# Synthesis of enynones from alkynes, alkynyl ketones and aromatic aldehydes using the $TiCl_4/Et_3N$ reagent system†

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Alkynyltitanium species, prepared *in situ* from alk-1-ynes using the $TiCl_4/Et_3N$ reagent system, react with aromatic aldehydes to give enynones **2** in 49–38% yields. Reaction of alkynyl aryl ketones with aromatic aldehydes and the $TiCl_4/Et_3N$ reagent gives the enynones **2** in 78–92% yields.

**Keywords:** alkynyl aryl ketones, titanium tetrachloride, triethylamine, enynones

Metal acetylides are an important versatile class of reactive intermediates widely used in organic synthesis.[1] During the course of investigations on the synthetic applications of the $TiCl_4/Et_3N$ reagent system,[2] we have reported that this reagent system reacts with 1-alkynes to produce alkynyltitanium reagents.[3] Since organotitanium reagents have proven synthetic applications,[4] we have examined the reaction of alkynyltitanium species produced *in situ* with electrophiles.

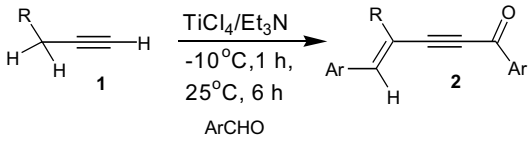
We have observed that alkynyltitanium species produced in this way react with two equivalents of an aromatic aldehyde to give the corresponding enynone **2** (Scheme 1). The formation of the enynone **2** was found to be general for a number alk-1-ynes.

In all reactions, the corresponding 1,3-diyne was isolated as minor product. For example, hept-1-yne gave the enynone **2a** in 49% yield besides the 1,3-diyne (10%), (Table 1, entry 1). Oct-1-yne and dec-1-yne produced the enynones in 45% and 41%, respectively, besides the corresponding 1,3-diynes (11% and 8%), (Table 1, entries 2 and 3).

This transformation can be explained by the mechanism shown in Scheme 2. The initially formed alkynyltitanium **A** could add to the aldehyde to give the alkoxy intermediate **B**, which could lose a '$HTiCl_3$' species giving the alkynyl ketone **C.** Further metalation by $TiCl_4/Et_3N$ would give the organometallic intermediate **D**, which could give the enynone **2a,** on reaction with benzaldehyde through the intermediate **E (**Scheme 2).

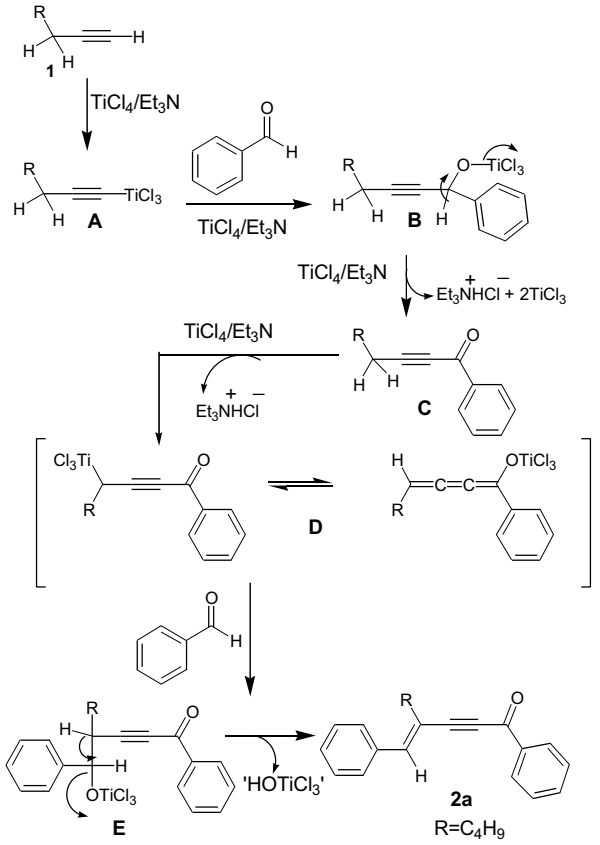
We have examined the reaction with phenylacetylene **3** as it cannot lead to the enynone since there is no methylene moiety attached to the acetylenic group (Table 1, entry 5). In this case, the corresponding ketone **3a** (31%) and the olefin **3b** (12%) were obtained (Scheme 3). Presumably, the corresponding propargyl alcohol derivative that is expected to be formed *in situ* is oxidised to the ketone **3a** by $TiCl_4$ and the $TiCl_3$ produced *in situ* in the medium gives the compound **3b** through reductive coupling.

