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STEREOSELECTIVE SYNTHESIS OF 1,6-DICHLORO-1,3,5-HEXATRIENE DERIVATIVES BY MCMURRY COUPLING OF β-CHLOROACRYLALDEHYDE DERIVATIVES

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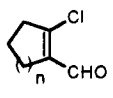
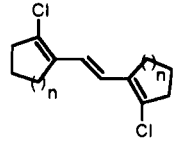
Abstract : A highly stereoselective synthesis of 1,6-dichloro-1,3,5-hexatriene derivatives by McMurry coupling of β-chloroacrylaldehydes have been developed.

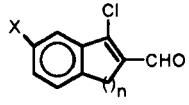
Reductive dimerisation of carbonyl compounds with low-valent titanium reagents developed by McMurry,[1] Mukayama[2] and Tyrlik[3] have been ventured by synthetic organic chemists. β-Chloroacrylaldehydes have been found to be good starting materials for the preparation of bioactive small ring heterocyclic compounds with exocyclic functionalities.[4] When we treated β-chloroacrylaldehydes with titanium tetrachloride ($TiCl_4$), zinc in dimethoxyethane (DME), we observed highly stereoselective formation of 1,6-dichloro-1,3,5-hexatrienes.



1a (n=1)
1b (n=2)

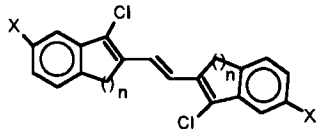


2a (n=1)
2b (n=2)

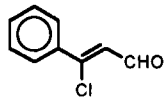


3a (n=1, X=H)
3b (n=2, X=H)
3c (n=2, X=Br)

*To whom correspondence should be addressed.



4a (n=1, X=H)
4b (n=2, X=H)
4c (n=2, X=Br)



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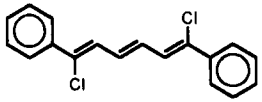

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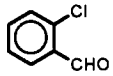

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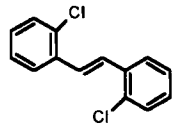
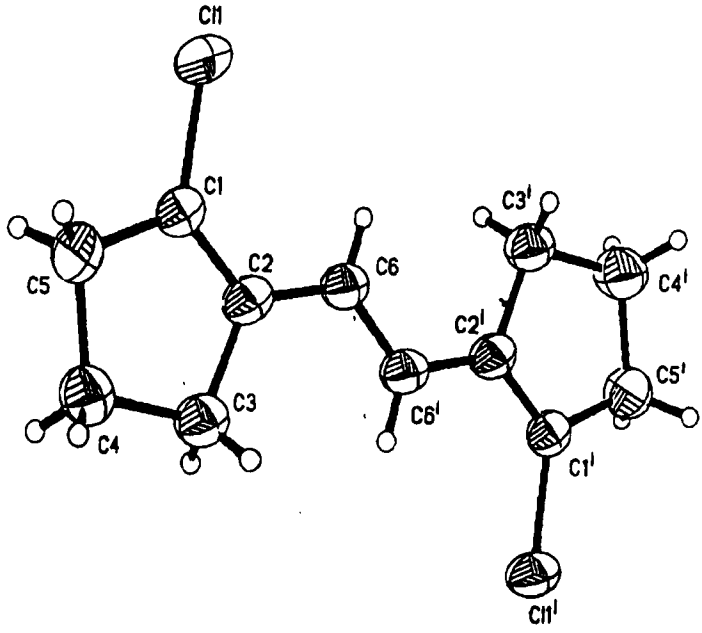


8

In reactions of carbonyl compounds with low valent Ti, the first step is simply a pinacol reaction and is not unique to low-valent Ti. It has been known that reducing metals are capable of adding an electron to a ketone or aldehyde carbonyl group, yielding an anion radical that dimerizes.[5-10] The evidence for this first step in the titanium induced coupling reaction is straight forward, as the intermediate pinacol can be isolated in high yield if the carbonyl coupling reaction is carried out at 0^0C. When the isolated pinacols are treated with low valent Ti at solvent reflux temp., deoxygenation occurs to produce the alkenes. Thus the second step of the carbonyl-coupling reaction to yield alkene is very interesting one because it was mechanistically unprecedented at the time of its discovery and is uniquely carried out by low valent Ti.[1-5]

