

# A New Titanium Tetrachloride Mediated Annulation of $\alpha$ -Aryl-Substituted Carbonyl Compounds with Alkynes: A Simple and Highly Efficient Method for the Regioselective Synthesis of Polysubstituted Naphthalene Derivatives

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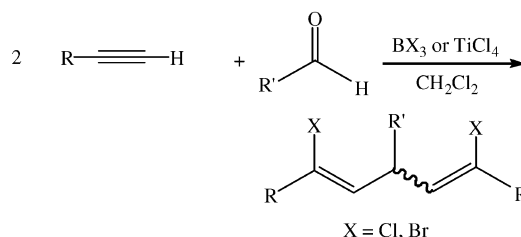
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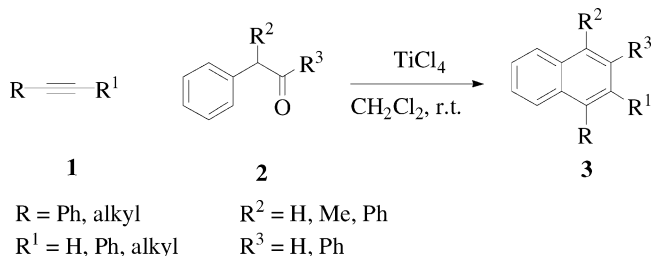
**Abstract:** A new straightforward procedure has been developed for the synthesis of polysubstituted naphthalene derivatives. The reaction of  $\alpha$ -aryl-substituted carbonyl compounds with terminal or internal alkynes in the presence of  $\text{TiCl}_4$  regioselectively generates substituted naphthalene derivatives in good to excellent yields.

Substituted naphthalene compounds are very important building blocks for the syntheses of pharmaceuticals<sup>1</sup> and polycyclic aromatic electronic materials.<sup>2</sup> The development of new and efficient methodologies for the synthesis of polysubstituted naphthalene derivatives has recently attracted much attention.<sup>3</sup> A variety of methods have been reported which include electrophilic substitution of naphthalenes,<sup>4</sup> annulation of benzene molecules bearing an unsaturated carbonyl side chain,<sup>5</sup> Suzuki coupling of halonaphthalenes with phenylboronic acids,<sup>6</sup> coupling of halonaphthalenes with organolithium or Grignard reagents,<sup>7</sup> reactions of aryl halides or arylmetal compounds with alkynes using transition metals,<sup>8</sup> cy-

## SCHEME 1



## SCHEME 2



clization of benzyne with alkynes,<sup>9</sup> annulations via Fisher carbenes,<sup>1c,10</sup> and cyclization of alkynes.<sup>11</sup> However, these methods involve either expensive catalysts and substrates or multistep syntheses. In some cases, the reactions produce mixtures of isomers.

During a recent study focused on boron and titanium halide-promoted carbon-carbon bond-forming reactions (Scheme 1),<sup>12</sup> we discovered that reactions of 2-phenyl-substituted aldehydes with alkynes in the presence of titanium tetrachloride generated substituted naphthalene derivatives with high regioselectivity (Scheme 2). This method provides a straightforward and efficient procedure for the synthesis of a variety of substituted naphthalene derivatives from readily available starting materials.<sup>13</sup>

$\text{TiCl}_4$  has been reported to react with alkynes to form haloalkenes after hydrolysis.<sup>14</sup> However, this reaction has not been used to generate new carbon-carbon bonds. Initially, we attempted to generate a titanium-carbonyl complex by adding 1 equiv of phenylacetaldehyde to  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  at room temperature. This was followed by the introduction of 1 equiv of phenylacetylene. The reaction solution immediately turned dark brown. Surprisingly, after several hours, 1-phenylnaphthalene was formed along with a small quantity of 2-phenylnaphthalene. None of the expected allyl alcohol was detected although aldehydes (without  $\alpha$ -aryl substituents) have been re-

