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One-Pot Synthesis of Nitriles from Aldehydes Under Microwave Irradiation: Influence of the Medium and Mode of Microwave Irradiation on Product Formation†

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Abstract: Chemoselective transformation of aldehyde to nitrile takes place in a one-pot reaction by treatment with $H_2NOH{\cdot}HCl$ in N-methyl-2-pyrrolidinone (NMP) under microwave irradiation using convection mode.

Transformation of aldehyde into nitrile is a highly valued reaction because of the versatility of nitriles as starting materials for synthesis of thiazoles, 2-oxazolines, tetrazoles, imidazoles, triazoles and benzamidines possessing a broad spectrum of biological activities[1]. Although a direct conversion would have been an attractive approach, the examples are rather limited[2] and recent developments include treatment with $NaN_3/AlCl_3$[3], $ClSi(N_3)_3$[4], and $H_2NOH{\cdot}HCl$/phthalic anhydride/Et_3N[5]. However, these procedures suffer from the limitations of use of costly reagents and/or harsh reaction conditions.

We report herein an efficient protocol for chemoselective transformation of aldehydes into nitriles by treatment with $H_2NOH{\cdot}HCl$ under microwave irradiation. Nitrile formation was found to be dependent on the reaction medium and the mode of microwave operation (Table 1) and could be best achieved in NMP using convection mode of operation with a preset temperature of 100°C (Method A). Inferior yields were obtained by irradiating the reactants admixed with neutral alumina[6] (entry 7), although, neat treatment (entry 8) afforded better results. Irradiation under micro mode of operation[7] (Method B) either in NMP or neat, instead, resulted in poor yields of nitrile (entries 10,11).

The progress of the reactions, during which oxime formation was detected, was monitored by GCMS. The overall transformation may be realised through Scheme I. The importance of activation of the oxime OH group prior to elimination was substantiated by the lack of formation of significant amount of nitrile when 1-naphthaldoxime, alone or in the presence of stoichiometric amount of LiCl, was subjected to microwave irradiation (entries 12,16) and was further supported by the formation of nitrile in good yield through the treatment of 1-naphthaldoxime with stoichiometric amount of HCl or $NaHSO_4$ (entries 14-16).

The general applicability of the protocol is demonstrated with various aldehydes (Table 2). Excellent chemoselectivity was observed in that methoxy (entries 1,10,13,14) and benzyloxy (entry 11) groups did not experience any ether cleavage despite the known α-nucleophilicity[8] of oxime and the ability of Cl^- to deprotect

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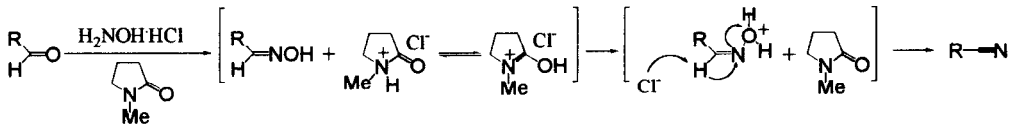
aryl methyl ether[9]. Substrates containing nitro (entries 6,7) and chloro (entry 2) groups also remain unaffected by competitive aromatic nucleophilic substitution[10]. However, substrates bearing strong electronwithdrawing group such as NO_2 (entries 6,7,20) require a longer reaction time as the extent of leaving group departure decreases with the electron-withdrawing ability of the β-aryl substituent[11]. In the case of citral (entry 24) a 1:1 *cis/trans* mixture resulted in the corresponding nitriles in 1:1 ratio indicating that no olefin isomerisation takes place under the experimental condition, further exemplifying the chemoselectivity of the process.

Table 1. Effect of Medium and Mode of Microwave Irradiation on Nitrile Formation.

