Notes

Direct Metalation of 1-Alkynes Using $TiCl_4/Et_3N$ and the Reactions of the Organotitanium Intermediates with Electrophiles

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Summary: Alkynyltitanium reagents are prepared in situ in the reaction of 1-alkynes with $TiCl_4/Et_3N$ and are used in the reaction with certain electrophiles.

Introduction

Metal acetylides are versatile synthetic intermediates in organic synthesis.[1] The readily accessible alkali metal acetylides are extremely basic and reactive. There has been continued interest in the development of alkynyl transition metal reagents for synthetic applications.[2] Organotitanium reagents have been proved to behave much more selectively than their lithium or magnesium counterparts.[3] In a continuation of our efforts toward the development of organotitanium reagents,[4] we report the formation of alkynyltitanium reagents in the reaction of terminal alkynes with $TiCl_4/Et_3N$ in CH_2Cl_2 under ambient conditions.

Results and Discussion

We have observed that the reaction of $TiCl_4$ with a mixture of terminal alkynes and trialkylamines readily produces the symmetrical 1,3-diynes (eq 1).

$$R-\equiv-H \xrightarrow[0\text{-}25\ ^\circ C,\ 6h,\ CH_2Cl_2]{TiCl_4/Et_3N} R-\equiv-\equiv-R \quad (1)$$

The reaction was carried out with several 1-alkynes, and the results are summarized in Table 1.

The diynes were isolated in 43−67% yields. Phenyl acetylene and 1-heptyne gave 62% and 67% yields, respectively (Table 1, entries 1 and 5).

1-Octyne, 1-dodecyne, 1-decyne, and 1-hexyne gave 64%, 51%, 49%, and 43% yields, respectively (Table 1, entries 2−4 and 6). The present conversion of 1-alkynes to symmetrical 1,3-diynes is convenient and easy to carry out from a synthetic point of view.

Table 1. The reaction of 1-Alkynes with $TiCl_4/R_3N$

No.	Substrate	Amine	Product[a]	Yield[b] (%)
1.	$C_6H_5-\equiv-H$	Et_3N	$C_6H_5-\equiv-\equiv-C_6H_5$ **1**	62
2.	$C_6H_{13}-\equiv-H$	Et_3N	$C_6H_{13}-\equiv-\equiv-C_6H_{13}$ **2**	64
3.	$C_{10}H_{21}-\equiv-H$	Et_3N	$C_{10}H_{21}-\equiv-\equiv-C_{10}H_{21}$ **3**	51
4.	$C_8H_{17}-\equiv-H$	Et_3N	$C_8H_{17}-\equiv-\equiv-C_8H_{17}$ **4**	49
5.	$C_5H_{11}-\equiv-H$	Et_3N	$C_5H_{11}-\equiv-\equiv-C_5H_{11}$ **5**	67
6.	$C_4H_9-\equiv-H$	Et_3N	$C_4H_9-\equiv-\equiv-C_4H_9$ **6**	43
7.	$C_5H_{11}-\equiv-H$	$^nBu_3N$	$C_5H_{11}-\equiv-\equiv-C_5H_{11}$ **5**	61
8.	$C_5H_{11}-\equiv-H$	$EtN(Pr^i)_2$	$C_5H_{11}-\equiv-\equiv-C_5H_{11}$ **5**	58
9.	$C_5H_{11}-\equiv-H$	$^nPr_3N$	$C_5H_{11}-\equiv-\equiv-C_5H_{11}$ **5**	59

[a] The products were identified by spectral (IR, ^1H NMR and ^{13}C NMR) and physical constant data and comparison with reported data. [b] The yields are based on the alkynes used.

The effect of various trialkylamines on the yields of diynes was also examined. The reactions using $^nBu_3N$, $EtN(^iPr)_2$, and $^nPr_3N$ gave 61%, 58%, and 59% yields of diyne when 1-heptyne was used (Table 1, entries 7−9). The reaction takes place at room temperature. However, the addition of $TiCl_4$ to the mixture of amine and alkyne was carried out at 0 °C. Chloroform can be used in place of dichloromethane without significant change in the yields. Reactions using pyridine and diethylamine did not give the diyne, and the alkyne remained unaffected.

