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A simple one-pot procedure for the direct conversion of alcohols into alkyl nitriles using TsIm

Mohammad Navid Soltani Rad,[a,*] Ali Khalafi-Nezhad,[b] Somayeh Behrouz[b] and Mohammad Ali Faghihi[a]

[a]*Department of Chemistry, Faculty of Basic Sciences, Shiraz University of Technology, Shiraz 71555-313, Iran*
[b]*Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran*

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Abstract—A convenient and efficient one-pot preparation of nitriles from alcohols using *N*-(*p*-toluenesulfonyl)imidazole (TsIm) is described. In this method, treatment of alcohols with a mixture of NaCN, TsIm and triethylamine in the presence of catalytic amounts of tetra-*n*-butylammonium iodide (TBAI) in refluxing DMF furnishes the corresponding alkyl nitriles in good yields. This methodology is highly efficient for various structurally diverse alcohols with selectivity for ROH: 1° > 2° > 3°.
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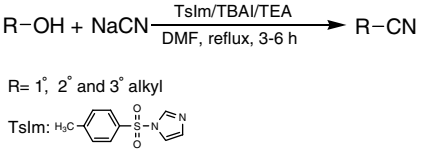
Alkyl nitriles[1] are useful intermediates in organic synthesis for the introduction of various functional groups as well as the construction of *N*-heterocycles.[2] The preparation of nitriles by nucleophilic substitution of alkyl halides and sulfonates with inorganic cyanides are common and well known procedures.[3] Furthermore, the introduction of nitrile into organic compounds can be achieved using different routes including: the direct conversion of aldehydes,[4] oxime ethers,[5] thioamides,[6] carboxylic acid and their esters,[7] dehydration of aldoximes[8] and amides[9] with various reagents, oxidation of amines,[10] and reduction of primary aliphatic nitro compounds,[11] enzymatic methods[12] and application of organoborane/diazoacetonitrile.[13] The direct conversion of alcohols into alkyl nitriles is an interesting and attractive reaction. This transformation is of synthetic importance allowing the elongation of an alkyl chain by one carbon. A few reports have appeared on the one-pot conversion of alcohols to nitriles.[14] The most common approach for this conversion is based on Mitsunobu conditions using HCN/Ph_3P/diethyl azodicarboxylate (DEAD).[15] However, the use of highly toxic HCN limits the applicability of this method.

Acetone cyanohydrin is used as an alternative cyanide source to HCN.[16] Other reported methods for the direct conversion of alcohols to nitriles include the use of CCl_4/Ph_3P/NaCN,[17a] *n*-Bu_3P/CCl_4/KCN/18-crown-6,[17b] and Ph_3P/*n*-Bu_4NCN/2,3-dichloro-5,6-dicyanobenzoquinine (DDQ),[17c] Me_3SiCl/NaI/NaCN[18] NH_3/I_2[19a] and NH_3/1,3-diiodo-5,5-dimethyl hydantoin.[19b] The aforementioned methods have several drawbacks such as non-generality for various types of alcohols, the use of expensive DEAD, low yields, long reaction times, tedious work-up as well as cumbersome separation from the generated $Ph_3P{=}O$ and unreacted Ph_3P. Hence, there is still a need to develop a practical and applicable method for the direct conversion of alcohols into nitriles. Recently, we reported TsIm as a highly efficient, cheap and stable reagent for the one-pot conversion of alcohols to alkyl azides.[20] Herein, we report that 1°, 2° and 3° alcohols can be converted efficiently into their corresponding alkyl nitriles using TsIm/NaCN in the presence of triethylamine (TEA) and catalytic amounts of TBAI in DMF (Scheme 1).



Scheme 1.

Keywords: Nitrile; Alcohol; *N*-(*p*-Toluenesulfonyl)imidazole (TsIm); Triethylamine (TEA); Tetrabutylammonium iodide (TBAI).
* Corresponding author. Tel.: +98 711 7261392; fax: +98 711 7354523; e-mail addresses: soltani@sutech.ac.ir; nsoltanirad@gmail.com

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Table 1. Effect of various solvents on the conversion of benzyl alcohol into benzyl cyanide

Entry	Solvent	Time (h)	Yield[b] (%)
1	DMSO	6	60
2	DMF	3	94
3	DMF[a]	6	67
4	THF	48	NR[c]
5	MeCN	12	20
6	HMPA	12	35
7	Toluene	48	NR
8	Acetone/H_2O[d]	24	Trace
9	H_2O	48	NR

[a] Anhydrous DMF.
[b] Isolated yield.
[c] No reaction.
[d] (1:1) ratio.

