3838 *J. Org. Chem.* **1994**, *59*, 3838–3840

Titanium(IV) Chloride Catalyzed Cyanation of Benzylic Halides With Trimethylsilyl Cyanide[1]

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Received February 1, 1994⊗

Six sterically hindered benzylic chlorides have been substituted with cyano groups in excellent yields with trimethylsilyl cyanide and titanium tetrachloride in methylene chloride. Both monochloro substrates such as diphenylmethyl chloride and triphenylmethyl chloride and dichloro substrates such as dichlorodiphenylmethane and *sym*-tetraphenylethylene dichloride were studied. Because isonitriles are plausible reaction intermediates, the isomerization of trityl isonitrile by $TiCl_4$ and by trityl tetrafluoroborate was studied at 0 and −78 °C. Both reagents catalyze conversion to triphenylacetonitrile at 0 °C while only trityl tetrafluoroborate is effective at −78 °C. It was also found that trityl tetrafluoroborate reacts with trimethylsilyl cyanide in the absence of $TiCl_4$ to give triphenylacetonitrile in 96% yield.

sym-Tetraphenylethylene dichloride, **1**, is a stable well-known compound which is easily available in 90% yields by adding chlorine to tetraphenylethylene.[2] As part of a synthetic effort to prepare tetraphenylethyl cations and study their subsequent reactions, we treated **1** with various silver salts as well as with trimethylsilyl cyanide.[1b]

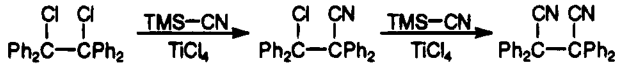
Trimethylsilyl cyanide (TMSCN) reacts with **1** in the presence of $TiCl_4$ at 0 °C for 2.0 h in CH_2Cl_2 to give a 93% yield of 3-chloro-2,2,3,3-tetraphenylpropanenitrile, **2**. See Scheme 1. Treatment of **1** with 2 mol each of TMSCN and $TiCl_4$ gave a 50% yield of tetraphenylsuccinonitrile, **3**, and tetraphenylethylene. However, if one premixes the TMSCN and **1** and adds $TiCl_4$ slowly, **2** can be secured unaccompanied by **3** and tetraphenylethylene. Treatment of **2** with 1 mol each of TMSCN and $TiCl_4$ gave a 90% yield of **3** after 4.5 h of reaction. Authentic **3** was prepared from diphenylacetonitrile by the literature procedure to confirm the structure (^1H and ^{13}C NMR, mp and undepressed mixed mp).[3]

That TMSCN substitutes the cyano group for chlorine in tertiary alkyl chlorides in the presence of $SnCl_4$ was shown by Reetz.[4] In that work it was found that $SnCl_4$ is more effective than such Lewis acids as zinc, bismuth, aluminum, iron, or titanium halides. Others have successfully cyanated 1-haloadamantane[5] and a chiral α-chloro thioether[6] with TMSCN and $SnCl_4$ in methylene chloride. Moreover, aryl iodides can be cyanated with TMSCN in the presence of tetrakis(triphenylphosphine)palladium(0) in triethylamine solvent.[7]

Results and Discussion

Inspired by the apparent ease of converting **1** into **2**, we sought to establish the generality of the cyanation process by studying a group of benzylic chlorides which are shown in Table 1. The most interesting substrate is that of the geminal dihalide, dichlorodiphenylmethane, which can be monocyanated to afford α-chlorodiphenylacetonitrile which in turn can be converted more slowly into diphenylmalononitrile, a compound not readily available from malonic ester or malononitrile. Benzyl chloride did not react and was recovered unchanged after 2 h. A reaction that was run at room temperature for 24 h gave a mixture of polymeric products.

Scheme 1

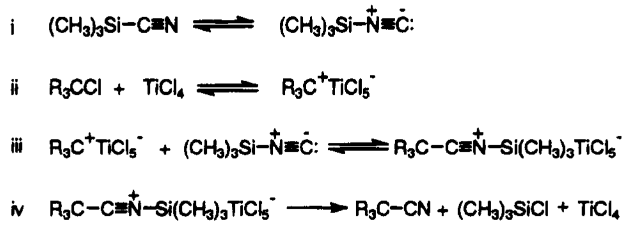


$$Ph_2\overset{Cl}{C}{-}\overset{Cl}{C}Ph_2 \xrightarrow[TiCl_4]{TMS{-}CN} Ph_2\overset{Cl}{C}{-}\overset{CN}{C}Ph_2 \xrightarrow[TiCl_4]{TMS{-}CN} Ph_2\overset{CN}{C}{-}\overset{CN}{C}Ph_2$$

1 2 3

Two alternative mechanisms[4b] have been considered as possible explanations for the formation of nitriles from tertiary alkyl halides. In mechanism 1 the fact that trimethylsilyl cyanide is in equilibrium with a small amount of trimethylsilyl isocyanide suggests that the isonitrile could undergo attack by a tertiary carbocation on carbon to form a nitrilium ion intermediate. See step iii in mechanism 1. This intermediate could break down to give the observed products.

