The Highly Efficient 1,4-Addition of TMSCN to Aromatic Enones Catalyzed by CsF with Water as the Additive

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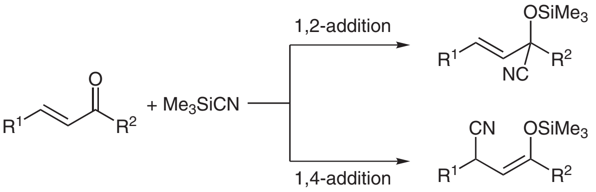
Abstract: An efficient 1,4-addition of TMSCN to aromatic enones has been achieved in excellent yields (91–99%) by CsF (1 mol%) as the catalyst and H_2O (4 equiv) as the additive in refluxing dioxane within 2–7 hours.

Key words: 1,4-addition reaction, enones, nitriles, regioselectivity, CsF

The conjugate addition of α,β-unsaturated carbonyl compounds is one of the supremely important C–C bond formation reactions in organic synthesis.[1] Unlike the well developed transition metal-catalyzed 1,4-addition of aryl[2] and alkyl reagents,[3] the regioselective 1,4-addition of weakly nucleophilic cyanide to α,β-unsaturated carbonyl compounds remains challenging (Equation 1).

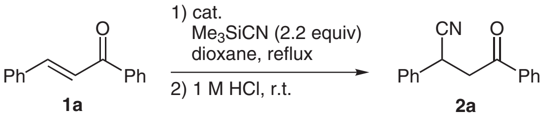


Equation 1

In the literature, 1,4-addition of cyanide to enones has been applied to syntheses of biologically active molecules[4] and complex natural products.[5] In this context, mild cyanide source such as TMSCN[6] and Et_2AlCN[7] are frequently employed with catalysts such as Et_3Al,[6,9a] $Pd(OAc)_2$,[8] and Lewis acids.[9] Ionic liquid and microwave have been utilized in this reaction in line of the concept of green chemistry.[10,11] Recently, Shibasaki and co-workers applied an entirely distinct Ni(0)–cyclooctadiene (COD) complex to the elegant synthesis of Tamiflu,[12] an important anti-influenza drug, and subsequent Ni(0) and $Gd(OTf)_3$ as the cooperative catalyst to the 1,4-addition of TMSCN to a wide variety of aliphatic enones.[13] The first synthetically useful catalytic enantioselective conjugate addition of cyanide to enones is also documented by Shibasaki.[14] Despite these achievements, practical regioselective 1,4-additon of TMSCN to enones is still demanding.[15] Herein, we report an efficient CsF-catalyzed 1,4-addition of TMSCN to aromatic enones in the presence of water.

In view of high affinity of silicon for fluoride anion,[16] we suppose that fluoride could activate TMSCN. Model experiments were conducted with chalcone (**1a**) and TMSCN to optimize the reaction conditions (Table 1). Initially, various fluorides were examined in dioxane at refluxing temperature. Thus, 41% yield was obtained with hydrated KF (20 mol%, entry 1). On the other hand, Bu_4NF gave an inferior 75% yield (entry 2). Surprisingly, the reaction proceeded smoothly in the presence of CsF[17] to afford the product **2a** in 92% yield (entry 3). Comparing the results of KF and CsF, a possible 'cesium effect' cannot be ruled out at present.[18] Nevertheless, a control

Table 1 Optimization of Reaction Conditions[a]



1a **2a**

Entry	Cat. (mol%)	Additive (equiv)[b]	Concn (M)[c]	Time (h)	Yield (%)[d]
1	KF·2H_2O (20)		0.1	5.5	41
2	Bu_4NF (20)		0.1	5.5	75
3	CsF (20)		0.1	5.5	92
4	CsCl (20)		0.1	5.5	16
5[e]	CsF (20)		0.1	5.5	30
6[f]	CsF (20)		0.1	5.5	7
7	CsF (20)	H_2O (4)	0.1	4	99
8	CsF (5)	H_2O (4)	0.3	4	99
9[g]	CsF (1)	H_2O (4)	0.3	4	99

[a] Unless otherwise noted, all reactions are conducted with 0.15 mmol (0.1 M) or 0.3 mmol (0.3 M) of chalcone (**1a**) in dioxane (1.5 mL or 1.0 mL, respectively) under argon.
[b] Relative to **1a**.
[c] Concentration of chalcone.
[d] Isolated yield.
[e] Performed in THF.
[f] Performed at 40 °C.
[g] Comparable results are obtained under open-air conditions.

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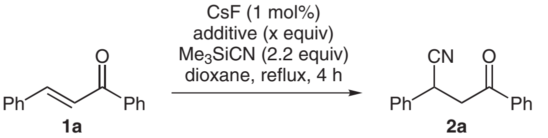
experiment using CsCl yielded the product in only 16% yield (entry 4). Subsequently, the effects of solvent and reaction temperature were investigated. The yield decreased sharply in THF (entry 5) and in other solvents,[19] or at lower temperature (entry 6).

Considering proton might be needed to complete the reaction sequence, the effect of water as an additive was studied (vide infra).[20] Dramatically, the reaction proceeded cleanly with four equivalents of water within four hours (entry 7). Further decreasing the catalyst loading down to 5 mol% and 1 mol% gave almost quantitative yields at slightly concentrated solutions (entries 8 and 9). Comparable results were obtained when the reaction was conducted under open-air conditions (entry 9).

