Metallation and Reaction of 4,5-Dicyanoimidazoles with Alkyllithium Reagents

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The conditions required for selective lithiation at the 2-position of 4,5-dicyanoimidazoles are described in detail. The course of the reaction of alkyllithium reagents with 4,5-dicyanoimidazoles depends on the temperature, the number of equivalents of alkyllithium and whether the 1-nitrogen is protected. Under certain circumstances, the alkyllithium reagent adds to one of the cyano groups giving cyanoimidazole ketones.

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Numerous examples of the metallations of imidazoles have been reported and reviewed [1]. We have recently reported on the copper(II) chloride promoted coupling reactions of 1-methyl-, 1-methoxymethyl-, and 1-benzyl-2-lithio-4,5-dicyanoimidazoles. These coupling reactions provide a novel route to derivatives of 4,4',5,5'-teracyano-2,2'-biimidazole [2]. Previously, there were no reports in the literature on the metallations of 4,5-dicyanoimidazoles or 1-protected-4,5-dicyanoimidazoles.

In this paper, we describe, in detail, the reactivity of alkyllithium reagents towards 4,5-dicyanoimidazoles, the conditions required for selective lithiation at the 2-position of 4,5-dicyanoimidazoles and the synthesis of new cyanoimidazole ketones by the reaction of alkyllithium reagents with one of the cyano groups.

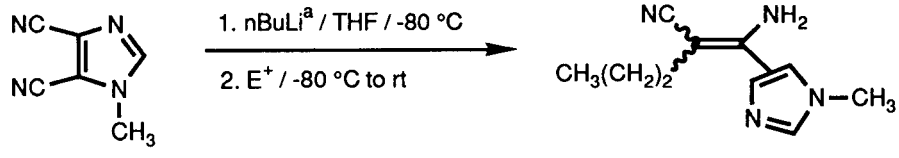
Results and Discussion.

Our initial strategy was to metallate directly at the 2-position (or C-2) of 1-protected-4,5-dicyanoimidazoles using *n*-butyllithium. First, protection of the 1-position of 4,5-dicyanoimidazole was necessary and was easily accomplished by methylation using dimethylsulfate or methyl iodide with triethylamine in tetrahydrofuran [2,3]. Addition of 1-methyl-4,5-dicyanoimidazole (**1**) to a solution of one equivalent of *n*-butyllithium (normal addition) in tetrahydrofuran at -80° followed by introduction of an electrophile gives several products. A major product comes from addition of *n*-butyllithium to a cyano group of **1** followed by an unusual rearrangement. No incorporation of the electrophile was observed. The structure of the product is shown (eq. 1).

The enaminonitrile **2** could have four possible regioisomeric configurations; a 4- or 5-(1-methylimidazole) and a *Z*- or *E*-configuration for the C=C bond of the enaminonitrile. Only one isomer of **2** was present (as determined by chromatography). The infrared and nmr data are consistent with reaction of *n*-butyllithium with a cyano group of **1** followed by a rearrangement to give the enaminonitrile **2**. The infrared spectrum of **2** shows N-H stretching bands at 3431 and 3330 cm^{-1}. The cyano group stretching band, at 2173 cm^{-1}, is consistent for a cyano group in conjugation with an amine. The stretching band of the enamine is at 1633 cm^{-1}. Almost identical wave numbers have been found for these stretching bands in other enaminonitriles [4]. The pmr spectrum of **2** clearly shows a *propyl group* and *two aromatic protons*. The cmr shows ten carbons (four in the aliphatic region) and mass spectrometry gives the expected molecular ion peak at m/z 190. Although this appears to be a novel rearrangement, cyclization of lithiated nitriles to form enaminonitriles has been reported [5].

Since normal base addition gives rearranged products, alternative modes of base addition were investigated. Addition of *n*-butyllithium to a solution of **1** in tetrahydrofuran (inverse addition) at -80° did not give **2**, nor did it give clean metallation at C-2. Mixtures of products were recovered upon reaction with electrophiles. As a control experiment, addition of *n*-butyllithium to **1** at -80° gives significant amounts of ketone **3** even after low temperature quenching (Scheme I, eq. 2). This suggests that nucleophillic attack of *n*-butyllithium on a cyano group is competitive with deprotonation at C-2 even when **1** is

(eq. 1)



1 **2** (26%)

[a] Normal addition of **1** to a solution of nBuLi in THF at -80 °C.

present in excess. No regioisomer assignment has been made for the cyanoimidazole ketone **3**.

