Organic LETTERS

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Skeletal Rearrangement of Cyano-Substituted Iminoisobenzofurans into Alkyl 2-Cyanobenzoates Catalyzed by $B(C_6F_5)_3$

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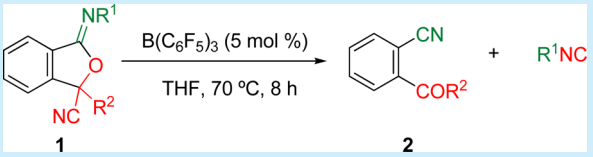
Supporting Information

ABSTRACT: An efficient method for the direct conversion of cyano-substituted iminoisobenzofurans into their corresponding alkyl 2-cyanobenzoates has been developed. This transformation proceeds via cleavage of C−C, C−O, and C−N bonds in starting iminoisobenzofurans. DFT study revealed that intermediate α-iminonitriles are produced in situ via C−C bond formation between 2-iminium benzoates and a cyanide ion. Generation of isocyanide as the byproduct in a more thermodynamic manner in DFT calculations also supports the experimental results.

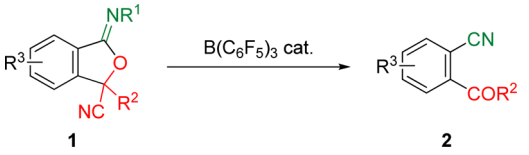


Cyano and ester groups are recognized as one of the most fundamental functional groups and are found in various bioactive molecules and functionalized materials.[1,2] In particular, nitriles can serve as versatile synthetic precursors such as amides,[3] carboxylic acids,[4] aldehydes,[5] and amines.[6] Because of broad transformations of a cyano group, the development of novel and efficient synthetic methods for the preparation of nitriles is of long-standing interest to organic chemists.[7]

Over the past few years, continuous efforts have been devoted to carbonylation or cyanation of aromatic rings.[8] Although there have been several synthetic methods of alkyl 2-cyanobenzoate, which bear both cyano and ester groups in the *o*-position, to the best our knowledge, the reported procedures for these variants to date have been rather routine.

Recently, our group has reported a versatile synthetic route to iminoisobenzofurans by the palladium-catalyzed three-component coupling of arynes, isocyanides, and cyanoformates.[9] On the other hand, transition-metal-catalyzed carbocyanation reactions of unsaturated organic compounds have been developed to synthesize highly functionalized nitriles, which allowed a simultaneous introduction of both a cyano group and other organic functionalities in highly regio-, stereo-, and chemoselective manners.[10] In this regard, we and other research groups have proved that acyl,[11,12] aryl,[13,14] allyl,[15] alkyl,[14,16] alkenyl,[14] and alkynyl[17] cyanides can participate in carbocyanation reactions. Although arynes are synthetically valuable intermediates and have been widely used in the preparation of 1,2-disubstituted arenes,[18] carbocyanation across arynes has not been reported. Herein, we report $B(C_6F_5)_3$-catalyzed reaction of a series of iminoisobenzofurans into the corresponding 2-cyanobenzoates as the exclusive products. Formally, an initial isocyanide moiety in the three-component coupling reaction is installed to the products as the CN source (Scheme 1).

Scheme 1. $B(C_6F_5)_3$-Catalyzed Transformation of Cyano-Substituted Iminoisobenzofurans 1 into 2-Cyanobenzoates 2



To our surprise, with the aid of several Lewis acids, we found that *N*-[3-cyano-3-ethoxy-1(3*H*)-isobenzofuranylidene]-2,4,4-trimethyl-2-pentanamine (**1a**), derived from the palladium-catalyzed three-component coupling reaction of benzyne, 1,1,3,3-tetramethylbutyl isocyanide, and ethyl cyanoformate, accidentally produced ethyl 2-cyanobenzoate (**2a**). A series of Lewis acids were investigated and the results are summarized in Table 1. The reaction did not proceed at all with 20 mol % of CuI in THF at 70 °C (entry 1). When other copper compounds such as CuBr, CuCl, or $Cu(OTf)_2$ were employed as the catalyst, **2a** was formed in moderate yields (entries 2−4). Although we further investigated employing other metal-containing Lewis acids such as $Sc(OTf)_3$, $InCl_3$, $Hf(OTf)_4$, and $AlCl_3$, lower yields of **2a** were obtained (entries 5−8). The reaction did not proceed with a stoichiometric amount of DIBAL-H (entry 9), which is quite different from the result of the formation of α-iminonitriles.[19] Subsequently, aluminum reagents such as AlF_3, $AlBr_3$, $AlCl_3$, and $AlPh_3$ at room temperature were also screened, but the substrate was recovered in all cases. Delightfully, when **1a** was treated with 20 mol % of $B(C_6F_5)_3$, the yield of **2a** was significantly improved to 93% (entry 10). Reducing the amount of $B(C_6F_5)_3$ to 5 mol % gave rise to the comparable yield (90%)

