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EFFICIENT AND HIGH-YIELDING PROTOCOL FOR THE SYNTHESIS OF NITRILES FROM ALDEHYDES

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An operationally simple and high-yielding procedure has been developed for the conversion of araldehydes into the corresponding nitriles using* p-*toluenesulfonic acid (*p-*TSA) (a mild catalyst) under microwave irradiation. The products are characterized by infrared spectral analysis and by comparison of the melting and boiling points with the reported values.

Keywords: Araldehydes; hydroxylamine hydrochloride; microwave irradiation; nitriles; *p*-TSA

INTRODUCTION

Nitriles are important key intermediates in organic synthesis.[1] It has been found that the cyano group is present HIV protease inhibitors, 5-lipoxygenase inhibitors, and many other bioactive molecules.[2] In addition, nitriles serve as useful precursors for the synthesis of carboxylic acids,[3] ketones,[4] amines,[5] amides,[6] and heterocyclic compounds.[7]

Synthesis of nitriles using the concept of green chemistry has been considered to be a great scientific challenge.[8] Usually synthesis of nitriles is accomplished by substitution reactions of alkyl and aryl halides with metal cyanides,[9] oxidation of primary amines,[10] dehydration of primary and secondary amides,[11] or dehydration of aldoximes with dehydrating agents.[12] Other reported methods for the synthesis of nitriles include a one-pot reaction of aldehydes and hydroxylammonium chloride using reagents such as I_2/NH_3/tetrahydrofuran (THF),[13] $NaN_3/AlCl_3$,[14] and dimethylsulfoxide (DMSO)–I_2.[15] However, the reagents or catalysts involved in these reactions are expensive, harmful, and difficult to handle, especially on a large scale. In the present work, our aim is to develop a rapid protocol without the use of any solvent that is simple and involves a readily available and environmentally compatible catalyst to get nitriles in a short duration.

RESULTS AND DISCUSSION

In continuation of our research work[16a–c] on the development of useful synthetic methodologies, we have recently reported the synthesis of nitriles from

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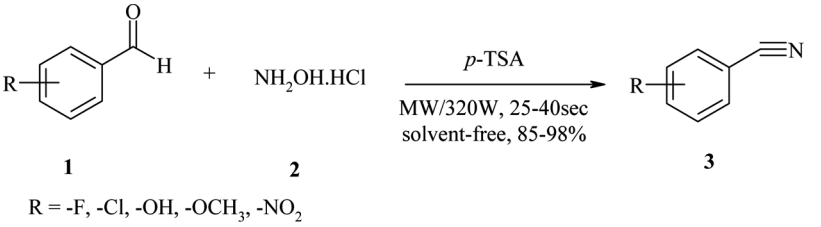


Scheme 1. *p*-TSA-catalyzed solvent-free synthesis of nitriles from araldehydes under microwave irradiation.

amides[16d] and from aldehydes[16e] using catalytic $ZnCl_2$ under microwave irradiation. Herein, we report a solvent-free conversion of araldehydes into corresponding nitriles employing *p*-toluenesulfonic acid (*p*-TSA) as catalyst under microwave irradiation (Scheme 1). It is found that microwave heating makes the reaction fast, clean, and high-yielding[17] (Table 1).

Initially, a model reaction was attempted by irradiating *p*-methoxybenzaldehyde (**1**, R = 4-OCH_3) and hydroxylamine hydrochloride (**2**) in the absence of *p*-TSA and any solvent in a microwave oven. Only a trace amount of *p*-methoxybenzonitrile was isolated after 120 s. When a catalytic amount of *p*-TSA (10 mol%) was introduced into the reaction mixture, the yield of the product was drastically increased to 85% in 40 s (Table 2).

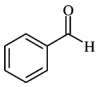
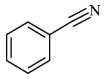
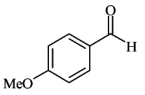
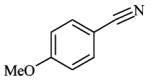
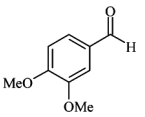
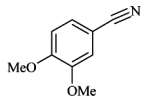
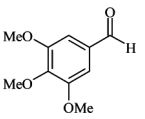
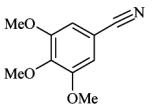
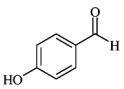
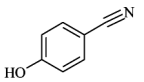
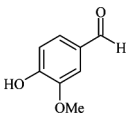
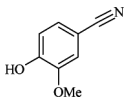
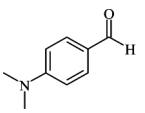
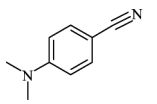
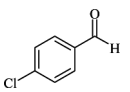
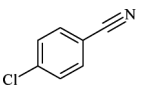
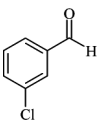
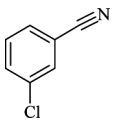
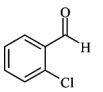
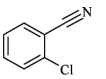
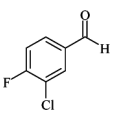
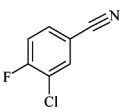
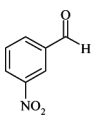
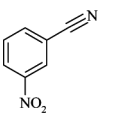
From Table 2, it is also clear that 10 mol% of *p*-TSA was sufficient for getting the corresponding 4-methoxybenzonitrile in 85% yield (Table 2, entry v). The product obtained was characterized by infrared spectral analysis (IR) which indicated the presence of a sharp signal at 2219.19 cm^{-1}, characteristic of a nitrile group.

