Organic LETTERS

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Ruthenium-Catalyzed Cyclization of Aromatic Nitriles with Alkenes: Stereoselective Synthesis of (*Z*)-3-Methyleneisoindolin-1-ones

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Supporting Information

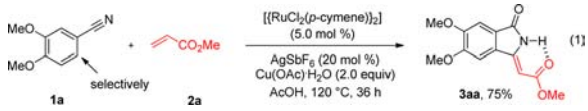
ABSTRACT: Aromatic nitriles underwent cyclization with activated alkenes in the presence of a ruthenium catalyst, $AgSbF_6$, and $Cu(OAc)_2{\cdot}H_2O$ providing substituted 3-methyleneisoindolin-1-ones with high *Z*-stereoselectivity. The *Z*-stereoselectivity of the 3-methyleneisoindolin-1-one moiety was controlled by the intramolecular hydrogen bonding.

Isoindolinone is a core structure unit present in various natural products and biologically active molecules.[1] In particular, the 3-methyleneisoindolin-1-one structural motif is found in several biologically active natural products and designed pharmaceutical molecules.[2] Traditionally, 3-methyleneisoindolin-1-ones are prepared by the reaction of phthalimides with Wittig reagents and nucleophilic addition of organometallic reagents into phthalimides followed by dehydration.[3] Alternatively, it can also be prepared by metal-catalyzed intramolecular cyclization of *o*-alkynylbenzamides, coupling of 2-halobenzamides with terminal alkynes, and intermolecular coupling of substituted ynamides or *o*-vinylbenzamides with aromatic boronic acids.[4] However, the control of regio- and stereoselectivity and the observation of competitive side products are critical problems in these reactions. In addition, preactivated halo-substituted aromatics are required to prepare the key starting materials.

Recently, isoindolinone derivatives have been efficiently prepared by metal-catalyzed oxidative cyclization of aromatic amides with alkenes without having any preactivated species on the aromatic moiety via chelation-assisted C−H bond activation.[5,6] *N*-Aryl- or -tosylbenzamides reacted with alkenes in the presence of palladium or rhodium catalysts yielding five-membered isoindolinones.[6a−c] *N*-Alkoxybenzamides reacted with activated alkenes in the presence of palladium catalyst yielding (*E*)-3-methyleneisoindolin-1-one derivatives.[6d,e] In the meantime, *N*-methylsubstituted benzamide or primary benzamides reacted with *n*-butyl acrylate to afford 3-methyleneisoindolin-1-ones.[6f] However, the corresponding reaction was studied with only two primary benzamides and a single 3-methoxy-*N*-methylbenzamide, and the observed yield was also very low. In fact, *N*-alkyl-substituted benzamides and primary benzamide are not suitable substrates for the cyclization with alkenes because of their sluggish reactivity. However, pyridine-substituted amides underwent cyclization with alkenes efficiently in the presence of rhodium catalyst affording *cis* and *trans* stereoisomeric mixtures of 3-methyleneisoindolin-1-ones.[6g−i] Apart from the benzamides, aromatic ketoximes reacted with isocyanates to give a mixture of *cis* and *trans* stereoisomeric 3-methyleneisoindolin-1-ones.[7]

By using the traditional methods and metal-catalyzed reactions,[3−7] isoindolinone and (*E*)-3-methyleneisoindolin-1-one derivatives are efficiently prepared, but, *Z*-stereoselective 3-methyleneisoindolin-1-one synthesis is not well demonstrated because of the rapid *Z* to *E* stereoselective isomerization.[8] Herein, we report a ruthenium-catalyzed annulation of aromatic nitriles[9] with activated alkenes to yield *Z*-stereoselective 3-methyleneisoindolin-1-ones in good yields in a highly regioselective manner. In the reaction, *Z*-stereoselectivity was controlled by the intramolecular hydrogen-bonding.

Treatment of 3,4-dimethoxybenzonitrile (**1a**) with methyl acrylate (**2a**) in the presence of $[[RuCl_2(p\text{-cymene})]_2]$ (5.0 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) in acetic acid (AcOH) at 120 °C for 36 h gave 3-methyleneisoindolin-1-one **3aa** in 75% isolated yield in a high *Z*-stereoselectivity (eq 1)



(for detailed optimization studies, see the Supporting Information). The *Z*-stereoselectivity of compound **3aa** was controlled by the intramolecular hydrogen bonding of the N−H group of **3aa** to the carbonyl group of the ester moiety of **3aa**. The catalytic reaction is also highly regioselective; the *ortho* C−H bond activation takes place selectively at a less hindered side of aromatic **1a**. It is important to note that until now methyleneisoindolin-1-ones have been prepared from substituted benzamides or aromatic ketoximes with alkenes. Here, we show the synthesis of methyleneisoindolin-1-ones from easily available aromatic nitriles.