To obtain optimized reaction conditions, we chose the reaction of benzyl alcohol with excess NaCN (2.0 equiv), freshly prepared TsIm (1.2 equiv)[20] and a catalytic amount of TBAI as a reaction model; the effect of various solvents on reaction times and yields was examined. The results are summarized in Table 1.

As the data in Table 1 indicate, DMF (entry 2) was the most appropriate solvent. Using DMSO and anhydrous DMF (Table 1, entries 1 and 3) afforded moderate yields of the corresponding nitrile. The choice of the base for activation of the alcohols was of great significance. In this case, we investigated the potency of several organic and inorganic bases on the reaction model (Table 2). The results in Table 2 demonstrate that among the employed bases, TEA (Table 2, entry 7) was the most efficient for activation of benzyl alcohol.

We also examined the role of phase transfer catalysts (PTC) on the model reaction (Table 3). In the absence of PTC the reaction occurred but only in moderate yield. In contrast to the azidation reaction using this method,[20] the presence of a catalytic amount of TBAI was not obligatory, however, using TBAI shortened the reaction time and enhanced the yield. Cyanation in the absence of TBAI can be attributed to the stronger nucleophilicity of CN^- in comparison with N_3^-.[21] Moreover, the use of an equal mixture of TBAI and TBAB (Table 3, entry 8) was less efficient. Other PTCs (Table 3, entries 2–4, 6 and 7) were not as effective as

Table 2. Effect of various bases on the conversion of benzyl alcohol into benzyl cyanide

Entry	Base	Time (h)	Yield[a] (%)
1	DBU	7	47
2	DABCO	7	45
3	DMAP	7	41
4	MgO	12	10
5	Cs_2CO_3	7	54
6	K_2CO_3	7	47
7	TEA	3	94
8	NaH	10	45

[a] Isolated yield.

Table 3. Effect of various PTCs on the conversion of benzyl alcohol into benzyl cyanide

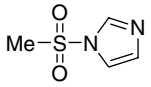
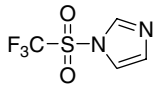
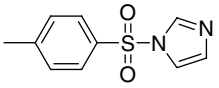
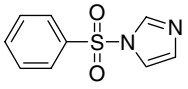
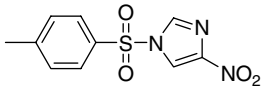
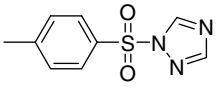
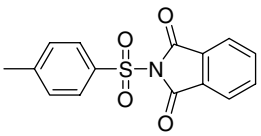
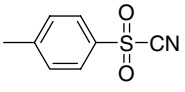
Entry	PTC	Time (h)	Yield[b] (%)
1	None	7	48[c]
2	TBAF	9	51
3	TBAC	9	55
4	TBAB	6	62
5	TBAI	3	94
6	$(n\text{-Bu})_4NHSO_4$[a]	9	43
7	$(n\text{-Bu})_4NCN$	10	51
8	TBAI/TBAB	7	70

[a] 2 equiv of TEA were used.
[b] Isolated yield.
[c] No reaction.

TBAI (Table 3, entry 5). We also examined other iodide sources including LiI, NaI and KI for the conversion of benzyl alcohol into its corresponding nitrile (40%, 47% and 50% yields were obtained, respectively). The optimized amount of TsIm was found to be 1.2–2.0 equiv per equivalent of alcohol. We also examined other TsIm analogues (Table 4).

As the data in Table 4 demonstrate, a higher yield of nitrile and short reaction time were obtained with TsIm

Table 4. Comparison of TsIm reactivity with analogues on the conversion of benzyl alcohol into benzyl cyanide

Entry	Reagent	Time (h)	Yield[a] (%)
1		12	20
2		12	32
3		3	94
4		7	60
5		12	54
6		12	48
7		48	NR[b]
8		48	NR

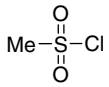
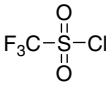
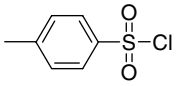
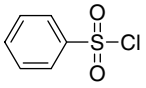
[a] Isolated yield.
[b] No reaction.

