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Improved synthesis of diethyl 2,6-dimethyl-4-aryl-4H-pyran-3,5-dicarboxylate under ultrasound irradiation

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ABSTRACT

Diethyl 2,6-dimethyl-4-aryl-4H-pyran-3,5-dicarboxylates (**1**) have been synthesized by the reaction of aryl aldehyde and 1,3-diketone catalyzed by $ZnCl_2$ under ultrasound irradiation. The effects of changes in the ultrasonic power, temperature, and reaction time are discussed. With the optimized reaction conditions, various aryl aldehydes were used to synthesize 4H-pyrans (**1**) under the influence of ultrasound irradiation. Compared with the conventional thermal methods, the remarkable advantages of this method are the simple experimental procedure, shorter reaction time and high yield of product.

1. Introduction

4H-pyrane and its derivatives are known as an important class of heterocyclic compounds in the pharmaceutical as well as synthetic chemistry [1,2]. A number of compounds containing the 4H-pyrane moiety are being developed in wide range of therapeutic areas [3–5], especially in the inhibition of the HIV-1 proteases [6]. Numerous methods have been reported for the synthesis of 4H-pyrane. Diethyl 2,6-dimethyl-4-aryl-4H-pyran-3,5-dicarboxylates (**1**) was produced via the reaction between the corresponding aldehyde and 1,3-diketone in 16 h with a yield of 30–50%, utilizing $ZnCl_2$ as a catalyst, acetic anhydride as the solvent, and column chromatography to purify the product [7–9]. To simplify the experimental procedures, the reaction was exposed to microwave irradiation for nearly 30 min, and the isolated yield did not increase significantly (<50%) [10] for the decomposition of ethyl acetoacetate [11].

Ultrasound irradiation has been established as an important technique in synthetic organic chemistry. It has been used as an efficient heating source for organic reactions. Shorter reaction time is the main advantage of ultrasound-assisted reactions. Simple experimental procedure, very high yields, increased selectivity and clean reactions of many ultrasound-induced organic transformations offers additional conveniences in the field of synthetic organic chemistry [12–14]. The beneficial effects of ultrasound irradiation are playing an increasing role in process chemistry, especially in cases where classical methods require drastic conditions or prolonged reactions times. As part of our program to investigated organic reactions amenable to sonochemistry, we report the ultrasound-assisted synthesis of diethyl 2,6-dimethyl-4-aryl-4H-pyran-3,5-dicarboxylates (**1**) (Scheme 1). The general procedure for synthesis of **1** is the reaction of aldehyde and 1,3-diketone in 16 h with a yield of 30–50%, $ZnCl_2$ was used as a catalyst, and acetic anhydride was the solvent. In our procedure the reactions were performed in an ultrasonic processor (GEX750-5C, USA). The effects of changes in the ultrasonic power, temperature, and reaction time are discussed. Our methodology offers several advantages including mild reaction conditions, good yields of products as well as a simple experimental and isolation procedure which makes it a useful and attractive process for the synthesis of these compounds.

2. Method

2.1. Apparatus and analysis

Melting points were determined by an X-5 instrument (made in China), and uncorrected. IR spectra were taken on a VERTEX70 (made in German) spectrometer by ATR. NMR spectra were measured on a Bruker AV 400 MHz (made in German) spectrometer. MS were determined on Esquire 6000 spectrometer (made in German). Sonication was performed in a GEX750-5C ultrasonic processor (made in USA) equipped with a 3 mm wide and 140 mm long

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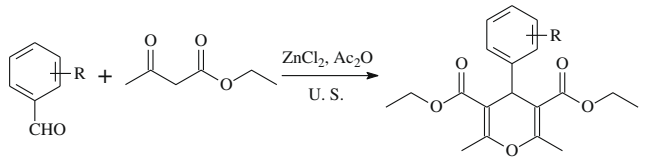

1

R= a: H; b: 4-CH_3; c: 4-Br; d: 4-OCH_3; e: 4-Cl; f: 3-Cl; g: 4-F; h: 4-NO_2; i: 3-NO_2; j: 4-OH; k: 3-Br; l: 3-$NHCOCH_3$; m: 4-$NHCOCH_3$; n: 2,3,4-triOCH_3; o: 2,4,5-triOCH_3.