Deprotonation of **1** using non-nucleophillic bases such as lithium diisopropylamide in tetrahydrofuran at -80° gives the anion at C-2 (not shown). A metal/halogen exchange reaction between *n*-butyllithium and 1-methyl-2-bromo-4,5-dicyanoimidazole (**4**) in tetrahydrofuran at -80° also gives the 2-anion (not shown). However, once the 2-anion is formed, it reacts with the cyano groups of other lithiated 4,5-dicyanoimidazoles, even in the presence of other electrophiles, producing oligomeric side-products.

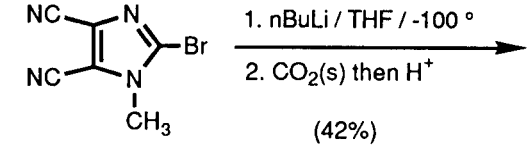
It is known that lower temperatures (-100° or lower) reduce the reactivity of alkyl- and aryllithium reagents and prevent undesired side reactions. For example, Parham [6] has reported clean metal/halogen exchange reactions of bromobenzonitriles at -100°. Similarly, metal/halogen exchange between *n*-butyllithium and **4** at -100° gives clean lithiation at C-2 [7]. After quenching, work-up and purification, **1** is recovered (Scheme I, eq. 3).

The reduced reactivity of *n*-butyllithium at -100° is apparent. When one equivalent of *n*-butyllithium is added to a solution of **1** at -100°, there is no evidence for addition of *n*-butyllithium to a nitrile (Scheme I, eq. 4). In this case, clean lithiation occurs at C-2 and quenching the reaction at low temperature gives only starting material. However, if two equivalents of *n*-butyllithium are added to **1** at -100°, the second equivalent adds to one of the cyano groups and the ketone **3** is recovered in good yield (Scheme I, eq. 5). Again, no regioisomer assignment has been made for **3** although the cyanoimidazole ketones recovered in equations 2 and 5 are identical as determined by chromatography, ir and nmr.

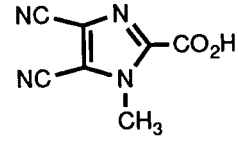
For selective lithiation at C-2, it is evident that the temperature should be kept at (or below) -100° and that only one equivalent of base should be added to the 1-protected-4,5-dicyanoimidazole.

The reaction of electrophiles with 1-methyl-2-lithio-4,5-dicyanoimidazole was found to give low yields of 2-substituted product. One example is shown in equation 6. Large excesses of electrophile give the best yields of 2-substituted product. Even under the most favorable conditions, however, yields are low [8]. Several explanations are plausible. At -100°, the reactivity of the 2-anion may be drastically reduced. The low reactivity observed in this system is consistent with literature reports on the reaction of metallated imidazoles with electrophiles [9]. Attempts to warm the solution after introduction of the electrophile, in order to increase the reactivity of the 2-anion, leads to side reactions and oligomer formation. Incomplete metallation at C-2 may also by contributing to the low yields observed.

(eq. 6)



4



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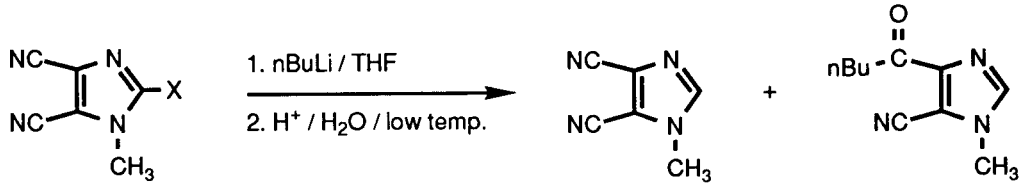
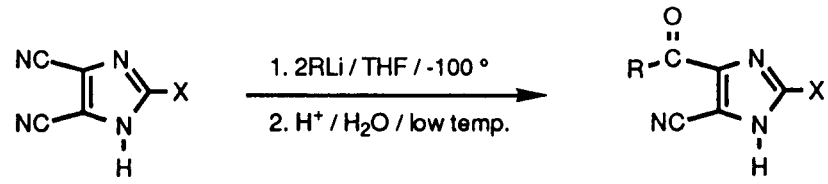
Scheme I



1, X= H; **4**, X= Br — **1** — **3**

eq.	compound	no. eq. nBuLi[a]	Temp.(°C)	**1**(%yield)	**3**(%yield)
2	**1**	one	-80	53	11
3	**4**	one	-100	48	-
4	**1**	one	-100	72	-
5	**1**	two	-100	-	53

Scheme II



6, X= H; 7, X= Br

8, R= nBu, X= H
9, R= tBu, X= H

eq.	compound	RLi	R(%yield)
7	6	nBuLi	8(72)
8	6	tBuLi	9(94)

It was hoped that formation of the 1,2-dianion starting from 4,5-dicyanoimidazole (**6**) or 2-bromo-4,5-dicyanoimidazole (**7**) would increase the reactivity of the 2-anion towards electrophiles by adding additional negative charge to the electron poor ring [10]. Disappointingly, clean formation of the 1,2-dianion from **6** or **7** was not possible [11].

