Microwave-assisted Heterogeneous Benzil–Benzilic Acid Rearrangement†

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A new procedure for carrying out the benzil–benzilic acid rearrangement in the solid state has been developed which provides a new route to synthesize the pharmacologically interesting anticonvulsant dilantin.

Some simple benzilic acid derivatives show pronounced pharmacological activity,[2] for example the sodium salt of 5,5′-diphenylhydantoin, the anticonvulsant Dilantin. In 1838 von Liebig[1] described the hydroxide ion induced transformation of benzil, an α-diketone, into benzilic acid, the salt of an α-hydroxy acid. In this hydroxide ion-catalyzed rearrangement reaction, the favoured solvents are water and aqueous ethanol. Heterogeneous conditions with hydroxide ion in organic solvents have also been employed.[3] The reactions may take up to 4 days when conducted at room temperature or 10 min to 24 h under reflux. Recently, Toda *et al.*[4] have developed a method for carrying out the benzil–benzilic acid rearrangement in the solid state at 80 °C (giving 0–95% yield in 0.1 h to 6 h) and some reactions were found to proceed more quickly than in solution. We report here the solid state microwave-enhanced benzil–benzilic acid rearrangement.[5]

If powdered KOH and benzil are ground together with a pestle and mortar, and irradiated in a domestic microwave over, they burnt due to the tendency of KOH to adsorb the microwave energy. Therefore, two drops of water were added to the KOH crystals to dissolve them, then benzil was added and the mixture ground with a pestle to form a milky material. Some Celite was added to absorb the milky material and it was ground again. The resulting solid <?show mixture was transferred to a Teflon beaker and irradiated in a household microwave oven for 15 s first and then for 10 s intervals for the indicated times (Table 1). The benzil rearrangement reactions proceeded safely using this sample preparation procedure. The results are outlined in Table 1.

Generally, without microwave irradiation, the benzil derivatives with electron-donating groups took a long time to complete the rearrangement reaction at 80 °C in the solid state; for example the *para*-methoxy derivative gives only 32% yield after 6 h.[4] In contrast, under microwave irradiation, there was not much difference between electron-donating and withdrawing groups on benzil; both reactions gave satisfactory yields in a very short time (< 1 min in most cases). In entry 5 the reason for the low yield from 4,4′-dibromobenzil is not clear. However, this compound was difficult to dissolve in common organic solvents probably due to the effect of its lattice energy.

In conclusion, the benzil–benzilic acid rearrangement reaction using microwave-irradiation not only shortens the reaction time but also increases yields. In addition the simple reaction protocol of microwave-irradiation also provides an advantage over the traditional heating method in organic solvents.

Experimental

Methanol, ethyl acetate, methylene chloride, diethyl ether, and dimethylformamide (HPLC grade and reagent grade) were obtained from a local supplier, the ALPS Chem. Co. (Taiwan). Potassium hydroxide, Celite, hydrochloric acid, and anhydrous sodium sulfate were purchased from Fluka A. G. (Switzerland). A Tatung microwave oven (model TMO-110, Tatung Co., Taipei, Taiwan) with adjustable power level was used for microwave irradiation. NMR spectra were taken on a Bruker AM-400 and chemical shifts of the ^{1}H NMR spectra were referenced to solvent peaks. *J* values are in Hz. TLC was performed on silica gel G pre-coated plates (E. Merck, Germany), HPLC was run on an Alcott 760-HPLC pump (Japan) with a Soma 3701 UV-Detector (Japan) and data collected on a Hewlett-Packard HP 3394A Integrator (USA).

General Procedures for Microwave-assisted Solid State Reaction.— To solid KOH (0.56 g, 10 mmol) was added water (0.1 ml) and the resulting solution allowed to stand for 2 min to dissolve the KOH. Powdered benzil (0.42 g, 2 mmol) was added to the KOH and the mixture was well-ground with a pestle to form a milky material. Then to this mixture, Celite (5 ml) was added and the resulting mixture was ground again. The final mixture was irradiated in a domestic microwave oven (70% of full power) for 15 s first and then three times for 10 s (compound **1**, five times; compound **2**, five times; compound **3**, four times; compound **4**, three times; compound **5**, eleven times and once for 15 s). Diethyl ether (5 ml) was added to the mixture, which was stirred for a while, filtered and the mixture acidified to pH 1.5 with 3 M HCl (25 ml) and then extracted with ethyl acetate (100 ml). The organic phase was dried over $MgSO_4$ and concentrated to give benzilic acid **1** as a white solid. Compound **1** (0.393 g, 86% yield), mp 146–148 °C (lit.,[6] mp 150–153 °C); δ_H (400 MHz, [^{2}H$_6$]DMSO) δ_H 7.35–7.24 (10 H, m), 3.38 (1 H, br).

In a similar procedure, compounds **2**–**5** were synthesized. Their yields and physical data are: compound **2** (0.642 g, 95% yield), mp 163–164 °C; δ_H (400 MHz, [^{2}H$_6$]DMSO) 7.87 (4 H, d, *J* 7.0), 6.85 (4 H, d, *J* 7.0), 3.71 (6 H, s), 3.38 (1 H, br); compound **3** (0.476 g, 93% yield), mp 127–128 °C; δ_H (400 MHz, [^{2}H$_6$]DMSO) 7.33–7.11 (8 H, m), 3.41 (1 H, br), 2.26 (6 H, s); compound **4** (0.585 g, 98% yield), mp 135–136 °C (lit.,[6] mp 136–138 °C); δ_H (400 MHz, [^{2}H$_6$]acetone) 7.49–7.31 (8 H, m), 3.40 (1 H, br); compound **5** (0.429 g, 56% yield), mp 216–218 °C; δ_H (400 MHz, [^{2}H$_6$]DMSO) 7.50 (4 H, d, *J* 6.9), 7.30 (4 H, d, *J* 6.9).

Table 1 Microwave-assisted heterogeneous benzil–benzilic acid rearrangements $Ar^1C(:O)C(:O)Ar^2 \rightarrow Ar^1C(OH)(CO_2H)Ar^2$

Entry	Ar^1	Ar^2	Irradiation time/s	Isolated yield (%)	Mp/°C
1	C_6H_5	C_6H_5	45	86	146–148
2	*p*-MeC_6H_4	*p*-MeC_6H_4	65	95	163–164
3	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	55	93	127–128
4	*o*-ClC_6H_4	*o*-ClC_6H_4	45	98	135–136
5	*p*-BrC_6H_4	*p*-BrC_6H_4	145	56	216–218

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