Entry	Substrate[a]	Reagent	Mode[b]	Medium	Time (min)	Distribution of Product (%)[c]		
						Nitrile[d]	Aldehyde	Oxime
1	1	$H_2NOH{\cdot}HCl$	A	NMP	15	100(98)		
2	1	$H_2NOH{\cdot}HCl$	A	DMPU	15	90(80)		2
3	1	$H_2NOH{\cdot}HCl$	A	DMEU	15	89(80)		
4	1	$H_2NOH{\cdot}HCl$	A	HMPA	15	37.5		47.5
5	1	$H_2NOH{\cdot}HCl$	A	DMF	15	61	2	37
6	1	$H_2NOH{\cdot}HCl$	A	Sulfolane	15	81(70)		5
7	2	$H_2NOH{\cdot}HCl$	A	Al_2O_3[e]	15	83(70)		16[f]
8	1	$H_2NOH{\cdot}HCl$	A	Neat	15	91.5(80)	7	1.5[g]
9	1	$H_2NOH{\cdot}HCl$	B	NMP	10	81(70)	13	
10	1	$H_2NOH{\cdot}HCl$	B	NMP	15	52[h]	3	
11	1	$H_2NOH{\cdot}HCl$	B	Neat	10	65(40)	30	
12	3	None	A	NMP	15	2		98
13	3	HCl[i]	A	NMP	15	89(80)		
14	3	$NaHSO_4$[i]	A	NMP	15	96.5(88)	3.5	
15	3	$NaHSO_4$[i]	A	Neat	15	79(56)		21[g]
16	3	LiCl[i]	A	NMP	15	17		83

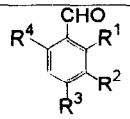
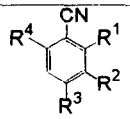
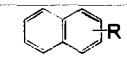
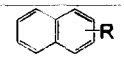
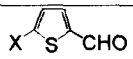
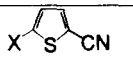
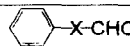
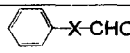
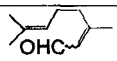
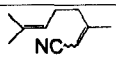
[a]1 = 4-Methoxybenzaldehyde; 2 = 2-Naphthaldehyde; 3 = 1-Naphthaldoxime. [b]A: Microwave irradiation using convection mode of operation with a preset temperature of 100°C; B: Microwave irradiation using micro mode of operation. [c]Determined by GCMS. [d]The figure in parenthesis represents the isolated yield. [e]The aldehyde and $H_2NOH{\cdot}HCl$ were ground with neutral alumina and mixed with a cyclomixer. [f]2:1 stereoisomeric mixture. [g]Stereoisomer of the starting oxime. [h]4-Cyanophenol was formed in 10% yield. [i]1.5 eq. was used.

Scheme I



In conclusion we have achieved an efficient method for the one-pot conversion of aldehydes to nitriles. The advantages of this protocol over the existing methods are summarised as (a) chemoselectivity, (b) high yield, (c) wide application - suitable for aromatic as well as aliphatic aldehydes, (d) replacement of a two stage operation by one-pot reaction, (e) easy work up and (f) requirement of no additional agents such as base, electrophilic/oxidising agents, metal catalysts etc.

Table 2. Chemoselective Transformation of Aldehydes to Nitriles.

Entry	Substrate	Product	Time (min)	Yield (%)[a,b,c]
				