However, *Z*-β-chloroacrylaldehyde derivatives when treated with $Zn/TiCl_4$ in DME at 0-5^0C produced exclusively *Z-E-Z* alkene derivatives. The stereochemistry was proved from the X-ray crystallographic analysis of the compound **2a** (fig. 1).[11]

Thus, when 2-chlorocyclopentene-1-carboxaldehyde (**1a**) was treated with



Compound (**2a**)

ORTEP DIAGRAM (fig. I)

$Zn/TiCl_4$ in DME produced exclusively the *E*-geometrical isomer (**2a**) [entry no I]. Under similar reaction conditions 2-chlorocyclohexene-1-carboxaldehyde (**1b**) produced the geometrical isomer (**2b**) as the only isolable product in 70% yield (entry no II). This reaction procedure when subjected to other chloroaldehydes **3a, 3b, 3c, 5** and **7** gave also only *E*-geometrical isomers **4a, 4b, 4c, 6** and **8** respectively in good yields [entry no III- VII].

It has been observed that organohalides are not reduced by low-valent titanium reagents under the above mentioned experimental conditions. Thus, the method described here provide a highly stereoselective synthesis of *Z,E,Z*-1,6-dichloro-1,3,5- hexatriene derivatives in high yields.

EXPERIMENTAL

All the melting points are uncorrected and were checked in one side open glass capillary using sulphuric acid bath. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Brucker FACF-200 FT NMR spectrometer using TMS as internal standard. Mass spectra were performed on Finnigan 4000 GC/MS machine at 70 ev. Elemental analysis have been performed from CDRI, Lucknow (India).

Typical Experimental Procedure: To an ice cooled suspension of active zinc dust (0.025 gm atom) in dimethoxyethane (8 ml) under argon, $TiCl_4$ (0.0126 mole) was injected slowly. It was then refluxed for two hours and then again cooled to 0^0C. To this, a solution of chloroaldehyde (0.003 mole) in DME (4ml) was added dropwisely with stirring at 0^0C. Stirring was continued at 0^0C for 30 min, then at room temperature and at refluxing temperature (vide Table). The cooled reaction mixture was then poured into an ice cooled saturated potassium carbonate solution and extracted with dichloromethane or benzene. The organic layer was washed thoroughly with water or brine solution several times, dried (sodium sulphate), and solvent was removed to give the product as colourless or yellow solids. It was further purified by recrystallisation from pet.ether (60-80^{0}C)-chloroform mixture.

Spectral and Analytical data :Compound **2a:** ^{1}H-NMR ($CDCl_3$) δ: 1.98 (dd, 2H, J= 7.2 and 14.9 Hz), 2.02 (dd, 2H, J=7.7 and 14.9 Hz), 2.56-2.72 (m, 8H), 6.43 (s, 2H), ^{13}C-NMR ($CDCl_3$) δ: 20.59, 30.69, 38.56, 123.50, 130.87, 134.98. MS(m/z): 233, 231, 229 (M^+), 196, 194, 168, 166, 158 (B^+), 156, 154, 152, 143, 132, 130, 116. Anal. Calcd. for $C_{12}H_{14}Cl_{12}$: C, 62.88; H, 6.11. Found: C, 62.66; H, 5.59.

Compound **2b:** ^{1}H-NMR ($CDCl_3$) δ: 1.70-1.79 (m, 8H), 2.31-2.39 (m, 4H), 2.44-2.51 (m, 4H), 6.88 (s, 2H). Anal Calcd. for $C_{14}H_{18}Cl_2$: C, 65.37; H, 7.00. Found: C, 65.24; H, 6.84.

