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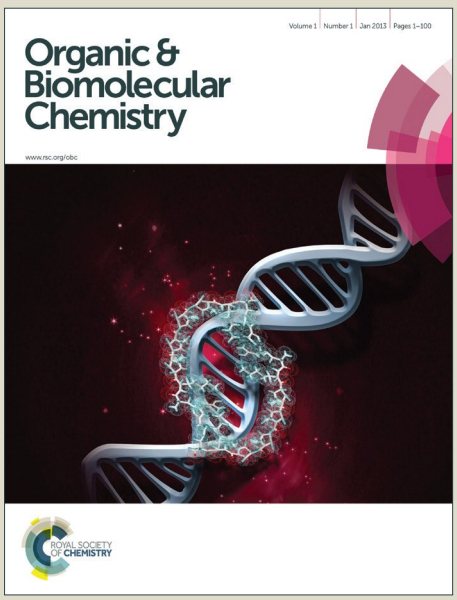

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An Efficient Aldol-Type Direct Reaction of Isatins with $TMSCH_2CN$

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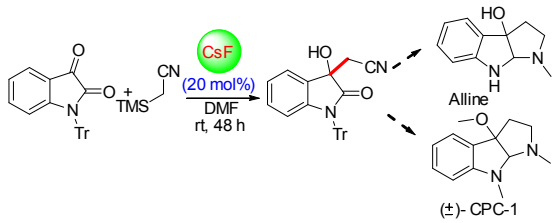
Cesium fluoride catalyzed direct cyanomethylation of various isatins by using trimethylsilyl acetonitrile (TMSAN) as a nucleophile has been developed. The reaction has been explored for a number of isatins, with various substitutions on its aromatic ring. Further, versatility of the reaction is demonstrated by converting the direct aldol adduct to corresponding intermediates of natural products and medicinally important compounds.



Aldol-type cyanomethylation of carbonyls by nucleophilic addition provides a direct access to β-hydroxy nitriles, an important synthon for the total synthesis of many small molecules.[1] Also, the easy convertibility of β-hydroxy nitriles to γ-amino alcohols and β-hydroxy carboxylic acid derivatives makes it a useful synthetic intermediate.[2] Typically, the synthesis of β-hydroxy nitriles involves base mediated deprotonation of alkyl nitrile followed by a nucleophilic addition,[3] α-halonitrile's Reformatasky reaction[4] or a α-metallonitrile's addition to carbonyls.[5] However, reversibility of the carbonyl addition, progression of the cyanomethylated product to α,β-unsaturated nitriles,[6] and restriction of the substrate scope to only certain class of carbonyls are some of the unresolved issues with cyanomethylation.

In the last two decades, a number of methods utilizing organosilicon derived nucleophile (α-cyanocarbanion) addition to carbonyls have emerged as a direct way for cyanomethylation.[7] In fact, the recently developed base promoted α–trimethylsilyl acetonitrile (TMSAN) addition to carbonyl has turned out to be the most efficient method for β-hydroxy nitrile synthesis.[8] Interestingly, the cyanomethylation of ketones with TMSAN remains less explored. This could be due to the poor reactivity and the steric challenges that the ketone structure imposes.

The very first report of α–cyanocarbanion addition, by Palomo and coworkers, has used tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)-promoted cyanomethylation in presence of TMSAN as a nucleophile precursor, giving moderate yield of the adduct.[7a] Subsequently, Shibasaki's group described a copper fluoride activated cyanomethylation of aldehydes and ketones in presence of $(EtO)_3SiF$.[7b] Later, Mukaiyama reported LiOAc catalyzed cyanomethylation of aldehydes and ketones in presence of TMSAN.[7c] Very recently, cyanomethylation of ketones in presence of α–alkylated (dimethylsilyl)acetonitrile using $MgCl_2$ or $CaCl_2$ as activating agent have been reported.[7d]

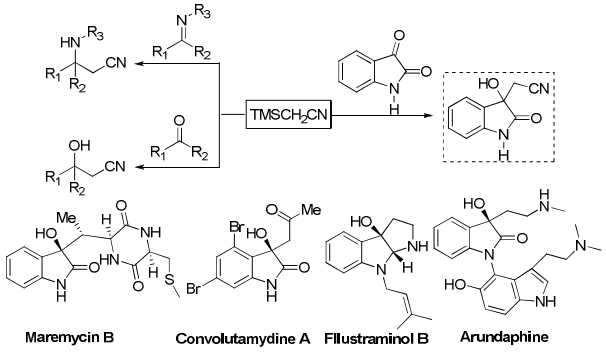


Figure 1 Cyanomethylation reaction of unsaturated compound for β-amino/hydroxy nitrile synthesis. Examples of bioactive natural products built on a 3-hydroxy-2-oxindole core.