Mechanism 1



i $(CH_3)_3Si{-}C{\equiv}N \rightleftharpoons (CH_3)_3Si{-}\overset{+}{N}{\equiv}\overset{-}{C}{:}$

ii $R_3CCl + TiCl_4 \rightleftharpoons R_3C^{+}TiCl_5^{-}$

iii $R_3C^{+}TiCl_5^{-} + (CH_3)_3Si{-}\overset{+}{N}{\equiv}\overset{-}{C}{:} \rightleftharpoons R_3C{-}C{\equiv}\overset{+}{N}{-}Si(CH_3)_3TiCl_5^{-}$

iv $R_3C{-}C{\equiv}\overset{+}{N}{-}Si(CH_3)_3TiCl_5^{-} \longrightarrow R_3C{-}CN + (CH_3)_3SiCl + TiCl_4$

In mechanism 2 the tertiary carbocation intermediate adds to the predominant form of TMSCN at nitrogen forming a nitrilium ion isomeric with that formed in mechanism 1. This nitrilium ion breaks down to produce the isonitrile of the starting halide. In the absence of carbocations one should be able to isolate the isonitrile providing its further rearrangement to yield nitrile is not faster than its formation. Indeed, adamantyl chloride is reported to react with TMSCN to give adamantyl isonitrile which is reported not to be rearranged to adamantyl

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⊗ Abstract published in *Advance ACS Abstracts*, June 1, 1994.

(1) Presented in part at the 207th ACS National Meeting, San Diego, CA, 1994, ORGN 486. (b) Details of the reaction of **1** with silver salts will appear in a separate paper.

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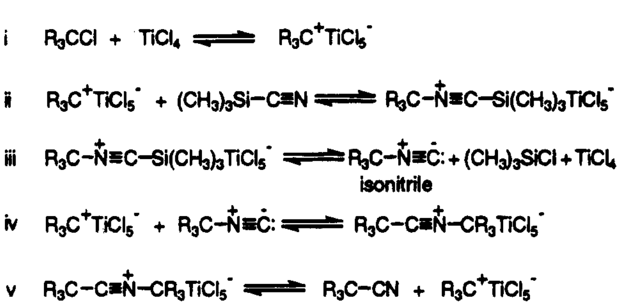
Table 1. Cyanation of Benzylic Chlorides by TMSCN and $TiCl_4$

entry	RCl[a]	$TiCl_4$ (mmol)	TMSCN (mmol)	RCN	yield[b] (%)
1	Ph_2CHCl	5.5	5.5	Ph_2CHCN	93
2	Ph_2CCl_2	5.0	5.0	$Ph_2C(Cl)CN$[c]	91
		11	11		98
3[d]	$Ph_2C(Cl)CN$	5.5	5.5	$Ph_2C(CN)CN$[e]	85
4	Ph_3CCl	5.5	5.5	Ph_3CCN[f]	95
5	$Ph_2C(Cl)C(Cl)Ph_2$	5.0	5.0	$Ph_2C(Cl)C(CN)Ph_2$	93
6[g]	$Ph_2C(Cl)C(CN)Ph_2$	5.5	5.5	$Ph_2C(CN)C(CN)Ph_2$[h]	90
7	$Ph_2C(Cl)C(Cl)Ph_2$	10	12	$Ph_2C(CN)C(CN)Ph_2$	53

[a] In all entries, 5 mmol of benzylic chlorides was used. [b] The yields are isolated yields. [c] See ref 12. [d] The reaction was run at 0 °C for 2 h and stirred overnight at room temperature. [e] See ref 13. [f] See ref 14. [g] The reaction was run at 0 °C for 2 h and stirred at room temperature for another 2.5 h. [h] See ref 3.

nitrile by titanium tetrachloride.[5b] Moreover, alkyl isonitriles are reported[8] to form complexes with $TiCl_4$ and $AlCl_3$ without generating cations that isomerize the isonitrile to nitrile. Benzylic halides appear to behave differently from the tertiary alkyl halides toward $TiCl_4$, and it appears that benzylic isonitriles may rearrange to nitriles much more readily than alkyl isonitriles.

