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Ruthenium-catalyzed intramolecular selective halogenation of *O*-methylbenzohydroximoyl halides: a new route to halogenated aromatic nitriles†

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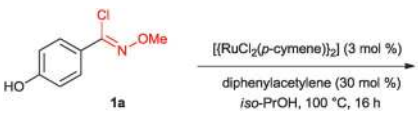
The intramolecular halogenation of *O*-methylbenzohydroximoyl halides in the presence of a Ru catalyst and the ligand diphenylacetylene afforded halo substituted aromatic nitriles in a highly regioselective manner. Further, substituted nitriles were converted into substituted tetrazole derivatives in the presence of NaN_3 and I_2.

Aromatic halides are synthetically useful compounds that have been widely used as precursors in various organic transformations and for synthesizing various organometallic reagents, heterocyclic compounds, natural products, biologically active molecules and organic materials.[1] Traditionally, substituted aromatic halides are prepared by aromatic electrophilic substitution of electron-rich aromatics.[2] However, many of these reactions generally provide mixtures of regioisomeric *ortho* and *para* substituted aromatic halides. Alternatively, *ortho*-halo substituted aromatics are efficiently prepared by chelation-assisted metal-base mediated C–H bond activation of substituted aromatics followed by halogen quenching.[3] Recently, metal-catalyzed directing group assisted transformation of *ortho* aromatic C–H bonds to C–X bonds by utilizing NXS sources (X = Cl, Br and I) or XOAc or CuX_2 has been reported.[4,5] By using these methods, various *ortho*-bromo and iodo substituted aromatic compounds are conveniently prepared. However, chlorobenzene synthesis is still a challenging task. In all reported reactions, halogenation of aromatics proceeded in an intermolecular fashion.

The *ortho* C–H bond activation of aromatics has been fairly studied in the literature.[4,5] But, the *meta* selective C–H bond activation of aromatics is much limited in the literature.[6] In this context, metal-catalyzed *meta* selective arylation and alkenylation of substituted aromatics have been reported by the groups of Gaunt, Yu and Sanford.[6a–d] In addition, Ru(II)-catalyzed *meta* selective sulfonation of 2-phenylpyridines has been demonstrated by Frost and co-workers in 2011.[6e] To date, no report has been available in the literature for halogenation at the *meta* C–H bond of substituted aromatics. In the meantime, there is also no example available in the literature for halogenation of aromatics in an intramolecular fashion. This, and also our continuous interest in the Ru(II)-catalyzed C–H activation reactions,[7,8] prompted us to explore the possibility of performing halogenation at the *meta* C–H bond of substituted aromatics in an intramolecular fashion. Herein, we wish to report for the first time, an unprecedented ruthenium-catalyzed intramolecular halogenation at the *meta* and *ortho* carbon positions of *O*-methylbenzohydroximoyl halides. It is noteworthy to say that the present halogenation reaction is conducted under base and oxidant free conditions. It is also important to point out that substituted aromatic nitriles are key structural units in various natural products and also key intermediates for synthesising various pharmaceutically active molecules, agricultural molecules, dyes and organic materials.[9]



(1)

The halogenation of 4-hydroxy-*N*-methoxybenzimidoyl chloride (**1a**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (3 mol%) and ligand diphenylacetylene (30 mol%) in iso-PrOH at 100 °C for 16 h gave 3-chloro-4-hydroxybenzonitrile (**2a**) in 83% isolated yield (eqn (1)). In the reaction, chlorination takes place very selectively at the *meta* carbon position of **1a** and the imidoyl moiety of **1a** is converted into the nitrile moiety (for detailed optimization studies, see ESI†).

