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APPLICATION OF ULTRASOUND IRRADIATION FOR THE REACTIONS OF N-HYDROXYMETHYLATION

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Abstract: A convenient and high yield method for the N-hydroxymethylation of substituted phthalimide and benzimidazole under ultrasound irradiation is reported.

In the recent years the application of ultrasound irradiation in organic reactions is rapidly increasing. It has been reported that a variety of reactions such as Diels-Alder[1], Arndt-Eistert reaction[2], Knoevenagel condensation[3], Wolf rearragement[4], oxidation[5], reduction[6], Reformatsky reaction[7], Cannizzarro reaction[8], substitution reaction[9] could be facilitated by ultrasound irradiation.

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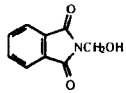
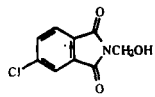
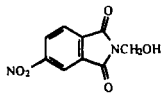
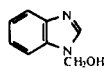
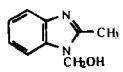
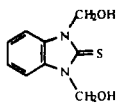
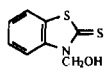
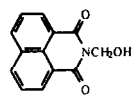
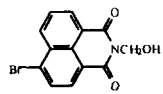
But there is no report of the use of sonication in the N-hydroxymethylation reaction of phthalimide and benzimidazole. We therefore decided to investigate the effect of ultrasound on such reaction.

The N-hydroxymethylation of phthalimide, benzimidazole and naphthalimide derivatives with formaldehyde soliution were carried out at reflux temperature in a directly immersion probe ultrasonic reactor similar to Herbert C. Brown's apparatus[10]. No catalyst was added. The progress of the reaction was monitored by thin layer chromatogrphy (TLC). The reaction results are summarized in table 1. The products were characterized by IR except those of entries 4 and 6 where ^{1}HNMR were used. In less than 20 minutes good yields (except entry 8 and 9) could been achieved for most of the reactions. In some cases, nearly quantitative yields of N-hydromethylation products with satisfying purtiy could been obtained after several minutes irradiation. As a contrast, much more time for the N-hydroxymethylation of phthalimide were needed under conventional conditions (called "silent" in sonochemstry) by mechanical stirring. For example, 4 hours were needed for the N-hydroxymethylation of phthalimide under "silent" condition[11], while only 4 minutes sufficed under ultrasound irradiation. Similar acceleration occurred even at room temperature when 2-mercaptobenzothiazole (entry 7) was used. By way of exception, no remarkable enhancement was observed for 1,8-naphthalimide and 4-bromide 1,8-naphthalimide.

Experimental

Melting points were taken in open capillary on WRS-1 digital point instrument and

Table 1. Results of N-hydroxymethylation reaction of some phthalimides and benzimidazoles

Entry	Product	Time (min)	Yield [a] (%)	solvents	m.p. (℃)	Lit. m.p. (℃)
1		4 240 [b]	97 90	water	144.9-145.3	138-141[11]
2		8	76	water	124.5-125.5	126-9[13]
3		24	83	water	160-160.5	159[14]
4		20 120 [b]	80 84	50% methanol	145.0-145.7	139-141[15]
5		20	81	50% methanol	153.4-154.2	—
6		10	98	50% ethanol	167.7-168.1	—
7		15 [c] 120 [b]	94 100 [d]	50% ethanol	130-131	128-130[17]
8		20	No product	water	—	—
9		20	No product	water	—	—

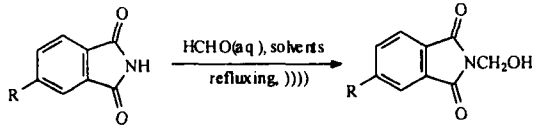
a: isolated yields

b: "silent" condition under reflux temperature

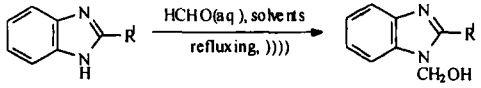
c: ultrasound irradiation at room temperature

d: crude yield

Scheme 1



R=H-, Cl-, NO_2-



R^1=H-, Me-, SH-

uncorrected. TLC was carried out on silical gel GF_{254}. IR spectra were recorded on a NICOLET MAGNA-IR500 spectrometer. ^{1}HNMR spectra were obtained with an AVANCE 500 spectrometer in DMSO solution using TMS as internal standard. The JHN-M-1 ultrasonic probe was made by Shanghai Jump Ultrasonic Co., Ltd.

Material

All phthalimides and benzimidazoles were prepared according to the literature[12,16]. Other reagents were available commercially.

General procedure

As an example, phthalimide (1.47 g, 10 mmol), 38% formaldehyde solution (2 mL), and water (8 mL) were added to a cylindrical flask similar to the apparatus in literature[10]. A tapered ultrasonic probe (100 W, 20±1 KHZ) was placed into the mixture so that the tip reached just below the surface. (It is important to ensure that the probe does not touch the glass of the flask). The oil

bath preset to 102-105℃ was placed around the flask to immerse the contents and the ultrasonic probe was switched on at half power (50 W). After 4 minutes irradiation, all of the phthalimide dissolved. The TLC showed just one point and the ultrasonic probe was switched off. After cooled to room temperature the mixture was filtered, washed with water (2×15 mL) and dried, 1.72 g (yield 97 %) white plate crystal with melting point: 144.9-145.3℃ was obtained. The IR spectra data of the product was identical to the standard IR spectra data[18,19]. In entries 2 to 5 and entry 7 recrystallization was needed after filtering to get satisfying purity. The solvents for recrystallization were benzene (entry 2, 3), ethanol-petroleum ether (entry 4, 5) and acetone (entry 7) respectively.

Spectral data of entry 1-7 are as follows

Entry 1 IR (KBr/cm^{-1}): 3500, 2950, 1770, 1700, 1610, 1460, 1425, 1395, 1351, 1330, 1055

Entry 2 IR (KBr/cm^{-1}): 3505, 2950, 1774, 1706, 1590, 1455, 1414, 1368, 1335, 1148, 1050

Entry 3 IR (KBr/cm^{-1}): 3510, 2950,1780, 1713, 1620, 1538, 1350, 1150, 1063

Entry 4 ^{1}HNMR (CD_3SOCD_3, δ ppm):

5.56 (d, 2H,-CH_2OH), 7.18-7.32 (m, 2H, ArH), 7.65 (m, 2H, ArH), 8.29 (s, 1H, -CH)

Entry 5 IR (KBr/cm^{-1}): 3100, 2850, 1615, 1518, 1462, 1394, 1055

Entry 6 ^{1}HNMR (CD_3SOCD_3, δ ppm):

5.70 (s,4H, -CH_2OH), 7.25 (m, 2H, ArH), 7.49 (m, 2H, ArH)

Entry 7 IR (KBr/cm^{-1}): 3250, 1662, 1580, 1500, 1427, 1328, 1220

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