Quaternary Carbon Centers

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Nitrile Alkylations through Sulfinyl–Metal Exchange**

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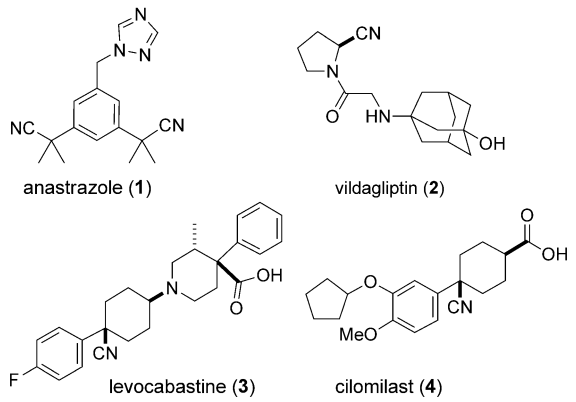
Nitriles play pivotal roles in a diverse range of pharmaceuticals.[1] The nitrile pharmacophore often engages in key hydrogen bonding, as in the blockbuster drug anastrazole (**1**),[2] in other cases a covalent attachment occurs, as in the anti-diabetic vildagliptin (**2**, Scheme 1).[3] Syntheses of many nitrile-containing pharmaceuticals, particularly of those bearing quaternary centers, such as anastrazole[1] and the cyclohexylnitriles levocabastine (**3**)[4] and cilomilast (**4**),[5] typically involve multiple alkylations.



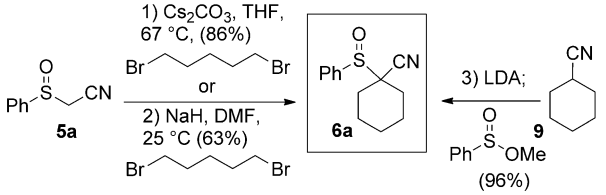
Scheme 1. Representative nitrile-containing pharmaceuticals.

Most alkylations of nitriles employ alkyllithium or metal amide bases,[6] in these cases, monoalkylation is often complicated by overalkylation.[7] A conceptually appealing solution for multiple controlled alkylations of acetonitrile includes two sequential alkylations of an activated acetonitrile (**5**→**6**) with a mild base followed by a functional group/metal exchange alkylation (**6**→**7**→**8**, Scheme 2). The execution of this strategy would allow three consecutive alkylations, require only one equivalent of strong base, and install quaternary centers, as can be found in numerous nitrile-containing pharmaceuticals.

Metal-exchange reactions[8] usually employ halides,[9] trialkylstannanes,[10] or sulfoxides[11] as transferrable precursors. Recently reported halogen–metal exchange reactions of bromo-, iodo-,[12] and even chloronitriles[13] with organolithium and Grignard reagents allow the selective generation of N-lithiated and C-magnesiated nitriles, respectively. Conceptually, an analogous sulfinyl–metal exchange[14] represents a significant advance by avoiding the aggressive reagents typically required for the synthesis of halonitriles, allowing the performance of two alkylations with mild base, and introducing a greater functional-group tolerance.

Scheme 2. Multiple alkylations of an acetonitrile trianion equivalent. M = metal.

Access to the symmetrical sulfinylnitrile **6a** was achieved by two complementary alkylations[15] of phenylsulfinylacetonitrile[16] (**5a**; Scheme 3, conditions 1 and 2). In each case, 1,5-dibromopentane was used as a prototypical bis-electrophile



Scheme 3. Complementary routes 1, 2, and 3 to sulfinylnitrile **6a**. DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamine, THF = tetrahydrofuran.

because the resulting nitrile **6a** contains the core cyclohexylnitrile motif embedded within several nitrile-containing pharmaceuticals (see **3** and **4** in Scheme 1). Heating **5a** and 1,5-dibromopentane with Cs_2CO_3 to reflux in THF smoothly provides **6a**, whereas the use of NaH in DMF allows the analogous alkylation at ambient temperature. Alternatively, the sulfinylnitrile **6a** can be prepared by sulfinylating nitrile **9** with methyl phenylsulfinate.[17] Sequential alkylation and oxidation of phenylthioacetonitrile provides another versatile route to sulfinyl nitriles that is ideal for nonsymmetrical substrates (see the Supporting Information for details).[18]