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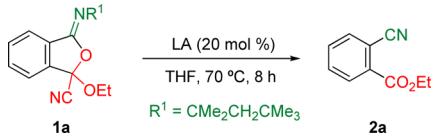
Table 1. Transformation of 1a to 2a Catalyzed by a Lewis Acid[a]



1a 2a

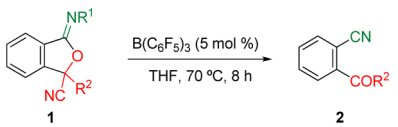
entry	Lewis acid	yield[b] (%)
1	CuI	0
2	CuBr	34
3	CuCl	57
4	$Cu(OTf)_2$	45
5	$Sc(OTf)_3$	>1
6	$InCl_3$	5
7	$Hf(OTf)_4$	>1
8	$AlCl_3$	7
9[c]	DIBAL-H	0
10	$B(C_6F_5)_3$	93
11[d]	**$B(C_6F_5)_3$**	**91 (90)**
12[d,e]	$B(C_6F_5)_3$	84
13	$BF_3{\cdot}Et_2O$	0
14	BPh_3	0

[a]The reactions were carried out using **1a** (0.1 mmol) and Lewis acid (20 mol %) in THF (0.5 mL) at 70 °C for 8 h. [b]Determined by the ^1H NMR spectra using CH_2Br_2 as an internal standard. An isolated yield is shown in parenthesis. [c]1 equiv of DIBAL-H was used. [d]5 mol % of $B(C_6F_5)_3$ was used. [e]The reaction was carried out at room temperature for 24 h.

of **2a** (entry 11). The transformation was also proceeded with 5 mol % of $B(C_6F_5)_3$ at room temperature to afford **2a** in 84% yield (entry 12). However, other boron reagents such as $BF_3{\cdot}Et_2O$ or BPh_3 did not produce **2a** (entries 13 and 14).

The scope of this transformation of a variety of cyano-substituted iminoisobenzofurans **1** into the corresponding alkyl 2-cyanobenzoates **2** is shown in Table 2. A series of iminoisobenzofurans **1a**–**f** bearing Et, Me, ^{n}Pr, ^{i}Pr, ^{n}Bu, and Bn substituents were transformed efficiently to afford the corresponding products **2a**–**f** in high to excellent yields (entries 1–6). Under identical reaction conditions, this reaction was not applicable to the formation of iminoisobenzofuran **1g**, prepared from a three-component coupling of the benzyne precursor,

Table 2. Scope of $B(C_6F_5)_3$-Catalyzed Synthesis of 2[a]



1 2

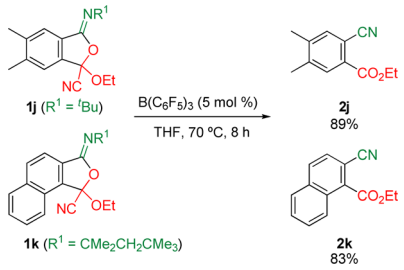
entry	1	R^1 =	R^2 =	product	yield[b] (%)
1	**1a**	$CMe_2CH_2CMe_3$	OEt	**2a**	90
2	**1b**		OMe	**2b**	99
3	**1c**		O^{n}Pr	**2c**	89
4	**1d**		O^{i}Pr	**2d**	94
5	**1e**		O^{n}Bu	**2e**	88
6	**1f**		OBn	**2f**	82
7	**1g**		Ph	**2g**	0
8	**1h**	^{t}Bu	OEt	**2a**	88
9[c]	**1i**	1-adamantanyl	OEt	**2a**	50

[a]The reactions were carried out using **1** (0.1 mmol) and $B(C_6F_5)_3$ (5 mol %) in THF (0.5 mL) at 70 °C for 8 h. [b]Isolated yields. [c]10 mol % of $B(C_6F_5)_3$ was used for 24 h.

1,1,3,3-tetramethylbutyl isocyanide, and benzoyl cyanide (entry 7). Other iminoisobenzofurans **1h** and **1i** bearing the different R^1 substituents could also participate in the reaction to afford **2a** in 88% and 50% yields, respectively (entries 8 and 9).

