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Brønsted Acid-Promoted Hydrocyanation of Arylalkenes

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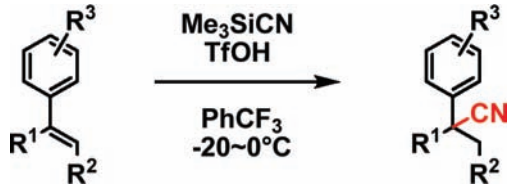
ABSTRACT



Nonactivated arylalkenes are effectively converted to tertiary benzylic nitriles in the presence of triflic acid and trimethylsilyl cyanide. The hydrocyanation reactions result in good to excellent yield when electron-donating groups are substituted on the benzene ring. The reaction conditions are mild and relatively safe, notably without need for handling hazardous hydrogen cyanide gas, providing simple and easy access to tertiary benzylic nitriles. The reaction was applied to the preparation of a PDE4 inhibitor (3) as well as a series of analogues.

Construction of an all-carbon-substituted quaternary center has been an important challenge in organic synthesis.[1] Tertiary benzylic nitriles have proven to be not only important building blocks[2] but also biologically important compounds, e.g., slow calcium channel antagonists[3] and phosphodiesterase (PDE) 4 inhibitors.[4] In general, this class of compounds has been prepared by double alkylations of benzylic nitrile,[4a] displacement of tertiary benzylic alcohol or halide with cyanide,[5,4b] or oxidative benzylic cyanation of aromatic hydrocarbons.[6] Recently, direct arylations of secondary nitrile anions with aryl halides such as SNAr-type substitution with aryl fluorides[7,4b] or Pd-catalyzed arylation with aryl halides[8] have become powerful alternatives but still have the limitation of requiring a strong base for generating the secondary nitrile anions.

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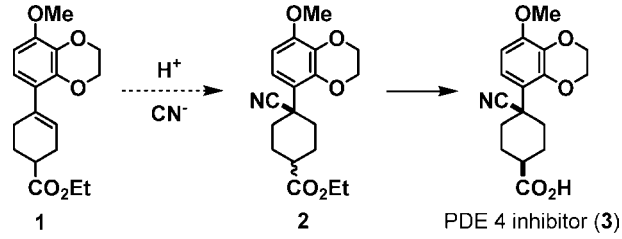
Hydrocyanations of arylalkenes provide a direct path to such benzylic nitriles and, moreover, have the advantage of easy access to starting materials. Transition-metal-free hydrocyanations had long been realized, with the only difficulty being a requirement of extremely high temperatures and pressures.[9] Transition-metal (Co, Ni, Pd) catalyzed hydrocyanations of alkenes to form primary or secondary nitriles have been established by both academia and industry.[10] However, their application to substituted aryl alkenes had been very limited.[11] In addition, most of the above procedures require handling of hazardous hydrogen cyanide, which critically limits applications for fine chemical synthesis.

In the course of synthetic study of a PDE 4 inhibitor (**3**),[4c] which featured a tertiary benzylic nitrile, we envisioned that 1-arylcyclohexene derivative **1** might be converted to nitrile **2** in presence of an appropriate Brønsted acid and cyanide source, despite the fact that such acid-promoted hydrocyanation has been very rare (Scheme 1).[12] This idea was based

Scheme 1. Retrosynthesis of a PDE 4 Inhibitor (**3**)



first on the assumption that the possible intermediate benzylic cation should be stabilized by the electron-donating substituents of **1**. In this paper, we describe a discovery and optimization of a Brønsted acid-promoted hydrocyanation of arylalkenes which provides a new and practical synthetic approach to tertiary benzylic nitriles.

Our study began with exploration of a Brønsted acid. To a dichloromethane solution of cyclohexene **1** (see the Supporting Information) and trimethylsilyl cyanide (Me_3SiCN), selected as an easily handled cyanide source, each of several Brønsted acids was added at room temperature. Both acids and trimethylsilyl cyanide were used in large excess (ca. 100 equiv) for the purpose of testing the concept. Use of inorganic acids (e.g., 36% HCl, 47% HBr, H_3PO_4, PPA) only gave recovered starting material. Sulfuric acid caused decomposition of substrate. With TFA, a trace of desired nitrile **2** was detected by HPLC. Both 60% $HClO_4$ and methanesulfonic acid gave **2** in moderate conversion. Finally, triflic acid (TfOH) was identified as the most effective promoter to provide **2** with high conversion.