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**TABLE 1. Synthesis of Substituted Naphthalene Derivatives (Scheme 1) via Reaction of Aldehydes with Alkynes in the Presence of  $\text{TiCl}_4$** 

entry	<b>1</b>		<b>2</b>		time (h)	<b>3</b>	yield <sup>a,b</sup> (%)
	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>			
1	Ph	H	H	H	3	<b>a</b>	88
2	Ph	H	Me	H	4	<b>b</b>	80
3	Ph	H	Ph	H	5	<b>c</b>	83
4	Ph	H	H	Ph	2	<b>d</b>	77
5	<i>p</i> -MePh	H	H	H	2	<b>e</b>	85
6	<i>p</i> -BrPh	H	H	H	3	<b>f</b>	73
7	<i>p</i> -ClPh	H	H	H	4	<b>g</b>	70
8	Ph	Me	H	H	4	<b>h</b>	82
9	Ph	Me	Me	H	4	<b>i</b>	75
10	Ph	Me	Ph	H	4	<b>j</b>	76
11	<i>n</i> -Pr	H	H	H	4	<b>k</b>	85
12	<i>n</i> -Pr	H	Me	H	2	<b>l</b>	88
13	<i>n</i> -Bu	H	H	H	12	<b>m</b>	88
14	<i>n</i> -Bu	H	Me	H	2	<b>n</b>	90
15	<i>n</i> -Bu	H	Ph	H	4	<b>o</b>	78
16	Ph	Ph	Me	H	10	<b>p</b>	65
17	Ph	Ph	Ph	H	12	<b>q</b>	65
18	<i>n</i> -Pr	<i>n</i> -Pr	H	H	5	<b>r</b>	80
19	<i>n</i> -Pr	<i>n</i> -Pr	Me	H	5	<b>s</b>	85
20	<i>n</i> -Pr	<i>n</i> -Pr	Ph	H	7	<b>t</b>	75

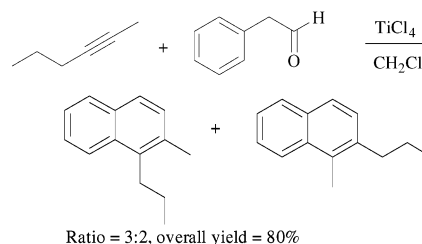
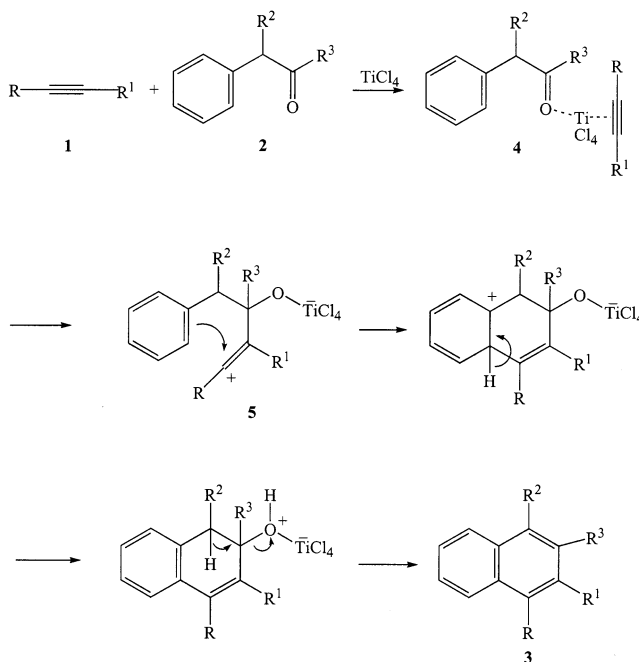
<sup>a</sup> Isolated yields based on starting carbonyl compounds. <sup>b</sup> All compounds were characterized by elemental analysis and NMR spectroscopy.

ported to react with alkynes in the presence of titanium tetrachloride to form allyl alcohols.<sup>12b</sup> To optimize the reaction conditions and minimize the self-condensation of phenylacetaldehyde, phenylacetylene and  $\text{TiCl}_4$  (1:1 ratio) were dissolved in  $\text{CH}_2\text{Cl}_2$  at room temperature. A dark brown solution formed to which 1 equiv of phenylacetaldehyde was added. 1-Phenylnaphthalene was isolated in excellent yield. A variety of alkynes including aryl, aliphatic, terminal, and internal alkynes were subjected to the reaction sequence. Essentially, all alkynes gave the desired naphthalene derivatives in good to excellent yields (Table 1).

