Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1955–1958

A simple $TiCl_4$ promoted arylation of orthoformate and benzyl ethers by *N*,*N*-dialkylarylamines

Mariappan Periasamy,* Neela Kishorebabu and K. Natarajan Jayakumar

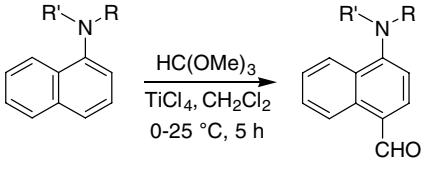
School of Chemistry, University of Hyderabad, Central University PO, Hyderabad 500 046, India

Received 24 May 2006; revised 10 January 2007; accepted 16 January 2007
Available online 19 January 2007

Abstract—*N*,*N*-Dialkylarylamines react with trimethyl orthoformate and $TiCl_4$ under ambient conditions to give the corresponding formyl derivatives in 75–89% yields, whereas the corresponding arylated products are obtained from benzyl ethers and acetals in 42–78% yields.

Although numerous methods are available for the formylation of arenes as a result of their importance in chemical and pharmaceutical syntheses,[1,2] there is still a need for reliable, highly regioselective synthetic methods for the introduction of a formyl group. It was reported from this laboratory that *N*,*N*-dialkylarylamines couple oxidatively to give the corresponding *N*,*N*,*N*,*N*-tetraalkylbenzidines in the presence of $TiCl_4$.[3] During the course of investigating the scope and limitations of the reactivity of the *N*,*N*-dialkylarylamines in the presence of $TiCl_4$,[4] we observed that these amines react with trimethyl orthoformate and $TiCl_4$ to give the corresponding formyl compound **1** (Scheme 1).

For example, the reaction of *N*,*N*-dimethyl-1-naphthylamine and trimethyl orthoformate with $TiCl_4$ produced 4-dimethylamino-1-naphthaldehyde **1a** in 89% yield (Table 1, entry 1), besides the corresponding benzidine derivative (10%). This transformation was carried out with other *N*,*N*-dialkylarylamines in the presence of $TiCl_4$ and the results are summarized in Table 1.[5]



1

Scheme 1.

We observed that in the reaction of $TiCl_4$ with 1-phenylethanol methyl ether and *N*,*N*-diethylaniline, the corresponding arylated product *N*,*N*-diethyl-4-(1-phenylethyl)aniline **2a** was obtained in 52% yield (Table 1, entry 5). In contrast, the reaction of benzaldehyde dimethyl acetal and *N*,*N*-diethylaniline with $TiCl_4$ produced the corresponding triarylmethane derivative **3a** in 72% yield (Scheme 2, Table 1, entry 6). Similarly, phenylacetaldehyde dimethyl acetal gave diaryl substituted product **3b** in 80% yield (Table 1, entry 7).

Interestingly, in the reactions using aryl ethers such as 1,2-dimethoxy-1,2-diarylethane **4**, the expected 1,2-disubstituted product was not formed. Instead, 1,1-disubstituted aryl derivative **5** was formed in 42–78% yields (Scheme 3). For example, the reaction of *N*,*N*-diethylaniline and $TiCl_4$ with 1,2-dimethoxy-1,2-diphenylethane produced **5a** in 78% yield. The reaction was generalized with other 1,2-dimethoxy-1,2-diarylethanes as well as using other arylamines and the results are summarized in Table 2. Product **5c** was also identified by X-ray crystal structure analysis (Fig. 1).

The transformations would be expected to proceed through initial substitution of the OCH_3 group in the orthoformate (Scheme 1) and benzyl ethers by the arylamine (Schemes 2 and 3). The formation of 1,1-disubstituted products **5** in the reaction of *N*,*N*-dialkylanilines and 1,2-dimethoxy-1,2-diarylethanes (Scheme 3) can be

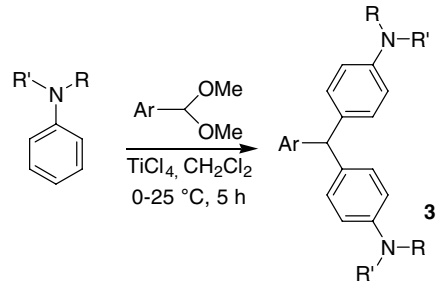
Keywords: *N*,*N*-Dialkylarylamines; Trimethyl orthoformate; Formylation; Titanium tetrachloride.
* Corresponding author. Tel.: +91 40 23134814; fax: +91 40 23012460; e-mail: mpsc@uohyd.ernet.in