The scope of the cyclization reaction was examined with various alkenes (Table 1). Ethyl acrylate (**2b**), *n*-butyl acrylate (**2c**), and cyclohexyl acrylate (**2d**) underwent cyclization with **1a**, yielding cyclization products **3ab**−**ad** in 67%, 70%, and 74% yields, respectively (entries 1−3). Interestingly, 2,2,2-trifluoroethyl

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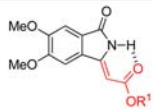
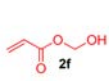
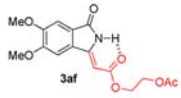
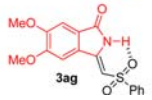
Table 1. Scope of the Activated Alkenes 2b–g[a]

entry	alkene **2**	product **3**	yield(%)[b]
			
1	**2b**: R^1 = Et	**3ab**: R^1 = Et	67
2	**2c**: R^1 = *n*-Bu	**3ac**: R^1 = *n*-Bu	70
3	**2d**: R^1 = cyclohexyl	**3ad**: R^1 = cyclohexyl	74
4	**2e**: R^1 = CH_2CF_3	**3ae**: R^1 = CH_2CF_3	62
5			61
6			65

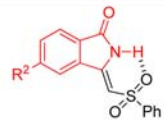
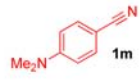
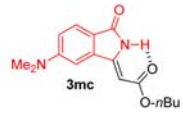
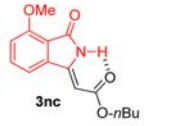
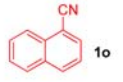
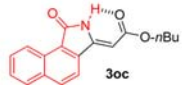
[a]All reactions were carried out using **1a**, alkenes **2b**,**c** (4.0 equiv), **2d**–**f** (3.0 equiv), and **2g** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2.H_2O$ (2.0 equiv) in AcOH (3.0 mL) at 120 °C for 36 h. [b]Isolated yield.

acrylate (**2e**) and 2-hydroxyethyl acrylate (**2f**) also efficiently reacted with **1a** giving cyclization products **3ae** and **3af** in 62% and 61% yields, respectively (entries 4 and 5). In the product **3af**, a free hydroxy group was converted into acetate group in the presence of AcOH. Surprisingly, vinyl sulfone (**2g**) also reacted efficiently with **1a**, providing cyclic compound **3ag** in 65% yield, respectively (entry 6). Next, the reaction was tested with other alkenes such as methyl vinyl ketone, acrylonitrile, and styrenes. However, in the reaction, no cyclization product was observed. It seems a good coordinating group such as ester and SO_2Ph-substituted alkenes were suitable for the reaction.

The present catalytic reaction was also successfully extended with various substituted aromatic nitriles (Table 2). Thus, electron-rich aromatic nitriles such as 4-hydroxy- (**1b**), 4-methoxy- (**1c**), and 4-methylbenzonitriles (**1d**) and benzonitrile (**1e**) efficiently reacted with phenyl vinyl sulfone (**2g**) to give isoindolinone derivatives **3bg**–**eg** in good to moderate yields in a highly *Z*-stereoselective manner (entries 1–4). The structure of compound **3cg** was supported by a single-crystal X-ray diffraction (see the Supporting Information). Halogen groups such as 4-iodo- (**1f**), 4-bromo- (**1g**), 4-chloro- (**1h**) and 4-fluorobenzonitriles (**1i**) were nicely involved in the reaction, providing cyclization products **3fg**–**ig** in good yields in a highly stereoselective manner (entries 5–8). Very interestingly, electron-deficient aromatic nitriles such as 4-nitrobenzonitriles (**1j**), 4-methyl ester benzonitriles (**1k**), and 4-formylbenzonitriles (**1l**) nicely reacted with phenyl vinyl sulfone (**2g**) affording products **3jg**–**lg** in 61%, 56%, and 52% yield, respectively, in a highly regio- and stereoselective manner (entries 9–11). It is important to note that a free OH and sensitive I, Br, ester, CHO, and NO_2 groups were not affected. Further, 4-(dimethylamino)benzonitrile (**1m**), sterically hindered *o*-methoxybenzonitrile (**1n**), and 1-naphthonitrile (**1o**) reacted with *n*-butyl acrylate (**2c**) providing cyclization products **3mc**–**oc** in 59%, 51%, and 56% yields, respectively (entries 12–14).

