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One-pot conversions of carboxylic acids into nitriles without solvent under microwave irradiation

Yu-Qing Cao*, Yuan-Yuan Jin, Chun-Ming Duan, Zhan Zhang

College of Pharmacy, Hebei University, Baoding-071002, (P.R.CHINA)

E-mail: pharm_hbu@yahoo.com

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ABSTRACT

In an environmentally benign solvent-free system, carboxylic acids were rapidly transformed into corresponding nitriles by amidation with ethyl carbamate via one-pot reactions in excellent yields under microwave irradiation. The most suitable condition was 18 minutes under the microwave power of 231 watt with the amount of zinc chloride of 0.5 equiv.

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KEYWORDS

Carboxylic acids;
Nitriles;
Ethyl carbamate;
Microwave;
Solvent-free.

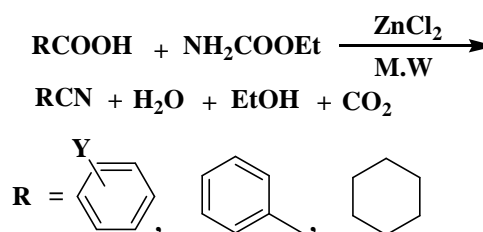
INTRODUCTION

Nitriles, important reagents for organic synthesis, had been known to chemists for a long time. In recent reports, it showed that nitriles could be converted to thiazole derivatives as inhibitors^[1] benzamidines possessing activity of fibrinogen antagonists^[2] tetrazole derivatives as anticoronavirus drugs and the commercially important angiotensin 1 receptor ligands, losartan and valsartan. Literature survey indicates that there were a large number of methods reported for the preparation of these useful classic compounds. The primary methods are the dehydration of aldoximes^[3] carboxylic acids and acyl amine^[4-5]; the Sandmeyer reaction of diazo salt; the ammoxidation of hydrocarbon, alcohols and aldehydes^[6-8] and so on.

In recent years, microwave had been widely used in organic synthesis^[9-11]. It had been reported^[12] that microwave activation for the one-pot synthesis of nitriles from aldehydes. But no report about microwave promote the synthesis of nitriles from carboxylic acids was found. In continuation of our ongoing programme

to develop environmentally benign reactions, we now wish to report a new method for the conversion of carboxylic acids to their corresponding nitriles by amidation with ethyl carbamate via one-pot reactions under microwave irradiation.

The general method is by the reaction of carboxylic acids and carbamide under melting conditions. The operation is too difficult to control, the reaction can not carry through completely and take too much time and low yields. With comparison to the general method, the yields are much higher for some products and save much time synchronously. The results shown in TABLE 1 indicate that the reaction is successful for a variety of carboxylic acids.



RESULTS AND DISCUSSION

Compared with other methods, ethyl carbamate was used to provide amidogen instead of carbamide. Ethyl carbamate was a low melting point reagent, it could be melted easily at low temperature and then carboxylic acids would be dissolved in it. Thus, the reaction would progress much more easily. Moreover, ethyl carbamate with steady character was easy to obtain. So it was more suitable to this reaction.

General method



A mixture of carboxylic acids, carbamide and amido sulfoacid are heated at 200-250 °C for 1-5h.

As shown in TABLE 1, several structurally different carboxylic acids could be converted to corresponding nitriles by amidation with ethyl carbamate under microwave irradiation at the absence of solvents in excellent yields. The substitutional groups of the phenyl could not only be the electron-donating groups such as -CH₃ and -OCH₃, but also the electron-withdrawing groups such as -Cl, -NO₂. At the presence of some of the substitutional groups which could be affected easily through other reactions, such as -I, -OH, -NH₂, the corresponding nitriles could also be gained normally. A longer reaction time was needed in the reactions of 4-aminobenzoic acid (**10**) because of the reduced solubility and lower reactivity of the zwitterionic amino acid compared with the other substrates.

As shown in TABLE 2, the power and time had an obvious effect to the yields. The most suitable condition was 18 minutes under the power of 231 watt. The causation may be that with the prolongation of time and the higher power input, the temperature is too high to make the reaction effectively carry through; On the other hand, if the power input is too low or the reaction time is too short, the reaction is unable to progress completely, so the yield is too low.