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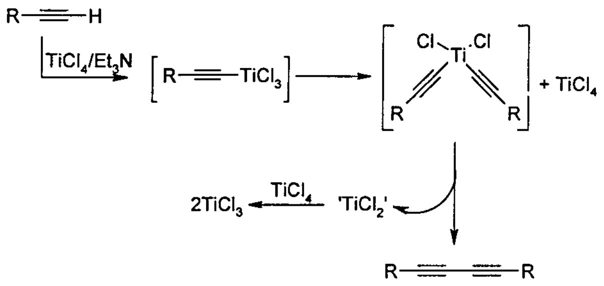
Scheme 1

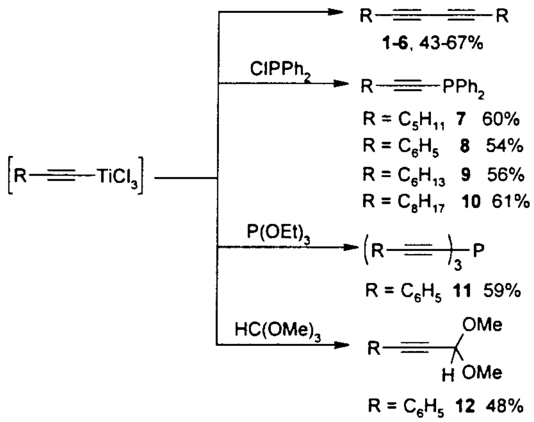


It was reported that alkynylcopper[5] and alkynylchromium[6] reagents undergo such dimerization reactions to give the symmetrical 1,3-diynes. The $TiCl_4/Et_3N$ combination has been extensively used for removal of an acidic hydrogen to generate titanium enolates in aldol condensation reactions.[7] Recently, it has been reported that certain ester enolates, prepared using $TiCl_4/Et_3N$, undergo coupling reactions with concomitant formation of Ti(III) species.[8] A similar mechanistic pathway can be considered to rationalize the present transformation (Scheme 1).

Previously, it has been reported that the alkynyltitanium is formed by transmetalation of alkynyllithium with $ClTi(O^iPr)_3$.[9] The method described here is interesting, since the alkynyltitanium reagent is formed directly from the alkyne without using organolithium reagents. Formation of 1,3-diyne was reported using 1-alkyne and CuX_2/pyridine,[5] but the utility of the organometallic intermediates was not demonstrated. The present method involving $TiCl_4/Et_3N$ leads to useful organotitanium intermediates that have proven synthetic applications. To examine the use of alkynyltitanium generated in situ in this way, reactions with various electrophiles were carried out (Scheme 2). The reaction with chlorodiphenylphosphine gives the corresponding alkynyl phosphines. In a run with 1-heptyne, the alkynyl phosphine **7** was isolated in 60% yield and the diyne was not formed. Phenylacetylene gave the corresponding phosphine **8** in 54% yield in addition to 2% of the 1,3-diyne. 1-Octyne and 1-decyne gave the corresponding phosphines **9** and **10** in 56% and 61% yields, respectively. These compounds were identified by comparison with authentic samples prepared following a reported method.[10]

When the triethyl phosphite was used as an electrophile, all three alkoxy groups were substituted, producing tris(phenylethynyl)phosphine (**11**) in 59% yield. This compound has been previously prepared by the reaction of phenylethynyllithium with PCl_3.[11] The alkynyltitanium also readily reacts with trimethyl orthoformate, yielding the acetal **12** in 48% yield. These results illustrate the synthetic potential of the alkynyltitanium reagent prepared in this way.

Scheme 2



Experimental Section

General. ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ unless otherwise stated, and TMS was used as reference ($\delta = 0$ ppm). Melting points are uncorrected. Dichloromethane was distilled over calcium hydride and dried over molecular sieves. Chromatographic purification was conducted by column chromatography using 100−200 mesh silica gel obtained from Acme Synthetic Chemicals, India. All reactions and manipulations were carried out under a dry nitrogen atmosphere. All yields reported are isolated yields of materials, judged homogeneous by TLC analysis.

Reaction of 1-Alkynes with $TiCl_4/Et_3N$. Formation of 1,3-Diynes. Dichloromethane (40 mL), Et_3N (15 mmol, 2.1 mL), and 1-alkyne (5 mmol) were stirred under an atmosphere of nitrogen. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column. Hexane eluted the 1,3-diyne. **1**: mp 87 °C (lit.[12] 87−88 °C); ^{13}C NMR (δ) 74.00, 81.60, 121.90, 128.42, 129.15, 132.50.[13] **2**: ^{13}C NMR (δ) 14.00, 19.20, 22.58, 28.39, 28.58, 31.35, 65.30, 77.40. **3**: ^{13}C-NMR (δ) 14.00, 19.11, 22.52, 28.21, 28.88, 29.00, 29.18, 29.48, 29.59, 31.91, 65.34, 77.41. **4**: ^{13}C NMR (δ) 14.02, 19.19, 22.62, 28.38, 28.86, 29.08, 29.68, 31.83, 65.34, 77.41. **5**: ^{13}C NMR (δ) 13.85, 19.15, 22.13, 28.05, 30.99, 65.31, 77.45. **6**: ^{13}C NMR (δ) 13.44, 18.84, 21.89, 30.42, 65.35, 77.32. The acetylenic carbon signals appear at (δ) 65.3 and 77.4. These values are similar to that reported for dodeca-5,7-diyne (**6**).[14]

