On the Preparation of Aryl Nitriles Using Tosyl Cyanide

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Introduction

As part of our investigation into the preparation of retrograde axonally transported fluorescent-imaging agents[1] (RATFIA), we desired an expedient method to convert aryl halides into benzonitriles.[2] The classic method is the Rosenmund synthesis which is not universally applicable because it requires empirical derivation of a unique set of reaction times and temperatures and solvents for each substrate.[3] More recent reports have dealt with the use of Pd(0)-mediated processes.[4] We needed a general aryl nitrile synthesis which could be extended to sterically hindered and oxygenated substances.

The initially reported cyanation of phenylmagnesium bromide by tosyl cyanide[5] has since been extended to aryl cyanation of lithiated imidazole,[6] vinyl cuprates,[7] and benzylzinc halides.[8] The yields with vinyl cuprates were reported to be far superior (>90%) to yields with other nucleophiles (approximately 60%). Additionally, it has been shown that "lower order" (LO) and "higher order" (HO) cyano cuprates often exhibit better selectivity and reactivity than the Gilman CuBr–Me_2S, CuI cuprate reagents, or aryllithiums.[9] In order to determine the best method for the reaction of aryl nucleophiles with electrophilic cyanide, the reactions of various aryllithium, arylcopper, diaryl cuprate, and LO and HO cyano cuprate nucleophiles with tosyl cyanide were investigated.

Results and Discussion

Preliminary reactions (Table 1) were monitored by GC–MS to select appropriate, general reaction conditions. *p*-Bromotoluene (**1a**) reactions revealed the expected nitrile (Ar-CN) and moderate amounts of oxidative coupling to biphenyl (Ar-Ar), protonation (Ar-H), and alkylation via benzyne chemistry (Ar-*t*-Bu, with undetermined regiochemistry). The ratio of cyanation to protonation was slightly higher for the phenyllithium (Ar-Li) than for the organocopper reagent (Ar-Cu). In addition, at −78 °C, both the HO and LO cyano cuprates showed a propensity toward oxidation, and all methods exhibited benzyne chemistry. The Ar-Cu and Ar-Li reagents demonstrated more efficiency than the Gilman diarylcopper lithium reagent (Ar_2-CuLi) or the HO and LO cyano cuprates.

Table 1. GC–MS Analysis of Nitrilation Methods

substrate	temp (°C)	method[a]	Ar-CN (%)	Ar-H (%)	Ar-*tert*-Bu[b] (%)	Ar-Ar (%)
1a	−78	A	95	5	trace	–
	−78	B	67	17	trace	15
	−78	C	68	17	trace	15
	−78	D	92	8	trace	–
	−78	E	71	20	trace	9
2	−78	A	70	30	–	–
	−78	B	73	18	–	9
	−78	C	46	46	–	8
	−78	D	69	31	–	–
	−78	E	51	44	–	5
3	−78	A	63	13	24	trace
	−78	B	43	22	35	trace
	−94	A	82	18	–	–
	−94	B	84	16	–	–
	−125	B	80	20	–	–

[a] A = Ar-Li prepared from Ar–Br reacted with 2 equiv of *t*–BuLi. B = HO cuprate prepared from A treated with 0.5 equiv of CuCN. C = LO cuprate prepared from A treated with 1.0 equiv of CuCN. D = Ar–Cu prepared from A treated with 1.0 equiv of CuBr–Me_2S. E = Ar-2-CuLi prepared from A treated with 0.5 equiv of CuBr–Me_2S. [b] Where peaks are detectable by expansion but below the treshold detection limit of 1%, amounts are designated as trace.

Reactions with mesityl bromide (**2**) were used to introduce a moderate amount of steric hinderance. The Ar-Li, Ar-Cu, and HO cyano cuprate were more effective than the LO cyano cuprate or the diarylcopper lithium reagents, both of which displayed unacceptable amounts of protonation to nitrilation (ca. 1:1). The Ar-Cu and Ar-Li species give similar amounts of nitrilation, but the Ar-Cu reagent requires one more experimental manipulation than the Ar-Li reagent. Moreover, the Ar-Li results are slightly better than the Ar-Cu nitrilations for the unhindered *para* toluene reagent. For these reasons, the Ar-Cu reagent was dismissed from further consideration. With the HO cyano cuprate, the ratio of cyanation to protonation was higher (ca. 3:1) as compared to both the Ar-Cu and Ar-Li (ca. 2:1) reagents. Protonation was assumed to be a potential complication for oxygenated reagents that might be mitigated by using the HO cuprates. Consequently, both the Ar-Li and HO cuprate reagents were carried on to the subsequent reactions.