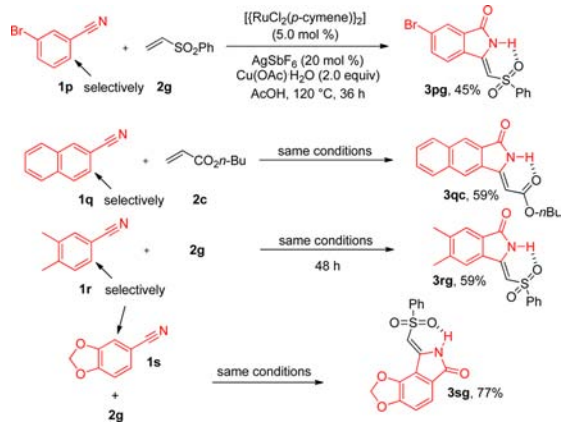
Next, the cyclization reaction was tested with unsymmetrical aromatic nitriles such as *m*-bromobenzonitrile (**1p**), 2-naphthonitrile (**1q**), and 3,4-dimethylbenzonitrile (**1r**) with **2c** or **2g** (Scheme 1). In these substrates, two different regioselective products are possible. However, the reaction is highly regioselective, and the *ortho* C–H activation takes place at the less hindered

Table 2. Cyclization of Nitriles 1 with Alkenes 2c or 2g[a]

entry	nitriles **1**	product **3**	yield (%)[b]
			
1	**1b**: R^2 = OH	**3bg**: R^2 = OH	61
2	**1c**: R^2 = OMe	**3cg**: R^2 = OMe	75
3	**1d**: R^2 = Me	**3dg**: R^2 = Me	41[c]
4	**1e**: R^2 = H	**3eg**: R^2 = H	72[d]
5	**1f**: R^2 = I	**3fg**: R^2 = I	69[d]
6	**1g**: R^2 = Br	**3gg**: R^2 = Br	71[d]
7	**1h**: R^2 = Cl	**3hg**: R^2 = Cl	67[d]
8	**1i**: R^2 = F	**3ig**: R^2 = F	65[c]
9	**1j**: R^2 = NO_2	**3jg**: R^2 = NO_2	61[e]
10	**1k**: R^2 = CO_2Me	**3kg**: R^2 = CO_2Me	56[c]
11	**1l**: R^2 = CHO	**3lg**: R^2 = CHO	52[c]
12			59
13			51[d]
14			56

[a]All reactions were carried out using **1a**–**o**, alkene **2g** (1.20 equiv) or **2c** (4.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2.H_2O$ (2.0 equiv) in acetic acid (3.0 mL) at 120 °C for 36 h. [b]Isolated yield. [c]Reaction was carried out for 42 h. [d]Reaction was carried out for 39 h. [e]Reaction was carried out for 45 h.

Scheme 1. Regioselective Studies



side, giving products **3pg**–**3rg** in 45%, 59%, and 59% yields, respectively (Scheme 1), whereas in the substrate **1s**, the *ortho* C–H bond activation takes place at the sterically hindered side, providing cyclization product **3sg** in 77% yield (Scheme 1).

Isoindolin-1-one derivatives are widely used as a fluorescent marker for labeling biomolecules.[2] To learn the optical behavior, we have performed the following reaction and monitored the absorbance and fluorescence of the product (eq 2). Treatment of pyrene-1-carbonitrile (**1t**) with **2g** provided cyclization product

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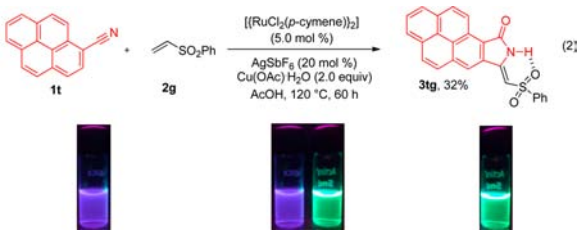
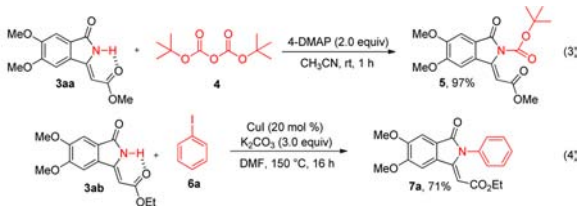


