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A Concise Synthesis of 2-(2-Hydroxyphenyl)acetonitriles *via* the *o*-Quinone Methides Generated from 2-(1-Tosylalkyl)phenols†

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A concise synthesis of 2-(2-hydroxyphenyl)acetonitriles has been developed through reaction of trimethylsilyl cyanide and the *o*-quinone methides *in situ* generated from 2-(1-tosylalkyl)phenols under basic conditions. In addition, 2-(2-hydroxyphenyl)acetonitriles could be conveniently transformed to benzofuranones.

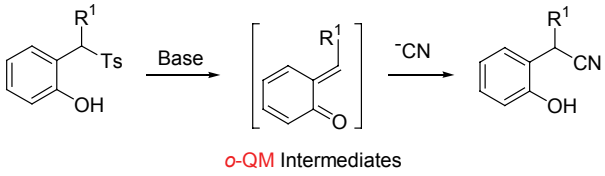
Keywords 2-(2-hydroxyphenyl)acetonitriles, *o*-quinone methides, 2-(1-tosylalkyl)phenols

Introduction

Nitriles are ubiquitous and prevalent in various biologically active compounds,[1] natural products[2] and industrial processes (polymer, agrochemicals, dyestuffs and pigments),[3] and are versatile intermediates for the synthesis of other functionalized compounds such as amines, carboxylic acid derivatives, aldehydes, ketones and *N*-heterocycles.[4] Therefore, the concise synthesis of nitriles has received extensive attention in the past decades and various efficient approaches for the construction of nitriles have been developed. Common routes for the preparation of nitriles contain Sandmeyer-type reaction,[5] cyanation of alkyl or aryl halides,[6] dehydration of amides or aldoximes,[7] metal-catalyzed cyanomethylation,[8] oxidation of primary amines,[9] hydrocyanation of alkenes or alkynes[10] and so on.[11] However, most of these existed routes have several drawbacks involving harsh reaction conditions, tedious processes, limited selectivity and unsatisfactory yields, impeding their wider application. Hence, developing a convenient, efficient and easy operating method for the rapid synthesis of nitriles is still highly desirable.

o-Quinone methides (*o*-QMs) are a prominent class of intermediates in numerous chemical and biological processes.[12] Consequently, several methods have been successfully developed for the generation of *o*-QMs, including tautomerization, oxidation, acid or base catalysis, thermolysis, photolysis and olefination of *o*-quinones.[13,14] Recently, we reported base-induced desulfonylation of 2-(1-tosylalkyl)phenols to generate *o*-QMs and the reaction of *o*-QMs with sulfur ylides to afford *trans*-2,3-dihydrobenzofurans.[15] Considering the *o*-QM intermediates could be conveniently generated from 2-(1-tosylalkyl)phenols under basic conditions, we speculated that *o*-QMs generated *in situ* could be rapidly trapped by cyanide anion to allow the formation of 2-(2-hydroxyphenyl)acetonitriles. Herein, we described a convenient and straightforward protocol for the rapid synthesis of 2-(2-hydroxyphenyl)acetonitriles through reaction of trimethylsilyl cyanide and the *o*-QMs generated from 2-(1-tosylalkyl)phenols under basic conditions (Scheme 1).

Scheme 1 A concise strategy for the synthesis of 2-(2-hydroxyphenyl)acetonitriles



Experimental

General procedure for synthesis of 2-(2-hydroxyphenyl)acetonitriles

A reaction mixture of 2-(1-tosylalkyl)phenol **1** (0.40 mmol), trimethylsilyl cyanide (60 μL, 0.48 mmol), TBAF (1 mol•L^{-1} in THF, 58 μL, 0.058 mmol) and K_2CO_3 (66 mg, 0.48 mmol) in acetonitrile (4 mL) was stirred at 80 ℃ for 12 h. The reaction mixture was cooled to room temperature. Then water (20 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with dichloro-

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methane (30 mL×3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using petroleum ether and ethyl acetate to give the desired product 2-(2-hydroxyphenyl)acetonitriles **2**.

