Direct Synthesis of Imides from Dicarboxylic Acids using Microwaves†

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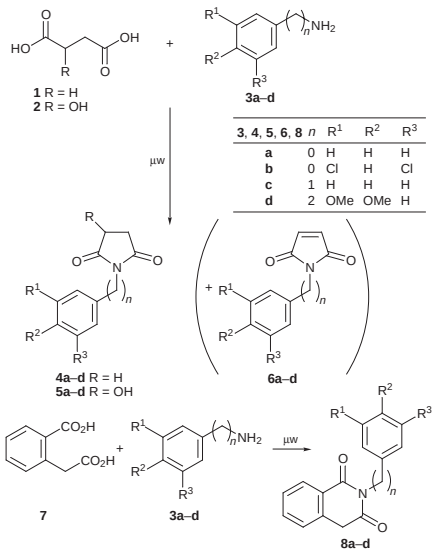
1,4- and 1,5-dicarboxylic acids, when treated with amines in a domestic microwave oven, afford good yields of the corresponding imides.

Imide derivatives are associated with a variety of uses due to their biological properties,[1,2] synthetic applications[3,4] and industrial uses.[5,6] Thus, *N*-arylsuccinimides have been examined as potential fungicides,[7] especially *N*-(3,5-dichlorophenyl)succinimide.[8] The 3-hydroxy derivatives are involved in their metabolic pathways,[9,10] 2-aryl-1,3(2*H*,4*H*)-dioxoisoquinolines are known as herbicides and plant growth regulators[11] and some show activities as aminopeptidase N inhibitors.[12] Despite their wide applicability, routes available for the synthesis of imide derivatives are limited. These syntheses usually start from the anhydride and give the corresponding amic acid, followed by cyclization under acidic conditions.[13–16]

In recent years the use of microwaves to 'emulate' classic organic reactions has become very popular amongst synthetic organic chemists[17–23] because microwave heating often leads to higher yields, cleaner reactions and shorter reaction times. These procedures are seriously limited because of the use of solvents in microwave ovens which gives rise to elevated temperatures and consequently high pressures, and in some cases may lead to dangerous explosions. Here we describe a microwave-induced synthesis of imides from dicarboxylic acids and amines in a one-pot reaction in the absence of solvents. One of us[24] already had used microwaves to prepare amides by pyrolysis of carboxylic acid salts of amines and we thought that this could be extended to the synthesis of imides. Recently a paper was published[25] where microwave irradiation is used to prepare cyclic imides from anhydrides in the presence of $TaCl_5$–SiO_2. Our method consists of heating the acid and amine mixture (molar ratio 1 : 1) until the starting material disappears in a domestic microwave oven. Thus, succinic acid **1** was heated with aniline for 20 min yielding *N*-phenylsuccinimide **4a** in 76% yield. When the amine employed was 3,5-dichloroaniline **3b** the required reaction time was 15 min to afford fungicide **4b** in 78% yield; with benzylamine a similar yield (78%) of compound **4c** was obtained after 15 min. To check the behaviour of a typical aliphatic amine the succinimide of homoveratryl amine **3d** was also prepared; after 15 min irradiation we obtained an 84% yield of the desired imide **4d**, showing the viability of our synthesis for the derivatization of β-phenethylamines as imides.

The synthesis of 3-hydroxy-2,5-pyrrolidinediones was also attempted. There has been several reports on their synthesis, all with several steps.[26,27] We started with malic acid **2** and the amines **3a–d**. In all four cases, together with the expected products **5a–d** in 59–72% yield, we found 14–19% of the corresponding maleimides **6a–d** (Scheme 1); this product obviously comes from the dehydration of the hydroxy compound. Our question was how to overcome its formation. First we tried to reduce the reaction time; however the NMR of the crude mixture showed a singlet at δ 6.89 corresponding to the vinyl proton in the pyrroline ring. As a second idea, we tried to lead the reaction to a complete dehydration; however longer heating times (45 min) did not change the ratio malimide:maleimide. We think the dehydration occurs in the first stages of the synthesis, prior to the cyclization, and may be helped by the presence of a free carboxylic acid function.



Scheme 1

Finally, we studied the extension of our procedure to the formation of six-membered imide rings by using homophthalic acid **7** with amines **3a–d** and obtaining imides **8a–d** 73–84% (Table 1) in 15 min. **8d** has been used as a precursor for protoberberine type alkaloids.[28]

Typical Procedure.—A mixture of succinic acid **1** (400 mg, 3.39 mmol) and aniline (315 mg, 3.39 mmol) in a test tube was heated in a domestic microwave oven (1000 W, 70% of total power) until no starting materials were observed by TLC (20 min). The crude reaction was purified by flash chromatography (ethyl acetate:hexane, 1 : 1) to afford *N*-phenylsuccinimide **4a** (448 mg, 76%) as a white solid.