3tg in 32% yield. Compound **3tg** shows absorbance at 415 nm and fluorescence at 470 nm (see the Supporting Information). The starting material pyrene-1-carbonitrile (**1t**) shows absorbance at 355 nm, and fluorescence shows three characteristic bands at 383, 402, and 425 nm. After installation of the isoindolin-1-one moiety, the fluorescence was enhanced 55 nm and a broad single emission band with red shift was observed.

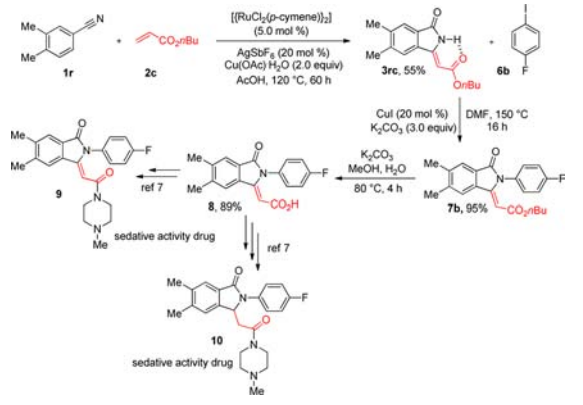
Next, the free N−H group of **3aa** was attempted to protect with di-*tert*-butyl dicarbonate (**4**) (2.0 equiv) in the presence 4-(dimethylamino)pyridine (4-DMAP) (2.0 equiv) in CH_3CN at room temperature for 1 h (eq 3). In the reaction, *N*-BOC-protected



compound **5** was observed in 97% yield. It is very interesting to note that in the product **5** alkene *Z*-stereoselectivity was retained (NOE experiments, see the Supporting Information). Similarly, the N−H group of **3ab** was tried by arylating with iodobenzene (**6a**) in the presence of CuI (20 mol %) and K_2CO_3 (3.0 equiv) in DMF at 150 °C for 16 h (eq 4). In the reaction, *N*-arylated product **7a** was observed in 71% yield, in which alkene *Z*-stereoselectivity was also retained.

The *N*-arylation reaction prompted us to explore the possibility of preparation of pharmaceutical molecules **9** and **10** (Scheme 2).[7,10] These molecules show sedative activity.[10]

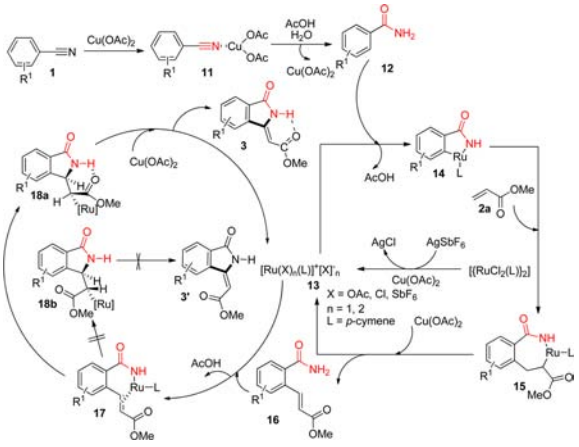
Scheme 2. Synthesis of Sedative Active Molecules



Treatment of 3,4-dimethylbenzonitrile (**1r**) with *N*-butylacrylate (**2c**) under the optimized reaction conditions provided cyclic compound **3rc** in 55% yield in a highly regio- and stereoselective manner (Scheme 2). Later, the free N−H group of compound **3rc** was arylated with 4-fluorophenyl iodide (**6b**) under similar reaction conditions, providing *N*-arylated product **7b** in 95% yield. Then, the ester group of compound **7b** was converted into COOH derivative **8** in 89% yield in the presence of 15% aqueous K_2CO_3 (2.0 mL) in MeOH at 80 °C for 4 h. It is known that the compound **8** can be easily converted into the pharmaceutical molecule **9** and **10**.[7]

A possible reaction mechanism is proposed in Scheme 3 to account for the present cyclization reaction.[5−9] Three different