Development of a direct method for the β-hydroxy nitrile synthesis will also enable easy routes for synthesizing many synthons from indole containing frameworks such as isatins. For instance, 3-functionalized-3-hydroxy-2-oxindole, a core unit in many natural products[9] and drug candidates, can be directly synthesized from isatins.

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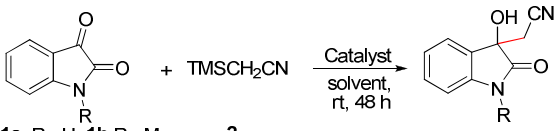
Table 1. Cyanomethylation of *N*-protected isatin **1** with trimethylsilyl acetonitrile **2** [a,b]



1a, R =H, **1b** R =Me; **1c**, R=Bn; **1d**, R = PMB; **1e**, R = Tr

2

3a-e

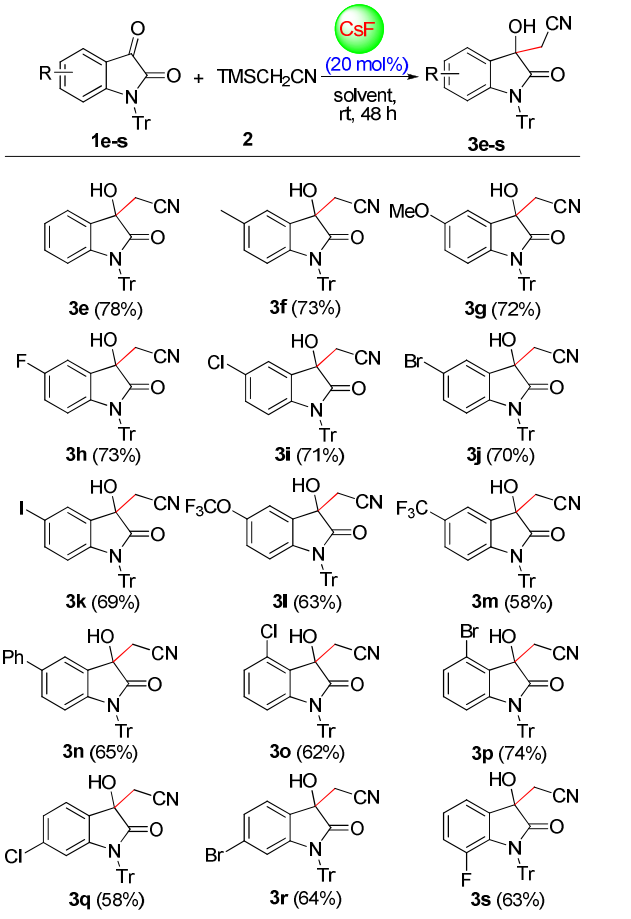
entry[a]	R	Catalyst	solvent	yield (%)[b]
1	H	Na_2CO_3	DMF	19
2	H	K_2CO_3	DMF	20
3	H	KOH	DMF	8
4	H	CsF	DMF	23
5	H	KF	DMF	25
6	Me	CsF	DMF	32
7	Me	KF	DMF	28
8	PMB	CsF	DMF	55
9	PMB	KF	DMF	30
10	Bn	CsF	DMF	71
11	Tr	CsF	DMF	78
12	Tr	CsF	DMSO	30
13	Tr	CsF	EtOH	0
14	Tr	DMAP	DMF	5
15	Tr	DABCO	DMF	0
16	Tr	KO^tBu	DMF	0
17	Tr	KOAc	DMF	55
18	Tr	CsOAc	DMF	69
19	Tr	NaOAc	DMF	58
20	Tr	NaOMe	DMF	24
21	Tr	KF	DMF	40

[a]Unless otherwise noted, the reactions were performed with 0.2 mmol of 1 and 0.3 mmol of 2 in 1.0 mL of solvent with 20 mol% of base under nitrogen. [b] Isolated yield.