Iminoisobenzofurans bearing substituents on the phenyl ring can also be transformed (Scheme 2). Treatment of **1j**, derived

Scheme 2. Substrate Scope

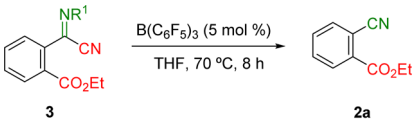


from 4,5-dimethylbenzyne, *tert*-butyl isocyanide, and ethyl cyanoformate with a catalytic amount of $B(C_6F_5)_3$, gave **2j** in 89% yield. Iminoisobenzofuran **1k** could also be applied to the present transformation, leading to product **2k** in 83% yield.

To gain insight into the reaction mechanism of this novel transformation, the time-course experiments were performed.[20] An NMR monitoring experiment was conducted using **1a** as a model substrate at 70 °C. Interestingly, iminoisobenzofuran **1a** was immediately transformed to the corresponding cyanobenzoate **2a** and α-iminonitrile **3a** in 31 and 41% yields, respectively. After 0.5 h, **1a** was completely consumed, while **3a** was increased to 47% yield, accompanied by **2a** in 34% yield. Later, **2a** was gradually generated along with **3a**. In contrast, the NMR-monitoring experiment performed at room temperature led to **2a** in less than 20% yield after 1 h, and **3a** was also formed slowly. After 14 h, the substrate **1a** was completely consumed and cyanobenzoate **2a** and α-iminonitrile **3a** were formed in 49 and 39% yields, respectively. Consequently, **3a** was gradually diminished until the reaction time was prolonged to 24 h, affording **2a** as the exclusive product.

Additional experiments were also performed, as shown in Scheme 3. When **3a** was treated with 5 mol % of $B(C_6F_5)_3$, **2a** was

Scheme 3. Effect of R^1 Group on $B(C_6F_5)_3$-Catalyzed Transformation of 3 to 2a



3 2a

3a: R^1 = $CMe_2CH_2CMe_3$, 97%
3b: R^1 = cyclohexyl, 0%

formed in 97% yield, whereas **3b** bearing the cyclohexyl imine substituent could not afford **2a** and the substrate was recovered completely, indicating that the substituent of imine strongly affects the success of this transformation.

It has been reported that Lewis acid induced reductive cleavage of furans, leading to the acyclic products,[21] and that a C–N bond of isocyanides can be cleaved.[22] On the basis of previous works reported, we carried out density functional theory (DFT) calculations for a plausible mechanism, as shown in Figure 1. Although this skeletal transformation includes two bond cleavages (C–C and C–O) and one bond formation (C=O), the activation barrier (**INT1** to **TS1**) is moderate (~50 kJ/mol),

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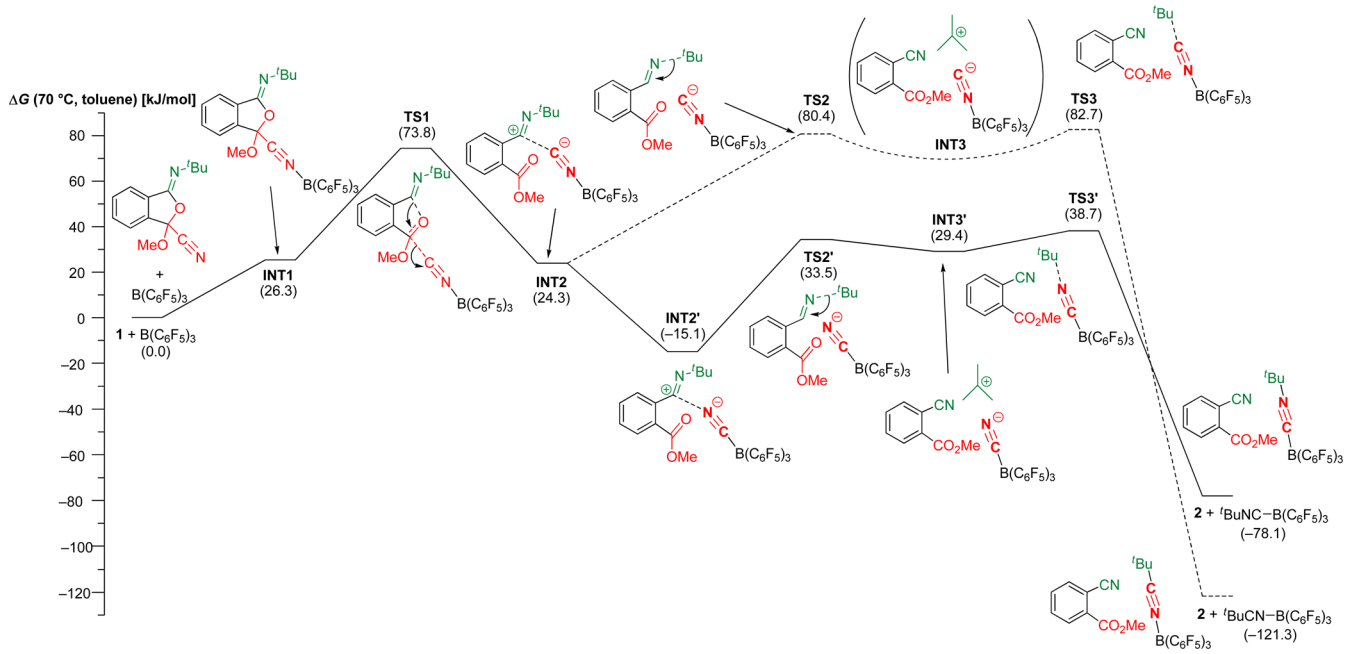
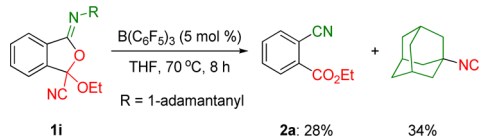