Reaction of Alkynyltitanium with Chlorodiphenylphosphine. Dichloromethane (40 mL), Et_3N (15 mmol, 2.1

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mL), 1-heptyne (5 mmol, 0.7 mL), and $ClP(C_6H_5)_2$ (5 mmol, 0.9 mL) were stirred under N_2. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. EtOAc/hexane (1:99) mixture eluted the alkynyl diaryl phosphine **7**: yield 60%; IR (cm^{-1}) 2179; ^1H NMR (δ) 0.91 (t, $J = 6.1$ Hz, 3H), 1.24−1.73 (m, 6H), 2.25 (t, $J = 5.8$ Hz, 2H); ^{13}C NMR (δ) 14.02, 20.42, 22.22, 28.31, 31.14, 75.93, 110.61, 128.42, 128.57, 128.81, 130.83, 131.05, 132.25, 132.65, 137.16, 137.30 (the spectral data of **7** showed 1:1 correspondence with data obtained for the authentic sample prepared using the reported procedure);[10] MS (EI) m/z 280 (M^+, 100%), 237 [($M^+ - C_3H_7$), 28%]. **8**: mp 42 °C (lit.[10] 43 °C); yield 56%; IR (cm^{-1}) 2115; ^1H NMR (δ) 7.14−8.32 (m, 15H); ^{13}C NMR (δ) 86.08, 86.21, 107.99, 122.96, 128.51, 128.71, 128.86, 129.05, 129.19, 131.97, 132.52, 132.95, 136.45, 136.57. **9**: yield 56%; IR (cm^{-1}) 2132; ^1H NMR (δ) 0.90 (t, $J = 6.18$ Hz, 3H), 1.23−1.71 (m, 8H), 2.42 (t, $J = 5.9$ Hz, 2H), 7.11−7.84 (m, 10H), the values are in accordance with reported values;[15] ^{13}C NMR (δ) 13.99, 20.39, 22.55, 28.55, 31.15, 31.30, 75.88, 110.5, 128.38−135.61, 137.14, 137.26. **10**: yield 61%; IR (cm^{-1}) 2179; ^1H NMR (δ) 0.92 (t, $J = 6.01$ Hz, 3H), 1.34−1.86 (m, 12H), 2.35 (t, $J = 6.21$ Hz, 2H), 7.31−8.20 (m, 10H); ^{13}C NMR (δ) 14.10, 20.42, 22.69, 28.62, 28.94, 29.11, 29.23, 31.85, 75.92, 110.57, 128.39, 128.54, 128.75, 130.81, 131.03, 132.02, 132.22, 132.64, 137.17, 137.32.

Reaction of Alkynyltitanium with Triethyl Phosphite. Dichloromethane (40 mL), Et_3N (15 mmol, 2.1 mL), phenyl acetylene (5 mmol, 0.5 mL), and $P(OEt)_3$ (5 mmol, 0.9 mL) were stirred under N_2. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column. EtOAc/hexane (1:99) mixture eluted the tris(2-phenyl-1-ethynyl)phosphine. **11**: mp 90 °C (lit.[16] 92 °C), IR (cm^{-1}) 2164; ^1H NMR (δ) 7.25−8.14 (m, 15H); ^{13}C NMR (δ) 79.85, 80.01, 106.04, 106.25, 122.50, 128.42, 129.51, 132.20; MS(EI) m/z 334 (M^+, 68%), 333 ($M^+ - 1$, 100%).

Reaction of Alkynyltitanium with Trimethyl Orthoformate. Dichloromethane (40 mL), Et_3N (15 mmol, 2.1 mL), phenyl acetylene (10 mmol, 1.1 mL), and trimethyl orthoformate (15 mmol, 1.6 mL) were stirred under an atmosphere of nitrogen. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column. EtOAc/hexane (1:99) mixture eluted the acetal **12**:[17] yield 48%; IR (cm^{-1}) 2226, 2189; ^1H NMR (δ) 3.45 (s, 6H); 5.38 (s, 1H); 7.31−7.72 (m, 5H); ^{13}C NMR (δ) 52.51 (OCH_3), 83.62 ($C{\equiv}C$), 85.78 ($C{\equiv}C$), 93.63 ($CH(OCH_3)_2$), 121.77 (quaternary), 128.28 (CH), 128.87 (CH), 131.92 (CH), (signal assignments are based on DEPT experiments).

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Supporting Information Available: ^{13}C NMR spectra of the compounds **1**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org

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