Aryltitanium Species through the Reaction of *N,N*-Dialkylarylamines with $TiCl_4$: Oxidative Coupling, *N*-Dealkylation, and Reaction with Electrophiles

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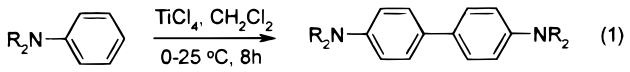
In alliance with tertiary amines, $TiCl_4$ is well-known to mediate aldol type condensation reactions[1] and oxidative coupling of certain ester enolates.[2] Recently, it was observed in this laboratory that the $TiCl_4/Et_3N$ reagent system is useful for the oxidative coupling of aryl methyl ketimines to 2,5-diarylpyrroles[3a] and for the direct metalation of 1-alkynes.[3b] Also, it was observed that trialkylamines are oxidized to iminium ions by $TiCl_4$ with concomitant formation of $TiCl_3$.[4a,b] Herein we report that the reaction of $TiCl_4$ with *N,N*-dialkylanilines gives the corresponding *N,N,N′,N′*- tetraalkylbenzidines (eq 1).

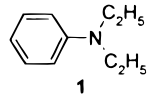
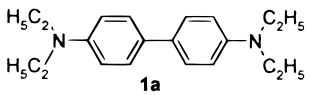
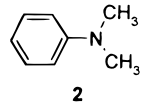
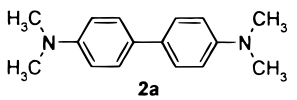
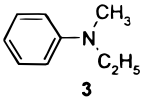
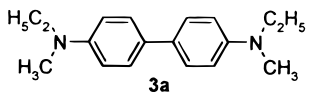
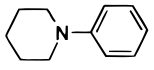
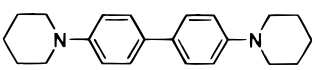
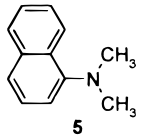
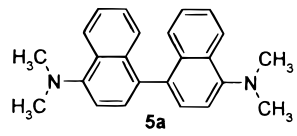


This transformation was found to be general for several amines. The results are summarized in Table 1. The *N,N*-dialkylarylamines, **1**−**5**, produced the corresponding *N,N,N′,N′*-tetraalkylbenzidines or naphthidines in good yields. However, *N,N*-dimethylaniline (**2**) and *N*-methyl-*N*-ethylaniline (**3**) gave lower yields of the corresponding tetraalkylbenzidines along with some unidentified polar compounds. In the case of amines, **2** and **3**, *N*-demethylated products were also isolated in 5% and 7% yields, respectively.

The transformation can be rationalized by the tentative mechanistic pathway outlined in Scheme 1, involving aryltitanium and radical cation intermediates. Reaction of the aryltitanium species with various electrophiles would result in the products **6**−**10**. The corresponding benzidines (**1a**−**5a**) could have formed through two reaction pathways as shown in Scheme 1.

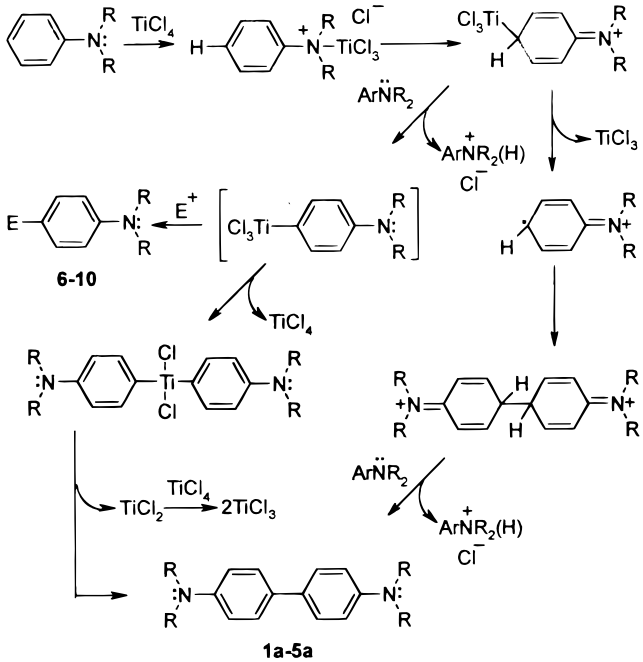
The products obtained in the presence of electrophiles such as benzophenone, methyl formate, chlorodiphenylphosphine, and benzaldehyde (Table 2) indicate that the reaction may go through organotitanium intermediates. Whereas the reaction with benzophenone produced the expected electrophilic addition product, the amino alcohol **6** (85% yield) in addition to the corresponding benzidine (16% yield), the reactions of methyl formate and benzaldehyde are interesting since in these cases the