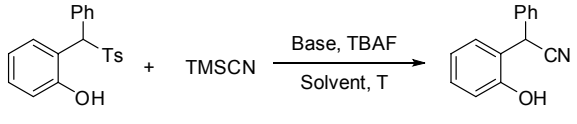
2-(2-Hydroxyphenyl)-2-phenylacetonitrile (2a) 94% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58—7.28 (m, 6H), 7.26—7.04 (m, 3H), 4.31 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.8, 150.2, 133.6, 130.1, 129.4, 127.6, 126.1, 123.2, 121.2, 117.5, 110.1, 94.4. HRMS calculated for $C_{14}H_{12}NO$ $[M+H]^+$ 210.0919, found 210.0908.

Results and Discussion

The initial investigation was conducted with 2-(phenyl(tosyl)methyl)phenol **1a** and trimethylsilyl cyanide (TMSCN) in the presence of K_2CO_3 (1.2 equiv.) and TBAF (0.12 equiv.) at room temperature. To our delight, the desired product **2a** was isolated in 33% yield (Table 1, Entry 1). Increasing the reaction temperature to 80 ℃, the reactivity was effectively improved and high yield was obtained (Entry 2). The base played a prominent role in the reaction and assisted desulfonylation to generate *o*-QM intermediates. Several common inorganic bases, such as Cs_2CO_3, K_3PO_4, NaOH and KO^{t}Bu, only delivered the desired product in moderate yields (Entries 3—6). Further evaluation of solvents revealed that the transformation was sensitive to the reaction medium. CH_3CN was proved to be the most favorable solvent giving an excellent yield (Entries 7—9). Therefore, the optimal conditions for this reaction were established by using K_2CO_3 (1.2 equiv.) as base, TBAF (0.12 equiv.) as initiator and CH_3CN as solvent at 80 ℃.

With the aforementioned reaction conditions in hand, we next sought to investigate the scope of the substrate generality in present reaction system. As summarized in Scheme 2, the transformations proceeded very well and moderate to excellent yields were achieved. For aryl substituents as R^1, electronic property had slight influence on the yield. For instance, the reactions provided the desired products **2a** and **2g** in 94% and 92% yields, respectively. However, when alkyl moieties were used as R^1, elimination of hydrogen cyanide from the nitrile products was very facile and that led to the resulting alkene compounds as the final products. The substituents on the benzene ring of the phenol did not affect the reaction. 2-(Phenyl(tosyl)methyl)naphthalen-1-ol **1j** was also a suitable reaction partner and provided the target product in moderate yield.

Table 1 Optimization for the reaction of 2-(phenyl(tosyl)methyl)-phenol **1a** with trimethylsilyl cyanide[a]

