

Arylthio-Metal Exchange of α -Arylthioalkanenitriles

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Supporting Information

ABSTRACT: The addition of BuLi, Bu₃MgLi, Et₂ZnBuLi, or Me₂CuLi to α arylthioalkanenitriles triggers an arylthio-metal exchange. NMR spectroscopic Ar-S analyses implicate organometallic attack on sulfur forming a three-coordinate sulfidate as the key intermediate. Electrophilic trapping affords tertiary and quaternary nitriles in high yield. The method addresses the challenge of improving the functional group tolerance and preventing polyalkylations.



etalated nitriles are powerful nucleophiles ideally suited for sterically demanding alkylations.¹ The exceptional nucleophilicity originates from the nitrile's small cylindrical diameter² and the high charge density on the formally anionic carbon.³ The combination of small steric demand⁴ and high nucleophilicity permits challenging alkylations even in cases where comparable enolate alkylations are unsuccessful.⁵

Deprotonating alkanenitriles 1 with lithium amide bases generate N-lithiated nitriles 2 in which the nitrile nitrogen is coordinated to lithium (Scheme 1).¹ A complementary





approach to metalated nitriles employs an exchange with a substituted nitrile 4, which allows selective generation of Nmetalated nitriles 2 or C-metalated nitriles 5. Organometallic addition to α -haloalkanenitriles⁶ (4, Y = Cl, Br, I) or α sulfinylnitriles⁷ (4, Y = PhSO) provides N- or C-metalated nitriles even in the presence of acidic esters, enoates, and nitriles.⁷ Despite the versatility of exchange-based syntheses of metalated nitriles, several challenges remain: greater precursor stability, improved functional group tolerance, and increased organometallic diversity.

Arylsulfides are attractive exchangeable groups because arylsulfides are readily manipulated, tolerate numerous reagents, and readily exchange with organometallics.⁸ Arylsulfides first served as organometallic precursors in the serendipitous attack of NaSPh on a phenylthio ketone,⁹ and were subsequently used to generate lactone enolates not accessible by conventional metal amide deprotonation.¹⁰ Until

recently¹¹ the development of arylsulfide-based exchange reactions stalled, perhaps because preferential attack of the organometallic on resident functionality can circumvent the exchange.12

Arylthioalkanenitriles are attractive metalated nitrile precursors¹³ because deprotonation is facile,¹⁴ unlike sulfinylni-triles¹⁵ they do not readily eliminate, and many are commercially available or easily synthesized.¹⁶ Exploratory foravs employed arylthioalkanenitriles 7 that were readily prepared by double alkylation of arylthioacetonitriles 6 (Scheme 2) or by sulfenylation of the corresponding



Ar_s 6 CN R ¹ X; R ² X	ArS CN R ¹ R ² 7	LDA; R ¹ (ArS) ₂ F	CN ⁷² 8
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alkanenitrile 8. These two strategies readily provided fourthrough six-membered phenylthio-, o-methoxyphenylthio-, and 2-pyridinethiocarbonitriles.

Initial sulfide-metal exchange reactions employed phenylthiocyclohexanecarbonitrile (7c) as a prototype because sixmembered nitriles feature in mechanistic studies¹⁷ and are a key motif in several nitrile containing pharmaceuticals.¹⁸ Although 7c did not react with *i*-PrMgCl, even after 12 h at rt, BuLi caused a complete exchange at -78 °C in less than 5 min. Trapping the intermediate with benzyl bromide affords the quaternary nitrile 3c in 98% yield (Figure 1). Presuming that the successful exchange with BuLi stems from an increased nucleophilicity relative to *i*-PrMgCl, the phenylthionitrile 7c was treated with the magnesiate Bu₃MgLi derived from Bu₂Mg and BuLi.¹⁹ Minimal exchange occurs at -78 °C, but warming to room temperature allowed complete exchange after 1 h. Cooling the reaction to -78 °C and addition of benzyl bromide gave nitrile 3c in 86% yield.