Accordingly, we have examined the reaction of the propargyl alcohol **4** with the $TiCl_4/Et_3N$ system. In this reaction, the enediyne **3b** was obtained in 68% yield (Scheme 4). The structure of **3b** was confirmed by X-ray crystal structure analysis (Fig. 1).

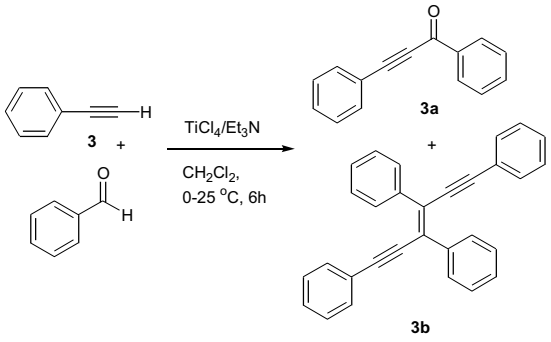



**Scheme 1** Reaction of alkynes and aromatic aldehydes with the $TiCl_4/Et_3N$ reagent system.

The formation of the enynones in the reaction of alkynyl titanium species and benzaldehyde would probably involve the titanium allenolate intermediate **D** formed *in situ* from the corresponding propargyl alcohol (Scheme 2). Accordingly,




**Scheme 2** Mechanism of reaction of alk-1-ynes and benzaldehyde with the $TiCl_4/Et_3N$ reagent system.




**Scheme 3** Reaction of phenyl acetylene and benzaldehyde with the $TiCl_4/Et_3N$ reagent system.

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† Dedicated to Professor M. Vivekananda Bhatt on the occasion of his 82nd birthday.

**Table 1** The reaction of alkynes and aromatic aldehydes with the $TiCl_4/Et_3N$ reagent system[a]

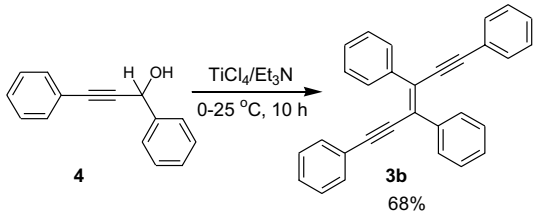
| Entry | Alkyne | Product[b,c] | Yield[d] |
|---|---|---|---|
| 1 | $C_4H_9—H_2C—\equiv—H$ **1a** | $C_4H_9$, O, H **2a** | 49 |
| 2 | $C_5H_{11}—H_2C—\equiv—H$ **1b** | $C_5H_{11}$, O, H **2b** | 45 |
| 3 | $C_7H_{15}—H_2C—\equiv—H$ **1c** | $C_7H_{15}$, O, H **2c** | 41 |
| 4[e] | $C_4H_9—H_2C—\equiv—H$ **1a** | $C_4H_9$, O, H **2d** | 43 |
| 5 | Ph—≡—H **3** | O **3a** | 38 |

[a]The hept-1-yne (5 mmol), $TiCl_4$ (10 mmol), $Et_3N$ (15 mmol) and benzaldehyde (10 mmol) were used.
[b]The products were identified by spectral and physical constant data (IR, $^1$H NMR, $^{13}$ C NMR and mass).
[c]$^{13}$C NMR data of the enynone derivates **2a-d** indicated that only one stereoisomer is obtained in all cases. $^1$H NMR (400 MHz) spectroscopic analysis indicates that the products have the *E*-stereochemistry (NOESY and carbon-hydrogen correlation experiments – olefinic hydrogen and the alkyl group are positioned *trans*).
[d]The yields are of isolated products.
[e]1-Naphthaldehyde (10 mmol) was used instead of benzaldehyde.