Previously, apart from catalytic aldol reactions of ketones and aldehydes with isatins,[10] the synthesis of 3-substituted-3-hydroxy oxindoles has mostly been achieved by metal mediated nucleophilic addition of boronic acids to 3-carbonyl of isatins,[11] catalytic Henry reaction of isatins with nitro alkanes and oxidation of 3-substituted oxindoles.[12] All of these strategies have been reported either on limited substrates or by using difficult to access expensive catalysts. Thus, undoubtedly a strategy for direct cyanomethylation of isatins by cheap catalytic system is highly desirable. Herein, we disclose a base catalyzed cyanomethylation of commercially available TMSAN with various *N*-trityl isatins. We demonstrate the versatility of the developed nucleophilic addition reaction by converting the direct aldol adduct to corresponding intermediates of natural products and medicinally important compounds.

Our initial study explored cyanomethylation reaction of isatin with trimethylsilyl acetonitrile (TMSAN) at room temperature with DMF as a solvent. We found that TMSAN alone did not give cyanomethylation of **1a**. However, when **1a** was treated with TMSAN and inorganic bases or metal fluoride as a promoter in DMF, the nucleophilic addition of cyanomethenes anion was observed leading to **3a**. The inorganic bases showed poor reactivity (table 1, entry 1-3) whereas metal fluoride showed slightly better reactivity (table 1, entry 4 and 5). As it is well established that fluoride anion can exert a silyl activation of TMSAN due to the high silicon-fluoride affinity, we planned to generate a cyanomethylene anion *in-situ* via this strategy. The anion thus generated can further proceed for a nucleophilic addition with isatin. At first, we carried out a reaction between isatin and TMSAN with 20 mol % of CsF as a promoter. We found that the desired β-hydroxy nitrile product **3a** was formed in 23% yield at room temperature.

Table 2. Cyanomethylation of various N-trityl isatins with trimethylsilyl acetonitrile [a,b]



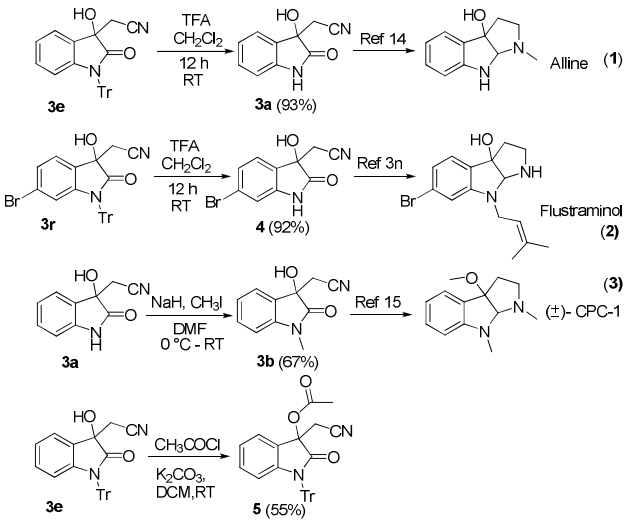
[a]Unless otherwise noted, reactions were performed with 0.2 mmol of 1 and 0.3 mmol of 2 in 1.0 mL of solvent with 20 mol% of CsF under nitrogen. [b] Isolated yield.

Since cesium fluoride is better nucleophile than potassium fluoride for the silicon activation,[13] it turned out to be a better promoter and gave higher yield for the cyanomethylation reaction (entry 4 vs entry 5 and entry 6 vs entry 7) in comparison with KF.

To further improve the yield of the reaction, we decided to investigate the impact of *N*-substitution of the isatin. Hence, we carried out CsF catalyzed aldol reaction for a series of *N*-protected isatin derivatives at room temperature. *N*-PMB isatin gave moderate yield (55 %, entry 8, table 1,), whereas *N*-benzyl isatin produced comparatively higher yield (71%, entry 10, table 1). Interestingly, a shift in *N*-protection to trityl group yielded best conversion for the CsF catalyzed aldol reaction

(78%, table 1, entry 11). Polar solvents such as, DMSO and EtOH were also tested for the aldol reaction of *N*-trityl isatin at room temperature (Table 1, entries 12 and 13). However, no improvement in the reactivity was observed in these cases. In order to improve the reactivity, various organic and inorganic bases such as DMAP, DABCO, KOAc, CsOAc, NaOAc, NaOMe and KF were screened as catalyst for aldol reaction of *N*-trityl isatin with TMSAN in DMF (entry 14 - 21). Surprisingly, none of the base showed better reactivity than CsF with DMF as a solvent.