Scheme 3. Proposed Mechanism

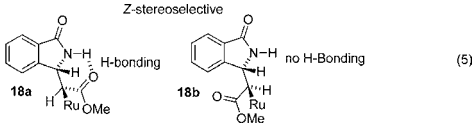


catalytic reactions were involved in the reaction. In the first step, $Cu(OAc)_2$ likely acts as a Lewis acid to which the nitrile group of benzonitrile **1** is coordinated to provide intermediate **11**. In this stage, the Lewis acid likely reduces the electron density of the nitrile group followed by hydration, providing benzamide **12**, and regenerates the active $Cu(OAc)_2$.[11a]

In the second catalytic cycle, $AgSbF_6$ likely removes the chloride ligand from $[[RuCl_2(p\text{-cymene})]_2]$ complex followed by the ligand exchange with $Cu(OAc)_2$ giving a cationic ruthenium species **13**. Coordination of the amide group of **12** into the ruthenium cationic species **13** followed by the *ortho*-metalation provides a five membered ruthenacycle **14** and AcOH.[11b,c] Coordinative insertion of alkene **2** into the Ru−carbon bond of ruthenacycle **14** affords ruthenacycle intermediate **15**. *β*-Hydride elimination of intermediate **15** in the presence of $Cu(OAc)_2$ provides alkenylated product **16** and regenerates the active ruthenium species **13**.

In the third catalytic cycle, the amide group of product **16** coordinates with ruthenium species **13** followed by the intramolecular coordination of double bond to afford intermediate **17** and AcOH. Intramolecular coordinative insertion of N−Ru bond of intermediate **17** into the alkene moiety via aza-Michael addition provides intermediate **18a**. Subsequent *β*-hydride elimination of intermediate **18a** in the presence of $Cu(OAc)_2$ provides product **3** and regenerates ruthenium species **16**.

In fact, in the intramolecular insertion of N−Ru bond of intermediate **17** into the double bond of alkene moiety, two different diastereoselective intermediates such as the ester moiety of alkene and cyclic tertiary C−N−H bond are *syn* to each other (**18a**) and *anti* to each other (**18b**) via aza-Michael addition (Scheme 3, eq 5). These intermediates only decide the nature of



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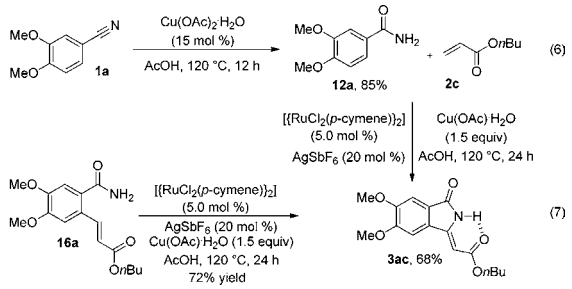
product. If ester and C−N−H are *syn* to each other as intermediate **18a**, only *Z*-stereoselective product **3** would be formed. If both are *anti* to each other as intermediate **18b**, *E*-stereoselective product **3′** would be expected. In the cyclization of aromatic nitrile **1** with **2**, intermediate **18a** was only formed (eq 5). This is mainly due to the intramolecular hydrogen bonding of C−N−H bond to C−O bond of intermediate **18a**.

To support the proposed mechanism, aromatic nitrile **3a** was treated with $Cu(OAc)_2{\cdot}H_2O$ (15 mol %) in acetic acid at 120 °C for 12 h, giving the corresponding benzamide **12a** in 85% yield (eq 6). Later, benzamide **12a** was treated with *n*-butyl acrylate



(**2c**) under similar reaction conditions, providing product **3ac** in 68% yield (eq 7). Further, *ortho*-alkenylated benzamide **16a** was prepared separately and treated with $[[RuCl_2(p\text{-cymene})]_2]$ (5.0 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv) in acetic acid at 120 °C for 24 h. In the reaction, product **3ac** was observed in 72% yield (eq 7). However, the corresponding conversion did not proceed in the absence of ruthenium catalyst with or without the Lewis acid.

In conclusion, we have demonstrated a highly regio- and stereoselective synthesis of (*Z*)-3-methyleneisoindolin-1-ones in good to moderate yields by a ruthenium-catalyzed annulation of aromatic nitriles with activated alkenes. In the reaction, *Z*-stereoselectivity was controlled by the intramolecular hydrogen bonding.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure, starting materials preparation, CIF, and characterization details. 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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