Table 1. The Reaction of *N,N*-Dialkylarylamines with $TiCl_4$

No.	Substrate	Product[a]	Yield[b](%)
1.	 **1**	 **1a**	92
2.	 **2**	 **2a**	57
3.	 **3**	 **3a**	77
4.	 **4**	 **4a**	71
5.	 **5**	 **5a**	91

[a] The products were identified using IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral analysis, and physical constant data and comparison with reported data. [b] Yields are based on the recovered starting material.

Scheme 1



(1) (a) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135. (b) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (c) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (d) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883. (e) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727 and references therein.

(2) (a) Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809. (b) Kise, N.; Tokioka, K.; Aoyama, Y.; Matsumura, Y. *J. Org. Chem.* **1995**, *60*, 1100. (c) Kise, N.; Kumada, K.; Terao, Y.; Ueda, N. *Tetrahedron* **1998**, *54*, 2697.

(3) (a) Periasamy, M.; Srinivas, G.; Bharathi, P. *J. Org. Chem.* **1999**, *64*, 4204. (b) Bharathi, P.; Periasamy, M. Unpublished results.

(4) (a) Bharathi, P.; Periasamy, M. *Org. Lett.* **1999**, *1*, 857. (b) Periasamy, M.; Srinivas, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577.

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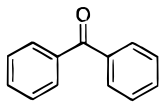
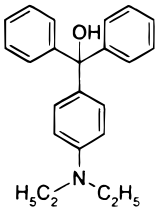
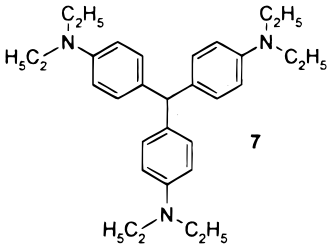
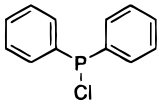
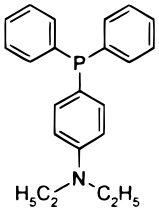
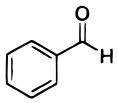
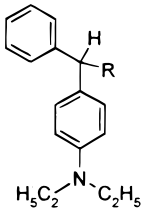
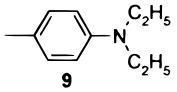
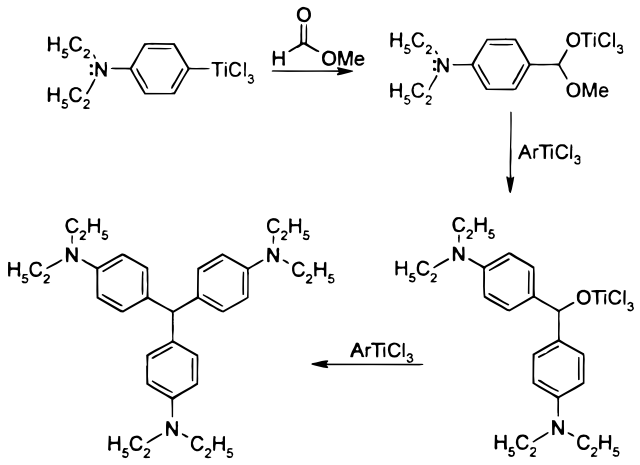
Table 2. The Reaction of Aryltitanium with Electrophiles

No.	Electrophile	Product[a]	Yield[b](%)
1.		 **6**	85
2.	$HCOOCH_3$	 **7**	34
3.		 **8**	72
4.		 R =  **9**; R = —OH **10**	91; 12

[a] The products were identified using IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral analysis, and physical constant data and comparison with reported data. [b] Yields are based on the recovered starting material.