Encouraged with this result, we moved on to solvent optimization employing 2.0 equiv of triflic acid and 1.5 equiv of trimethylsilyl cyanide. As shown in Table 1, the use of polar solvents such as DMSO did not provide **2** (entries 1−5). Hydrocarbon solvents afforded a moderate yield of **2** (entries 8 and 9) but seemed unsuitable because of the forming heterogeneous reaction mixture. Halogenated solvents such as dichloromethane gave the best results (entries 10−12). Trifluorotoluene (entry 11) was selected for further optimization, particularly from an environmental viewpoint.[13]

Table 1. Solvent Effects[a]

			assay yield[b] (%)		
entry	solvent	time (h)	**1**	**2**	(*cis*/*trans*)[c]
1	DMSO	72	81	0	
2	DMF	72	82	0	
3	EtOH	24	84	0	
4	DME	24	78	0	
5	EtOAc	24	65	3	(52/48)
6	CH_3CN	5	2	14	(65/35)
7	TFA	9	4	23	(66/34)
8	Hexane	2	5	29	(63/37)
9	Toluene	2	0	36	(70/30)
10	EDC[d]	2	0	45	(62/38)
11	$PhCF_3$	2	0	54	(63/37)
12	CH_2Cl_2	2	0	56	(63/37)

[a] Conditions: **1** (0.05 mmol), Me_3SiCN (1.5 equiv), TfOH (2.0 equiv), solvent (0.5 mL), rt. [b] HPLC yield. [c] Ratio of *cis*/*trans* isomers of **2** was determined by HPLC. [d] Ethylene dichloride.

Optimal stoichiometry of triflic acid and trimethylsilyl cyanide was examined (Table 2). Triflic acid treatment (absence of trimethylsilyl cyanide) caused degradation of **1**, mainly giving a dimer **4** (entry 1).[14] Minimizing exposure to triflic acid, solution of **1** was added last and slowly (entries 2−6). Use of a slightly excess equivalent of triflic acid compared to trimethylsilyl cyanide was essential for reducing dimer formation and provided a higher yield of **2**, which implies that residual triflic acid plays a key role. Alternative cyanide sources were also examined. Acetone cyanohydrin, a less expensive cyanide source, provided a lower yield and slower reaction rate (entry 9), while sodium cyanide and zinc

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(12) $AlCl_3$/HCl-mediated hydrocyanation of 1,1-diphenylethylene was described in ref 9.

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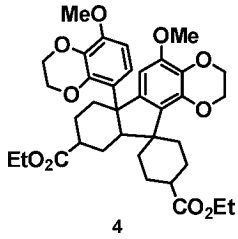
Table 2. Cyanide Source and Reagent Stoichiometry[a]



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entry	CN source	(equiv)	TfOH (equiv)	assay yield (%)[e] 1	4	2	(*cis*/*trans*)[f]
1	none		1.0	5	72	0	
2	Me_3SiCN	(1.5)	0.5	89	0	2	(45/55)
3[b]	Me_3SiCN	(1.5)	2.0	3	10	82	(65/35)
4[c]	Me_3SiCN	(1.2)	1.3	8	7	81	(57/43)
5[c]	Me_3SiCN	(2.0)	2.1	3	4	90	(59/41)
6[d]	Me_3SiCN	(5.0)	5.2	2	3	93	(62/38)
7	NaCN	(5.0)	6.0	<1	NT	15	(74/26)
8	ZnCN	(1.5)	2.0	<1	NT	1	(65/35)
9[c]	ACH[g]	(4.4)	3.5	7	12	69	(62/38)

[a] Reaction conditions: CN source, TfOH, $PhCF_3$ (5 mL), then **1** (0.5 mmol), 20 °C. [b] −20 to −5 °C. [c] −20 to 0 °C. [d] −20 °C. [e] HPLC yield. [f] Ratio of *cis*/*trans* isomers of **2** was determined by HPLC. [g] Acetone cyanohydrin.

cyanide turned out to be ineffective for this transformation (entries 7 and 8).

We investigated the scope and limitation of this reaction by applying it to various arylalkene derivatives (Table 3). As expected from the proposed mechanism, arylalkenes that were substituted by electron-donating groups provided high yield (entries 3−7), as well as tolyl substrate (entry 2). Interestingly, simple phenyl substrate gave the nitrile, in spite of the lack of electron-donating substitute (entry 1). Linear substrate and a more complicated steroid skeleton were allowed (entries 8 and 9).

A plausible mechanism for the reaction is presented in Scheme 2. When an equimolar amount of triflic acid to trimethylsilyl cyanide had been added to the substrate **1**, the mixture turned red, which probably indicated generation of benzylic cation, and then the reaction started. This observation suggests that after formation of trimethylsilyl triflate and hydrogen cyanide the residual triflic acid protonates the aryl alkene to form the benzylic cation. Subsequent cyanide attack would afford the product and regenerate triflic acid. To prove this catalytic role of triflic acid, we demonstrated this reaction using 0.2 equiv of triflic acid with 20 equiv of hydrogen cyanide, which was distilled from mixture of sodium cyanide and sulfuric acid, in trifluorotoluene at −5 °C. Almost equal results in reaction rate, *cis*/*trans* selectivity (63/37), and yield of **2** (74%) were obtained, strongly supporting the proposed mechanism.[15] In addition, the failure with polar solvents (Table 1 entries 1−6) was presumed to have occurred because the Lewis basicity of these solvents should reduce the protonating ability of triflic acid to inhibit generation of the benzylic cation.