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.01.079

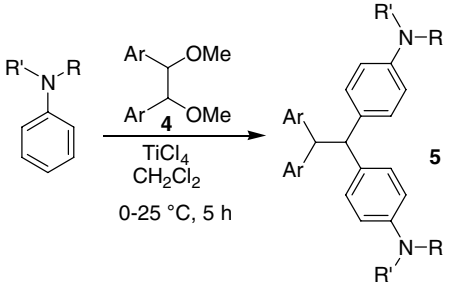
Table 1. Reaction of $TiCl_4$ and *N*,*N*-dialkylarylamines with orthoformates and benzyl ethers[a]

Entry	ArNRR′	Electrophile	Product[b]	Yield[c] (%)
1	Ar = 1-naphthyl R = R′ = Me	$HC(OMe)_3$	**1a**	89
2	Ar = 1-naphthyl R = R′ = $-C_5H_{10}-$	$HC(OMe)_3$	**1b**	85
3	Ar = Ph R, R′ = Et	$HC(OMe)_3$	**1c**	75
4	Ar = Ph, R = Et R′ = *n*-butyl	$HC(OMe)_3$	**1d**	82
5[d]	Ar = Ph R = R′ = Et	$PhCH(OMe)CH_3$	**2a**	52
6[e]	Ar = Ph R = R′ = Et	$PhCH(OMe)_2$	**3a**	72
7[e]	Ar = Ph R = R′ = Et	$PhCH_2CH(OMe)_2$	**3b**	80

[a] The reactions were carried out using arylamine (5 mmol), trimethyl orthoformate (7.5 mmol) and $TiCl_4$ (10 mmol, 1:1 solution of $TiCl_4/CH_2Cl_2$).
[b] The products were identified by ^1H, ^{13}C NMR spectral data and compounds **1d** and **3b** were also identified from mass spectral data.[5,6]
[c] The yields are of isolated products.
[d] The reaction was carried out using the ether (2.5 mmol), amine (5 mmol) and $TiCl_4$ (10 mmol, 1:1 solution of $TiCl_4/CH_2Cl_2$).
[e] The reactions were carried out using acetals (2.5 mmol), amine (7.5 mmol) and $TiCl_4$ (10 mmol, 1:1 solution of $TiCl_4/CH_2Cl_2$).



Scheme 2.



Scheme 3.

explained in terms of substitution of one OCH_3 group in the 1,2-dimethyl ether followed by the rearrangement of the aryl group to give the carbocation and subsequent reaction with the arylamine to produce compound **5** (Scheme 4).

Previously, it was reported from this laboratory that $TiCl_4$ reacts with *N*,*N*-dialkylarylamines at 0–25 °C to give the corresponding benzidines in 57–91% yields.[3] Tentative mechanistic pathways involving oxidation of the arylamines to the corresponding radical cations or formation of aryltitanium $R_2N–Ph–TiCl_3$ species followed by dimerization were considered to rationalize

Table 2. Reaction of $TiCl_4$ and arylamines with 1,2-dimethoxy-1,2-diarylethane **4**[a]

Entry	ArNRR′	**4**	Product[b]	Yield[c] (%)
1	R = R′ = Et	Ar = Ph	**5a**	78
2	R = R′ = $-C_5H_{10}-$	Ar = Ph	**5b**	55
3	R = R′ = Et	Ar = 1-naphthyl	**5c**	72
4	R = R′ = $-C_5H_{10}-$	Ar = 1-naphthyl	**5d**	42

[a] The reactions were carried out using arylamine (7.5 mmol), 1,2-dimethoxy-1,2-diarylethane **4** (2.5 mmol) and $TiCl_4$ (10 mmol, 1:1 solution of $TiCl_4/CH_2Cl_2$).
[b] The products were identified by ^1H NMR and ^{13}C NMR spectral data and product **5c** was also characterized by X-ray crystal structure analysis.[5]
[c] The yields are of isolated products.