(Table 4, entry 3) in comparison with other sulfonyl analogues. Replacing the tolyl group in TsIm with methyl, trifluromethyl and phenyl did not afford satisfactory results (Table 4, entries 1, 2 and 4). Furthermore, other azole analogues of TsIm were not as efficient as imidazole (Table 4, entries 5 and 6). *N*-Tosyl phthalimide and tosyl cyanide (Table 4, entries 7 and 8) were inactive for the conversion of benzyl alcohol into benzyl cyanide even after reflux for 48 h.

Various sulfonyl chlorides were also examined instead of TsIm (Table 5). On using these sulfonylating agents, lower yields of benzyl cyanide were observed. The sulfonyl cyanides were obtained as the major product in most cases. This may be due to the high reactivity and hence low selectivity of sulfonyl chlorides in reactions with alcohols.

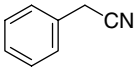
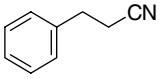
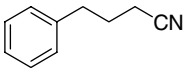
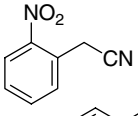
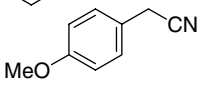
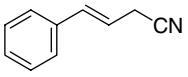
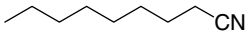
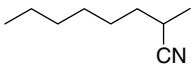
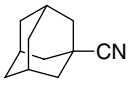
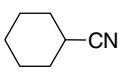
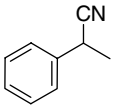
To explore the generality and versatility of this method, we applied the optimized conditions for the conversion of structurally diverse alcohols into their corresponding nitriles (Table 6). As the results in Table 6 indicate, this method is suitable for various alcohols including: primary, secondary and tertiary alcohols. The generality

Table 5. Effect of various sulfonyl chlorides on the conversion of benzyl alcohol into benzyl cyanide

Entry	Sulfonyl chloride	Time (h)	Yield[a] (%)
1		10	33
2		10	42
3		10	31
4		10	28

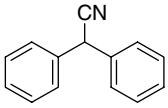
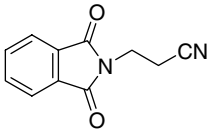
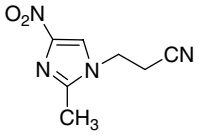
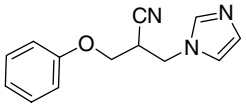
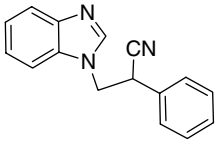
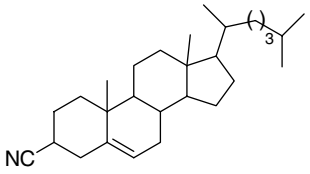
[a] Isolated yield.

Table 6. One-pot conversion of alcohols to nitriles using TsIm/TBAB/TEA in refluxing DMF

Entry[Ref.]	R–CN[a]	ν (cm^{-1})[b]	Time (h)	Yield[c] (%)
1[3c,f,g,16a,17b,c,18a]		2212	3	94
2[3f,7c,8g,16a,17b,c]		2202	3	93
3[17c]		2245	3	91
4		2200	3	87
5[17c]		2212	3	90
6[17b,18b]		2235	4	81
7[3f,4c,d,17b,c]		2230	4	89
8[3g,i,16a,17c,18a]		2222	4	64
9[4b,17c,18a]		2231	4	53
10[17c,18a]		2206	5	51
11[3d,17c,18a]		2206	4	77
12[4b,17c]		2202	4	73[d]

(*continued on next page*)

Table 6 (*continued*)

Entry[Ref.]	R–CN[a]	ν (cm^{-1})[b]	Time (h)	Yield[c] (%)
13[16a,17c]		2210	6	71
14		2243	5	90
15		2204	6	88
16		2208	6	62
17		2213	6	52
18[15c,18a]		2253	6	40