1	$R^1 = R^2 = R^4 = H$; $R^3 = OMe$	$R^1 = R^2 = R^4 = H$; $R^3 = OMe$	15	98
2	$R^1 = R^2 = R^4 = H$; $R^3 = Cl$	$R^1 = R^2 = R^4 = H$; $R^3 = Cl$	15	95
3	$R^1 = OH$; $R^2 = R^3 = R^4 = H$	$R^1 = OH$; $R^2 = R^3 = R^4 = H$	30	80
4	$R^1 = R^2 = R^4 = H$; $R^3 = OH$	$R^1 = R^2 = R^4 = H$; $R^3 = OH$	15	100(70)
5	$R^1 = R^3 = R^4 = H$; $R^2 = OH$	$R^1 = R^3 = R^4 = H$; $R^2 = OH$	15	85
6	$R^1 = R^2 = R^4 = H$; $R^3 = NO_2$	$R^1 = R^2 = R^4 = H$; $R^3 = NO_2$	30	90(25)
7	$R^1 = R^3 = R^4 = H$; $R^2 = NO_2$	$R^1 = R^3 = R^4 = H$; $R^2 = NO_2$	30	97
8	$R^1 = R^2 = R^4 = H$; $R^3 = NMe_2$	$R^1 = R^2 = R^4 = H$; $R^3 = NMe_2$	15	100
9	$R^1 = R^4 = H$; $R^2 = R^3 = OH$	$R^1 = R^4 = H$; $R^2 = R^3 = OH$	15	89
10	$R^1 = R^4 = H$; $R^2 = R^3 = OMe$	$R^1 = R^4 = H$; $R^2 = R^3 = OMe$	15	96
11	$R^1 = R^4 = H$; $R^2 = R^3 = OCH_2Ph$	$R^1 = R^4 = H$; $R^2 = R^3 = OCH_2Ph$	15	85
12	$R^1 = R^3 = OH$; $R^2 = R^4 = H$	$R^1 = R^3 = OH$; $R^2 = R^4 = H$	30	70
13	$R^1 = R^4 = H$; $R^2 = OMe$; $R^3 = OH$	$R^1 = R^4 = H$; $R^2 = OMe$; $R^3 = OH$	15	80
14	$R^1 = R^3 = R^4 = OMe$; $R^2 = H$	$R^1 = R^3 = R^4 = OMe$; $R^2 = H$	15	100
				
15	R = 1-CHO	R = 1-CN	15	100
16	R = 2-CHO	R = 2-CN	15	90(80)
				
17	R = 3-CHO	R = 3-CN	15	70
18	R = 4-CHO	R = 4-CN	15	80
				
19	X = H	X = H	15	80
20	X = NO_2	X = NO_2	30	76(28)
				
21	X = *trans*- CH = CH	X = *trans*- CH = CH	15	100(85)
22	X = CH_2	X = CH_2	15	100
23	X = $(CH_2)_2$	X = $(CH_2)_2$	15	100
				
24			15	80

[a]Isolated yields. [b]Reactions were carried out in microwave irradiation using convection mode of operation with a preset temperature of 100°C. [c]Figures under paranthesis are the corresponding yields in absence of the solvent.

EXPERIMENTAL

The aldehydes were available commercially. The solvents were distilled before use. $NH_2OH{\cdot}HCl$ used was procured from S. d. Fine chemicals, India.

General procedure for the nitrile formation

Method A. A mixture of 4-methoxybenzaldehyde (0.32 g, 2.5 mmol), $H_2NOH{\cdot}HCl$ (0.26 g, 3.75 mmol) in NMP (2.5 ml) was heated in a domestic microwave oven using convection mode of operation[7] with a preset

temperature of 100°C for 15 mins. The cold reaction mixture was diluted with water (25 ml) and extracted with Et_2O (2 x 20 ml) to afford 4-methoxybenzonitrile (Mp = 60°C, 326 mg, yield = 98%) and was found to be identical with an authentic sample[12].

GCMS (m/z) : 133 (M, 100), 118 (M-CH_3, 9), 103 (M-CH_2O, 45), 90 (C_6H_4N, 51), 76 (C_6H_4, 15).

Method B. A mixture of 4-methoxybenzaldehyde (0.32 g, 2.5 mmol), H_2NOH·HCl (0.26 g, 3.75 mmol) in NMP (2.5 ml) was heated in a domestic microwave oven using the micro mode of operation[7] for 10 mins. The crude product, obtained after usual work up, was purified through chromatography (silica gel, eluent 5% EtOAc-hexane) to afford 4-methoxybenzonitrile (Mp = 60°C, 233 mg, yield = 70%) and was found to be identical with an authentic sample[12].

Method A was followed for the remaining substrates and on each occasion the product was found to be identical (^{1}H NMR, FTIR and GCMS) with an authentic sample. In most of the cases the product was isolated in pure form[13] and whenever required, purification was accomplished through chromatography.

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† NIPER Communication No. 38

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13. The crude products obtained using NMP as the solvent provided cleaner spectra (GCMS) compared to those of the products of the corresponding reactions carried out neat.