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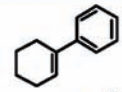
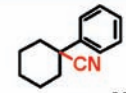
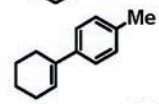
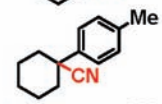
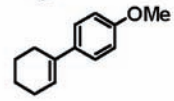
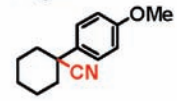
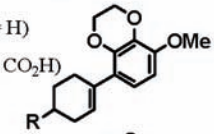
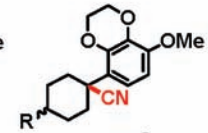
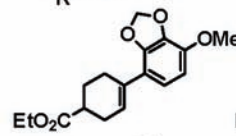
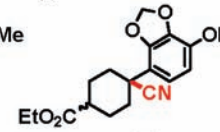
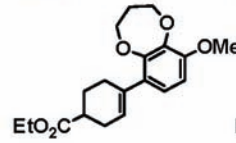
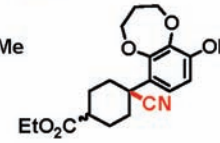
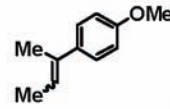
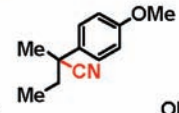
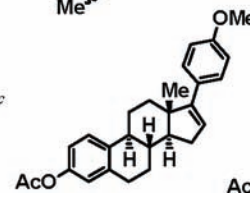
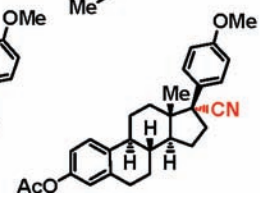
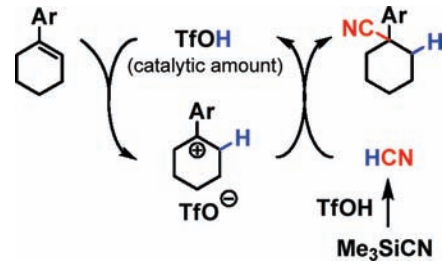
Table 3. Hydrocyanation of Various Arylalkenes[a]

entry	alkene	nitrile	yield (%)[d]
1			30
2			79
3			95
4 (R = H)			97
5 (R = CO_2H)			71 (72/28)[e]
6			49 (64/36)[f]
7			82 (62/38)[f]
8[b]			75
9[c]			48

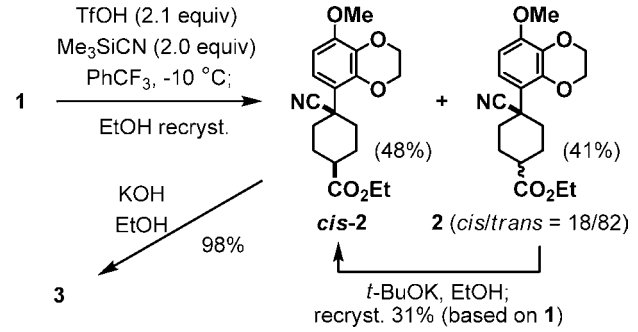
[a] Conditions: alkene (0.5 mmol), TfOH (5.2 equiv), Me_3SiCN (5.0 equiv), $PhCF_3$ (5 mL), −20 to 0 °C (equiv of TfOH−Me_3SiCN were 10.5−10.0 equiv for entry 5 and 2.1−2.0 equiv for entry 6). [b] *E*/*Z* ratio is 6/4. [c] CH_2Cl_2 was used as solvent. [d] Isolated yields. [e] Yield and ratio of *cis*/*trans* isomers were determined by HPLC. [f] Ratio of *cis*/*trans* isomers was determined by NMR.

Scheme 2. Proposed Mechanism



We employed the optimal conditions of Table 2, entry 5, for large-scale campaign (Scheme 3). The hydrocyanation

Scheme 3. Synthesis of a PDE 4 Inhibitor (**3**)



proceeded smoothly to result in *cis*/*trans* mixture **2** (*cis*/*trans* = ca. 6/4), which was readily separated by crystallization to obtain pure ***cis*-2** crystals. *Trans*-rich mother liquor could be converted via base-induced isomerization to ***cis*-2**, achieving 79% combined yield. Hydrolysis afforded multigram quantities of **3** in satisfactory purity (see the Supporting Information). More details about this process will be reported in forthcoming papers.

In summary, we found and optimized the Brønsted acid-promoted hydrocyanation of arylalkenes. The reaction was effectively promoted by triflic acid in the presence of trimethylsilyl cyanide, resulting in fair to excellent yields. The reaction is dependent upon the electron-donating nature of substituent on the benzene ring. The reaction conditions are mild and relatively safe compared to the known classical hydrocyanations, notably without need for handling hazardous hydrogen cyanide gas, providing simple and easy access to tertiary benzylic nitriles. The reaction was applied to the synthesis of a PDE 4 inhibitor (**3**) and its analogues. Further extension and investigation in the field of medicinal chemistry are currently ongoing.

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Supporting Information Available: Reaction procedures, substrate synthesis, and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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