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A New One Pot Method for the Conversion of Aldehydes into Nitriles Using Hydroxyamine and Phthalic Anhydride

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Abstract : The aryl and alkyl aldehydes were readily converted to give the corresponding nitriles in good yields using hydroxyamine and phthalic anhydride as reagents in one pot.

Nitriles, important reagents for organic synthesis have been known to chemists for a long time. In recent reports, it showed that nitriles could be converted to thiazole derivatives as inhibitors of superoxide,[1] condensed with β-amino alcohol in the presence of catalyst to give new chiral 2-oxazolines as FLC dopants,[2a] or as protecting group[2b], converted to antipicornavirus tetrazoles analogues,[3] transferred to 1,2-diarylimidazoles as potent antiinflammatory agents,[4] as a starting material for synthesizing triazolo[1,5-c]pyrimidines with potential antiasthma activity,[5] and as a starting material for the preparation of benzamidines possessing activity of fibrinogen antagonists.[6] Furthermore, vanillylamine readily obtained by the reduction of vanillylonitrile,[7] could be reacted with corresponding acyl chlorides to give several capsaicinoids. In order to find an more efficient synthetic route for capsaicinoids, it prompts us to reexamine the methods for the preparation of nitriles. According to the literatures, it can be divided mainly into two routes : one is by the dehydration of aldoximes,[8] and the other is by treating aldehydes with a variety of chemicals such as free sulfimide,[9] N-tosylimines,[10] S,S-dimethylsulfurdiimide,[11] trimethylsilyl azide,[12] triazidochlorosilane,[13] O-(2-aminobenzoyl) hydroxyamine,[14] hydroxyamine / polyphosphoric acid,[15] hydroxylamine hydrochloride / formic acid,[16] hydroxylamine hydrochloride / selenium dioxide,[17] hydroxylamine hydrochloride / $MgSO_4$ / ToSOH,[18] hydroxylamine hydrochloride / pyridine in refluxing toluene,[19] ammonium chloride / copper(0) powder / oxygen / pyridine,[20] aq. ammonia / $NiSO_4$ / $K_2S_2O_8$ / NaOH,[21] ammonia / copper salt / strong base in the presence of various oxidizing agents ranging from oxygen,[22] lead tetraacetate[23] and iodine[24] respectively. However, a lot of drawbacks may be encountered in using some of these reagents such as low yields, harsh reaction conditions, tedious workup procedures, opaque reaction mechanism and with some limitations. In addition some of them are corrosive, toxic, expensive or commercially unavailable. Therefore, it is necessary to develop a practical and applicable method for this conversion. Herein we wish to report a new, simple and efficient one pot preparation of nitriles from aldehydes using hydroxyamine and phthalic anhydride (**Scheme 1**). The mechanism of our method could be briefly proposed as follows: (1) hydroxyamine was released from its hydrochloride salt by triethylamine, (2) followed by the reaction with aldehydes to give aldoximes in situ, (3) subsequently the ring of phthalic anhydride was opened by the nucleophilic attack from the hydroxy group of aldoximes, and (4) finally

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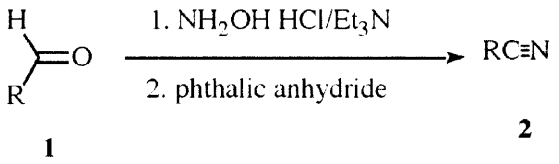
by *via* a proposed six-membered transition state and undergoing an intramolecular 1,2-elimination to give nitriles.

Scheme 1



1 **2**

We found that aryl and alkyl aldehydes were readily converted to give the corresponding nitriles in good yields using hydroxyamine hydrochloride : triethyl amine : phthalic anhydride (1: 1.1: 1.05) in acetonitrile under reflux.The results obtained were compiled in **Table 1**.

Table 1 Conversion of aldehydes into nitriless with hydroxyamine hydrochloride, triethyl amine, and phthalic anhydride in one pot

Entry	Aldehydes (**1**)	reaction time (hrs)	Nitriles (**2**)	Yield(%)	References
a	3-Benzyloxybenzaldehde	7	3-Benzyloxybenzonitrile	95	25
b	4-Benzyloxybenzaldehde	7	4-Benzyloxybenzonitrile	94	26
c	4-methoxybenzaldehyde	7	4-methoxybenzonitrile	92	9, 20
d	4-O-allyl-3-methoxybenzaldehde	7.5	4-O-allyl-3-methoxybenzyloxy benzonitrile	90	-
e	3,5-dimethoxy-4-hydroxy benzaldehde	7	3,5-dimethoxy-4-hydroxy benzonitrile	92	27
f	4-Benzyloxy-3-methoxybenzaldehde	7	4-Benzyloxy-3-methoxybenzonitrile	95	28
g	3-Benzyloxy-4-methoxybenzaldehde	7	4-Benzyloxy-3-ethoxybenzonitrile	92	29
h	3,4-dimethoxybenzaldehde	8	3,4-dimethoxybenzonitrile	91	18
i	3,4-diethoxybenzaldehde	8	3,4-diethoxybenzonitrile	93	30
j	4-Hydroxybenzaldehyde	7	4-Hdroxybenzonitrile	91	10, 18
k	Cinnamaldehyde	7.5	Cinnamonitrile	92	9, 19
l	2-Pyrrolecarboxaldehyde	8	2-Pyrrolecarbonitrile	83	18
m	Nonylaldehyde	8	Nonylonitrile	80	31
n	4-O-MEMbenzaldehyde	8	4-O-MEMbenzonitrile	83	32
o	4-O-MOMbenzaldehyde	8	4-O-MOMbenzaldehyde	80	33