The reaction of aromatic alkynes with aldehydes containing an electron-donating group on the phenyl ring tend to proceed rapidly. Reactions of aliphatic alkynes are faster than aryl alkynes and produce higher yields. It was also noted that the reactions of terminal alkynes generate higher yields of products than internal alkynes. Several  $\alpha$ -aryl-substituted aldehydes such as phenylacetaldehyde, diphenylacetaldehyde, and 2-phenylpropionaldehyde were also used in the reaction, and the corresponding naphthalenes were obtained in high yields. Deoxybenzoin also gave the corresponding substituted naphthalene in good yield. For terminal alkynes, the reaction exclusively generated 1-substituted naphthalene derivatives. Internal alkynes such as 1-phenylpropyne produced 1-phenyl-substituted naphthalene derivatives, whereas unsymmetrical aliphatic internal alkynes such as 2-hexyne gave mixtures of regioisomers (Scheme 3).

Alkynes containing functional groups such as ester, nitro, nitrile, and amino groups were also examined, but none of the desired naphthalenes formed. A variety of solvents such as hexane, toluene,  $\text{CH}_2\text{Cl}_2$ , diethyl ether, and THF were evaluated, and  $\text{CH}_2\text{Cl}_2$  was found to produce the best yields.

To investigate the reaction mechanism, a mixture of phenylacetaldehyde and phenylacetylene was monitored

**SCHEME 3****SCHEME 4**

by NMR spectroscopy. Phenylacetylene and  $\text{TiCl}_4$  (1:1 ratio) were dissolved in  $\text{CDCl}_3$  in an NMR tube, and the reaction solution immediately turned dark brown. The NMR spectra revealed only resonances corresponding to the alkyne group. Then, 1 equiv of phenylacetaldehyde was introduced into the reaction solution. The NMR data indicated that 1-phenylnaphthalene gradually formed. No intermediate was observed. In a separate experiment, phenylacetaldehyde and  $\text{TiCl}_4$  (1:1 ratio) were mixed in  $\text{CDCl}_3$  in a NMR tube to form a yellow  $\text{TiCl}_4$ -carbonyl complex.<sup>15</sup> Phenylacetylene was then added to the complex. Again, 1-phenylnaphthalene formed. However, if 2 equiv of phenylacetaldehyde was added to  $\text{TiCl}_4$  (to form the  $\text{TiCl}_4$ -bis(carbonyl) complex) followed by introduction of phenylacetylene, no reaction occurred. This result suggests that coordination between the alkyne and titanium is an essential step in the reaction. Based on these experiments, the reaction presumably involves the coordination of the aldehyde and alkyne to titanium to form complex **4** followed by cyclization to afford the final product **3** (Scheme 4). Functional groups presumably interfere with formation of titanium-alkyne complex by generating unreactive hexacoordinated titanium species.

In conclusion, we have developed a new, simple, regioselective, and efficient synthesis of substituted naphthalene derivatives via the reaction of  $\alpha$ -aryl substituted carbonyl compounds with alkynes in the presence of  $\text{TiCl}_4$  at room temperature. The reaction is

applicable to both terminal and internal, aliphatic and aromatic alkynes.

## Experimental Section

**General Considerations.** All glassware was dried in an oven at 120 °C and flushed with dry argon. All reactions were carried out under an argon atmosphere.  $\text{CH}_2\text{Cl}_2$  was distilled from  $\text{CaH}_2$ . All aldehydes and alkynes were purchased and used as received. Titanium tetrachloride (1 M in  $\text{CH}_2\text{Cl}_2$ ) was used as received. All products were purified by flash chromatography using silica gel (60 Å, 230–400 mesh) with hexane as eluent.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were recorded in  $\text{CDCl}_3$  (250 MHz) with chemical shifts reported relative to TMS. HRMS data for new compounds were obtained using an EAB-ZQ mass spectrometer.