Mechanism 2



$$\text{i}\quad R_3CCl + TiCl_4 \rightleftharpoons R_3C^+TiCl_5^-$$

$$\text{ii}\quad R_3C^+TiCl_5^- + (CH_3)_3Si{-}C{\equiv}N \rightleftharpoons R_3C{-}\overset{+}{N}{\equiv}C{-}Si(CH_3)_3TiCl_5^-$$

$$\text{iii}\quad R_3C{-}\overset{+}{N}{\equiv}C{-}Si(CH_3)_3TiCl_5^- \rightleftharpoons \underset{\text{isonitrile}}{R_3C{-}\overset{+}{N}{\equiv}\overset{-}{C}{:}} + (CH_3)_3SiCl + TiCl_4$$

$$\text{iv}\quad R_3C^+TiCl_5^- + R_3C{-}\overset{+}{N}{\equiv}\overset{-}{C}{:} \rightleftharpoons R_3C{-}C{\equiv}\overset{+}{N}{-}CR_3TiCl_5^-$$

$$\text{v}\quad R_3C{-}C{\equiv}\overset{+}{N}{-}CR_3TiCl_5^- \rightleftharpoons R_3C{-}CN + R_3C^+TiCl_5^-$$

Trityl isonitrile (Ph_3CNC), **4**, is a stable compound obtained by the dehydration of *N*-tritylformamide.[9] Treatment of isonitrile **4** with $TiCl_4$ at 0 °C for 2.0 h in CH_2Cl_2 gave triphenylacetonitrile, **5**, in 90% yield. Similarly, treatment of **4** with trityl tetrafluoroborate under the cyanation reaction conditions of Table 1 again produced nitrile **5** (95%) and triphenylmethanol (95%). These experiments show that if the isonitrile **4** is an intermediate, either $TiCl_4$ or the benzylic cation intermediate derived from the benzylic chlorides would have rapidly rearranged it to the nitrile. Perhaps the isomerization of **4** to **5** by $TiCl_4$ should not be so surprising for the benzylic systems shown in Table 1 because the carbocations formed are all doubly or triply benzylic. In addition, they are sterically hindered with bulky phenyl groups.

Another fact about isonitriles is that they thermally rearrange to nitriles upon heating at 200 °C in unimolecular fashion.[10] It is possible that π-complexation with $TiCl_4$ merely causes this isomerization to occur at a lower temperature.

Trityl tetrafluoroborate (1.0 mmol) in the absence of $TiCl_4$ reacts with TMSCN (1.0 mmol) to give the nitrile **5** (96%). This suggests that in the TMSCN reaction of benzylic halides the function of $TiCl_4$ is primarily that of cation generation.

When **4** and $TiCl_4$ were combined at −78 °C for 2.0 h in CH_2Cl_2, followed by quenching with methanol, **4** was recovered unchanged; this showed that $TiCl_4$ cannot isomerize the isonitrile at −78 °C. In contrast, when **4** was treated with $Ph_3C^+BF_4^-$ at −78 °C for 2 h and hydrolyzed with water, nitrile **5** (93%) and triphenylmethanol (91%) were secured. A reaction of TMSCN, Ph_3CCl, $TiCl_4$, and CH_2Cl_2 at −78 °C was quenched with methanol and gave methyl trityl ether; this seems to suggest that the trityl cation−titanium pentachloride anion does not react with TMSCN at −78 °C.

In conclusion, it has been shown that doubly benzylic chlorides are substituted by the cyano group with TMSCN and $TiCl_4$ in excellent yields. In addition, the dichloro substrates dichlorodiphenylmethane and **1** can be mono- or disubstituted as desired in 85−90% yields. Finally, the experiments run on trityl isonitrile can be interpreted in terms of the mechanisms proposed earlier for tertiary alkyl halides, but not as distinguishing whether the carbocation intermediate attacks the isonitrile or nitrile form of trimethylsilyl cyanide.[4b]

Experimental Section

CH_2Cl_2 was distilled over CaH_2 prior to use. Benzyl chloride, chlorodiphenylmethane, and dichlorodiphenylmethane were purified by vacuum distillation. Chlorotriphenylmethane was recrystallized from benzene−acetyl chloride. $TiCl_4$ (1.0 M in CH_2Cl_2), trimethylsilyl cyanide, and $Ph_3C^+BF_4^-$ were obtained from Aldrich Chemical Co. and used as supplied. *sym*-Tetraphenylethylene dichloride (**1**) was prepared according to the literature procedure.[2] *N*-Tritylformamide was obtained as described by Theilig and his co-workers[11] in 81% yield, mp 201−203 °C. NMR spectra were recorded on a Brucker 250-MHz FT NMR spectrometer. Infrared spectra were taken using a Perkin-Elmer Model 1320 spectrometer. Flash chromatography was performed on silica gel (230−400 mesh). Elemental analyses were done by Desert Analytics. Melting points were uncorrected.