All niriles have satisfactory spectral data such as mass, ^{1}H-NMR and ^{13}C-NMR comparing with known compounds except 4-O-allyl-3-methoxybenzyloxybenzonitrile (**2d**) and 3,5-dimethoxy-4-hydroxy-benzonitrile (**2e**).[27]

In each case of reaction the appearance of nitrile is monitored by tlc analysis (ethyl acetate : n-hexane = 1 : 5). This monitoring also showed that the reaction proceeded *via* dehydration of the respective aldoximes. If acetic anhydride was used for replacing phthalic anhydride in our method, only aldoximes with the recovery of aldehydes were observed.[34] Not only with the recovery of aldehydes but also obtained phenolic acetate of oxime[35] in entry **j**, and *N*-acetyl-2-pyrrolecarbonitrile[36] in entry **l**.

From the practical point of view, the advantages of our new approach for the facile conversion of nitriles from aldehydes are : (1). with high yields, (2) one pot to give nitriles without the isolation of aldoximes, (3) easy for working up and purification, (4) readily available and inexpensive for all reagents, and (5) no limitation to aliphatic, heterocyclic and phenolic aldehydes or pyrrolecarboxaldehydes.

Conversion of aldehydes 1 into nitriles 2 ; general procedure :

To a cold solution of hydroxylamine hydrochloride (0.38 g, 5.5 mmol) in anhydrous acetonitrile (50 mL), triethylamine (distilled from KOH) (0.77 mL, 5.5 mmol), and aldehyde **1** (5 mmol) were added and stirred for about 30 min., then phthalic anhydride (0.75 g, 5.05 mmol) was successively added under nitrogen. The resulting mixture was heated under the reflux for about 7-8 h. Then the solution was concentrated under reduced pressure, and the resulting residue was added and stirred with cold CH_2Cl_2 (30 mL X 3), and then filtered. The combined filtrates were washed with 5% ammonia water to remove phthalic acid completely. The separated organic layer was dried with $MgSO_4$, and then evaporized under reduced pressure. Finally the residue was recrystallized from n-hexane / ethyl acetate or purified by passing it through a short silica gel column using $CHCl_3$ as eluting solvent to give pure nitrile, **2a** (95 %), **2b** (94 %), **2c** (91 %), **2d** (95 %), **2e** (92 %), **2f** (95 %), **2g** (92 %), **2h** (91 %), **2i** (93 %), **2j** (91 %), **2k** (93 %), **2l** (83 %), **2m** (80 %), **2n** (83 %) and **2o** (80 %). The physical and spectral data of compound **2d**, mp 59-60 °C; Rf = 0.47 (EtOAC : n-Hexane = 1 : 5), IR ν_{CN} = 2239.5 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 3.89 (s, 3H, OCH_3); 4.66 (dd, $J_{vicinal}$ = 5.4 Hz, $J_{4\text{-bond}}$ = 1.2 Hz, 2H, allylic H); 5.33 (ddd, J_{cis} = 10.7 Hz, J_{gem} = 3.0 Hz, $J_{4\text{-bond}}$ = 1.2Hz, 1H, terminal vinylic H), 5.43(ddd, J_{trans} = 17.2Hz, J_{gem} = 3.0 Hz, $J_{4\text{-bond}}$ = 1.2 Hz, 1H, terminal vinylic H), 6.06 (m, 1H, internal vinylic H); 6.90 (d, J_{ortho} = 8.4 Hz, 1H, Ar-H), 7.09 (d, J_{meta} = 2.0 Hz, 1H, Ar-H), 7.24 (dd, J_{ortho} = 8.4 Hz, J_{meta}=2.0 Hz, 1H, Ar-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 55.94 (OCH_3), 69.52 ($O\underline{C}H_2CH=CH_2$), 103.78, 112.72, 114.12, 118.53, 118.97, 126.01, 131.90, 149.29 and 151.68; MS(EI), *m/z* 189 (M^+); *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.48; H, 5.83; N, 7.31. Compound **2e**, mp 117-118 °C; Rf = 0.36 (EtOAC : n-Hexane = 1 : 2); IR ν_{CN} = 2225.7 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ : 3.91 (s, 6H, 2 X OCH_3), 6.36 (br s, 1H, OH), 6.87 (s, 2H, Ar-H); ^{13}C-NMR (200 MHz, $CDCl_3$) δ : 56.24 (OCH_3), 56.36 (OCH_3), 101.81 (C-1), 109.03 (C-2), 119.11 (CN), 139.29 (C-4) and 147.06 (C-3); MS *m/z* 179 (M^+); *Anal.* Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.56; H, 4.98; N, 7.71.

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34. When entry **d** (5 mmol) was treated with Ac_2O, it gave oxime (0.56 g, 77 %) with the recovery of aldehyde (0.29 g); in entry **f**, it gave oxime (0.35 g, 52 %) with the recovery of aldehyde (0.58 g).
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