However, it was found that addition of two equivalents of alkyllithium (*n*-butyllithium or *t*-butyllithium) to **6** gave the cyanoimidazole ketones **8** and **9** in high yield (Scheme II, eq. 7 and 8). Once again, the second equivalent of alkyllithium adds to one of the cyano groups. No substitution at the 2-position was observed when electrophiles were introduced into the reaction mixtures. In contrast to *n*-butyllithium and *t*-butyllithium, methyllithium gave only low yields of what was apparently the cyanoimidazole ketone as determined by chromatography and nmr but in this example, starting material **6** is the major product recovered. Finally, addition of two equivalents of alkyllithium to **7**, followed by introduction of an electrophile, gave mixtures of several products. These products arise, in part, from attack of *n*-butyllithium on one of the cyano groups of **7** and from alkylation of the 1- and 2-positions of 4,5-dicyanoimidazole.

Conclusions.

Clean metallation at the 2-position of 1-protected-4,5-dicyanoimidazoles is possible. Conditions must be carefully controlled, however, to prevent undesired side reactions. Reaction of the 2-anion with electrophiles gives the corresponding 2-substituted products. Although the reactivity of the 2-anion towards most electrophiles is low, transmetallation with copper salts occurs readily at low temperatures [2]. These aryl copper intermediates have been oxidatively coupled to give new tetracyanobiimidazole derivatives in good yields [2]. As a result, it is possible to functionalize the 2-position of 4,5-dicyanoimidazoles selectively. These methodologies compliment our recent reports on the nucleophillic aromatic substitution reactions of **4** [3a,12].

Furthermore, during the course of this investigation, new cyanoimidazole ketones have been synthesized *via* addition reactions of alkyl lithium reagents to one of the cyano groups. Novel cyanoimidazole derivatives are now accessible.

EXPERIMENTAL

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Thin layer chromatography was done on Eastman Kodak silica gel sheets containing fluorescent indicator. Column chromatography was done using 70-230 or 230-400 mesh silica gel (Aldrich). Infrared spectra were recorded on a Nicolet 5-DX FTIR spectrophotometer. The pmr (300 MHz) and cmr (75 MHz) were recorded on a Bruker AM-300 spectrometer. Chemical shift values are reported relative to tetramethylsilane in the appropriate solvent. All cmr were done under broad band proton decoupling. Nominal mass spectra were recorded on a Finnigan model 4021 mass spectrometer. Elemental analysis were done at the University of Michigan on a Perkin-Elmer 2400 CHN analyzer or by Oneida Research Services, Inc., Whitesboro, NY. Tetrahydrofuran was distilled under nitrogen from sodium benzophenone ketyl. 4,5-Dicyanoimidazole (**6**) was obtained from Nippon Soda Co., Ltd., recrystallized from water and dried prior to use. Other 4,5-dicyanoimidazoles **1**, **4** and **7** were synthesized from **6** as reported [2,3]. Alkyllithium and other reagents were used as purchased from Aldrich Chemical Co.

Reaction of *n*-Butyllithium with **1** at -80° (followed by warming to room temperature). 2-Propyl-3-amino-3-(4-(or 5)-1-methylimidazolyl)propenenitrile (**2**).

A flask was charged with 0.80 ml of *n*-butyllithium (2.2 mmoles, 1.0 eq) in 3 ml of tetrahydrofuran and cooled to -80°. A solution of 0.286 g of **1** (2.18 mmoles) in 8 ml of tetrahydrofuran was added dropwise slowly (20 minutes) to the solution of alkyllithium at -80°. The reaction turned yellow, dark orange and then brown. After 15 minutes at low temperature, 0.2 ml of 1-methoxy-2-chloroethane (1.0 eq) in 3 ml of tetrahydrofuran was added. After 30 minutes, the reaction was allowed to slowly warm to room temperature and quenched with water. The clear orange solution was partitioned between water (20 ml) and ethyl acetate (40 ml). The layers were separated and the aqueous layer extracted with ethyl acetate (15 ml). The organics were combined, washed with water and brine, and dried (sodium sulfate). Solvent was removed to give an orange solid which was subjected to column chromatography (2/1 ethyl acetate/hexanes). The major component was collected from fractions #2-7 and concentrated to give 0.107 g of **2** as a pale yellow solid (26%), tlc 2/1 ethyl acetate/hexanes R_f 0.27, mp 133-136°; ir (potassium bromide): 3431, 3330, 3230, 2961, 2931, 2173, 1633, 1581, 1552, 1398, 1326, 979 cm^{-1}; ^{1}pmr (acetone-d_6): δ 7.87 (d, 1 H, J = 1.0 Hz), 7.59 (s, 1 H), 5.85 (br s, 2 H), 3.82 (s, 3 H), 2.21 (t, 2 H, J = 7.4 Hz), 1.58 (m, 2 H), 0.98 (t, 3 H, J = 7.3 Hz); cmr (acetone-d_6): δ 150.3, 138.3, 136.9, 125.0, 122.4, 73.0, 33.9, 30.3, 22.1, 13.9; ms: (EI) (m/e) 190 (M^+), 175, 161 (100%), 132, 108, 96, 83, 67, 52, 42.