The 2-(3-bromophenyl)-1,3-dioxolane compound (**3**) was used as a representative oxygenated substrate. These reactions demonstrated a marked change in the product distribution. The protonation pathway, while still significant, was no longer the major competitive process. Rather, there was a pronounced increase in benzyne chemistry, presumably accelerated by preferential coordination of the alkyllithium base with dioxolane oxygens. The sensitivity of cyanocuprate chemistry to temperature[10] and the intrusion of benzyne products mandated examination of lower reaction temperatures. Reactions

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Table 2. Nitrilation Results of Aryllithium Substrates

compd	product[a]	yield[b]	mp (°C)	IR[c]
1a	*p*-tolunitrile	65	oil	2227
1b	*m*-tolunitrile	71	oil	2228
1c	*o*-tolunitrile	78	oil	2223
2	2,4,6-trimethylbenzonitrile	75	50–52	2219
3	2-(3-cyanophenyl)-1,3-dioxolane	66	oil	2230
4	2,5-di-*tert*-butylbenzonitrile	50	62.5–63.5	2223
5	2,4,6-tri-*tert*-butylbenzonitrile	34	147–148	2212
6a	*p*-methoxybenzonitrile	65	59.5–61.5	2229
6b	*m*-methoxybenzonitrile	76	oil	2231
6c	*o*-methoxybenzonitrile	58	oil	2228
7	4-(methylthio)benzonitrile	65	62.5–64.5	2222
8	2-cyanothiophene	59	oil	2221

[a] The characterization of commercially available products (**1a–c** and **6–8**) by MS and ^{1}H NMR was routine. The characterization of other products (**2–5**) is described in the Experimental Section. [b] Yields are reported for chromatographically pure materials. [c] IR data for the CN bond are reported in cm^{-1}.

were run in THF at −78 °C and −94 °C and in 2-methyltetrahydrofuran at −125 °C. The use of lower temperatures is known to be superior for "kinetically" formed mixed HO cyano cuprates to prevent scrambling of the ligands. Additionally, the structure of the complex, while still debatable,[11] has been shown to be different at lower temperatures.[10] This structural difference in the composition of the cuprate matrix apparently has a limited effect on the nucleophilicity of the reagent with tosyl cyanide.

At −94 °C, the benzyne pathway is excluded for both reagents. While the HO cyano cuprate did give a slightly larger percentage of nitrilation at lower temperatures, the extra handling required in the use of the HO cyano cuprate is not adequately compensated for with an increased degree of nitrilation. The results point to the use of the aryllithium nucleophile at −94 °C, as the most expedient, general method. As has been previously reported,[10] we found that fresh *tert*-butyllithium was required for reproducible HO cyano cuprate chemistry and for aryllithium chemistry. Older *tert*-butyl lithium from bottles that have been penetrated more than five times results in a higher percentage of protonation with respect to nitrilation.

Numerous alkylated and oxygenated substrates were prepared utilizing this methodology. The results (Table 2) indicate the general applicability of the procedure. Of particular note are the reactions involving 2,5-di-*tert*-butylbromobenzene and 2,4,6-tri-*tert*-butylbromobenzene.[12] GC–MS analysis of the crude di-*tert*-butylbromobenzene cyanation reaction indicated 70% nitrilation (**4**) and 30% protonated material. The tri-*tert*-butylbromobenzene initially resulted in 52% product (**5**) and 43% protonation. The latter compound offers a severe test for steric hinderance in the nitrilation process with only a 2.5 Å clearance between the nitrile and closest *tert*-butyl group.[13]

The effect of steric compression on the IR frequency of the nitrile stretch,[14a] is confirmed and extended in this study. In a separate account,[14b] the trend in IR data is not apparent, with reported frequencies of 2220 cm^{-1} for 2-*tert*-butylbenzonitrile, 2200 cm^{-1} for 2,4-di-*tert*-butyl- and 2,6-di-*tert*-butylbenzonitriles, and 2280 cm^{-1} for 2,4,6-tri-*tert*-butylbenzonitrile. The contradictory data are recorded as mull suspensions, while the confirmatory data are recorded in $CDCl_3$ solutions. To exclude the possibility of a strong lipophilic interaction in the mull of these arenes that might perturb the steric effect, we ran two IR's (**4** and **5**) in mull using white paraffin oil and obtained the same values as reported for KBr pellet.