Compound **4a:** ^{1}H-NMR ($CDCl_3$) δ: 3.75 (s, 4H), 7.04 (s, 2H), 7.23-7.38 (m, 6H), 7.42-7.45 (m, 2H). Anal. Calcd. for $C_{20}H_{14}Cl_2$: C, 73.85; H, 4.31. Found: C,73.75; H, 4.18.

Table:

Entry No.	Reactant*	Reaction conditions	Product (colour)	Melting Point** (^{0} C)	Isolated Yield (%)
I	**1a**[12]	0-5^{0}C/ 1hr, r.t. 4 hrs., then reflux, 2 hrs.	**2a** (light yellow solid)	130-132	50
II	**1b**[13]	0-5^{0}C/ 30 min. then reflux, 3 hrs.	**2b** (colour-less solid)	148-150	70
III	**3a**[14]	0-5^{0}C/ 1hr, r.t. 2 hrs then reflux, 2 hrs.	**4a** (yellow solid)	263-265	60
IV	**3b**[15]	0-5^{0}C/ 30 min. then reflux, 4 hrs.	**4b** (yellow solid)	186-188	92
V	**3c**[16]	0-5^{0}C /30 min. then reflux, 4 hrs.	**4c** (yellow solid)	> 270	84
VI	**5**[17(a,b)]	0-5^{0}C/ 30 min. then reflux, 3 hrs	**6** (yellow solid)	196-198	79
VII	**7**	0-5^{0}C/ 30 min. then reflux, 3 hrs	**8** (colour-less solid)	98-100	85

* The β-chloroacrylaldehyde derivatives (**1a-5**) were prepared following the published procedure.[12-17] 2-Chlorobenzaldehyde (**7**) was purchased from Aldrich Chemical Company (USA).

** All the compounds were recrystallised from pet. ether (60-80^{0}C) - chloroform mixture.

Compound **4b:** ^{1}H-NMR ($CDCl_3$) δ: 2.73-2.82 (m, 4H) , 2.89-2.97 (m, 4H), 7.13-7.23 (m, 6H), 7.32 (s, 2H), 7.69 (dd, 2H, J=7.0 and 1.8Hz), ^{13}C-NMR ($CDCl_3$) δ: 25.22, 27.66, 125.14, 126.78, 126.96, 128.12, 130.0, 132.60, 133.64, 136.62.

Compound **4c:** ^{1}H-NMR ($CDCl_3$) δ : 2.73-2.79 (m, 4H), 2.79-2.87 (m, 4H), 7.03 (d, 2H, J=7.7 Hz), 7.26 (s, 2H), 7.33 (dd, 2H, J=1.5 Hz and 7.7 Hz), 7.81 (d, 2H, J=1.5 Hz). MS (m/z) : 514, 513, 512, 511, 510 (M^+), 509, 508 (B^+), 507, 506, 440 (M - 2 ×Cl), 438, 436, 395, 393, 360, 359, 358, 357, 356, 280, 279, 278, 277, 276, 275.

Compound **6:** ^{1}H-NMR ($CDCl_3$) δ: 6.95-7.02 (m, 4H), 7.33-7.42 (m, 5H), 7.35 (s, 2H), 7.66-7.71 (m, 3H). MS (m/z): 304, 303, 302, 301, 300 (M^+) , 267, 265 (M-Cl), 232, 231, 230 (M- 2×Cl), 229 (B^+) [M-Cl-HCl], 228, 227, 226, 215, 203, 202, 190, 189, 164, 163, 162. Anal. Calcd. for $C_{18}H_{14}Cl_2$: C, 71.76; H, 4.65. Found: C, 71.69; H, 4.55.

Compound **8:** ^{1}H-NMR ($CDCl_3$) δ: 7.17-7.28 (m, 4H), 7.38 (dd, 2H, J=1.9 and 7.4 Hz), 7.47 (s, 2H), 7.73 (dd, 2H, J= 1.9 and 7.4 Hz), MS (m/z): 252, 251, 250, 249, 248 (M^+), 215, 214, 213 (M-Cl), 212, 179 (B^+), 178 (M- 2 ×Cl), 177, 176.

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