Figure 1. Computed Gibbs free energies (kJ/mol) at 70 °C and 1 atm for $B(C_6F_5)_3$-catalyzed transformation pathway from iminoisobenzofurans **1** to cyanobenzoates **2**. Gibbs energies in kJ/mol are shown, relative to **1** + $B(C_6F_5)_3$.

presumably owing to high stability of generated a tertiary carbocation as well as a strong Lewis acidity of $B(C_6F_5)_3$.

Subsequently, we found that both **INT2** and cyanide-inverted **INT2′** possess electrostatic interactions (C−CN = 3.07 Å for **INT2**; C−NC = 2.90 Å for **INT2′**) but that inverted **INT2′** is more preferable ($\Delta\Delta G$ = 39.4 kJ/mol). It is noteworthy that the direct C−CN bond formation in **INT2** generates α-iminonitriles **3**.[19] The ^{1}H NMR time-course experiments indicate that α-iminonitrile **3** is formed as the intermediate during this transformation. The activation barrier of C−N bond cleavage from **INT2′** is also moderate (~50 kJ/mol) with a release of a tertiary carbocation. Given that the secondary α-iminonitrile **3b** could not afford the corresponding 2-cyanobenzoate (Scheme 3), **INT3′** is reasonable from the viewpoint of the stable tertiary carbocation.[23] Finally, C−N bond formation affords ^{t}BuNC, not ^{t}BuCN, which is consistent with the experimental result, as shown in Scheme 4. When iminoisobenzofuran **1i** was treated with 5 mol % of $B(C_6F_5)_3$ at 70 °C for 8 h, **2a** was formed in 28% yield, accompanied by 1-adamantanyl isocyanide in 34% yield.

Scheme 4. $B(C_6F_5)_3$-Catalyzed Transformation of 1i to 2a with the Formation of Isocyanide



In summary, we have disclosed the $B(C_6F_5)_3$-catalyzed transformation of cyano-substituted iminoisobenzofurans into the corresponding alkyl 2-cyanobenzoates in good yields. In this transformation, the original isocyanide moiety acts as the CN source via the C−N bond cleavage of the tertiary imine substituents. This novel synthetic method may open a new window for the synthesis of alkyl 2-cyanobenzoates. Further studies on a direct synthesis of alkyl 2-cyanobenzoates by the palladium-catalyzed cyanoesterification of arynes are currently underway.

Computational Methodology

All calculations in the present study were performed with the Gaussian 09 program[24] using the Becke three parameter plus Lee−Yang−Parr (B3LYP) density functional theory (DFT) method.[25] For all geometry optimizations and normal coordinate analyses at stationary points, we used the 6-31G(d) basis set for all atoms.[26] We also employed a larger basis set for single-point energy calculations, 6-311+G(d) for all atoms.[27,28] In the single-point energy calculations, the polarized continuum method (PCM),[29,30] with a dielectric constant of 7.58 (THF), was also used. Corrections for Gibbs energy were calculated from the normal coordinate analyses of the stationary points at the thermal state (70 °C, 1 atm).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full characterizations 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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