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A Novel Titanium Tetrahalide-Mediated Carbon–Carbon Bond-Forming Reaction: Regioselective Synthesis of Substituted (*E,Z*)-1,5-Dihalo-1,4-dienes

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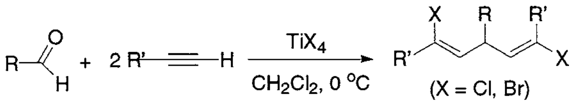
ABSTRACT



Reactions of aldehydes with 2 equiv of alkyne in the presence of TiX$_4$ (X = Cl, Br) regioselectively generated 1,5-dihalo-1,4-dienes in moderate to good yields with high (*E,Z*)-stereoselectivity.

Titanium(IV) halides are very versatile reagents in organic synthesis.[1] TiCl$_4$ is widely used in many carbon−carbon bond-forming reactions, including the coupling of carbonyl and aldimine compounds,[2] aldol condensations,[3] alkynylations of carbonyl compounds,[4] and ene reactions.[5] Other syntheses involve the additions of allylsilane,[6] allyltin,[7] propargylsilane,[8] and 2,4-pentadienylsilane[9] reagents to aldehydes, ketones, α-keto esters, and ketals. Titanium(IV) chloride is also used in the carbocyclization of active methane compounds with alkyne groups,[10] Claisen rearrangements,[11] as well as Baylis−Hillman[12] and Friedel−Crafts reactions.[13] In addition, numerous organic functional group transformations have been achieved using TiCl$_4$. Examples include conversion of propargylic alcohols to α,*β*-acetylenic aldehydes,[14] alkyl azides and ketones to amides,[15] α-nitro ketones

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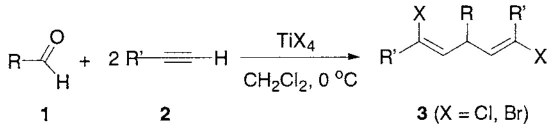
to *anti*-β-nitro alcohols,[16] ketamines to pyrroles,[17] carbonyl compounds to acetals,[18] acetals and ketals to carbonyl compounds,[19] ethers to alcohols,[20] and enamines to anilines.[21]

$TiCl_4$ and $TiBr_4$ are reported to react with alkynes to produce (*E*)-2-halo-1-alkenes after hydrolysis.[22] However, the vinyl-titanium intermediates have not been utilized in carbon−carbon bond-forming reactions other than the reaction of 3,3,3-trifluoro-1-propynylamines with carbonyl compounds to generate the corresponding α-(trifluoromethyl)-α,β-unsaturated amides[23] and addition of alkynes to expoxides.[24] We felt that titanium(IV) might be useful for reactions involving the addition of alkynes to carbonyl compounds to generate new carbon−carbon bonds, a reaction we previously reported for borane reagents.[25] We investigated the reaction of aldehydes with alkynes in the presence of titanium(IV) halides and discovered that (*E,Z*)-1,5-dihalo-1,4-dienes were generated (Scheme 1). These dihalodiene compounds are potentially useful intermediates in organic synthesis due to the number of functional groups present in the molecules, which can subsequently be transformed through coupling, substitution, and cyclization reactions.[26] In this paper, we report the preliminary results of our study.

Scheme 1



The reaction was first carried out by introducing 1 equiv of $TiCl_4$ to a mixture of phenylacetylene and 4-chlorobenzaldehyde (1:1 ratio) in CH_2Cl_2. (*E,Z*)-1,5-Dichloro-3-(4-chlorophenyl)-1,5-diphenyl-1,4-pentadiene was formed in modest yield. When 2 equiv of phenylacetylene and 1 equiv of 4-chlorobenzaldehyde were allowed to react with 1 equiv of $TiCl_4$, (*E,Z*)-1,5-dichloro-3-(4-chlorophenyl)-1,5-diphenyl-1,4-pentadiene was formed along with a trace amount of the (*Z,Z*)-isomer. Reactions carried out using $TiBr_4$ also generated the corresponding (*E*,Z)-1,5-dibromodiene compounds.

A series of aldehydes and alkynes were subjected to the new reaction. All reactions successfully produced the corresponding 1,5-dihalodiene derivatives in moderate to good yields (Table 1). All compounds were characterized by elemental analyses and NMR spectroscopy. The ^1H and ^{13}C NMR spectra of the products indicate that they are (*E*,*Z*)-dienes except for compounds **3p** and **3q**. A single crystal of compound **3b** was analyzed by X-ray crystallography.[27] The X-ray data for **3b** confirmed the NMR assignment. As can be seen from the data contained in Table 1, the reactions of substrates bearing electron-withdrawing groups tend to proceed more slowly. The low yields of bromo products, when compared to the chloro analogues, may be due to the low solubility of $TiBr_4$. Solvents such as diethyl ether, tetrahydrofuran, methylene chloride, hexane, and toluene were also examined. Methylene chloride produced the highest yields. Reactions in diethyl ether and THF gave poor yields with low stereoselectivity. A series of internal alkynes were also examined. However, only monoaddition of the alkyne to the aldehyde occurred, producing the allylic alcohol product. In addition, ketones did not give desired products. $SnCl_4$, $AlCl_3$, and $FeCl_3$ were also examined, but none produced the desired dienes.