In this reaction, we use zinc chloride as catalyst and dehydrating agent. ZnCl₂ can give excellent yields, and the amount was reduced to 0.5 equiv. So ZnCl₂ was more suitable for this reaction. The amount of zinc chloride played an important role. Under the microwave irradiation of 231 watt and 18 minutes, the yield was promoted with the addition of zinc chloride, and it would reach peak at the amount of 1.70g(0.5 equiv).

TABLE 1: Conversions of carboxylic acids into nitriles

| Entry | R | Time (min) | Yield(%) | | m.p./°C | |
|-----------------|--|------------|----------|---------|---------|---------------------|
| | | | M.W | General | Find | Report [13,14] |
| 1 ^a | C ₆ H ₅ | 18 | 93 | 65 | 186-9 | 188 ^[15] |
| 2 | 4-HOC ₆ H ₄ | 20 | 88 | 65 | 111-3 | 113 |
| 3 | 4-ClC ₆ H ₄ | 20 | 86 | 74 | 92-6 | 94-6 |
| 4 | 2-ClC ₆ H ₄ | 20 | 85 | 80 | 43-6 | 43-6 |
| 5 | 4-O ₂ NC ₆ H ₄ | 19 | 84 | 71 | 146-9 | 149 |
| 6 | 3-O ₂ NC ₆ H ₄ | 21 | 91 | 76 | 116-8 | 118 |
| 7 | 4-CH ₃ C ₆ H ₄ | 20 | 83 | 65 | 27-9 | 29 |
| 8 | 4-IC ₆ H ₄ | 21 | 85 | 72 | 126-9 | 128-9 |
| 9 | 4-H ₃ COC ₆ H ₄ | 21 | 78 | 68 | 53-6 | 54-6 |
| 10 | 4-H ₂ NC ₆ H ₄ | 23 | 75 | 46 | 86-9 | 88 |
| 11 ^a |  | 21 | 89 | 83 | 233-4 | 233-4 |
| 12 ^a |  | 20 | 81 | 70 | 117-9 | 117-9 |

^aBoiling points were determined

TABLE 2 : Effect of the power and time

| Compound | Power (W) | Time (min) | Yield (%) | Power (W) | Time (min) | Yield (%) |
|--------------|-----------|------------|-----------|-----------|------------|-----------|
| Benzoic acid | 119 | 15 | 11 | 231 | 23 | 78 |
| Benzoic acid | 119 | 25 | 23 | 385 | 5 | 45 |
| Benzoic acid | 119 | 40 | 39 | 385 | 10 | 36 |
| Benzoic acid | 231 | 13 | 24 | 539 | 5 | 12 |
| Benzoic acid | 231 | 18 | 93 | 539 | 10 | 7 |

So the suitable amount of zinc chloride was 0.5 equiv.

EXPERIMENTAL

All reactions were performed in a commercial domestic microwave oven (Midea PJ21C-BF). TLC was used to monitor the reaction process. TLC was GF₂₅₄ thin layer chromatography with petroleum ether/ethyl acetate (4/1) used as eluent. Melting points were determined on a microscopy apparatus and uncorrected. ¹H-NMR spectra were obtained on a Bruker AVANCE (400MHz) spectrometer using TMS as internal standard and CDCl₃ as solvent. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). All the liquid parent materials are fresh distilled. The products were also characterized by comparison of their Melting points and boiling points with the literature values.

General procedure for the preparation of benzo nitrile (entry 1, TABLE 1)

A mixture of benzoic acid (3.05g, 0.025mol), ethyl carbamate (2.67g, 0.03mol), zinc chloride (1.7g,

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0.0125mol) was irradiated at middle low power(231W) in a 50mL one-necked, round-bottomed flask equipped which was placed into a 200mL beaker covered with a evaporating dish. The progress of the reaction was monitored by TLC. Upon completion, the solids were extracted by alcohol, distilled to eliminate solvent. The benzonitrile 2.4g (93% yield) was collected at 186-189°C by distillation at atmospheric pressure. ¹H-NMR (CDCl₃): δ: 7.44 (d, 2H, 2×CH), 7.51 (d, 2H, 2×CH), 7.54 (t, 1H, CH); IR (KBr) v: 3067, 2229, 1599, 1490, 1447, 1287, 1223, 1178, 1070, 1026, 927, 760, 688, 548 cm⁻¹

Some other results were shown as follows:

Compound (entry 2, TABLE 1) ¹H-NMR (CDCl₃)