Conclusion

After various alternatives were invesetigated, it was concluded that the reaction of Ar-Li with tosyl cyanide at −94 °C was the most efficient and expedient methodology of those investigated for the nitrilation of aryl halides. In general, cyano aryl cuprates gave slightly lower product formation and required more experimental manipulation. The nitrilation of aryllithiums is applicable with a wide variety of substrates and should prove to be a reliable method.

While the origin of the observed steric effect on alkylated benzonitriles is still unresolved, the presence of the effect is substantiated. This may prove useful as a complimentary tool for probing the structure of the active site of proteins.[15] The correlation shows that a single ortho alkyl substituent (**1c**), even a *tert*-butyl group (**4**), lowers the frequency by about 5 cm^{-1}, while sandwiching the nitrile between two methyls (**2**) reduces the frequency by nearly 10 cm^{-1}, and squeezing the nitrile between two *tert*-butyls (**5**) lowers the frequency by 15 cm^{-1}. In comparison, the nitrile appears to be less sensitive to electronic effects. Electronic effects of the methoxy group do not vary significantly among the *ortho* (**6c**), *meta* (**6b**), or *para* (**6a**) isomers, but the electronic effect of a sulfur with the nitrile (**7** and **8**) does lower the frequency by about 5 cm^{-1}.

Experimental Section

Unless otherwise stated, all chemicals are commercially available. Melting points were determined on a Mel-Temp or Fisher-Johns apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian 400XL FT-NMR using $CDCl_3$ with TMS as an internal standard and a secondary reference to trace $CHCl_3$ in $CDCl_3$ at 2907.5 Hz. IR spectra were recorded on a Mattson Polaris FT-IR. GC analysis was performed on a Hewlett-Packard Series II 5890 GC fit with a 15 m J&W DB-5 0.2 mm × 0.33 μm column using a HP 5971A mass selective detector and a HP 7673 auto injector. Sample preparation for GC–MS was 2 mL of solvent per 0.01 g of analyte. Most compounds were purified by preparative HPLC and then analyzed for purity on an analytical HPLC, Waters Millennium HPLC system (600E pump, PDA detector, 717 Autosampler, radial compression cartridges, 10 × 100 mm analytical/1.5 mL per minute, 40 × 100 mm prep/27 mL per minute). Normal phase HPLC was performed on μPorasil. Reverse phase HPLC was performed on μBondapak. Short path distillations were performed on a Kugelrohr apparatus. A Firestone[16] valve with mineral oil was used to maintain inert atmospheres. All glassware and cannula were oven dried (48 h at 120 °C) and then flame dried under a positive pressure of argon passed through a tower of copper wire. All reaction vessels were repetitively (2–3 times) evacuated (0.5 mmHg) and

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charged with argon. THF and 2-methyletrahydrofuran were freshly distilled from sodium/benzophenone under Ar prior to use. Yields are reported as isolated chemical yields of purified materials based on the average of at least two runs.

Representative Nitrilation Procedure

The aryl bromide (2.5 mmol) and THF (6 mL) are added by syringe to a 25 mL round bottom flask under positive argon. The magnetically stirred solution is cooled to −94 °C (internal temperature) in a liquid N_2/hexanes slush bath, at which time fresh *tert*-butyllithium (3.0 mL, 1.7 M in hexanes, 2.0 equiv) is added slowly by syringe. The solution is maintained at −94 °C for 30 min. To a dried, 50 mL, three-neck round bottom flask is added tosyl cyanide (0.90 g, 5.0 mmol, 2.0 equiv) and dry THF (11 mL) under positive argon. The TsCN flask is magnetically stirred and cooled to an internal temperature of −94 °C. The Ph−Li solution is then transfered by cannula into the TsCN solution. Subsequently, the reaction mixture is allowed to come to room temperature, at which time the reaction is quenched with concentrated NH_4OH (3 mL) and the mixture stirred for 15 min. The mixture is then poured into 1 M NaOH (150 mL) and extracted with ether (3 × 50 mL), washed with brine (1 × 25 mL), and dried with $MgSO_4$. Products are purified and characterized as described below. Characterization of commercially available compounds by GC−MS, FT-IR, and NMR was routine. Pertinent characterizations for the remaining compounds are provided.