Reaction of **1** or **4** with *n*-Butyllithium. General Procedure.

A solution of **1** or **4** (1-5 mmoles) in 8-12 ml of tetrahydrofuran was cooled to -80° or -100°. *n*-Butyllithium (1.0-2.0 eq, 2.5 *M* in hexanes) was added dropwise slowly (see Scheme I for starting substrate, equivalents of alkyllithium and temperature). The solution was stirred at low temperature for 30 minutes and then poured into aqueous hydrochloric acid or water. The aqueous layer was extracted with diethyl ether or ethyl acetate. The organics were combined, washed with water, dried (magnesium sulfate or sodium sulfate) and concentrated to give the crude product(s).

Reaction of *n*-Butyllithium with **1** at -80° (followed by low temperature quench). 4-(or 5)-(Pentanoyl)-1-methylimidazole-5-(or 4)-carbonitrile (**3**).

The crude yellow residue was chromatographed (1/1 ethyl acetate/hexanes to 2/1 ethyl acetate/hexanes). Collected fractions #15-19 and removed solvent to give **3** as a colorless oil (11%), tlc 1/1 ethyl acetate/hexanes R_f 0.58; ir (neat): 3117, 2961, 2934, 2874, 2236, 1677, 1516, 1505, 1382, 1359, 1299, 1037 cm^{-1}; pmr (deuteriochloroform): δ 7.60 (s, 1 H), 3.96 (s, 3 H), 3.09 (t, 2 H, J = 7.3 Hz), 1.73 (m, 2 H), 1.43 (m, 2 H), 0.96 (t, 3 H, J = 7.3 Hz); cmr (deuteriochloroform): δ 191.1, 143.0, 135.5, 119.4, 114.6, 41.0, 35.9, 26.1, 22.2, 13.8; ms (m/e) 191 (M^+), 176, 162 (100%), 149, 134, 121, 106, 86, 84, 79, 57.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.98. Found: C, 62.12; H, 6.59; N, 21.65.

Collected fractions #26-34 and removed solvent to give a white crystalline solid identified as **1** (53%), tlc 1/1 ethyl acetate/hexanes R_f 0.33, mp 86-88° (lit mp 89-90°); ir (potassium bromide): 3126, 2240, 1507, 1317, 1181, 1033, 751, 633, 505 cm^{-1} (identical to authentic sample of **1**).

Metal/Halogen Exchange in **4**.

The crude solid was collected, rinsed with hexanes and dried to give **1** (48%). Recrystallization from 95% ethanol gives pure product; pmr (deuteriochloroform): δ 7.69 (s, 1 H), 3.89 (s, 3 H) (identical to authentic sample of **1**).

Reaction of *n*-Butyllithium with **1** at -100°.

The product was recrystallized from 95% ethanol to give white crystals of **1** (72%), tlc 1/1 ethyl acetate/hexanes R_f 0.30, mp 87-89° (lit mp 89-90°); ir (potassium bromide): 3126, 2240, 1517, 1363, 1317, 1247, 1180, 1033, 860, 751, 633, 505 cm^{-1} (identical to authentic sample of **1**). There was no evidence of *n*-butyllithium to a cyano group (by tlc, ir or pmr).

Reaction of 2.0 Equivalents of *n*-Butyllithium with **1** at -100°. 4-(or 5)-(Pentanoyl)-1-methylimidazole-5-(or 4)-carbonitrile (**3**).