δ: 5.40 (s, 1H, OH), 6.91 (d, 2H, 2×CH), 7.34 (d, 2H, 2×CH); IR (KBr, cm⁻¹) v: 3250, 2220, 1610, 1580, 1500, 1280, 1220, 1160, 835cm⁻¹

Compound (entry 3, TABLE 1) ¹HNMR (CDCl₃)

δ: 7.45(d, 4H, 4×CH); IR (KBr, cm⁻¹) v: 3091, 2225, 1591, 1483, 1397, 1088, 1015, 828, 585, 542cm⁻¹

Compound (entry 4, TABLE 1) ¹HNMR (CDCl₃)

δ: 7.77 (d, 1H, CH), 7.80 (m, 1H, CH), 7.83(m, 1H, CH), 8.37(d, 1H, CH).

Compound (entry 5, TABLE 1) ¹HNMR (CDCl₃)

δ: 7.77 (d, 2H, 2×CH), 8.37 (d, 2H, 2×CH); IR (KBr, cm⁻¹) v: 3106, 3073, 3052, 2231, 1603, 1527, 1488, 1437, 1350, 1293, 1236, 859, 747, 682, 539cm⁻¹

Compound (entry 6, TABLE 1) ¹HNMR (CDCl₃)

δ: 7.77 (d, 1H, CH), 7.80 (m, 1H, CH), 7.83(m, 1H, CH), 8.37(d, 1H, CH)

Compound (entry 7, TABLE 1) ¹HNMR (CDCl₃)

δ: 2.35(s, 3H, CH₃), 7.24 (d, 2H, 2×CH), 7.39 (d, 2H, 2×CH); IR (KBr, cm⁻¹) v: 3039, 2953, 2925, 2228, 1608, 1508, 1451, 1384, 1176, 1040, 818, 546cm⁻¹

Compound (entry 10, TABLE 1) ¹HNMR (CDCl₃)

δ: 7.32 (m, 1H, CH), 7.48 (m, 1H, CH), 7.45(d, 2H, 2×CH); IR (KBr, cm⁻¹) v: 3094, 3073, 2232, 1590, 1471, 1435, 1268, 1165, 1133, 1059, 1035, 955, 762, 677, 555, 460cm⁻¹

CONCLUSION

In summary, the microwave promoted conversions of various carboxylic acids into Nitriles by amidation with ethyl carbamate under solvent-free conditions with excellent yields in very short reaction time. The neutral conditions and rapid reaction conditions together with eco-friendly solvent-free conditions should make present protocol an important alternative to other classical methods.

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REFERENCES

- [1] E.C.Wang, G.J.Lin; Tetrahedron Lett., **39**, 4047-4050 (1998).
- [2] B.D.Judkins, D.G.Allen, T.A.Cook, B.Evans, T.E.Sardharwala; Synth.Comm., **26**, 4351-4367 (1996).
- [3] J.Brnrko; Synth.Comm., **1**, 189 (1989).
- [4] W.Brackman, P.J.Smit; Rec.Trav.Chim, **82**(8), 757 (1963).
- [5] H.T.Clarke, R.R.Read; 'Organic Synthesis Collective', John Wiley; New York, **1**, (1941).
- [6] G.A.Olah, T.Keumi; Synthesis, 112 (1979).
- [7] F.Cavani, F.Trifiro; Chim.Ind., **70**(4), 58 (1988).
- [8] F.Cavani, G.Centi, F.Trifiro; Chim Ind, **74**(3), 182-193 (1992).
- [9] R.Q.Li, H.Yan; Chinese Journal of Synthetic Chemistry, **13**(6), 597-599 (2005).
- [10] Y.W.Sha, T.Han, L.Shen, R.Chen; Speciality Petrochemicals, **6**, 21-24 (2000).
- [11] J.Wang, F.C.Jiang; Chinese Journal of Organic Chemistry, **22**(3), 212-219 (2002).
- [12] D.Subhas Bose, A.Vencor Narsaiah; Tetrahedron Lett., **39**, 6533-6534 (1998).
- [13] D.H.Liao, B.Wu; Huaxueshijie, **7**, 373-375 (2000).
- [14] D.H.Liao, Q.M.Xu, Z.H.Xue; Journal of East China University of Science and Technology, **23**, 426-430 (1997).
- [15] S.J.Yuan, H.L.Fang; Materials Protection, **30**, 12-15 (1997).