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Figure 1. Sequential PhS-lithium exchange alkylation. ^{*a*} An 86% yield was obtained when the exchange was performed with Bu₃MgLi.

Upon adopting BuLi as the optimal organometallic, a series of phenylthioacetonitriles were subjected to the exchange and alkylated with an array of electrophiles (Figure 1). Sequential exchange-benzylations with four-, five-, and six-membered phenylthioalkanenitriles afforded the benzyl-substituted nitriles 3a-c in uniformly excellent yield. Using the phenylthionitrile 7c as a prototype and varying the electrophile allowed alkylations with reactive alkylbromide and carbonyl electrophiles (3d-f) as well as with less reactive propyliodide (3g).

Modulating the electronic environment of the aryl sulfide does not influence the exchange—alkylation efficiency. Sequential treatment of the electron-rich 2-methoxyphenylsulfide 7d with BuLi and BnBr gave nitrile 3c in 91% yield (eq 1), virtually the same yield as the phenyl sulfide (98%, Figure 1), together with sulphide 9a.



Exchange–alkylations with the electron-deficient 2-pyridinethiocarbonitriles are particularly efficient (Figure 2). Sequential treatment of 2-pyridinethiocarbonitriles with BuLi and alkyl halide or carbonyl electrophiles efficiently installs quaternary centers in 3c and 3i-l.

Mechanistically, adding BuLi to an arylthioalkanenitrile could trigger an $S_N 2$ type displacement passing through a tricoordinate sulfur as a transition state or as a discrete intermediate (Scheme 3). Insight into the mechanism was obtained by acquiring ¹³C NMR spectra from a -78 °C, THF solution of 7c to which BuLi was added. Particularly revealing is the signal for the nitrile carbon because the chemical shift is







Figure 2. Sequential ArS-lithium exchange alkylation. ^{*a*} The reaction was allowed to warm to rt over 2 h prior to addition of NH₄Cl. Addition of NH₄Cl at -78 °C affords 3l (36%) and the uncyclized isomer (49%).

diagnostic for the coordination mode: *N*-lithiated nitriles resonate downfield $(\delta = 142-164)^{20}$ whereas *C*-metalated nitriles typically resonate upfield $(\delta = 120-140)$.²¹ The addition of BuLi to 7c generates a signal for the nitrile carbon at $\delta = 128.9$, significantly upfield from that of lithiated cyclohexanecarbonitrile (2c, $\delta = 163.6$),²² and consistent with formation of sulfidate **10c**.

The efficiency of the exchange–alkylation of 7c with propyl iodide to afford 3g in 87% yield (Figure 1) suggests that the alkylation does not proceed through the sterically congested sulfidate 10c. Although the sulfidate is the major solution species, an equilibrium may exist with a small fraction of the more nucleophilic lithiated nitrile 2c from which alkylation occurs. The existence of an equilibrium between the sulfidate and an N-lithiated nitrile was probed by preparing the lithiated cyclohexanecarbonitrile 2c (Scheme 3) and adding butylphenylsulfide. The diagnostic nitrile carbon signal at $\delta = 163.6$ in 2c shifts upfield to $\delta = 128.3$, close to the normal range for neutral cyclohexanecarbonitriles ($\delta = 118-127$).²³ Consistent with the rapid sulfidate-N-lithiated nitrile equilibration is the loss of configuration at the nitrile-bearing stereocenter during the exchange and benzylation of the norbornene carbonitrile diastereomers 7f and 7g which converge to a single stereoisomer 3h (eq 2).

A series of competitive sulfide exchanges were performed to determine the relative exchange rates of phenylthio, 2-pyridinethio, and 2-methoxyphenylthio substituents.²⁴ The exchange rate decreases in the order 2-pyridylsulfide > *ortho*-methoxyphenylsulfide > phenylsulfide. Chelation of BuLi to the pyridine nitrogen²⁵ or the methoxy oxygen is likely responsible for the rate acceleration, rather than electronic effects, because the pyridinethionitriles are electron deficient relative to the phenylthionitriles, whereas 7d is electron rich.