Each of the following compounds was purified as indicated by normal phase HPLC and subsequently found by analytical HPLC and GC to be greater than 98% pure: *m*-tolunitrile (**1b**), *o*-tolunitrile (**1c**), *o*-methoxybenzonitrile (**6c**), and 2,4,6-trimethylbenzonitrile (**2**) with 50% CH_2Cl_2:hexanes; *p*-tolunitrile (**1a**) with 15% EtOAc:hexanes; *m*-methoxybenzonitrile (**6b**) with 10% EtOAc:cyclohexane; *p*-methoxybenzonitrile (**6a**) with 15% EtOAc:cyclohexane; 4-(methylthio)benzonitrile (**7**) with CH_2Cl_2. 2,5-Di-*tert*-butylbenzonitrile (**4**) and 2,4,6-tri-*tert*-butylbenzonitrile (**5**) were purified by preparative reverse phase HPLC with 15% MeOH:water and subsequently found by analytical HPLC and GC to be greater than 98% pure. 2-cyanothiophene (**8**) was purified by flash chromatography with 15% EtOAc:hexanes and subsequently found by analytical HPLC and GC to be greater than 98% pure. 2-(3-cyanophenyl)-1,3-dioxlane (**3**) was purified by short path distillation 125 °C/0.5 mmHg or by normal phase HPLC in 15% EtOAc:cyclohexane with comparable efficieny and subsequently found by analytical HPLC and GC to be greater than 98% pure.

2,4,6-Trimethylbenzonitrile[17] (**2**): mp 50−52 °C; IR 2219 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.48 (s, 6H), 6.93 (br s, 2H).

2-(3-Cyanophenyl)-1,3-dioxolane[18] (**3**): bp 125 °C/0.5 mmHg. MS (relative intensity) *m*/*z* 176 (3), 175 ($[M]^+$ 33), 174 (100), 144 (18), 130 (42), 103 (23), 102 (26), 73 (61); ^1H NMR ($CDCl_3$) δ 4.10 (m, 4H), 5.83 (s, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.66 (td, J = 7.8, 1.5 Hz, 1H), 7.71 (td, J = 7.8, 1.5 Hz, 1H), 7.80 (t, J = 1.5 Hz, 1H). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.42; H, 5.21; N, 7.94.

2,5-Di-*tert*-butylbenzonitrile[14a] (**4**): mp 62.5−63.5 °C. IR 2223 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.50 (s, 9H), 7.39 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 8.5, 2.3 Hz, 1H), 7.66 (d, J = 2.3 Hz, 1H).

2,4,6-Tri-*tert*-butylbenzonitrile[3b,14] (**5**): mp 147−148 °C. IR 2212 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.57 (s, 18H), 7.38 (s, 2H).

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Additions and Corrections

Vol. 54, 1989

Philip Hughes* and Jon Clardy. Total Synthesis of 3(*S*)-Carboxy-4(*S*)-hydroxy-2,3,4,5-tetrahydropyridazine, an Unusual Amino Acid Constituent of Luzopeptin A.

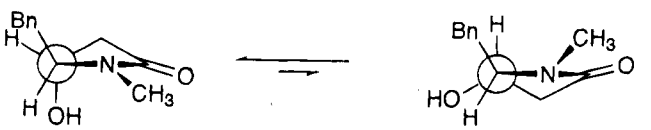
Page 3260. The optical rotation for the title compound **2** was incorrectly reported to be minus. The rotation of **2** should have been reported as $[\alpha]^{25} = +57.5°$ (c = 53 mg/mL, MeOH).

JO954004B

Vol. 59, 1994

Klemens Stratmann, David L. Burgoyne, Richard E. Moore,* Gregory M. L. Patterson, and Charles D. Smith. Hapalosin, a Cyanobacterial Cyclic Depsipeptide with Multidrug-Resistance Reversing Activity.

Page 7222. Since **5a** is the major conformer and **5b** is the minor conformer, the arrows in the equation should be reversed as follows.



5a **5b**

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