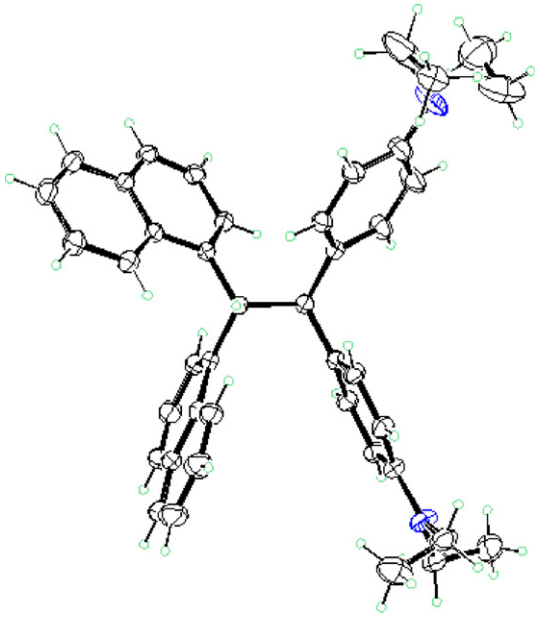
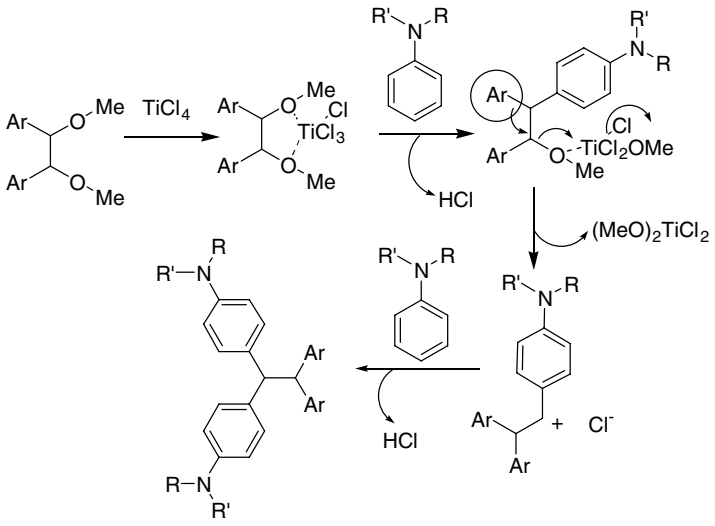


Figure 1. ORTEP diagram of compound **5c**.



Scheme 4.

this transformation, since $TiCl_4$ is known to oxidize amines[7–9] and Lewis acids such as BCl_3 are known to react with aromatic rings to give the corresponding Ar–BCl_2 species.[10] In order to examine whether such aryltitanium species are involved in the transformations reported here, we carried out an experiment using *N*,*N*-dialkylaniline and $TiCl_4$ at −40 °C and quenched the reaction mixture after 6 h with D_2O. In this case, the corresponding benzidine was obtained in 10% yield and the recovered *N*,*N*-dialkylaniline did not contain deuterium. Presumably, the aryltitanium species is not formed here or it is not stable even at −40 °C.

$TiCl_4$ has been used earlier in combination with MeO-$CHCl_2$[11] for the formylation of diphenols,[12] 3-substituted thiophenes,[13] and for the O-formylation of phenols.[14] On the other hand, it was reported that hydrolysis of 2-arylbenzo-1,3-dithiols using mercury(II) chloride and mercury(II) oxide in boiling aqueous tetrahydrofuran produced **1a** in 37% yield.[15] Also, compounds **1a** and **1c** were obtained in only 32% and 22% yields, respectively, following a method using hexamine.[16] Previously, such formyl derivatives of *N*,*N*-dialkylarylamines have been used for the synthesis of dyes containing a dialkylaminostyryl moiety.[17] Since these formyl derivatives are readily accessed using the $TiCl_4$/$(MeO)_3CH$ reagent system, the procedures described here have considerable synthetic potential.

Acknowledgements

N.K.B. and K.N.J. are thankful to the CSIR (New Delhi), for a fellowship. Support of the UGC (New Delhi) under the 'University of Potential for Excellence' (UPE) and 'Center for Advance Study' (CAS) programs are gratefully acknowledged. We are also thankful to the DST (New Delhi) for providing the 400 MHz NMR facility under the FIST program. A research grant to M.P. from ILS-UOH-MOU is also gratefully acknowledged.