With the propensity of pyridylsulfides toward exchange discovered, a series of organometallics were screened and Bu₃MgLi was identified as the optimal reagent for the

exchange.²⁴ Acyclic and cyclic 2-pyridinethiocarbonitriles exchange equally well, and the exchange–alkylation is effective in generating the *alkene*nitrile **3q** (Figure 3). Exchange–



Figure 3. 2-Pyridinethionitrile exchange—alkylation. ^{*a*} The yield was 92% when the exchange was performed with BuLi, and butyl(2-pyridyl)sulfide was isolated in 96% yield. ^{*b*} A yield of 82% was obtained from the diastereomeric nitrile.

benzylations with the diastereomeric norbornene carbonitriles **7f** and **7g** converge to the same carbonitrile **3h**, indicating that the intermediate magnesiated nitrile is configurationally labile. The piperidinecarbonitrile **3k** is readily generated from the acylation with methyl cyanoformate. An analogous alkylation with benzyl bromide affords the quaternary nitrile **3i** in 54% yield accompanied by 32% of the nitrile resulting from exchange and protonation. Evidently the reactivity of the intermediate magnesiated nitrile is diminished, at least in this case, relative to the corresponding lithiated nitrile (cf. Figure 2).

Particularly remarkable are the exchange reactions with nitriles 7m-7p (Figure 3, lower quadrant). Secondary nitriles 7m and 7n, bearing a relatively acidic methine proton, efficiently undergo an exchange–alkylation forming tertiary nitriles 3t and 3u without overalkylation. Bu₃MgLi-induced exchange with nitrile 7o generates a magnesiated nitrile that

does not cyclize onto, or eliminate adjacent to, the pendant chloride $(70 \rightarrow 3v)$. An analogous exchange-acylation, $7p \rightarrow 3w$, proceeds smoothly at the tertiary carbon without interference from the pendant nitrile, despite the ease with which metalated nitriles can equilibrate.²⁶

The facile pyridinethio-magnesium exchange stimulated a search for an exchange with less reactive organometallics. Although BuZnCl·LiCl and Bu₂Zn·LiCl do not react with 7e, a clean exchange occurs in 5 min at 0 °C with $Et_2ZnBuLi$.²⁷ An analogous exchange with $Et_2ZnBuLi$ ·LiCl did not proceed cleanly. The zincated nitrile derived from 7e smoothly alkylates propyliodide and propylene oxide to afford 3g and 3x, respectively (Scheme 4).



Despite there being scant precedent for arylthio-cuprate exchange,²⁸ Bu₂CuLi triggers a complete exchange of 7e within 5 min at 0 °C. In a preparative experiment, trapping the copper intermediate generated from 7e with allyl bromide very efficiently affords 3y (Scheme 4). The analogous copper exchange with piperidinecarbonitrile 7h generates a cuprated nitrile that acylates methyl cyanoformate to afford 3k.

 α -Arylthioalkanenitriles engage BuLi, Bu₃MgLi, BuMgCl, Et₂ZnBuLi, and even Me₂CuLi in a highly unusual arylthiometal exchange. NMR analysis suggests formation of a sulfidate in equilibrium with a small fraction of the corresponding lithiated nitrile. Trapping the metalated intermediates efficiently affords tertiary, quaternary, and alkenenitriles even in the presence of relatively acidic and electrophilic functionality. The arylthio-metal exchange reactions of α -arylthioalkanenitriles address several long-standing challenges with metalated nitriles: selective access to N- or C-metalated nitriles, functional group tolerance, and the formation of tertiary nitriles without polyalkylation.

ASSOCIATED CONTENT

Supporting Information

¹H and ¹³C NMR spectra and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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