The sulfinyl–metal exchange of **6a** is remarkably facile. *i*PrMgCl triggers a rapid exchange that is complete within 5 minutes at −78 °C.[19] In sequential sulfinyl–magnesium exchange alkylations, quaternary centers are efficiently installed by the reaction of the magnesiated nitriles with a diverse range of electrophiles (Table 1). Carbonyl-containing ketone, ester, and acid chloride electrophiles all acylate

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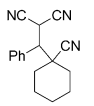
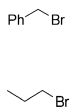
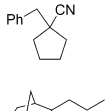
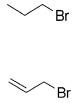
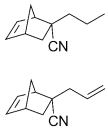
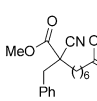
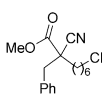
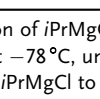
Table 1: Sulfinyl-exchange alkyations of nitriles **6**.[a]

Entry	Sulfinylnitrile	Electrophile	Quaternary nitrile	Yield[a] [%]
1	**6a**		**8a**		92[b]
2	**6a**		**8b**		91[b]
3	**6a**		**8c**		90[b]
4	**6a**		**8d**		77
5	**6a**		**8e**		92[b]
6	**6a**		**8f**		90
7	**6a**		**8g**		91
8	**6a**		**8h**		92
9	**6b**		**8i**		93
10	**6c**		**8j**		99
11	**6d**		**8k**		90
12	**6e**		**8l**		92
13	**6e**		**8m**		96
14	**6f**		**8n**		94
15	**6g**		**8o**		94[b]
16	**6h**		**8p**		91[b]
17	**6i**		**8q**		92[b]

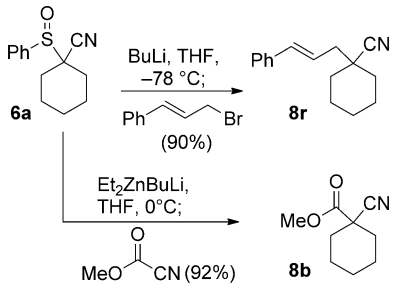
[a] Reactions performed by sequential addition of *i*PrMgCl and electrophile to a solution of sulfinyl nitrile in THF at −78 °C, unless otherwise noted. [b] Reaction performed by addition of *i*PrMgCl to a solution of electrophile and sulfinyl nitrile in THF at −78 °C.

magnesiated nitriles efficiently (Table 1, entries 1–3 and 15–17). Diphenyldisulfide (Table 1, entry 4), alkyl halides (entries 5–6 and 9–14), and benzylidene malononitrile (entry 8) similarly provide high yields in nucleophilic alkylations of nitriles.

Cyclic (Table 1, entries 1–13) and acyclic sulfinylnitriles (entries 14–17) engage in sulfinyl exchange alkylations with essentially the same efficiencies. The alkylation with isopropyl iodide is particularly interesting because the exchange installs vicinal tertiary–quaternary centers in 90% yield (Table 1, entry 6). Unlike lithiated nitriles, the magnesiated nitrile derived from **6a** alkylates propylene oxide to afford hydroxynitrile **8g** without any observable formation of the lactone that results from internal cyclization (Table 1, entry 7).[20]