Under similar reaction conditions, the catalytic reaction was examined with various substituted *O*-methylbenzohydroximoyl chlorides **1b–h** (Table 1). Thus, 4-methoxy **1b**, 4-ethoxy **1c**, 4-*n*-propoxy **1d** substituted *N*-methoxybenzimidoyl chlorides underwent chlorination selectively at the *meta* carbon position yielding the corresponding *meta*-chlorobenzonitriles **2b–d** in excellent 85%, 90% and 92% yields, respectively (entries 1–3). The structure of **2c** was confirmed using single crystal X-ray diffraction (see ESI†). 4-Dimethylamino **1e** and 4-methylamino **1f** substituted *N*-methoxybenzimidoyl chlorides also proceeded smoothly under similar reaction conditions affording the corresponding *meta*-chlorobenzonitriles **2e** and **2f** in excellent 84% and 91% yields, respectively (entries 4 and 5). In these reactions also, chlorination takes place at the *meta* carbon position

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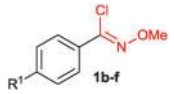
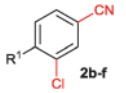
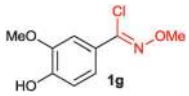
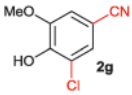
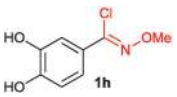
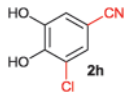
† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectroscopic data. CCDC 924191 and 924192. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc41124a

Table 1 Scope of the selective *meta*-chlorination reaction[a]

Entry	1b–h	Product 2b–h	Yield[b] (%)
	 1b-f	 2b-f	
1	**1b**: R^1 = OMe	**2b**: R^1 = OMe	85
2	**1c**: R^1 = OEt	**2c**: R^1 = OEt	90
3	**1d**: R^1 = O-*n*Pr	**2d**: R^1 = O-*n*Pr	92
4	**1e**: R^1 = NMe_2	**2e**: R^1 = NMe_2	84
5	**1f**: R^1 = NHMe	**2f**: R^1 = NHMe	91[c]
6	 1g	 2g	85
7	 1h	 2h	87

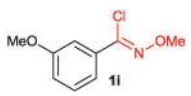
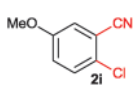
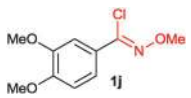
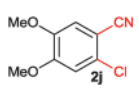
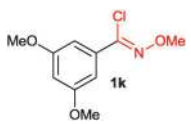
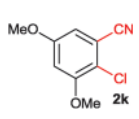
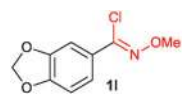
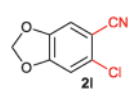
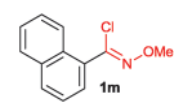
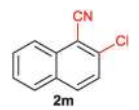
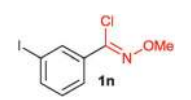
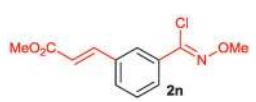
[a] All reactions were carried out using **1b–h** (1.0 mmol), diphenylacetylene (30 mol%) and [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol%) in iso-PrOH (3.0 mL) at 100 °C for 16 h. [b] Isolated yield. [c] The reaction was conducted in the presence of methyl acrylate (50 mol%).

of **1e** and **1f** exclusively. Interestingly, 4-hydroxy-3-methoxy **1g** and 3,4-dihydroxy **1h** substituted *N*-methoxybenzimidoyl chlorides provided substituted *meta*-chlorobenzonitriles **2g** and **2h** in 85% and 87% yields, respectively, also in which chlorination takes place at the *meta* carbon position of **1g** and **1h** (entries 6 and 7).

Next, the scope of the regioselectivity of the chlorination of substituted unsymmetrical *N*-methoxybenzimidoyl chlorides **1i–n** was examined under the optimized reaction conditions (Table 2). Initially, the reaction was tested with 3-methoxy substituted *N*-methoxybenzimidoyl chloride **1i**. In contrast to the previous reactions (Table 1), surprisingly, in this reaction, chlorination takes place selectively at the less hindered *ortho* carbon position of **1i** providing 2-chloro-5-methoxybenzonitrile (**2i**) in 93% yield (Table 2, entry 1). Like **1i**, 3,4-dimethoxy **1j** and 3,5-dimethoxy **1k** substituted *N*-methoxybenzimidoyl chlorides underwent chlorination at the less hindered *ortho* carbon position of **1j** and **1k** affording the corresponding substituted *ortho*-chlorobenzonitriles **2j** and **2k** in 81% and 89% yields, respectively (entries 2 and 3). Similarly, 1,3-dioxale group substituted *N*-methoxybenzimidoyl chloride **1l** yielded *ortho*-chloro piperonylonitrile **2l** in 85% yield (entry 4). The structure of **2l** was confirmed using single crystal X-ray diffraction (see ESI†). Further, *N*-methoxy-1-naphthimidoyl chloride (**1m**) provided 2-chloro-1-naphthonitrile (**2m**) in 81% yield (entry 5). Next, the reaction was tested with 3-iodo substituted *N*-methoxybenzimidoyl chloride **1n** (entry 6). In the reaction, the C–I bond of **1n** underwent a Heck-type alkenylation with the methyl acrylate ligand giving an alkene derivative **2n** in 42% yield.

