : 112 °C; ^{1}H NMR ($CDCl_3$) δ 6.27 (1, $\frac{1}{2}$AB J = 6.0 Hz), 5.92 (1, $\frac{1}{2}$AB), 3.68 (1, $\frac{1}{2}$AB J = 9.6 Hz), 3.33 (1, $\frac{1}{2}$AB), 1.30 (3, s), 1.25 (3, s), 1.09 (3, s), 0.95 (3, d J = 0.8 Hz); ^{13}C NMR δ 171.80 (s), 171.70 (s), 135.98 (d), 135.34 (d), 67.19 (s), 65.68 (s), 60.40 (s), 53.27 (d), 48.42 (d), 39.26 (t), 33.87 (s), 28.93 (q), 27.85 (t), 22.79 (q), 18.41 (t), 17.99 (q), 11.52 (q).

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