Scheme 2



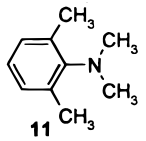
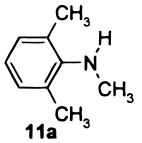
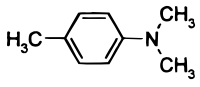
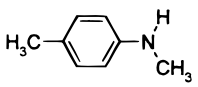
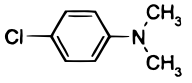
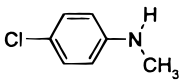
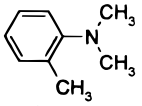
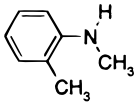
initially formed addition product undergoes further arylations to give the triaryl-, and phenyldiarylmethane derivatives, respectively (Scheme 2).

Also, in the presence of chlorodiphenylphosphine, the diphenyl-arylphosphine **8** is obtained (72% yield). Clearly, this observation indicates the presence of the aryltitanium intermediate in the transformations described here.

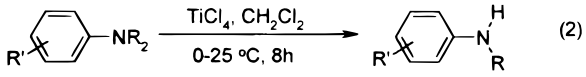
It is of interest to note that the commercially important dye precursor leuco ethyl crystal violet **7** is readily prepared following this method. It compares favorably with the multistep synthesis employed previously.[5]

When the experiment was carried out using some substituted *N*,*N*-dimethylanilines, the mono *N*-dealkylation was the predominant reaction (eq 2, Table 3).

Table 3. *N*-Demethylation of Aromatic Amines using $TiCl_4$

No.	Substrate	Product[a]	Yield[b](%)
1.	 **11**	 **11a**	85
2.	 **12**	 **12a**	72
3.	 **13**	 **13a**	86
4.	 **14**	 **14a**	81

[a] The products were identified using spectral (IR, ^{1}H-NMR, ^{13}C-NMR) data and comparison with authentic samples prepared using reported procedure.[12] [b] Yields are based on the recovered starting material.



(2)

It appears that in these cases, metalation of the ring becomes difficult and dealkylation takes place through the intermediacy of iminium ions.[4a,b]

In conclusion, simple methods of conversion of *N*,*N*-dialkylarylamines to *N*,*N*,*N*′,*N*′-tetraalkylbenzidines and naphthidines through oxidative coupling using $TiCl_4$ and demethylation of *N*,*N*-dimethylarylamines have been developed. Previously, such oxidative coupling reactions have been reported using electrochemical oxidation,[6] cerium sulfate oxidation in acid aqueous solution,[7] peroxidase,[8] iodosobenzene acetate,[9] and VCl_4.[10] Also, a molten mixture of $AlCl_3$−NaCl−KCl was reported to mediate coupling reactions of amines in the presence of

(5) Venkatraman, K. *The Chemistry of Synthetic Dyes*; Academic Press: New York, 1952; Vol. II, p 705.
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O_2.[11] The one-pot conversions described here using $TiCl_4$ involving aryltitanium intermediates have good synthetic potential in such applications.

Experimental Section

General. ^{1}H 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). The chemical shifts are reported in ppm on the δ scale relative to $CDCl_3$ (77.0 ppm). Melting points are uncorrected. Dichloromethane was distilled over calcium hydride and dried over molecular sieves. Aromatic tertiary amines were prepared by the reported procedure[12] and were distilled over CaH_2. *N*-Phenylpiperidine was prepared from aniline and 1,5-dibromopentane.[13] 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, adjudged homogeneous by TLC analysis.

Representative Procedure for the Reaction of *N,N*-Dialkylarylamines. Oxidative Coupling of *N,N*-Diethylaniline. In CH_2Cl_2 (25 mL), *N,N*-diethylaniline (1.6 mL, 10 mmol) was added at 0 °C under N_2. $TiCl_4$ (3.3 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$, 15 mmol) in 10 mL of CH_2Cl_2 was added dropwise for 5 min. The reaction mixture was stirred at 0 °C for 0.5 h and stirred further at 0−25 °C for 8 h. A saturated K_2CO_3 solution (20 mL) was added and stirred for 0.5 h. The reaction mixture was filtered through a Buchner funnel. 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. The unreacted amine was eluted using 1:99 EtOAc/hexane mixture. The benzidine **1a** was isolated using 2:98 EtOAc/hexane mixture as eluent (0.65 g, 92%).