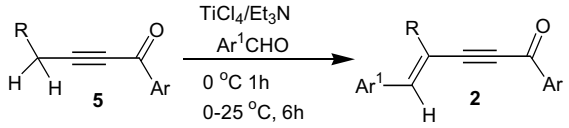
**Table 2** The reaction of alkynyl ketones with aromatic aldehydes in the presence of the $TiCl_4/Et_3N$ reagent system[a]

| Entry | Alkynyl ketone | Product[b] | %Yield[c] |
|---|---|---|---|
| 1 | $C_4H_9—H_2C—\equiv$, O **5a** | $C_4H_9$, O, H **2a** | 87 |
| 2 | $C_5H_{11}—H_2C—\equiv$, O **5b** | $C_5H_{11}$, O, H **2b** | 92 |
| 3 | $C_7H_{15}—H_2C—\equiv$, O **5c** | $C_7H_{15}$, O, H **2c** | 91 |
| 4[d] | $C_4H_9—H_2C—\equiv$, O **5a** | $C_4H_9$, O, H **2e** | 78 |

[a]The reagents were used in the following quantities: $TiCl_4$ (10 mmol), $Et_3N$ (15 mmol), alkynylketone (10 mmol) and benzaldehyde (10 mmol).
[b]The products were identified by spectroscopic and physical constant data (IR, $^1$H NMR, $^{13}$ C NMR and mass).
[c]The yields are of isolated products.
[d]1-Naphthaldehyde (10 mmol) was used instead of benzaldehyde.




**Scheme 4** Reaction of propargyl alcohol **4** with the $TiCl_4/Et_3N$ reagent system.




**Scheme 5** Reaction of alkynyl aryl ketones and aromatic aldehydes with the $TiCl_4/Et_3N$ reagent system.

it should be possible to obtain these enynones starting from the corresponding alkynyl phenyl ketones. Indeed, when the reactions were carried out using the alkynyl arylketones **5** and aromatic aldehydes, the corresponding enynones **2** were isolated in good yields (78–92%) (Scheme 5). The results are summarised in Table 2.

The *E*-stereochemistry was assigned for the enynones obtained (Table 1 and 2) based on the $^1$H NMR-NOESY studies which indicate that the olefinic hydrogen and the $CH_2$ of the alkyl groups are not *cis* to each other. Presumably, the elimination of the $HOTiCl_3$ fragment takes place (Scheme 2) to give selectively the *E*-isomer. The stereochemistry of this elimination process (*syn* or *anti*) and the steric requirements of the groups involved in the transition state are not clearly understood at this stage.

The enynones are a useful class of compounds. For example, certain enynone derivatives were previously used for the preparation of Red Ginseng, a biologically active molecule which can serve as an analeptic, erythropoietic or cytotoxic agent.[5] Some enynone derivates were used as intermediate precursors for the total synthesis of pumiliotoxin B,[6a] phomactin,[6b] (-)-borrelidin,[6c] anti-helicobacter pylori agent,[7a] vitamin D (calciferol),[7b] methylenomycin B,[7c,d] furanoid fatty ethers[7e] and neocarzinostation.[7f] Some enynones can be readily converted into phenols,[8a] methylenecyclopentenone s,[8b] and *Z*-dienones.[8c] Therefore, the method described will serve as a good addition to the pool of reagents reported for the synthesis of enynones.[7e,9]

*General procedure for the synthesis of enynones from benaldehyde and hept-1-yne using the $TiCl_4/Et_3N$ reagent system*

Hept-1-yne **1a** (0.48 g, 0.5 ml, 5 mmol), $TiCl_4$ (1.9 g, 1 ml, 10 mmol) and triethylamine (1.2 g, 1.7 ml, 12 mmol) were taken in dichloro-

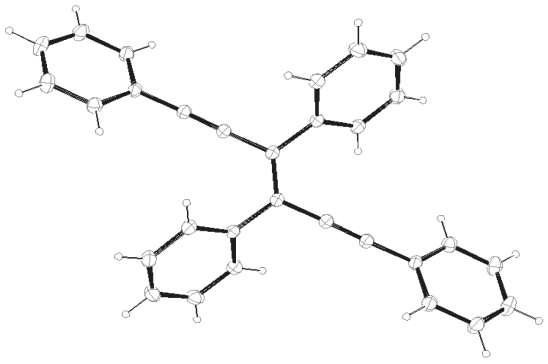


**Fig. 1** ORTEP representation of enediyne **3b**.

methane (35 ml) at 0°C under a $N_2$ atmosphere, and benzaldehyde (1.1 g, 1 ml, 10 mmol) was added. This reaction mixture was stirred for 1 h at –10°C and was further stirred for 6 h at 25°C. A saturated $NH_4Cl$ solution (20 ml) was added and the mixture stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 15 ml). The combined organic extract was washed with brine solution (10 ml) and dried over anhydrous $Na_2SO_4$. The solvent was removed and the residue was chromatographed on a silica gel column with 1% ethyl acetate/hexane mixture to isolate the enynone **2a** (0.14 g, 49%).