The generality of the reaction was confirmed by carrying out the reaction using various substituted araldehydes, and we found that the reactions proceed well irrespective of the substituents. Araldehydes having electron-donating substituents $-OCH_3$, $-OH$, and $-N(CH_3)_2$ groups (entries b–g) and electron-withdrawing groups such as $-NO_2$ and halides (entries h–n) were found to afford the corresponding nitriles in excellent yield; results of these studies are presented in Table 1. From Table 1, it is also clear that all the conversions went to completion within 25–40 s under solvent-free microwave irradiation. The structures of all the products were confirmed from their IR spectral analysis and found to be in agreement with the IR spectral data of the authentic samples.

EXPERIMENTAL

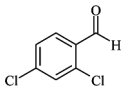
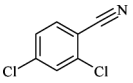
Araldehydes, hydroxylamine hydrochloride, *p*-TSA, and other chemicals were commercial. All reactions were conducted in a LG domestic microwave oven [model MS-1947C/01 (230 V/320 W/2450 MHz)]. Reactions were monitored using thin-layer chromatography (TLC, ethyl acetate/petroleum ether). IR spectra were recorded using a Shimadzu Fourier transform (FT)–IR-8400 s, and ^1H NMR ($CDCl_3$ as solvent and tetramethylsilane [TMS] as an internal standard) spectra were

Table 1. Solvent-free synthesis of nitriles from the araldehydes in the presence of 10 mol % *p*-TSA under microwave irradiation at 320 W

Entry	Substrate (**1**)	Product[a] (**3**)	Time (sec)	Yield (%)[b]	Mp/Bp (°C) (lit.)
a			25	98	186–187 (187)
b			40	87	57–58 (57–59)
c			25	91	62 (63)
d			30	85	93 (92–94)
e			30	87	110 (111–113)
f			20	87	85 (85–87)
g			40	90	73 (75–77)
h			35	91	90–92 (91–93)
i			40	88	95 (95–96)
j			35	92	42 (43–46)
k			40	85	69 (69–71)
l			35	85	113–114 (115)

(*Continued*)

Table 1. Continued

Entry	Substrate (**1**)	Product[a] (**3**)	Time (sec)	Yield (%)[b]	Mp/Bp (°C) (lit.)
m			35	85	105 (107–111)
n			30	88	59 (58–60)

[a]All the products are known and were characterized by IR spectral analysis and comparison of their melting and boiling points with the authentic samples prepared by the reported method [Ref. 15].
[b]Isolated yield.

Table 2. Optimization of the amount of *p*-TSA required for catalytic activity

Entry	*p*-TSA (mol %)	Time (s)	Yield[a] (%)
i	No catalyst	120	Trace
ii	1	80	40
iii	2	70	50
iv	5	70	60
v	10	40	87
vi	15	40	85

[a]Isolated yield (column chromatography).

recorded on a Bruker AMX (200-MHz) spectrophotometer. Melting points were measured on a Büchi B-540 apparatus, and boiling points were recorded at 690 mm torr using the open capillary method. Both are corrected.

General Experimental Procedure

A mixture of araldehyde (10 mmol), hydroxylamine hydrochloride (10 mmol) and *p*-TSA (10 mol%) were taken in a screw-capped Pyrex cylindrical tube, homogenized, and irradiated at 320 W in a unmodified domestic microwave oven. At the end of irradiation (25–40 s; Table 1), the mixture was cooled to room temperature and extracted with dichloromethane (2×5 ml). The organic layer was dried over fused calcium chloride, and the solvent was removed under vacuum. The crude product was chromatographed on a short column of silica gel using light petrol as eluent to get pure nitrile.

p-Methoxybenzonitrile (3b)

Mp 57–58 °C (lit. 62–63 °C); IR (KBr) (ν cm^{-1}): 2219; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.73 (3H, s, CH_3), 6.95 (2H, d, $J = 9.1$ Hz, H-Ar), 7.40 (2H, d, $J = 9.1$ Hz, Hz, H-Ar).

CONCLUSION

In conclusion, we have developed a simple, efficient, and green method for the synthesis of a small library of nitriles from araldehydes in excellent yield using a catalytic amount of *p*-TSA, a mild, acidic, and inexpensive catalyst. The present method has advantages compared to those reported in the literature,[11–15] including the avoidance of using harmful organic solvents, the simplicity of the methodology, and short reaction times. The method is as efficient as our previous method.[16e]

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