Scheme 1.

probe, which was immersed directly into the reaction mixture. The operating frequency was 24 kHz and the output power was 0–750 W through manual adjustment.

2.2. Typical procedure

A mixture of benzaldehyde (0.06 mol), ethyl acetoacetate (0.12 mol), in acetic anhydride (9.0 mL) was irradiated by an ultrasonic processor at 50 °C and 100 W. After the indicated time (see Table 2), the mixture was cooled to the room temperature, ice water was added and the solution was neutralized (pH 7–8) by an aqueous solution of NaOH. The organic phase was extracted with dichloromethane, washed with water and dried with Na_2SO_4. The solvent was removed under reduced pressure to afford **1**. The crude products were purified by recrystallation (ethyl acetate and petroleum ether) with enough purity for spectral analysis.

Compound **1a**: white solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.20 (t, 6H, $2CH_2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.09 (m, 4H, $2CH_2CH_3$), 4.75 (s, 1H, Ar-CH), 7.13–7.26 (m, 5H, Ar-H).

Compound **1b**: white solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21 (t, 6H, $2CH_2CH_3$), 2.28 (s, 3H, Ar-CH_3), 2.35 (s, 6H, $2CH_3$), 4.08 (m, 4H, $2CH_2CH_3$), 4.70 (s, 1H, Ar-CH), 7.04 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.12 (d, 2H, *J* = 8.0 Hz, Ar-H).

Compound **1c**: white solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (t, 6H, $2CH_2CH_3$), 2.37 (s, 6H, $2CH_3$), 4.11 (m, 4H, $2CH_2CH_3$), 4.73 (s, 1H, Ar-CH), 7.12 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.36 (d, 2H, *J* = 8.4 Hz, Ar-H).

Compound **1d**: white solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (t, 6H, $2CH_2CH_3$), 2.36 (s, 6H, $2CH_3$), 3.77 (s, 3H, OCH_3), 4.10 (m, 4H, $2CH_2CH_3$), 4.71 (s, 1H, Ar-CH), 6.80 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.28 (d, 2H, *J* = 8.8 Hz, Ar-H).

Table 1
The ultrasound yields of **1d** under ambient conditions.

Temp (°C)	30			50			70		
Time (min)	Power (W)								
	50	100	150	50	100	150	50	100	150
10	32.1	47.2	46.9	77.3	78.3	74.5	76.5	77.7	77.2
30	39.7	52.3	53.1	64.6	88.5	74.7	83.3	86.1	76.9
50	42.5	55.4	57.6	85.3	88.5	76.3	86.2	85.7	72.7

Compound **1e**: white solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (t, 6H, $2CH_2CH_3$), 2.37 (s, 6H, $2CH_3$), 4.10 (m, 4H, $2CH_2CH_3$), 4.74 (s, 1H Ar-CH), 7.20 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.29 (d, 2H, *J* = 8.4 Hz, Ar-H).

Compound **1f**: white solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, 6H, $2CH_2CH_3$), 2.39 (s, 6H, $2CH_3$), 4.11 (m, 4H, $2CH_2CH_3$), 4.74 (s, 1H, Ar-CH), 7.14–7.17 (m, 4H, Ar-H).

Compound **1g**: white solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.20 (t, 6H, $2CH_2CH_3$), 2.35 (s, 6H, $2CH_3$), 4.09 (m, 4H, $2CH_2CH_3$), 4.73 (s, 1H, Ar-CH), 6.91 (m, 2H, Ar-H), 7.20 (m, 2H, Ar-H).

Compound **1h**: yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.20 (t, 6H, $2CH_2CH_3$), 2.38 (s, 6H, $2CH_3$), 4.08 (m, 4H, $2CH_2CH_3$), 4.86 (s, 1H, Ar-CH), 7.41 (d, 2H, *J* = 8.7 Hz, Ar-H), 8.10 (d, 2H, *J* = 8.7 Hz, Ar-H).

Compound **1i**: yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21 (t, 6H, $2CH_2CH_3$), 2.41 (s, 6H, $2CH_3$), 4.11 (m, 4H, $2CH_2CH_3$), 4.88 (s, 1H, Ar-CH), 7.41–8.12 (m, 4H, Ar-H).