*Typical procedure for the synthesis of enynones from alkynyl ketones using the $TiCl_4/Et_3N$ reagent system*

Hept-1-ynylketone **5** (0.4 g, 2 mmol), $TiCl_4$ (0.38 g, 0.2 ml, 2 mmol) and triethylamine (0.4 g, 0.56 ml, 4 mmol) were taken in dichloromethane (35 ml), at 0°C under a $N_2$ atmosphere and benzaldehyde (0.21 g, 0.2 ml, 2 mmol) was added. The reaction mixture was stirred for 1 h at 0°C and was further stirred for 6 h at 25°C. A saturated $NH_4Cl$ solution (20 ml) was added and the mixture stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 15 ml). The combined organic extract was washed with brine solution (10 ml) and dried over anhydrous $Na_2SO_4$. The solvent was removed and the residue was chromatographed on a silica gel column with 1% EtOAc/hexane mixture to isolate the enynone **2a** (0.25 g, 87%).

*Procedure for the synthesis of enediyne* **3b** *from propargyl alcohol using the $TiCl_4/Et_3N$ reagent system*

$TiCl_4$ (0.38 g, 0.22 ml, 2 mmol) and $Et_3N$ (0.3 g, 0.42 ml, 3 mmol) were taken in dichloromethane (35 ml), at 0°C under $N_2$. To this 1,3-diphenyl-2-propyn-1-ol **4** (0.42 g, 2 mmol) was added and the mixture was stirred for 10 h at 25°C. Saturated $NH_4Cl$ solution (10 ml) was added and the mixture stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 15 ml). The combined organic extract was washed with brine solution (5 ml) and dried over anhydrous $Na_2SO_4$. The solvent was removed and the residue was chromatographed on a silica gel column using hexane. The enediyne **3b** was isolated in 0.26 g (68%) yield.

*Physical and spectroscopic data for compounds*

**2a:** TLC $R_f$ = 0.8 (9 : 1 hexane/EtOAc); IR (neat); ($cm^{-1}$) 2214, 1664; $^1H$ NMR (400 MHz, $CDCl_3$, δ ppm): 1.03 (t, $J$ = 6.7 Hz, 3H), 1.42–1.76 (m, 4H), 2.53 (t, $J$ = 6.88 Hz, 2H), 7.26 (s, 1H), 7.04–7.55 (m, 6H), 7.90–7.94 (m, 2H), 8.03–8.06 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$, δ ppm): 13.5, 19.7, 21.9, 30.2, 78.1, 103.1, 121.8, 128.0, 128.4, 129.7, 130.0, 130.2, 132.3, 134.9, 137.3, 143.9, 194.2; MS (EI) $m/z$ = 288, Anal. Calcd for $C_{21}H_{20}O$; C, 87.5%; H, 7.0%; Found: C, 87.5%, H, 7.0% (yellow viscous liquid). **2b**: TLC $R_f$ = 0.8 (9 : 1 hexane/EtOAc); IR (neat); ($cm^{-1}$) 2209, 1662; $^1H$ NMR (400 MHz, $CDCl_3$, δ ppm): 1.05 (t, $J$ = 6.4 Hz, 3H), 1.12–1.81 (m, 6H), 2.43 (t, $J$ = 6.8 Hz, 2H), 7.31 (s, 1H), 7.34–7.52 (m, 6H), 7.87–7.91 (m, 2H), 8.01–8.04 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$, δ ppm): 13.9, 20.0, 22.5, 27.9, 31.0, 78.7, 103.3, 121.9, 126.7, 130.2,137.1, 137.4, 138.2, 138.7, 139.3, 143.2, 194.6; MS (EI) $m/z$ = 302. Anal. Calcd for $C_{22}H_{22}O$; C, 87.4%; H, 7.3%; Found: C, 87.4%, H, 7.35% (yellow viscous liquid). **2c**: TLC $R_f$ = 0.8 (9 : 1 hexane/EtOAc); IR (neat); ($cm^{-1}$) 2212, 1663; $^1H$ NMR (400 MHz, $CDCl_3$, δ ppm): 0.85 (t, $J$ = 6.6 Hz, 3H), 1.2–1.9 (m, 10H), 2.4 (t, $J$ = 6.75 Hz, 2H), 7.40 (s, 1H), 7.32–7.49 (m, 6H), 7.84–7.89 (m, 2H), 7.93–8.02 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$, δ ppm): 14.0, 20.0, 22.6, 28.7, 28.4, 28.1, 31.4, 78.1, 103.3, 130.1, 132.3, 135.0, 137.3, 143.8, 194.1; MS (EI) $m/z$ = 330. Anal. Calcd for $C_{24}H_{26}O$; C, 87.2%; H, 7.9%; Found: C, 87.25%, H, 7.95% (yellow viscous liquid).