Table 1. Synthesis of (*E,Z*)-1,5-Dihalo-1,4-dienes via Reactions of Aldehydes with Alkynes in the Presence of TiX_4 (X = Cl, Br)

R	R′	X	time (h)	% yield[a,b]
Ph	Ph	Cl	10	56 (**3a**)
p-Cl-Ph	Ph	Cl	16	55 (**3b**)
o-F-Ph	Ph	Cl	24	54 (**3c**)
p-NC-Ph	Ph	Cl	24	50 (**3d**)
p-Me-Ph	Ph	Cl	8	56 (**3e**)
p-Cl-Ph	*p*-F-Ph	Cl	20	52 (**3f**)
p-Cl-Ph	*p*-Me-Ph	Cl	14	45 (**3g**)
n-hexyl	Ph	Cl	20	51 (**3h**)
n-hexyl	*n*-butyl	Cl	24	68 (**3i**)
n-hexyl	*p*-F-Ph	Cl	26	63 (**3j**)
p-F-Ph	Ph	Br	24	40 (**3k**)
p-Cl-Ph	Ph	Br	14	45 (**3l**)
p-Me-Ph	Ph	Br	8	40 (**3m**)
p-Cl-Ph	*p*-Me-Ph	Br	12	44 (**3n**)
p-Me-Ph	*p*-Cl-Ph	Br	14	52 (**3o**)
n-hexyl	*p*-Me-Ph	Br	12	50 (**3p**)[c]
n-hexyl	Ph	Br	10	59 (**3q**)[c]

[a] Isolated yields. [b] All products were characterized by elemental analyses and NMR spectroscopy. [c] (*Z,E*):(*Z,Z*) ratio = 1:1.

Reactions were monitored by NMR spectroscopy. In one experiment, $TiCl_4$ and 2 equiv of phenylacetylene were dissolved in $CDCl_3$ in a NMR tube. The reaction solution immediately turned dark. However, the ^1H and ^{13}C NMR spectra of the reaction mixture revealed only resonances corresponding to the alkyne moiety at 3.04 ppm (^1H) as well as 83.7 and 77.2 ppm (^{13}C). The NMR data revealed that no vinyl intermediate formed even after a week at room temperature. However, the hydrolysis of the reaction mixture resulted in formation of α-chlorostyrene. In a separate

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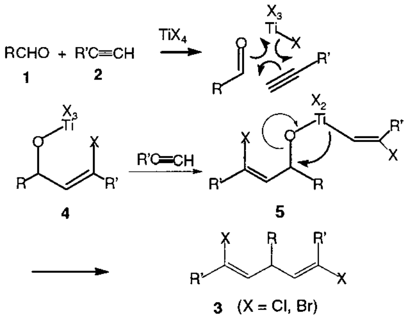
(27) For details of the X-ray crystal structure and data for **3b**, see Supporting Information.

Scheme 2



experiment, 2 equiv of phenylacetylene were added to a mixture of $TiCl_4$ and 4-chlorobenzaldehyde in $CDCl_3$.[28] The NMR spectra of the reaction mixture revealed the disappearance of the aldehyde and displayed new resonances corresponding to the (*E*,*Z*)-1,5-dichloro-3-(4-chlorophenyl)-1,5-diphenyl-1,4-pentadiene. On the basis of these experiments, we postulate the mechanism presented in Scheme 2. The reaction presumably undergoes a concerted six-membered ring transition state to form haloallyloxide intermediate **4**, which could then react with a second molecule of alkyne to generate **5**, followed by migration of vinyl group to afford final product **3**. Alternatively, intermediate **4** might generate an allylic cation that could add to alkyne **2** in an anti fashion to form **3**. In a control experiment, $TiCl_4$ was added to a mixture of 4-chlorobenzaldehyde and phenylacetylene (1:1 ratio), and (*Z*)-3-chloro-3-phenyl-1-(4-chlorophenyl)propenol was isolated upon hydrolysis. This result suggests the presence of intermediate **4** in the reaction.

In conclusion, we have developed a novel carbon−carbon bond-forming reaction involving titanium(IV) tetrahalides. The reaction is applicable to both aromatic and aliphatic substrates and produces (*E*,*Z*)-1,5-dihalo-1,4-dienes. Efforts to elucidate the reaction mechanism and to utilize titanium halides to synthesize a variety of monohalogenated and nonhalogenated 1,4-dienes are currently underway.

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Supporting Information Available: General experimental procedures and characterization data for all compounds prepared and details of the X-ray diffraction data and structure of compound **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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