References and notes

1. Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671–686.
2. Olah, G. A.; Kuhn, S. J. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley-Interscience: New York, 1964; Vol. III, Part II, p 1153.
3. Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *J. Org. Chem.* **2000**, *65*, 3548–3550.
4. Periasamy, M.; KishoreBabu, N.; Jayakumar, K. N. *Tetrahedron Lett.* **2003**, *44*, 8939–8941.
5. *Representative procedure for the arylation of orthoformate*: *N*,*N*-Dimethyl-1-naphthylamine (0.8 mL, 5 mmol) and trimethyl orthoformate (0.81 mL, 7.5 mmol) were taken at 0 °C in CH_2Cl_2 (25 mL) under N_2. $TiCl_4$ (2.2 mL of a 1:1 solution of $TiCl_4$/CH_2Cl_2, 10 mmol) in 10 mL CH_2Cl_2 was added dropwise over 5 min. The reaction mixture was stirred at 0 °C for 0.5 h and then stirred further at 0–25 °C for 5 h. Saturated K_2CO_3 solution (15 mL) was added and the reaction was 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 × 20 mL). The combined organic extract was washed with brine (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, and the benzidine side product were eluted using 2:98 EtOAc/hexane mixture. 4-Dimethylamino-1-naphthaldehyde **1a** in 89% yield (0.51 g) was eluted using 3:97 EtOAc/hexane mixture. Spectral data: Compound **1a**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 10.11 (s, 1H), 9.37 (d, 1H, $J = 8.8$ Hz), 8.13 (d, 1H, $J = 8.8$ Hz), 7.73 (d, 1H, $J = 7.8$ Hz), 7.67–7.42 (m, 2H), 6.90 (d, 1H, $J = 7.8$ Hz), 2.94 (s, 6H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 192.0, 157.1, 138.8, 132.5, 128.6, 127.4, 125.5, 125.1, 111.5, 44.5. Compound **1b**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 10.23 (s, 1H), 9.34 (d, $J = 8.8$ Hz, 1H), 8.18 (d, 1H, $J = 8.8$ Hz), 7.67 (d, 1H, $J = 8.8$ Hz), 7.90–7.55 (m, 2H), 7.10 (d, 1H, $J = 8.8$ Hz), 3.21 (t, $J = 6.8$ Hz, 4H), 1.95–1.87 (m, 4H), 1.76–1.72 (m, 2H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 192.5, 157.4, 138.6, 132.3, 128.6, 128.3, 125.9, 125.8, 125.4, 124.5, 112.7, 54.2, 26.2, 24.4. Compound **1c**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 9.70 (s, 1H), 7.70 (d, $J = 8.6$ Hz, 2H), 6.65 (d, $J = 8.7$ Hz, 2H), 3.45 (q, $J = 6.8$ Hz, 4H), 1.25 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 189.7, 152.1, 132.1,