Synthesis of 3-Chloro-2,2,3,3-tetraphenylpropanenitrile (2) (Entry 5, Table 1). General Procedure. To a solution of *sym*-tetraphenylethylene dichloride (**1**) (2.02 g, 5.0 mmol) and trimethylsilyl cyanide (0.50 g, 5.0 mmol) in 25 mL of dry CH_2Cl_2 was added $TiCl_4$ (5.0 mL, 1.0 M in CH_2Cl_2) dropwise with stirring at 0 °C. After 2.0 h, the reaction was quenched with 10 mL of CH_3OH, and the product was extracted with CH_2Cl_2. The organic layer was washed with water, 10% $NaHCO_3$ solution, and water and then dried over Na_2SO_4. The solvent was removed, and the crude product was recrystallized from acetone to afford 1.84 g (93%) of compound **2**, mp 140 °C dec. ^1H NMR ($CDCl_3$): δ 7.12−7.32 (m). ^{13}C NMR ($CDCl_3$): δ 61.26, 81.07, 122.33, 126.93, 127.18, 127.91, 128.14, 131.07, 131.63, 138.40, 142.18. Anal. Calcd for $C_{27}H_{20}NCl$: C, 82.33; H, 5.12; N, 3.56; Cl, 9.00. Found: C, 82.80; H, 5.21; N, 3.29; Cl, 8.65.

Attempted Cyanation of Benzyl Chloride. Under the above reaction conditions benzyl chloride remained inert and 90% was recovered by a bulb-to-bulb distillation.

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Cyanation of Chlorodiphenylmethane (Entry 1, Table 1). Similarly, chlorodiphenylmethane (1.01 g, 5.0 mmol) was cyanated with TMSCN (0.55 g, 5.5 mmol) and $TiCl_4$ (5.5 mmol) to give diphenylacetonitrile (0.89 g, 93% yield), mp 71–72 °C.

Cyanation of Dichlorodiphenylmethane (Entry 2, Table 1). Under the same reaction conditions, dichlorodiphenylmethane (1.19 g, 5.0 mmol) reacted with TMSCN (0.50 g, 5.0 mmol) and $TiCl_4$ (5.0 mmol) to yield α-chlorodiphenylacetonitrile (1.03 g, 91%) as a colorless oil after being purified by flash chromatography (CH_2Cl_2–hexane 1:2). The ^{13}C NMR data in the literature[12] for this compound inadvertently omitted one signal. The complete spectral data are as follows. ^1H NMR ($CDCl_3$): δ 7.36–7.38 (m, 6H), 7.54–7.58 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 63.34, 118.47, 127.07, 128.84, 129.57, 138.01; IR (neat, cm^{-1}) 2250, 1490, 1445, 1180, 829, 740, 689.

In another run, when 5.0 mmol of dichlorodiphenylmethane was treated with 11.0 mmol each of TMSCN and $TiCl_4$, a 98% yield of α-chlorodiphenylacetonitrile was obtained.

Cyanation of α-Chlorodiphenylacetonitrile (Entry 3, Table 1). A solution of α-chlorodiphenylacetonitrile (1.14 g, 5.0 mmol) and TMSCN (0.55 g, 5.5 mmol) in 25 mL of dry CH_2Cl_2 was treated with $TiCl_4$ (5.5 mL, 1.0 M in CH_2Cl_2) at 0 °C. After being stirred for 2.0 h, the reaction mixture was allowed to warm to room temperature, and stirring was continued overnight. It was then quenched with 5 mL of CH_3OH and extracted with CH_2Cl_2. The organic phase was washed with water, $NaHCO_3$ solution, and water and then dried over Na_2SO_4. Removal of the solvent and recrystallization of the crude product from CH_3OH–H_2O yielded 0.93 g of diphenylmalononitrile (85% yield), mp 83–85 °C (lit.[13] mp 87.5 °C). ^1H NMR ($CDCl_3$): δ 7.44–7.48 (m, 6H), 7.49–7.54 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 46.25, 114.73, 126.57, 129.73, 129.97, 133.56.

Cyanation of Chlorotriphenylmethane (Entry 4, Table 1). Following the general procedure, 1.39 g (5.0 mmol) of chlorotriphenylmethane and 0.55 g (5.5 mmol) of TMSCN in 25 mL of CH_2Cl_2 were treated with $TiCl_4$ (5.5 mmol). Recrystallization of the crude product from hexane yielded 1.28 g (95%) of triphenylacetonitrile (**5**), mp 127–129 °C (lit.[14] mp 127–128 °C). ^1H NMR ($CDCl_3$): δ 7.21–7.24 (m, 6H), 7.32–7.35 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 57.40, 123.41, 128.10, 128.62, 128.78, 140.19.