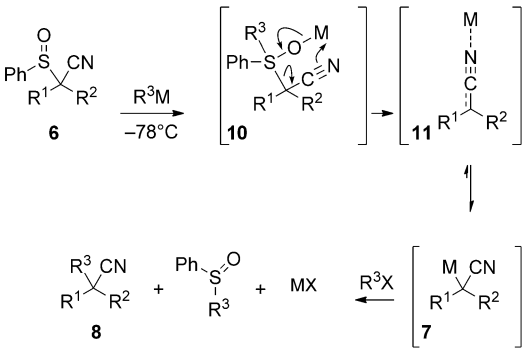
The sulfinyl–magnesium exchange is remarkably tolerant toward functional groups. Addition of *i*PrMgCl to a solution of methyl cyanoformate and the ester-containing sulfinyl nitrile **6g** (Table 1, entry 15) affords the bisester nitrile **8o** in 94% yield without observable intramolecular or intermolecular deprotonation or addition to the ester functionality. The selective generation of a magnesiated nitrile in the presence of an enolizable carbonyl functionality is highly unusual.[21] The sulfinyl–magnesium exchange of bisnitrile **6h** similarly allows the selective formation and acylation of a magnesiated nitrile in the presence of a potentially acidic alkylnitrile (Table 1, entry 16). The incorporation of a remote chloride within nitrile **6i** does not interfere with the exchange alkylation, despite the potential for intramolecular alkylation or elimination (Table 1, entry 17). Functional-group tolerance is further demonstrated by several in situ exchange alkylations in which *i*PrMgCl is added to a solution of the sulfinyl nitrile and the electrophile in THF at −78 °C (Table 1, entries 1–3, 5, and 15–17). A premature reaction of *i*PrMgCl and the electrophile was not observed in any case.

The sulfinylnitrile **6a** readily engages in sulfinyl–metal exchanges with other organometallic compounds (Scheme 4). Sequential addition of BuLi and cinnamyl bromide efficiently generates the alkylated nitrile **8r** via a lithiated nitrile intermediate. Lithium butyldiethylzincate[22] triggers a sulfoxide–metal exchange to form a putative zincate that acylates methyl cyanoformate to afford ester nitrile **8b** (Scheme 4). The isolation of both phenylbutylsulfoxide and phenylethylsulfoxide from the reaction indicates that either alkyl group of the zincate can initiate the exchange.



Scheme 4. Sulfinyl–lithium and sulfinyl–zinc exchange reactions.

The exchange is presumed to occur via the sulfurane **10** (Scheme 5). Prior mechanistic studies of related exchange processes demonstrate sulfoxide inversion,[23] which is consistent with an initial complexation between magnesium and the sulfoxide oxygen atom, followed by an invertive attack on the sulfur atom.[24] The interaction between the metal and the nitrile in sulfurane **10** might transfer the metal from the oxygen to the nitrogen atom with a minimal build-up of charge. During the exchange with BuLi, the N-lithiated nitrile **11** would form directly from sulfurane **10**. The analogous exchange with *i*PrMgCl requires a rapid "conducted tour"[25] equilibration from the N-magnesiated nitrile **11** (M = MgCl) to the C-magnesiated nitrile **7** (M = MgCl). Consistent with this sequence, near-quantitative isolation of *i*PrSOPh is observed in all the exchange procedures employing *i*PrMgCl. Alkylation products derived from this sulfoxide were not observed despite the presence of acidic protons in *i*PrSOPh.



Scheme 5. Sulfinyl–metal exchange mechanism.

Sulfinylnitriles readily exchange with Grignard reagents, organolithium reagents, and zincates in highly efficient metalation–alkylation sequences. The requisite sulfinylnitriles are prepared by several routes, which include the consecutive alkylation of phenylsulfinylacetonitrile with Cs_2CO_3; this route avoids the use of strong base typically required in alkylations of alkane nitriles. The sulfinyl–magnesium exchange is remarkably tolerant toward functional groups and allows alkylations with ester-, nitrile-, and chloro-substituted sulfinyl nitriles without competitive addition or deprotonation. A diverse range of electrophiles efficiently installs quaternary centers as found in numerous cyclohexylnitrile-containing pharmaceuticals. The sulfinyl–metal exchange is rapid and allows sequential alkylations of acetonitrile equivalents under very mild conditions.

Experimental Section

General deprotonation–alkylation procedure: A solution of the Grignard reagent (1.05 equiv) in THF was added to a stirred solution of the sulfinyl nitrile **6** in THF at −78 °C. After 5 minutes, neat electrophile (1.0 equiv) was added to the mixture, the reaction was allowed to warm to room temperature, and a saturated aqueous solution of NH_4Cl was added. The crude product was extracted with EtOAc, dried over $MgSO_4$, concentrated, and purified by radial chromatography (EtOAc/hexanes) to afford analytically pure material.

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