124.6, 110.5, 44.5, 12.3. Compound **1d**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 9.98 (s, 1H,), 7.68 (d, $J = 9.0$ Hz, 2H), 6.64 (d, $J = 8.8$ Hz, 2H), 3.54–3.28 (m, 4H), 1.70–1.48 (m, 2H), 1.46–1.20 (m, 2H), 1.18 (t, $J = 6.8$ Hz, 3H), 0.95 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 189.8, 152.4, 132.2, 124.6, 110.6, 50.2, 45.1, 29.5, 20.2, 13.9, 12.2, mass GC–MS (m/z) 205 (M^+). Compound **2a**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 7.50–6.70 (m, 9H), 4.23 (q, $J = 7.2$ Hz, 1H), 3.52 (q, $J = 6.8$ Hz, 4H), 1.75 (d, $J = 7.2$ Hz, 3H) 1.32 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 147.5, 146.6, 133.5, 128.4, 128.3, 127.7, 125,5, 112.2, 44.5, 43.9, 22.2, 12.8. Compound **3a**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 7.50–6.90 (m, 13H), 5.70 (s, 1H), 3.60 (q, $J = 6.8$ Hz, 8H), 1.50 (t, $J = 6.8$ Hz, 12H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 146.4, 146.0, 132.1, 130.4, 129.7, 128.3, 125.9, 112.1, 55.4, 44.6, 13.0. Compound **3b**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 7.30–6.60 (m, 13H), 4.15 (t, $J = 6.8$ Hz, 1H), 3.45–3.25 (m, 10H), 1.25 (t, $J = 6.8$ Hz, 12H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 146.2, 141.4, 132.8, 129.2, 128.7, 127.9, 125.7, 112.3, 51.1, 44.4, 42.8, 12.7, mass (EI) (m/z) 400 (M^+). Compound **5a**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 7.32–7.06 (m, 14H), 6.56 (d, $J = 8.8$ Hz, 4H), 4.79 (d, $J = 11.7$ Hz, 1H), 4.67 (d, $J = 11.7$ Hz, 1H), 3.32 (q, $J = 6.8$ Hz, 8H), 1.19 (t, $J = 6.8$ Hz, 12H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 148.8, 144.5, 131.8, 129.1, 128.6, 127.9, 125.4, 112.2, 56.9, 54.2, 44.2, 12.5. Compound **5b**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 6.36–6.08 (m, 14H), 5.78 (d, $J = 8.6$ Hz, 4H), 4.84 (d, $J = 11.7$ Hz, 1H), 4.72 (d, $J = 11.7$ Hz, 1H), 2.21 (t, $J = 5.0$ Hz, 8H), 0.80–0.62 (m, 12H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 149.9, 144.0, 134.9, 128.8, 128.5, 127.9, 116.2, 56.7, 54.6, 50.6, 25.9, 24.2. Compound **5c**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 8.14–7.20 (m, 14H), 6.71 (d, $J = 8.4$ Hz, 4H), 6.29 (d, $J = 8.4$ Hz, 4H), 4.90 (br s, 1H), 4.78 (br s, 1H), 3.15 (q, $J = 6.8$ Hz, 8H), 0.99 (t, $J = 6.8$ Hz, 12H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$)140.4, 133.6, 132.2, 129.5, 128.4, 126.6, 126.4, 125.4, 125.1, 124.6, 123.7, 112.4, 55.9, 44.6, 12.3. Compound **5d**: ^{1}H NMR: (200 MHz, δ ppm, $CDCl_3$) 8.06 (d, $J = 8.8$ Hz, 2H), 7.66 (d, $J = 8.8$ Hz, 2H), 7.55 (d, $J = 6.8$ Hz, 2H), 7.31–7.17 (m, 4H), 6.71 (d, $J = 8.6$ Hz, 4H), 6.47 (d, $J = 8.8$ Hz, 4H), 6.22 (d, $J = 8.8$ Hz, 4H), 4.89 (br s, 1H), 4.76 (br s, 1H), 2.88 (t, $J = 6.0$ Hz, 8H), 1.70–1.86 (m, 12H); ^{13}C NMR: (50 MHz, δ ppm, $CDCl_3$) 150.0, 140.1, 134.4, 133.5, 132.2, 129.2, 128.4, 126.4, 125.4, 125.0, 124.6, 123.5, 116.0, 56.1, 50.7, 25.6, 24.2. *Crystal data for amine* (**5c**): $C_{42}H_{44}N_2$, $M_W = 576.79$, triclinic, space group: P-1, $a = 11.2663(8)$ Å, $b = 13.1471(9)$ Å, $c = 13.8028(9)$ Å, $\alpha = 102.9260(10)°$, $\beta = 111.8580(10)°$, $\gamma = 108.1940(10)°$ $V = 1663.3(2)$ Å^3, $Z = 2$, $\rho_c = 1.152$ mg m^{-3}, $\mu = 0.066$ mm^{-1}, $T = 298(2)$ K. Of the 19,581 reflections collected, 7789 were unique [R(int) = 0.0415]. Refinement on all data converged at $R_1 = 0.0710$, $wR_2 = 0.1950$ (CCDC Deposition Number 293540).

6. Balme, G.; Gore, J. *J. Org. Chem.* **1983**, *48*, 3336–3338.
7. Bharathi, P.; Periasamy, M. *Org. Lett.* **1999**, *1*, 857–859.
8. Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *Chem. Commun.* **2001**, 1728–1729.
9. Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *J. Org. Chem.* **2005**, *70*, 5420–5425.
10. Bujwid, Z. J.; Gerrard, W.; Lappert, M. F. *Chem. Ind.* **1959**, 1091.
11. Groos, H.; Rieche, A.; Mattey, G. *Chem. Ber.* **1963**, *96*, 308–314.
12. Scarpat, M. L.; Bianco, A.; Mascitelli, L.; Passacantilli, P. *Synth. Commun.* **1990**, *20*, 2565–2572.
13. Meth-Cohn, O.; Ashton, M. *Tetrahedron Lett.* **2000**, *41*, 2749–2752.
14. Garcia, O.; Nicolas, E.; Albericio, F. *Tetrahedron Lett.* **2003**, *44*, 4961–4963.
15. Nakayama, J. *Synthesis* **1975**, *3*, 170–172.
16. (a) Duff, J. C. *J. Chem. Soc.* **1945**, 276–277; (b) Duff, J. C.; Furness, V. I. *J. Chem. Soc.* **1951**, 1159–1164.
17. Banerji, J. C.; Sanyl, S. A. *Indian J. Chem.* **1968**, *6*, 346–350.