In conclusion, we have demonstrated the validity of this procedure for the synthesis of imides from 1,4- and 1,5-dicarboxylic acids. Our method can be considered as an improvement over those previously described[25] since it does not use anhydrides, which are always more expensive than acids and sometimes not easily synthesized. The use of heavy metals was also avoided, which is really a matter of environmental concern when trying to extend a method to a multigram scale synthesis. Our work constitutes a good example of the better performance of microwaves *versus*

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Table 1 Synthesis of imides from dicarboxylic acids and amines by microwave heating

Acid	Amine	Prod.	*t*/min	Yield (%)	δ_u(300 MHz)	δ_c(C=O)	ν_{max}/ cm^{-1}	*m/z* M^+ (%)	Mp (lit.)/°C
1	**3a**	**4a**	20	76	2.88 (s, 4H)	176.3	1705	175(100)	153–155 (153–154[29])
1	**3b**	**4b**	15	78	2.92 (s, 4H), 7.29 (s, 2H), 7.41 (s, 1H)	175.3	1700–1720	247(11) 245(65) 243(100)	135–136 (136.5–137.5[8])
1	**3c**	**4c**	15	78	2.72 (s, 4H), 4.67 (s, 2H),	176.9	1695	189(100)	98–99/ (98-99[30])
1	**3d**	**4d**	15	84	2.72 (s, 4H), 2.84 (t, 2H), 3.73 (t, 2H)	177.1	1705	263(20)	125–127 (126.5–127.5[31])
2	**3a**	**5a**	15	62	2.90 (dd 1H), 3.26 (dd, 1H), 4.83 (m, 1H)	179.2, 176.0	3430, 1700	191(50)	178–180 (179–180[32])
		(+**6a**)		(+19)	6.88 (s, 2H)	169.6	1710	173(100)	88–89 (89—90[33])
2	**3b**	**5b**	10	60	2.88 (dd 1H), 3.26 (dd, 1H), 4.82 (dd, 1H)	176.6, 172.2,	3530 1695–1730	263(6) 261(37) 259(55)	131–132 (144–145[27])
		(+**6b**)		(+19)	6.89 (s, 2H), 7.36 (s, 3H)	168.5	1720	245(11) 243(67) 241(100)	132–133 (141–142[8])
2	**3c**	**5c**	10	72	2.69 (dd, 1H), 3.07 (dd, 1H), 4.58–4.66 (m, 3H)	178.2, 173.8	3360, 1700	205(71)	105–106 (101–103[26])
		(+**6c**)		(+14)	4.67 (s, 2H), 6.69 (s, 2H)	170.5	1700	187(100)	69–70 (68.5–70[34])
2	**3d**	**5d**	15	59	2.64 (dd, 1H), 2.85 (t, 2H), 3.03 (dd, 1H), 3.75 (t, 2H), 4.58 (dd, 1H)	178.4, 174.1,	3365, 1690–1715	279(16)	131.3–133.2[a]
		(+**6d**)		(+16)	2.86 (t, 2H), 3.76 (t, 2H), 6.68 (s, 2H)	170.6	1705	261(24)	139.4–140.6[b]
7	**3a**	**8a**	15	74	4.23 (s, 2H)	170.0, 163.9	1715, 1670	237(61)	186.5–188.2 (188–189[35])
7	**3b**	**8b**	15	75	4.24 (s, 2H)	169.5, 164.6	1720, 1675	309(3), 307(16) 305(25)	228.0–228.7 (230.5–232.5[35])
7	**3c**	**8c**	15	84	4.04 (s, 2H), 5.18 (s, 2H)	169.9, 164.9	1705, 1665	251(79)	126.9–128.4 (127[36])
7	**3d**	**8d**	15	73	2.88 (t, 2H), 4.04 (s, 2H), 4.21 (t, 2H)	169.8, 164.8	1710, 1665	325(5)	143.3–144.6[c]

[a] Found: C, 59.98; H, 6.64; N, 4.96. $C_{14}H_{17}NO_5$ requires C, 60.21; H, 6.14; N 5.01%. [b] Found: C, 64.22; H, 6.14; N, 5.48. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36%. [c] Found: C, 70.46; H, 5.74; N, 3.94. $C_{19}H_{19}NO_4$ requires C, 70.14; H, 5.89; N, 4.30%.

conventional heating, since when we compared our procedure with heating at 160 °C, we always found shorter reaction times and yields similar or better than those obtained by conventional heating.

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