**Representative Procedure for the Synthesis of Compounds 3a–t.** Phenylacetalene (0.41 g, 4.0 mmol) was placed in a dry argon-flushed, 50 mL round-bottomed flask equipped with a stirring bar and dissolved in dry  $\text{CH}_2\text{Cl}_2$  (20 mL). Titanium tetrachloride (3.0 mmol, 3.0 mL of a 1.0 M  $\text{CH}_2\text{Cl}_2$  solution) was added via a syringe at room temperature. The reaction solution immediately turned dark brown. Then, phenylacetaldehyde (0.36 g, 3 mmol) was added via a syringe at room temperature. The reaction mixture was allowed to stir for 3 h and then was hydrolyzed with water. The mixture was extracted into hexanes, and the organic layer separated, dried over anhydrous  $\text{MgSO}_4$ , concentrated under reduced pressure, and purified by flash column chromatography to afford **3a** as a colorless liquid (0.54 g, 88%).

(15) For the structures of  $\text{TiCl}_4$ -carbonyl complexes, see: Cozzi, P. G.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Chem Ber.* **1996**, *129*, 1361.

The physical properties and NMR data of all known compounds are in accord with literature values (Supporting Information). Data for new compounds are listed below.

**1-Methyl-4-propylnaphthalene (3l).** Colorless oil.  $^1\text{H}$  NMR:  $\delta$  8.06–7.97 (m, 2H), 7.50–7.46 (m, 2H), 7.21–7.18 (m, 2H), 3.00 (t, 2H,  $J = 7.5$  Hz), 2.64 (s, 3H), 1.80–1.71 (m, 2H), 1.01 (t, 3H,  $J = 7.3$  Hz).  $^{13}\text{C}$  NMR:  $\delta$  136.8, 132.9, 132.0, 126.2, 125.6, 125.2, 124.8, 124.4, 35.1, 24.0, 19.4, 14.3. HRMS: calcd for  $\text{C}_{14}\text{H}_{16}$  184.1252, found 184.1251.

**4-Methyl-1,2-diphenylnaphthalene (3p).** White solid. Mp: 137–138 °C.  $^1\text{H}$  NMR:  $\delta$  7.86 (dd, 2H,  $J = 8.3$  Hz), 7.50–7.13 (m, 13H), 2.25 (s, 3H).  $^{13}\text{C}$  NMR:  $\delta$  142.1, 139.2, 138.0, 136.0, 133.7, 132.8, 131.9, 131.6, 130.0, 129.1, 127.7, 127.5, 127.4, 126.6, 126.1, 125.9, 125.5, 124.0, 19.5. HRMS: calcd for  $\text{C}_{23}\text{H}_{18}$  294.1409, found 294.1408.

**4-Phenyl-1,2-di(propyl)naphthalene (3t).** Colorless oil.  $^1\text{H}$  NMR:  $\delta$  8.07–7.19 (m, 10H), 3.12–3.05 (m, 2H), 2.83–2.77 (m, 2H), 1.78–1.66 (m, 4H), 1.13 (t, 3H,  $J = 7.3$  Hz), 1.03 (t, 3H,  $J = 7.3$  Hz).  $^{13}\text{C}$  NMR:  $\delta$  141.1, 138.0, 137.0, 134.9, 132.5, 130.6, 10.1, 129.5, 128.9, 128.4, 128.1, 126.9, 126.5, 125.5, 124.5, 124.2, 35.8, 30.5, 24.8, 24.3, 14.7, 14.3. HRMS: calcd for  $\text{C}_{22}\text{H}_{24}$  288.1878, found 288.1884.

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**Supporting Information Available:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all known compounds prepared. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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