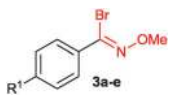
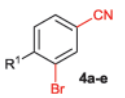
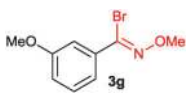
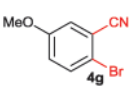
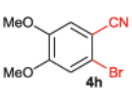
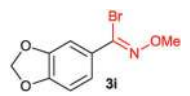
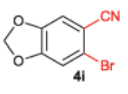
The current method can also be successfully extended to prepare various *meta* and *ortho* bromo substituted benzonitriles **4a–i** (Table 3). The bromination at the *meta* carbon position of 4-hydroxy substituted *N*-methoxybenzimidoyl bromide **3a** proceeded smoothly under the optimized reaction conditions affording 3-bromo-4-hydroxybenzonitrile (**4a**) in 93% yield in a highly regioselective manner (Table 3, entry 1). Similar to **3a**, 4-methoxy **3b**, 4-ethoxy **3c**, and 4-*n*-propoxy **3d** substituted *N*-methoxybenzimidoyl bromides gave the corresponding *meta*-bromo substituted benzonitriles **4b–d** in 96%, 96% and 97% yields, respectively (entries 2–4), in a highly regioselective manner. Similarly, 4-dimethylamino substituted

Table 2 Scope of the selective *ortho*-chlorination reaction[a]

Entry	1i–n	Product 2i–n	Yield[b] (%)
1	 1i	 2i	93[c]
2	 1j	 2j	81
3	 1k	 2k	89[c]
4	 1l	 2l	85
5	 1m	 2m	81[c]
6	 1n	 2n	42[c]

[a] All reactions were carried out using **1i–n** (1.0 mmol), diphenylacetylene (30 mol%) and [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol%) in iso-PrOH (3.0 mL) at 100 °C for 16 h. [b] Isolated yield. [c] The reaction was conducted in the presence of methyl acrylate (50 mol%).

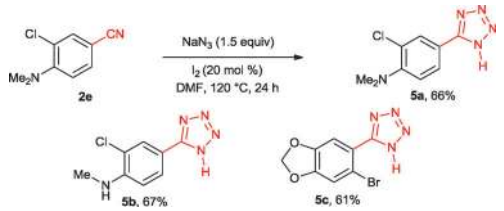
Table 3 Scope of the selective *meta* and *ortho* bromination reaction[a]

Entry	3	Product 4	Yield[b] (%)
	 3a-e	 4a-e	
1	**3a**: R^1 = OH	**4a**: R^1 = OH	93
2	**3b**: R^1 = OMe	**4b**: R^1 = OMe	96
3	**3c**: R^1 = OEt	**4c**: R^1 = OEt	96
4	**3d**: R^1 = O-*n*Pr	**4d**: R^1 = O-*n*Pr	97
5	**3e**: R^1 = NMe_2	**4e**: R^1 = NMe_2	84
6	 3f	 4f	88
7	 3g	 4g	94[c]
8	 3h	 4h	83
9	 3i	 4i	85

[a] All reactions were carried out using **3a–i** (1.0 mmol), diphenylacetylene (30 mol%) and [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol%) in iso-PrOH (3.0 mL) at 100 °C for 16 h. [b] Isolated yield. [c] The reaction was conducted in the presence of methyl acrylate (50 mol%).