1a: mp 85 °C (lit.[14] mp 85 °C); ^{13}C NMR δ146.40, 129.01, 127.19, 112.43, 44.58, 12.85; ^{1}H NMR δ 7.5 (d, 4H), 6.8 (d, 4H), 3.5 (q, 8H), 1.3 (t, 12H); mass: M^+ (*m*/*e*) 297.

2a: mp 197−198 °C (lit.[14] mp 195 °C); ^{13}C NMR δ 149.40, 130.01, 127.03, 113.25, 40.83; ^{1}H NMR δ 7.6 (d, 4H), 6.9 (d, 4H), 3.1 (s, 12H).

3a: mp 108 °C (lit.[15] mp 110 °C); ^{13}C NMR δ 147.82, 129.49, 127.06, 112.94, 47.02, 37.60, 11.39; ^{1}H NMR δ 7.6 (d, 4H), 6.9 (d, 4H), 3.5 (q, 4H), 3.0 (s, 6H), 1.2 (t, 6H).

4a: mp 208 °C; ^{13}C NMR δ 150.78, 132.02, 127.02, 116.75, 50.79, 25.87, 24.36; ^{1}H NMR δ 7.5 (d, 4H), 7.1 (d, 4H), 3.2 (s, 8H), 1.6−1.8 (m, 12H); mass: M^+ (*m*/*e*) 320.

5a: mp 135 °C (lit.[16] mp 130 °C); ^{13}C NMR δ 150.54, 134.48, 133.59, 128.86, 128.04, 127.37, 125.74, 125.03, 124.34, 113.68, 45.45; ^{1}H NMR δ 8.4 (d, 2H), 7.2−7.6 (m, 10H), 3.1(s, 12H).

Representative Procedure for the Electrophilic Reaction. Reaction of *N,N*-Diethylaniline with Benzophenone. In CH_2Cl_2 (25 mL), *N,N*-diethylaniline (1.6 mL, 10 mmol) and benzophenone (0.92 g, 5 mmol) were added at 0 °C under N_2. $TiCl_4$ (3.3 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$, 15 mmol) in 10 mL of CH_2Cl_2 was added dropwise for 5 min. The reaction mixture was stirred at 0 °C for 0.5 h and stirred further at 0−25 °C for 8 h. A saturated K_2CO_3 solution (20 mL) was added and stirred for 0.5 h. The reaction mixture was filtered through a Buchner funnel. 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. The unreacted amine was eluted using 1:99 EtOAc/hexane mixture. The alcohol **6** was isolated using 3:97 EtOAc/hexane mixture as eluent (1.15 g, 85%).

6: mp 71−72 °C (lit.[19] mp 73 °C); IR (cm^{-1}): ν_{O-H} 3474; ^{13}C NMR δ 147.61, 147.03, 133.92, 129.26, 127.99, 127.77, 126.90, 111.03, 81.87, 44.35, 12.71; ^{1}H NMR δ 7.3 (m, 10H), 7.1 (d, 2H), 6.6 (d, 2H), 3.3 (q, 4H), 2.8 (s, 1H), 1.2 (t, 6H); mass: M^+ (*m*/*e*) 331.

7: mp 75 °C; ^{13}C NMR δ 146.08, 132.88, 130.16, 111.90, 54.14, 44.46, 12.78; ^{1}H NMR δ 7.0 (d, 6H), 6.7 (d, 6H), 5.3 (s, 1H), 3.3 (q, 12H), 1.2 (t, 18H); (Structure was also confirmed by X-ray crystal structure analysis).

8: mp 110 °C; ^{13}C NMR δ 148.45, 139.12, 138.90, 136.13, 135.69, 133.54, 133.17, 128.37, 128.22, 128.13, 119.94, 111.73, 111.57, 44.29, 12.66; ^{1}H NMR δ 3.4 (q, 6H), 1.2 (t, 4H); mass: M^+ (*m*/*e*) 333.