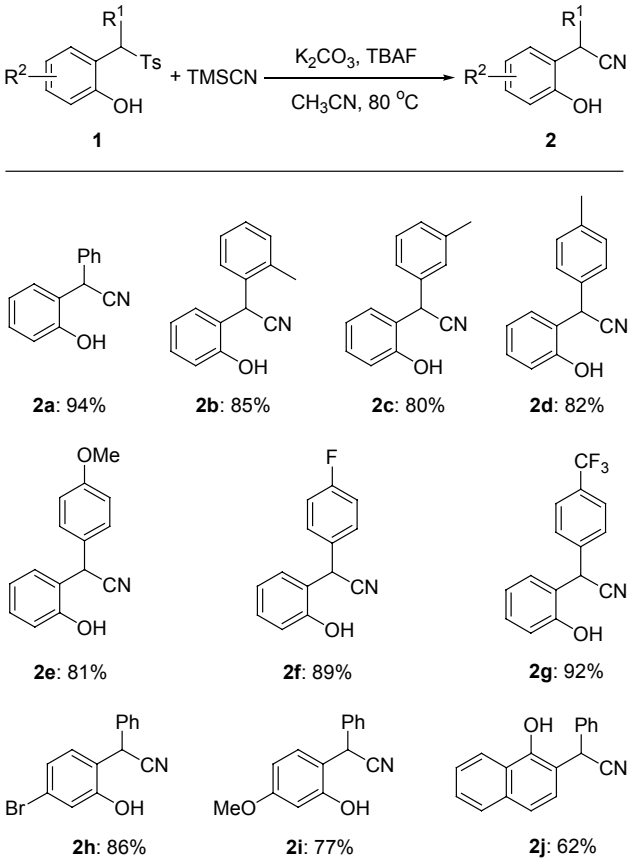


1a **2a**

Entry	Base	Solvent	*T*	Yield[b]/%
1	K_2CO_3	CH_3CN	r.t.	33
2	K_2CO_3	CH_3CN	80 ℃	94
3	Cs_2CO_3	CH_3CN	80 ℃	77
4	K_3PO_4	CH_3CN	80 ℃	54
5	NaOH	CH_3CN	80 ℃	77
6	KO^{t}Bu	CH_3CN	80 ℃	69
7	K_2CO_3	Toluene	80 ℃	36
8	K_2CO_3	DMF	80 ℃	81
9	K_2CO_3	Dioxane	80 ℃	15

[a] Conditions: **1a** (0.40 mmol), TMSCN (0.48 mmol), base (1.2 equiv.), TBAF (0.12 equiv.), solvent (4 mL), 12 h. [b] Isolated yields. TMSCN: trimethylsilyl cyanide; TBAF: tetrabutylammonium fluoride.

Scheme 2 Scope for the reaction of 2-(1-tosylalkyl)phenols **1** with trimethylsilyl cyanide[a]

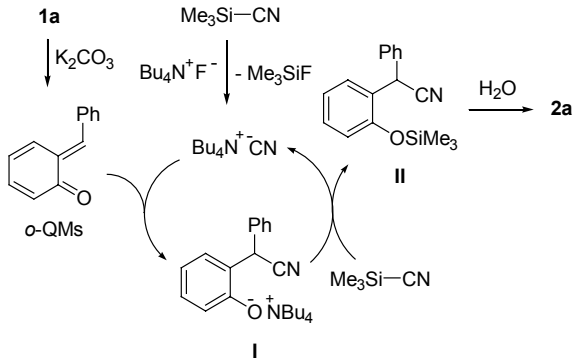


[a] Conditions: **1** (0.40 mmol), TMSCN (0.48 mmol), K_2CO_3 (1.2 equiv.), TBAF (0.12 equiv.), CH_3CN (4 mL), 80 ℃, 12 h. Isolated yields.

Based on the above experimental results and previous studies on fluoride-triggered autocatalysis mechanism of the Sakurai-Hosomi reaction reported by Dai and Hou,[16] a plausible mechanism was illustrated in Scheme 3. Firstly, the fluoride ion serves as an initiator to generate cyanide anion. Subsequently, the cyanide anion undergoes Michael addition with *o*-QM intermediate generated *in situ* to deliver the intermediate **I**, which activates trimethylsilyl cyanide to regenerate active cyanide anion and afford the intermediate **II**, fol-

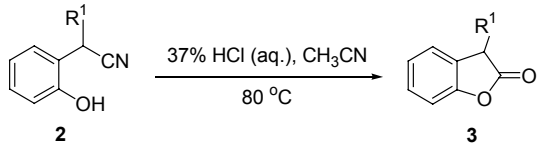
lowed by hydrolysis of intermediate **II** to afford the desired product **2a**.

Scheme 3 A plausible mechanism



The product, 2-(2-hydroxyphenyl)acetonitrile could be further transformed into the corresponding benzofuranone,[17] which is an essential scaffold in a plethora of important natural products and shows a wide range of biological activities. In the presence of hydrogen chloride, 2-(2-hydroxyphenyl)acetonitrile products **2a**—**2c** were smoothly converted to benzofuranones **3a**—**3c** in high yields (Scheme 4).

Scheme 4 Synthesis of benzofuranones **3**



R^1	Ph	4-MeC_6H_4	4-$MeOC_6H_4$
Yield/%	77 (**3a**)	82 (**3b**)	86 (**3c**)

Conclusions

In conclusion, we have developed a concise protocol for the rapid synthesis of 2-(2-hydroxyphenyl)acetonitriles by using trimethylsilyl cyanide and 2-(1-tosylalkyl) phenols *via* the formation of *o*-QM intermediates under basic condition to give moderate to excellent yields. Moreover, 2-(2-hydroxyphenyl)acetonitriles could be conveniently transformed to benzofuranone derivatives in the presence of hydrogen chloride.

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