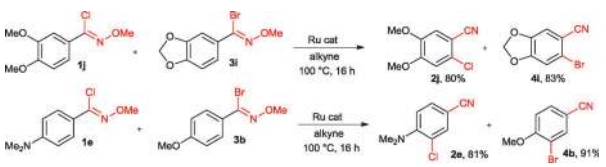
N-methoxybenzimidoyl bromide **3e** provided the corresponding *meta*-bromo substituted benzonitrile **4e** in 84% yield (entry 5). Likewise, in the reaction of 4-hydroxy-3-methoxy substituted *N*-methoxybenzimidoyl bromide **3f**, bromination took place regioselectively at the *meta* carbon position yielding **4f** in 88% yield (entry 6). The structure of **4f** was confirmed by single crystal X-ray diffraction (see ESI†). In contrast to **3a–f**, 3-methoxy, 3,4-dimethoxy and 1,3-dioxale substituted *N*-methoxybenzimidoyl bromides **3g–i** provided *ortho*-bromo substituted benzonitriles **4g–i** in 94%, 83% and 85% yields, respectively, in a highly regioselective manner (entries 7–9).

To demonstrate the utility of CN groups in organic synthesis, the [3+2] cycloaddition of aromatic nitriles with NaN_3 was carried out (eqn (2)). The cycloaddition of aromatic nitrile **2e** with NaN_3 (1.5 equiv.) in the presence of a catalytic amount of I_2 (20 mol%) in DMF at 120 °C for 24 h yielded the corresponding substituted tetrazole **5a** in 66% yield. Similarly, aromatic nitriles **2f** and **4i** also underwent cycloaddition with NaN_3 under similar reaction conditions giving tetrazoles **5b** and **5c** in 67% and 61% yields, respectively.



(2)

At present, the exact mechanism for the halogenation of **1** or **3** is not very clear to us. Possibly, the imidoyl moiety of **1** or **3** is converted into a cyano group[9b] followed by halogen transfer *via* electrophilic substitution at the aromatic carbon of **1** or **3** in the presence of a ruthenium catalyst. The exact role of the co-catalyst diphenylacetylene or methyl acrylate is unclear to us. It might be possible that this ligand coordinates with ruthenium metal and decreases the electron-density on the metal *via* π-back bonding. In fact the halogenation reaction was tested with various *para* and *meta* I, Br, Cl, F, CF_3 and NO_2 substituted *N*-methoxybenzimidoyl halides. However, in these reactions, no halogenation product was observed. This is probably due to the electron-withdrawing nature of these substituents. In the meantime, no halogenation product was observed in the reaction of 4-methyl or 4-*tert*-butyl substituted *N*-methoxybenzimidoyl halides. These results clearly revealed that in the present halogenation reaction, electron mesomeric donating groups such as OH, OR, NHR and NR_2 are highly important compared to the electron inductive donating groups such as alkyls. In all reactions, halogenation takes place selectively at the *ortho* and *meta* carbon of aromatics **1** and **3**. This is most likely due to the *ortho* and *para* directing nature of OH, OR, NHR and NR_2 groups in the electrophilic aromatic substitution reaction.



(3)

To see whether the halogenation reaction proceeds in an inter- or intramolecular manner, the following competitive reactions were performed (eqn (3)). The reaction of **1j** was conducted with **3i** under the optimized reaction conditions. In the reaction, if cross products **4h** and **2l** are observed in addition to the expected **2j** and **4i**, the reaction should be intermolecular. However, in the reaction, as expected, only compounds **2j** and **4i** were observed exclusively in 80% and 83% yields, respectively, and no cross products were observed. Similarly, in the reaction of **1e** with **3b**, only compounds **2e** and **4b** were observed exclusively in 81% and 91% yields, respectively, and no cross products **4e** and **2b** were observed. These results very clearly revealed that the present halogenation reaction proceeds in an intramolecular fashion.

In conclusion, we have described ruthenium-catalyzed intramolecular halogenation of *O*-methylbenzohydroximoyl halides. The catalytic reaction is highly regioselective, yielding substituted halo aromatic nitriles under base and oxidant free conditions. Further extension of the C–H bond activation of other chelating group substituted aromatics and functionalization with other π-components and the detailed mechanistic investigation are in progress.

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