9: mp 60 °C (lit.[17] mp 62 °C); ^{13}C NMR δ 146.45, 146.08, 132.15, 130.46, 129.71, 128.30, 125.99, 112.13, 55.45, 44.66, 13.02; ^{1}H NMR δ 6.9−7.5 (m, 13H), 5.7 (s, 1H), 3.6 (q, 8H), 1.5 (t, 12H); mass: M^+ (*m*/*e*) 386.

10: IR (cm^{-1}): ν_{O-H} 3385; ^{13}C NMR δ 147.48, 144.55, 131.09, 128.28, 128.13, 127.07, 126.48, 111.87, 76.02, 44.44, 12.67; ^{1}H NMR δ 7.5−7.3 (m, 5H), 7.2 (d, 2H), 6.7 (d, 2H), 5.8 (s, 1H), 3.4 (q, 4H), 1.2 (t, 6H); mass: M^+ (*m*/*e*) 255.

Representative Procedure for *N*-Demethylation. Reaction of *N,N*,2,6-Tetramethylaniline. In CH_2Cl_2 (25 mL), *N,N*,2,6-tetramethylaniline (1.6 mL, 10 mmol) was added at 0 °C under N_2. $TiCl_4$ (3.3 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$, 15 mmol) in 10 mL of CH_2Cl_2 was added dropwise for 5 min. The reaction mixture was stirred at 0 °C for 0.5 h and stirred further at 0−25 °C for 8 h. A saturated K_2CO_3 solution (20 mL) was added and stirred for 0.5 h. The reaction mixture was filtered through a Buchner funnel. 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. The unreacted amine was eluted using 1:99 EtOAc/hexane mixture. The compound **11a** was isolated using 2:98 EtOAc/hexane mixture as eluent (0.55 g, 85%).

11a: IR (cm^{-1}): ν_{N-H} 3387; ^{13}C NMR δ 147.99, 129.37, 129.17, 122.06, 35.52, 18.50; ^{1}H NMR δ 7.3 (d, 2H), 7.1 (m, 1H), 3.4 (s, 1H), 3.1 (s, 3H), 2.6 (s, 6H).

12a: IR (cm^{-1}): ν_{N-H} 3412; ^{13}C NMR δ 147.36, 129.83, 126.49, 112.75, 31.16, 20.52; ^{1}H NMR δ 7.1 (d, 2H), 6.6 (d, 2H), 3.5 (s, 1H), 2.9 (s, 3H), 2.4 (s, 3H).

13a: IR (cm^{-1}): ν_{N-H} 3427; ^{13}C NMR δ 148.12, 129.06, 121.63, 113.57, 30.77; ^{1}H NMR δ 7.1 (d, 2H), 6.5 (d, 2H), 3.6 (s, 1H), 2.8 (s, 3H).

14a: IR (cm^{-1}): ν_{N-H} 3435; ^{13}C NMR δ 147.50, 129.98, 127.26, 122.50, 116.97, 109.28, 30.80, 17.32; ^{1}H NMR δ 7.3−7.1 (m, 2H), 6.8−6.6 (m, 2H), 3.0 (s, 3H), 2.2 (s, 3H).

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Supporting Information Available: ^{13}C NMR spectra for compounds **1a**−**5a**, **6**−**10, 11a**−**14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) *N*-Phenylpiperidine was prepared by adding aniline (4.6 mL, 50 mmol), 1,5-dibromopentane (6.8 mL, 50 mmol), and K_2CO_3 (6.9 g, 50 mmol) to 50 mL of acetonitrile, and the mixture was refluxed for 12 h. The reaction mixture was filtered through a Buchner funnel, and the CH_3CN solvent was removed. The organic residue was extracted with ether (2 × 30 mL) and washed with water. The aqueous layer was extracted with ether (2 × 20 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and the amine was distilled under reduced pressure, bp 96−98 °C/5 mm (lit.[18] 95−98 °C/5 mm).

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