To examine the effect of additives, water and other proton sources were added to the reaction mixture (Table 2). Without any proton additive, the yield was 52% (entry 1). Increasing the amount of H_2O from 0.3 to 1 equivalent, the yield of **2a** increased gradually from 59% to 70% (entries 2 and 3). Other proton sources such as alcohols and phenols (2,6-dimethylphenol) gave inferior yields (entries 4 and 5). It implied that H_2O was not only used to provide proton.[20] The optimum yield was obtained with four equivalents of water (entry 6). However, using excessive amount of H_2O reduced the product yield (entry 7).

Table 2 Effect of Protonic Additive

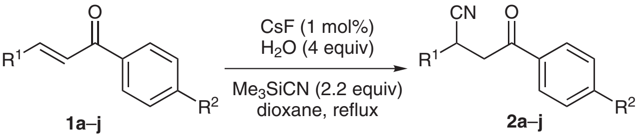


Entry[a]	Additive (equiv)[b]	Yield (%)[c]
1[d]	none	52
2[d]	H_2O (0.3)	59
3	H_2O (1)	70
4[d]	*i*-PrOH (1)	55
5[d]	DMPh (1)	64
6	H_2O (4)	99
7	H_2O (0.3 mL)	77

[a] Conditions: **1a** (62.5 mg, 0.3 mmol), CsF (0.5 mg, 0.003 mmol, 1 mol%), TMSCN (84 μL, 0.66 mmol, 2.2 equiv), dioxane (1.0 mL), under argon, 4 h.
[b] Relative to **1a**.
[c] Isolated yield.
[d] Quenched with 1 M HCl; DMPh = 2,6-dimethylphenol.

Under the optimized reaction conditions, the substrate scope of the CsF-catalyzed 1,4-addition of TMSCN to enones was evaluated (Table 3).[19,21] In general, chalcone derivatives gave excellent yields (91–97%) at varying reaction rate (entries 1–9). With electron-donating substituents, the reactions proceeded slowly than chalcone (entries 2–5 vs. entry 1). On the other hand, electron-deficient α,β-unsaturated enones were converted into β-cyanoketones much faster (entries 6–9). β-Alkyl-substituted enone **1j** also gave excellent yields under the optimal reaction conditions (entry 10). However, aliphatic enones could not be converted into the product under these conditions.

Table 3 Scope of Substrate



Entry[a]	Product	Time (h)	Yield (%)[b]
1[c]	**2a** R^1 = Ph, R^2 = H	4	99
2	**2b** R^1 = 2-$MeOC_6H_4$, R^2 = H	7	99
3	**2c** R^1 = 3-$MeOC_6H_4$, R^2 = H	5	99
4	**2d** R^1 = 4-$MeOC_6H_4$, R^2 = H	7	99
5	**2e** R^1 = 4-MeC_6H_4, R^2 = H	6	99
6	**2f** R^1 = 2-ClC_6H_4, R^2 = H	1.5	99
7	**2g** R^1 = 2,4-$Cl_2C_6H_3$, R^2 = H	1.5	99
8	**2h** R^1 = 3-$O_2NC_6H_4$, R^2 = H	1.5	91
9	**2i** R^1 = 2-ClC_6H_4, R^2 = O_2N	1	93
10	**2j** R^1 = Me, R^2 = H	1.5	97

[a] Conditions: enones (0.3 mmol), CsF (0.5 mg, 0.003 mmol, 1 mol%), TMSCN (84 μL, 0.66 mmol, 2.2 equiv), H_2O (22 μL, 1.2 mmol, 4 equiv), dioxane (1.0 mL), under argon.
[b] Isolated yield.
[c] Comparable results are obtained under open-air conditions.

In conclusion, the highly regioselective 1,4-addition of TMSCN to aromatic enones had been achieved with good substrate generality. The 1,4-adducts were obtained in excellent yields with 1 mol% of CsF as the catalyst and four equivalents of H_2O as the additive. Further studies to elucidate the reaction mechanism and extension to asymmetric version of this protocol are under way in our group.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) **Preparation of 2a**
The solution of CsF (0.5 mg, 0.003 mmol, 1 mol%) and enone (**1a**, 62.5 mg, 0.3 mmol) in dioxane (1 mL) is added TMSCN (84 μL, 0.66 mmol, 2.2 equiv) and H_2O (22 μL, 1.2 mmol, 4 equiv) subsequently in a dry Schlenk tube equipped with cold finger under argon. The reaction mixture is stirred at reflux temperature until the reaction is completed (monitored by TLC). 1 M HCl (0.3 mL) is added to quench the reaction with additional 20 min stirring at r.t. The resulting mixture is extracted with EtOAc (5 mL) (Caution! HCN generated in the reaction mixture is highly toxic. Those operations should be conducted in a well-ventilated hood). The extract is washed with H_2O, brine, dried over anhyd Na_2SO_4, and concentrated. The crude product is purified by flash chromatography on silica gel (PE–EtOAc, 20:1) to afford **2a** as white solid in 99% yield.
Nitrile **2a**: mp 120–122 °C (lit.: 122–125 °C).[11] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.52$ (dd, $J = 6.0, 18.0$ Hz, 1 H, NCCHCH_AH$_B$CO), 3.74 (dd, $J = 8.0, 18.0$ Hz, 1 H, NCCHCH$_A$$\mathit{H}_B$CO), 4.57 (dd, $J = 6.0, 8.0$ Hz, 1 H, NCC*H*CH$_A$H$_B$CO), 7.34–7.49 (m, 7 H, ArH), 7.58–7.62 (m, 1 H, ArH), 7.92–7.94 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.9$, 44.5, 120.6, 127.5, 128.1, 128.4, 128.8, 129.3, 133.9, 135.3, 135.8, 194.6 ppm. IR (KBr): $\nu = 1681, 2236$ cm^{-1}.