Compound **1j**: white solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.29 (t, 6H, $2CH_2CH_3$), 2.42 (s, 6H, $2CH_3$), 4.18 (m, 4H, $2CH_2CH_3$), 4.80 (s, 1H, Ar-CH), 6.80 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.15 (d, 2H, *J* = 8.8 Hz, Ar-H), 8.22 (s, 1H, Ar-OH).

Compound **1k**: white solid, IR (ATR, cm^{-1}): 2973, 1678, 1544, 1412, 1190, 1137, 1023, 790; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, 6H, $2CH_2CH_3$), 2.39 (s, 6H, $2CH_3$), 4.12 (m, 4H, $2CH_2CH_3$), 4.73 (s, 1H, Ar-CH), 7.10–7.31 (m, 4H, Ar-H); MS: 410 (M+1).

Compound **1l**: brown solid, IR (ATR, cm^{-1}): 3299, 2980, 1705, 1609, 1552, 1485, 1369, 1189, 1126, 1026, 779; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (t, 6H, $2CH_2CH_3$), 2.16 (s, 3H, $COCH_3$), 2.37 (s, 6H, $2CH_3$), 4.11 (m, 4H, $2CH_2CH_3$), 4.76 (s, 1H, Ar-CH), 7.00–7.23 (m, 4H, Ar-H), 7.47 (s, 1H, $NHCOCH_3$); MS: 410 (M+23).

Compound **1m**: brown solid, IR (ATR, cm^{-1}): 3296, 2979, 1703, 1554, 1408, 1188, 1125, 1023, 778; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21 (t, 6H, $2CH_2CH_3$), 2.15 (s, 3H, $COCH_3$), 2.36 (s, 6H, $2CH_3$), 4.10 (m, 4H, $2CH_2CH_3$), 4.74 (s, 1H, Ar-CH), 6.98–7.48 (m, 4H, Ar-H), 7.12 (s, 1H, $NHCOCH_3$); MS: 388(M+1).

Table 2
The yields of **1** under ultrasonic irradiation.

Entry	R	Time (min)/yield[a] (%)	Time (h)/yield (%)	Mp (°C)	Mp (°C)
1a	H	35/89.4	24/48.4 [9]	74.0–74.7	74.0–75.0 [9]
1b	4-CH_3	20/80.8	16/13.1 [8]	81.9–82.2	79.0–84.0 [8]
1c	4-Br	35/71.2	14/50.8[b]	81.3–81.8	81.2 [20]
1d	4-OCH_3	30/88.5	21/36.7 [9]	83.0–84.6	84.0–85.0 [9]
1e	4-Cl	40/87.2	16/49.8 [8]	63.2–64.8	63.0–66.0 [8]
1f	3-Cl	45/80.3	11/50.2[b]	62.2–63.8	62.5–63.2 [20]
1g	4-F	45/83.1	13/52.7[b]	69.9–71.5	68.9–69.9 [20]
1h	4-NO_2	45/90.0	13/58.7[b]	84.5–85.9	84.5–86.8 [20]
1i	3-NO_2	40/84.9	24/44.4[b]	88.6–89.6	89.0 [9]
1j	4-OH	50/79.2	15/46.2[b]	140.6–142.1	106.0 [9]
1k	3-Br	40/78.2	–	70.8–72.1	–
1l	3-$NHCOCH_3$	55/70.7	–	110.1–111.9	–
1m	4-$NHCOCH_3$	60/74.7	–	135.7–136.2	–
1n	2,3,4-triOCH_3	50/78.2	–	97.2–97.7	–
1o	2,4,5-triOCH_3	50/75.0	–	99.0–100.1	–

[a] Isolated yield.
[b] Synthesised based on the method of Urbahns [8,9,15].

Compound **1n**: white solid, IR (ATR, cm^{-1}): 2979, 2935, 1706, 1620, 1487, 1369, 1286, 1188, 1095, 1038, 793; ^1H NMR ($CDCl_3$, 400 MHz), δ = 1.23 (t, 6H, $2CH_2CH_3$), 2.33 (s, 6H, $2CH_3$), 3.91 (t, 9H, $3OCH_3$), 4.14 (m, 4H, $2CH_2CH_3$), 4.82 (s, 1H, Ar-CH), 6.51 (d, 1H, J = 8.8 Hz, Ar-H), 6.80 (d, 1H, J = 8.8 Hz, Ar-H); MS: 443 (M+23).