Cyanation of 3-Chloro-2,2,3,3-tetraphenylpropanenitrile (2) (Entry 6, Table 1). In a like manner, 1.97 g (5.0 mmol) of **2** and 0.55 g (5.5 mmol) of TMSCN in 35 mL of CH_2Cl_2 were treated with $TiCl_4$ (5.5 mmol). The reaction mixture was stirred at 0 °C for 2.0 h and another 2.5 h at room temperature, followed by methanol quenching. The crude product was recrystallized from acetic acid to afford 1.73 g (90%) of 2,2,3,3-tetraphenylsuccinonitrile (**3**), mp 219–222 °C (lit.[3] mp 222–224 °C). ^{13}C NMR ($CDCl_3$): δ 59.20, 121.09, 128.04, 128.54, 130.08, 136.99.

Dicyanation of Dichloride 1 (Entry 7, Table 1). Similarly, dichloride **1** (5 mmol) could be dicyanated with TMSCN (11.2 mmol) and $TiCl_4$ (15 mmol) to give a 54% yield of **3**.

Preparation of Trityl Isonitrile (4). A modified literature procedure[9] was used to prepare **4**. *N*-Tritylformamide (10.0 g, 34.8 mmol) in 40 mL of dry pyridine was treated with *p*-toluenesulfonyl chloride (8.25 g). The reaction mixture was stirred at room temperature for 6.0 h, and then cold water was added. After filtration, the solid was washed with water and recrystallized from hexane (or diethyl ether) to afford 4.33 g (46%) of purified **4**, mp 127–130 °C (lit.[9] mp 130–133 °C). ^1H NMR ($CDCl_3$): δ 7.22–7.24 (m, 6H), 7.31–7.43 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 74.97, 128.08, 128.25, 128.31, 141.64, 157.82.

The Reaction of 4 with $TiCl_4$ at 0 and −78 °C. To a solution of **4** (0.27 g, 1.0 mmol) in 10 mL of CH_2Cl_2 was added $TiCl_4$ (1.0 mL, 1.0 M in CH_2Cl_2) at 0 °C. After 2.0 h, the reaction was quenched with 10 mL of CH_3OH, followed by aqueous workup. Recrystallization of the crude product from hexane yielded 0.24 g (90%) of triphenylacetonitrile (**5**), mp 127–129 °C.

When the same reaction was run at −78 °C, **4** was recovered in 91% yield.

The Reaction of 4 with $Ph_3C^+BF_4^-$ at 0 and −78 °C. Trityl tetrafluoroborate (0.33 g, 1.0 mmol) was added to a solution of **4** (0.27 g, 1.0 mmol) in 10 mL of CH_2Cl_2 at 0 °C. After being stirred for 2 h, the reaction was quenched with 10 mL of cold water. The products were extracted with CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4 and concentrated. The solid residue was subjected to flash chromatography, and the following results were obtained: triphenylacetonitrile (**5**), 0.26 g, 95% yield; CH_2Cl_2–hexane 3:7; triphenylmethanol, 0.25 g, 95% yield; CH_2Cl_2–hexane 7:3.

Similarly, when the reaction was carried out at −78 °C, **5** and triphenylmethanol were isolated in 93% and 91% yields, respectively.

The Reaction of TMSCN with $Ph_3C^+BF_4^-$. TMSCN (0.099 g, 1.0 mmol) in 10 mL of CH_2Cl_2 was treated with $Ph_3C^+BF_4^-$ (0.33 g, 1.0 mmol) at 0 °C for 2 h. After aqueous workup and recrystallization from hexane, a 96% yield of **5** was obtained.

Cyanation of Chlorotriphenylmethane with TMSCN and $TiCl_4$ at −78 °C. The general cyanation procedure was followed, except that the reaction was run at −78 °C. After the reaction was quenched with 20 mL of CH_3OH, followed by aqueous workup, 1.31 g (96% yield) of methyl trityl ether was obtained (recrystallized from 95% ethanol), mp 79–81 °C (lit.[15] mp 82.6–82.9 °C).

Acknowledgment. This research was supported by the City University Faculty Research Award Program through PSC-CUNY Grant 6-63277. We gratefully acknowledge this support.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for **2**–**5**, α-chlorodiphenylacetonitrile, diphenylmalononitrile, and methyl trityl ether (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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