Chromatography of the crude residue (1/1 ethyl acetate/hexanes) gave two components. Fractions #10-15 gave **3** as a colorless oil (52%). The full characterization of **3** is given above. Fractions #24-27 gave a solid which was further purified by recrystallization from ethanol. A white crystalline solid was recovered (<1%) and tentatively assigned as the other regioisomer of the cyanoimidazole ketone, tlc 1/1 ethyl acetate/hexanes R_f 0.30, mp 74-78°; ir (potassium bromide): 3126, 2963, 2242, 1693, 1651, 1515, 1502, 1470, 1454, 1365, 1348, 1302, 1198, 921 cm^{-1}.

1-Methyl-4,5-dicyanoimidazole-2-carboxylic Acid (**5**).

A flask was charged with 0.236 g of **4** (1.12 mmoles) in 15 ml of tetrahydrofuran. The solution was cooled to -100° and 0.40 ml of *n*-butyllithium (1.0 eq, 2.9 *M* in hexanes) was added dropwise. The clear, yellow solution was poured onto solid carbon dioxide and the mixture allowed to warm to room temperature. The clear solution was partitioned between diethyl ether water. The ethereal layer was removed and washed with water. All of the aqueous layers were combined, acidified to a *p*H of 1 and extracted with ethyl acetate (2 x 10 ml). The ethyl acetate extracts were combined, dried (sodium sulfate) and concentrated to give 0.125 g of **5** as a white solid, tlc 1/1 ethyl acetate/hexanes R_f 0.00, mp 85-90° (with gas evolution); ir (potassium bromide): 3200-2500 (v br), 2247, 1729, 1476, 1230, 1196 cm^{-1}; pmr (acetone-d_6): δ 4.23 (s); ms: (m/z) 176 (M^+), 158, 132, 44 (100%).

Reaction of **6** with Alkyllithium Reagents. General Procedure for the Synthesis of Cyanoimidazole Ketones **8-9**.

A flask was charged with **6** (1.0-2.0 mmoles) in 10 ml of tetrahydrofuran and cooled to -100°. To this was added 2.0 equivalents of alkyllithium reagent (*n*-butyllithium, 2.5 *M* in hexanes; *t*-butyllithium, 1.7 *M* in pentanes). The cloudy, yellow solution was stirred at -100° for 30-60 minutes and then poured into dilute aqueous hydrochloric acid. The aqueous layer was extracted with diethyl ether. The ethereal layers were combined, washed with water, dried (magnesium sulfate) and concentrated to give the product.

4(5)-(Pentanoyl)imidazole-5(4)-carbonitrile (**8**).

Recrystallization of the crude product from 95% ethanol gave **8** as a white solid (72%), tlc 4/1 ethyl acetate/methanol R_f 0.68, mp 156-157°; ir (potassium bromide): 2961, 2800-2300 (br), 2237, 1682, 1551, 1486, 1401, 1258, 966 cm^{-1}; pmr (acetone-d_6): δ 8.05 (s, 1 H), 3.06 (t, 2 H, J = 7.3 Hz), 1.71 (m, 2 H), 1.43 (m, 2 H), 0.95 (t, 3 H, J = 7.3 Hz).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.73. Found: C, 61.19; H, 6.45; N, 22.69.

4(5)-(2,2-Dimethylpropanoyl)imidazole-5(4)-carbonitrile (**9**).

Recrystallization from water gave an analytically pure sample of **9** as a white solid (94%), tlc 3/1 ethyl acetate/hexanes R_f 0.21, mp 156-158°; ir (potassium bromide): 3129, 3000-2600 (br), 2233, 1674, 1333, 975, 972 cm^{-1}; pmr (acetone-d_6): δ 8.05 (s, 1 H), 1.40 (s, 12 H); ms: (m/z) 177 (M^+), 162, 149, 121, 93, 66, 57 (100%), 41.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.73. Found: C, 60.75; H, 6.22; N, 23.53.

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[7] Clean metallation at C-2 can be monitored by the appearance of the reaction. Upon addition of *n*-butyllithium to a solution of 1-protected-4,5-dicyanoimidazole in tetrahydrofuran, the solution containing the 2-anion turns orange-red and remains clear. If metallation is not clean, the solution turns dark brown, almost black, and becomes cloudy. In some cases, polymeric materials begin to precipitate from solution.

[8] Methyl iodide and other alkyl halides typically gave low yields (0-20%) of 2-substituted product(s). Various attempts were made to enhance the reactivity of the 2-anion towards electrophiles. The example shown in equation 6 is one of the higher yield reactions.

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[10] 4,5-Dicyanoimidazoles are known to be electron deficient. In fact, we have studied this class of compounds as electron acceptors and as components in charge-transfer complexes. See references [2] and [3b].

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Note Added in Proof:

The yields of many of the *n*-butyllithium reactions can be improved by the addition of a small amount of tetramethylethylenediamine.