Compound **1o**: white solid, IR (ATR, cm^{-1}): 2982, 2833, 1704, 1627, 1513, 1462, 1291, 1191, 1080, 1031, 812; ^1H NMR ($CDCl_3$, 400 MHz), δ = 1.23 (t, 6H, $2CH_2CH_3$), 2.37 (s, 6H, $2CH_3$), 3.89 (t, 9H, $3OCH_3$), 4.14 (m, 4H, $2CH_2CH_3$), 4.81 (s, 1H, Ar-CH), 6.42 (s, 1H, Ar-H), 6.71 (s, 1H, Ar-H); MS: 421 (M+1), 443 (M+23).

3. Results and discussion

In order to obtain the optimum experimental conditions, the reaction of 4-methoxy benzaldehyde with ethyl acetoacetate under ultrasonic irradiation has been considered as a standard model reaction (Table 1). To determine the appropriate time of the reaction, we investigated the model reaction at different times (10, 30, 50 min). The product was formed in lower yield at 10 min, and higher at 30 min and 50 min. This indicates that 30 min was sufficient for the result. When the reaction was at 50 and 70 °C, the product was in similar yields after 30 min. When the reaction was performed with an ultrasonic power of 50 W, a lower yield was achieved, with starting material remaining. The reaction yield was improved under sonication at 100 and 150 W. The best yield for **1d** was obtained by ultrasonic irradiation at a temperature of 50 °C and a power of 100 W. The product was obtained within 30 min in 88.5% yield. In conventional method, the yield **1d** was gained in 36.7% after heating 16 h at 60 °C [15]. It was observed that the reaction under ultrasonic irradiation had significantly improved yields.

The advantages on the synthesis of **1d** by such ultrasound is frequently attributed to cavitation (mechanical) effects, the physical processes that creates, enlarges, and implodes gaseous and vapor-phase cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer, thus producing a variety of high energy species in solution [16–18]. It has been observed that a favorable acceleration in reaction rate occurs when compared to classical conditions (i.e. under reflux). The addition of catalytic amounts of $ZnCl_2$ further facilitates the reaction, thereby indicating a synergistic effect of ultrasound on the tri-phase catalyst system. However, the successful reaction with sonication in the absence of catalyst indicates that ultrasound can indeed substitute for a phase transfer catalyst, thereby providing an attractive alternative for the nucleophilic substitution reactions [19].

To establish the generality with respect to the aryl aldehydes under the influence of ultrasound irradiation, various aryl aldehydes were used for the synthesis of 4H-pyran (**1**) with substituents such as –Cl, –OH, $–NO_2$, –Me, –OMe and so on. Under the optimized conditions previously described, the reaction of the aryl aldehydes under the influence of ultrasound irradiation was carried out. The corresponding 4H-pyrane (**1**) were formed in excellent yields. The results are summarized in Table 2. It was observed that **1** was formed faster (20–60 min) with yields of 70–90% using ultrasound. This is compared with the time required (11–24 h) and yields (40–60%) under thermal processing (Table 2, entries **1a**–**1j**).

We also examined the synthesis of 3-bromobenzaldehyde (**1k**), 3-acetamidobenzaldehyde (**1l**), 4-acetamidobenzaldehyde (**1m**), 2,3,4-trimethoxyl-benzaldehyde (**1n**), 2,4,5-trimethoxylbenzaldehyde (**1o**) under ultrasound. Compounds **1k**, **1l**, **1m**, **1n**, and **1o** were obtained in yields 70–78% in 40–60 min, and no significant formation was observed under literature conditions even after 16 h.

As shown in Table 2, a series of **1** were synthesized by ultrasonic irradiation in a simple experimental procedure, with a short reaction time, high yield, and ease of product isolation. The compounds **1a**–**1j** were characterized by ^1H NMR and matched with literatures. The compounds **1k**, **1l**, **1m**, **1n** and **1o** were characterized by ^1H NMR, IR and MS spectrum, respectively.

4. Conclusion

The diethyl 2,6-dimethyl-4-aryl-4H-pyran-3,5-dicarboxylates (**1**) have been synthesized under ultrasound irradiation. The present method has many advantages to those reported in the literature, the procedure is carried out in a shorter time, easier work-up and good yields, especially the generality to the various substituted 4H-pyrans.

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