A one-pot conversion of carboxylic acids into nitriles catalysed by PEG400 under microwave irradiation

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A new efficient method for the synthesis of nitriles is reported. Carboxylic acids were converted into nitriles by a one-pot reaction with hydroxylamine sulfate and zinc catalysed by PEG400 under microwave irradiation in excellent yields. The most suitable condition was 20 minutes under the microwave power of 231 W with 5 mol% PEG400.

Keywords: carboxylic acids, nitriles, hydroxylamine sulfate, PEG400, microwave irradiation

Nitriles are important reagents for organic synthesis, which serve as a pharmacophore and intermediate for pharmaceuticals, agricultural chemicals, dyes, and material sciences. In recent years, it showed that nitriles could be converted to thiazole derivatives as inhibitors of superoxide,[1] benzamidines possessing activity of fibrinogen antagonists,[2] tetrazole derivatives as antipicornavirus drugs[3] and the commercially important angiotensin II receptor antagonist, losartan and valsartan.[4] A number of methods are known for the preparation of this useful class of compounds. They can be divided into three routes: (1) by dehydration of aldoximes,[5–7] or directly from aldehydes via hydroxylamine hydrochloride/phthalic anhydride,[8] ammonia/$MgSO_4$/MnO_2[9] or hydroxylamine hydrochloride/KF/Al_2O_3;[10] (2) by treating acids chlorides with sulfonamide;[11] and (3) by treating carboxylic acids with urea/aminosulfonic acid,[12–16] ethyl carbamate/thionyl chloride[17] or diphosphorus tetraiodide/ammonium carbonate.[18] Among all of the reactants, carboxylic acids are more stable and inexpensive. In addition, a number of drawbacks may be encountered using some of the above methods, such as low yields, harsh reaction conditions, tedious work-up procedures, and opaque reaction mechanism.

Microwave irradiation has been widely applied in organic synthesis.[19–21] Microwave activation has been reported for the one-pot synthesis of nitriles from aldehydes.[22–24] However, only one method for conversion of carboxylic acids into nitriles under the microwave was found by our team.[25] We now report a new method for the one-pot conversion of carboxylic acids into nitriles with hydroxylamine sulfate as amidation reagent and zinc as reductant catalysed by PEG400 under microwave irradiation and the results shown in Table 2. In this method, the yields are higher for some products and save much time with comparison to the general methods.

Results and discussion

These reactions are very difficult, and there may even be no reaction if there is no catalyst. So, PEG400 as a phase transfer to this reaction has been studied and the best amount to use is 5 mol%. It was found that a lower dosage of PEG400 did not catalyse the reaction effectively and a higher dosage would undoubtedly lead to more loss of products during the washing procedure. In our opinion, PEG400 should work as a solvent and disperse reactants hence making the reactions easier.

As shown in Table 1, the power of microwave had an obvious effect on the yields. The most suitable condition for benzoic acid was 20 minutes with the power of 231W. The reason may be the higher power input, the energy is too high to make the reaction completely effective, some of others chemical bonds or compounds (hydroxylamine sulfate) would be broken at the same time; On the other hand, if the power input is too low, hydroxylamine would decompose so the reaction would be unable to progress completely and the yield would be too low.

$$\mathrm{RCOOH} \xrightarrow[\mathrm{PEG400/MW}]{(\mathrm{NH_2OH})_2\cdot \mathrm{H_2SO_4/Zn}} \mathrm{RCN}$$

Scheme 1

Table 1 Effect of the power to benzoic acid

Entry	Power/W	Time/min	Yield/%
1	119	20	45
2	119	40	57
3	119	60	61
4	231	15	78
5	231	20	93
6	231	25	92
7	385	10	55
8	385	15	63
9	385	20	62

In Table 2, most of aromatic (entries 1–12) and heteroaromatic (entries 13–15) carboxylic acids could be converted to the corresponding nitriles in excellent yields. The aryl carboxylic acids with electron-donating groups such as $–CH_3$ and $–OCH_3$ are more reactive than those with electron-withdrawing groups such as –Cl, –I, $–NO_2$ in the aromatic ring, mainly because electron-donating groups increased the electron density of carbonyl promoting the easier reaction, and producing heteroaromatic carboxylic acids. The amino group as an electron-donating group resulted in 4-aminobenzoic acid