[a] All products were characterized by ^{1}H and ^{13}C NMR, IR, CHN and MS analysis.
[b] IR signal of nitrile in wavenumbers (cm^{-1}).
[c] Isolated yield.
[d] Also obtained from optically pure *R*-(+)-1-phenylethanol, $[\alpha]_D^{20}$ +45 (*c* 5 in MeOH) in 56% ee.

of the method was confirmed with respect to allylic (Table 6, entry 6), benzylic (Table 6, entries 1, 4, 5, 12, 13, 17), aliphatic (Table 6, entries 7–9), alicyclic (Table 6, entries 10, 11, 18) and other alcohols containing *N*-heterocycles (Table 6, entries 14–17). Furthermore, the conversion of cholesterol into the corresponding nitrile was possible using this method (Table 6, entry 18).

We applied this method to optically pure *R*-(+)-1-phenylethanol (Table 6, entry 12) for conversion into its corresponding nitrile, however, a reduction in optical purity (56% ee) occurred. Mechanistically this can be explained as a result of partial inversion and retention at the same time from direct reaction of cyanide and two successive nucleophilic substitutions of iodide and cyanide ions with the alkyl tosylate. It is interesting to note that there was a remarkable tendency for TsIm to react with alcohols rather than nucleophiles present in the reaction mixture: no tosyl cyanide was observed in these reactions even in trace amounts.

In conclusion, a convenient and efficient method has been established for the one-pot conversion of alcohols into the corresponding nitriles using TsIm/TEA/TBAI (cat.) in refluxing DMF. This method is applicable to primary, secondary and tertiary alcohols with selectivity $1^{\circ} > 2^{\circ} > 3^{\circ}$.

General procedure for the one-pot conversion of alcohols to nitriles: To a double-necked round bottom flask (100 mL) equipped with a condenser was added a mixture of alcohol (0.01 mol), TsIm (0.012 mol),[20] TEA (0.02 mol), NaCN (0.02 mol) and a catalytic amount of TBAI (0.1 g) in DMF (30 mL). The mixture was refluxed, and in most cases, darkening of the reaction mixture occurred. Reflux was continued until TLC monitoring indicated no further improvement in the conversion (Table 6). The solvent was evaporated under vacuum and the remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2×100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by col-

umn chromatography on silica gel eluting with *n*-hexane/EtOAc (10:1).[22]

Acknowledgement

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22. Selected data for *N*-(2-cyanoethyl)phthalimide and 3-(2-methyl-4-nitro-imidazol-1-yl)propionitrile (Table 6, entries 14 and 15). *N*(2-*Cyanoethyl*)*phthalimid*e: White crystals; R_f (EtOAc/*n*-hexane) (1:1) 0.54; mp 143.1 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ_{ppm}: 2.70 (t, 2H, $J = 6.8$ Hz, CH_2CN), 3.88 (t, 2H, $J = 6.8$ Hz, NCH_2), 7.64–7.66 (m, 2H, aryl), 7.73–7.75 (m, 2H, aryl); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm}: 16.91, 33.50, 117.07, 123.54, 131.58, 134.39, 167.48; IR (KBr) ν cm^{-1}: 2243 (CN); MS(EI) [*m*/*z* (%)]: 200.19 (53.8); Anal. Calcd for $C_{11}H_8N_2O_2$: C, 66.00; H 4.03; N 13.99. Found: C, 66.08; H, 3.98; N, 14.01. 3-(2-*Methyl*-4-*nitro-imidazol*-1-*yl*)*propionitrile*: Pale yellow crystals; R_f (EtOAc/*n*-hexane) (4:1) 0.21; mp 155.5 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ_{ppm}: 2.40 (s, 3H, Me), 3.64 (t, 2H, $J = 6.2$ Hz, CH_2CN), 5.19 (t, 2H, $J = 6.2$ Hz, NCH_2), 8.96 (s, 1H, C(5)–H, imidazole); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm}: 13.12, 49.51, 60.76, 120.66, 145.23, 146.68, 150.28; IR (KBr) ν cm^{-1}: 2204 (CN); MS(EI) [*m*/*z* (%)]: 180.16 (70.3); Anal. Calcd for $C_7H_8N_4O_2$: C, 46.67; H, 4.48; N, 31.10. Found: C, 46.71; H, 4.45; N, 31.05.