**2d**: TLC $R_f$ = 0.8 (9: 1 hexane/EtOAc); IR (neat); ($cm^{-1}$) 2215, 1660; $^1H$ NMR (400 MHz, $CDCl_3$, δ ppm): 0.89 (t, 3H, $J$ = 8.1 Hz), 1.28–1.36 (m, 2H), 1.46–1.55 (m, 2H), 2.22–2.26 (m, 2H), 6.89 (s, 1H), 7.39–7.91 (m, 9H), 8.01–8.12 (m, 3H), 8.16 (d, 1H, $J$ = 7.8 Hz), 8.31 (d, 1H, $J$ = 7.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$, δ ppm): 13.5, 19.6, 21.9, 30.2, 78.3, 101.9, 123.4, 125.0, 126.0, 126.7, 128.1, 129.8, 130.3, 131.5, 132.4, 133.6, 137.4, 141.2, 194.7; MS (EI) $m/z$ = 388, Anal.Calcd for $C_{29}H_{24}O$; C, 89.7%; H, 6.2%; Found: C, 89.6%, H, 6.3% (yellow viscous liquid). **3a**[10a]: TLC $R_f$ = 0.9 (9.5: 0.5 hexane/EtOAc); IR (neat); ($cm^{-1}$) 2221, 1664; $^1H$ NMR (400 MHz, $CDCl_3$, δ ppm): 7.52–7.23 (m, 10H), $^{13}C$ NMR (100 MHz, $CDCl_3$, δ ppm): 81.3, 90.9, 128.8, 129.5, 133.3, 132.4, 134.4, 134.7, 173.5 (colourless semisolid at 25°C).

**3b**[10b]: TLC $R_f$ = 0.9 (9.5: 0.5 hexane/EtOAc); IR (neat); ($cm^{-1}$) 2219, 1379; $^1H$ NMR (200 MHz, $CDCl_3$, δ ppm): 7.12–7.82 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$, δ ppm): 99.9, 98.6, 123.3, 127.8, 128.3, 124.4, 128.7, 129.2, 131.4, 139.1. M. p.: 164–166°C (Colourless solid).

*Crystal data*

For the enediyne **3b:** $C_{30}H_{20}$, MW = 380.46, monoclinc, space group: $P2_1/n$, $a$ = 9.1453(18) Å, $b$ = 9.1141(18) Å, $c$ = 12.567(3) Å, α = α = 90°, β = 99.15(3)°; γ = 90°, V = 1034.1(4) Å $^3$, Z = 4, $\rho_c$ = 1.222 Mg/$m^3$, μ = 0.069 $mm^{-1}$, $T$ = 298 K, of the 11647 reflections collected, 2467 were unique [$R_{int}$ = 0.0217]. Refinement on all data converged at $R_1$ = 0.0458, $wR_2$ = 0.1173. CCDC 603903 contains the supplementary crystallographic data for **3b**. They can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_reqest.cif.

**2e**: TLC $R_f$ = 0.8 (9: 1 hexane/EtOAc); IR (neat); ($cm^{-1}$) 2218, 1664; $^1H$ NMR (400 MHz, $CDCl_3$, δ ppm): 0.87 (t, 3H, $J$ = 7.2 Hz), 1.22–1.27 (m, 2H), 1.27–1.33 (m, 2H), 1.47–1.53 (m, 2H), 6.89 (s, 1H), 7.10 (d, 1H, $J$ = 6.5 Hz), 7.28–7.73 (m, 10H), 7.82 (d, 1H, $J$ = 7.2 Hz), 7.99 (d, 1H, $J$ = 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$, δ ppm): 13.8, 18.7, 22.0, 28.1, 30.9, 77.7, 102.1, 122.6, 124.1, 125.2, 126.2, 127.0, 128.4, 128.7, 130.9, 131.3, 133.5, 148.8, 193.3; MS (EI) $m/z$ = 338. Anal. Calcd for $C_{25}H_{22}O$; C, 88.7%; H, 6.55%; Found: C, 88.7%, H, 6.6% (yellow viscous liquid).

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