Table 2 Conversions of carboxylic acids into nitriles

Entry	Carboxylic acids	Time /min	Yield /%	M.p./°C	
				Found	Report[12,13,26]
1	$C_6H_5.COOH$	20	93	187–189[a]	188–191
2	$4\text{-}HO.C_6H_4.COOH$	19	91	110–112	110–113
3	$4\text{-}Cl.C_6H_4.COOH$	24	89	92–95	94–96
4	$4\text{-}O_2N.C_6H_4.COOH$	27	85	146–149	146–149
5	$2\text{-}CH_3.C_6H_4.COOH$	17	93	204–206[a]	205
6	$4\text{-}H_3CO.C_6H_4.COOH$	14	96	55–57	57–59
7	$3\text{-}O_2N.C_6H_4.COOH$	27	87	115–117	115–117
8	$4\text{-}I.C_6H_4.COOH$	22	88	126–128	128–129
9	$2\text{-}Cl.C_6H_4.COOH$	25	90	43–45	43–46
10	$4\text{-}H_2N.C_6H_4.COOH$	25	82	83–85	83–85
11	$C_6H_5.CH_2COOH$	20	92	232–234[a]	233–234
12	$C_6H_5.CH_2CH_2COOH$	20	90	259–260[a]	261
13	$3\text{-}C_5H_4N.COOH$	25	89	50–51	50–52
14	$2\text{-}C_4H_3S.COOH$	14	93	190–192[a]	192
15	$3\text{-}C_4H_3O.COOH$	16	91	149–151[a]	151
16	$(CH_3)_3C.COOH$	20	80	104–105[a]	105–106
17	$CH_3CH_2CH_2CH_2.COOH$	21	88	138–140[a]	139–141

[a] Boiling points were determined.

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(**10**) having a lower yield than other acids. The aliphatic carboxylic acids (entries 16–17) have lower yields and longer reaction periods, especially for pivalic acid (**16**). We suggest that the main reason for the low yields of pivalic acid (**16**) is volatilisation and decarboxylation to form the hydrocarbon.

In summary, a new method for the conversion of carboxylic acids into nitriles catalysed by PEG400 under microwave irradiation in satisfactory yields with hydroxylamine sulfate as amidation reagent and zinc as reductant has been developed. This method is inexpensive, practical and with less pollution and easy work-up.

Experimental

All reactions were performed in a commercial domestic microwave oven (Midea PJ21C-BF). The reaction process was monitored by GF254 TLC using petroleum ether/ethyl acetate (10:1 v/v) as the eluant. Melting points were determined on a microscopy apparatus (SGW X-4) and uncorrected. ^{1}H NMR spectra were obtained on a Bruker Avance (400MHz) spectrometer using TMS as internal standard and CDCl$_3$ as solvent. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). All the liquid parent materials were freshly distilled. The products were also characterised by comparison of their melting points and boiling points with the literature values.

Benzonitrile; general preparation

A mixture of benzoic acid (2.44 g, 20 mmol), hydroxylamine sulfate (2.46 g, 15 mmol), zinc dust (1.94 g,30 mmol) and PEG400(5 mol%) was irradiated at middle low power(231W) for 20 min. Upon completion, the solids were filtered and extracted with dried dichloromethane (2×10 mL).The organic phase was washed with H$_2$O (3×10 mL) and dried with magnesium sulfate. After the solvent was removed by distillation, the benzonitrile 1.92 g (93% yield) was collected at 187–189^{0}C. ^{1}H NMR(CDCl$_3$,) δ: 7.44 (d, 2H, 2×CH), 7.51 (d, 2H, 2×CH),7.54 (t, 1H, CH); IR (KBr) ν: 3067, 2229, 1599, 1490, 1447, 1287, 1223, 1178, 1070, 1026, 927, 760, 688, 548 cm^{-1}.

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