Scheme 1. Transformation of cyanomethyl adduct.



We next explored the reaction scope of the developed methodology by studying various electronically different substituents on the benzene ring of *N*-tritylisatins **1** (table 2). We were pleased to observe good yields (58-78%) for both electron-donating as well as for electron withdrawing substituents (see table 2, **3e**-**s**) thus, indicating no specific trend for the reactivity of this reaction with respect to the electronic effect of the substituent. The reaction of *N*-trityl isatins bearing electron donating groups or halo-substituents at the 5-position of the benzene ring (**3e**-**3k**) gave good yields.

However, -OCF_3, -CF_3 and phenyl substituted isatins (**3l**, **3m** and **3n**) showed slightly lower yield. The isatins containing a Cl or Br substituent at the C6-position showed higher reactivity (**3q** and **3r**) than the substrates with the same substituents at the C4- position (**3o** and **3p**) (Table 2). We also examined the reaction of 7-fluoro *N*-trityl isatin (**1s**) with TMSAN, which gave **3s** in good yield.

After establishing the substrate scope we next focused our efforts to elucidate the synthetic efficacy of this methodology. We carried out transformations of the isatin-derived cyanomethylated adduct to yield intermediates that can be easily converted into various natural products, such as (±)-alline, (±)-flustraminol B and (±)-CPC-1 (Scheme 1). As demonstrated in eqs 1-3, we efficiently converted the adduct to corresponding intermediates **3a**, **4** and **3b**, which can be transformed to aimed natural products *via* known protocols. The cyanomethyl adducts **3e** and **3r** when subjected to detritylation by exposing it with TFA in CH_2Cl_2, yielded the corresponding compounds **3a** and **4** in 93% and 92% yield respectively. Both the products can be efficiently converted to (±)-alline and Flustraminol *via* known methods.[14] Methylation of compound **3a** with NaH and CH_3I gave 67% of *N*-methylated compound **3b**, which could be easily converted to (±)-CPC-1 *via* reported procedure.[15] To demonstrate the reactivity of tertiary hydroxyl group of the adduct **3e**, we transformed it into corresponding acetate **5** by treating it with CH_3COCl and K_2CO_3 in CH_2Cl_2.

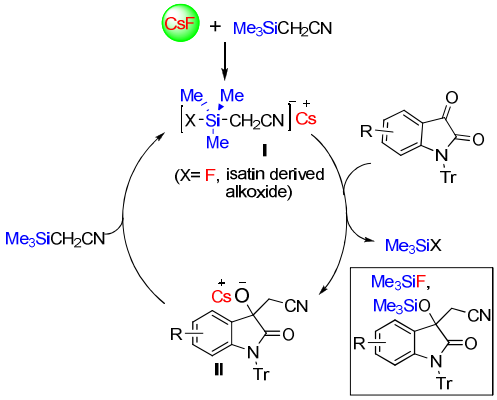


Figure 2 Plausible mechanism for CsF catalyzed Cyanomethylation of *N*-trityl isatin.

A plausible mechanism of this transformation is explained in Figure 2. In the proposed catalytic cycle, the fluoride ion of CsF first attacks the silicon atom of the trimethylsilyl acetonitrile, which leads to the formation of silicate **I** (hypervalent species). The increased nucleophilicity of the hypervalent complex formed increases its reactivity towards the carbonyl group of *N*-trityl isatin. This leads to the formation of a corresponding cesium alkoxide **II** and trimethylsilyl fluoride (TMSF). Further alkoxide **II** reacts with another molecule of trimethylsilyl acetonitrile to give silicate **I** which reacts with another molecule of isatin to generate *O*-silyl ether along with the another cesium alkoxide **II** thus, beginning another catalytic cycle (Figure 2).

In conclusion, we have described a practically simple and highly efficient CsF mediated cyanomethylation of various *N*-tritylisatins with TMSAN for the synthesis of 3-hydroxy-3-cyanomethyl oxindoles. We have also demonstrated the synthetic utility of this methodology by applying this protocol in the efficient assembly of intermediates of medicinally important 3-hydroxy indole natural products.

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