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Ultrasound promoted one-pot synthesis of 3-aza-6,10-diaryl-2-oxa-spiro[4.5]decane-1,4,8-trione

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ABSTRACT

One-pot synthesis of 3-aza-6,10-diaryl-2-oxa-spiro[4.5]decane-1,4,8-trione from 1,5-diaryl-1,4-pentadien-3-one can be carried out in good yields at 50 °C under ultrasound irradiation. This method provided several advantages such as simple work-up procedure, shorter reaction time and higher yield.

1. Introduction

Spiro compounds having cyclic structures fused at a central carbon are of recent interest due to their interesting conformational features and their structural implications on biological systems [1]. The title compound was prepared via two-step reactions in classical method, bischalcone was converted into the corresponding dimethyl 2,6-diaryl-4-ketocyclohexane-1,1-dicarboxylate at first, which was then reacted with hydroxylamine hydrochloride [2–4]. Reddy et al. reported that the synthesis of 2,6-diaryl-4-ketocyclohexane-1,1-dicarboxylate was carried out in 66–80% yield under refluxing via the condensation of bischalcone with dimethyl malonate, which was reacted with hydroxylamine hydrochloride to form 3-aza-6,10-diaryl-2-oxa-spiro [4.5]decane-1,4,8-trione in 65–76% yield in methanol in the presence of sodium methoxide [3], but the reaction needed a long reaction time (14–22 h). Compared with two-step strategies, one-pot reaction provides useful products without isolation of any intermediate, and thus reduces time, saves both energy and raw materials.

Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the last three decades. A large number of organic reactions can be carried out in higher yield, shorter reaction time or milder conditions under ultrasonic irradiation [5–10]. Herein, we wish to report an efficient one-pot synthesis of 3-aza-6,10-diaryl-2-oxa-spiro[4.5]decane-1,4,8-trione from bischalcones, dimethyl malonate and hydroxylamine hydrochloride catalyzed by sodium hydroxide under ultrasound irradiation (Scheme 1).

2. Method

2.1. Apparatus and analysis

Dimethyl malonate was purified by distillation prior to use. 1,5-Diaryl-1,4-pentadien-3-one were prepared according to the literature [11]. Melting points were uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal standard. MS were determined on VG70E-HF spectrometer (EI, 70 eV) or SHIMADZU GCMS-QP2010 spectrometer (ESI). Sonication was performed in Shanghai Branson BUG25-06 (or 40-06) ultrasonic cleaner (with a frequency of 25 or 40 kHz and a nominal power 250 W), the total acoustic power injected into the sample solution was found to be 0.63 (or 1.53) W by calorimetry [12]. The reaction flasks were immersed in every place of the cleaner in such way that the surface of reactants is slightly lower than water in the cleaner, and the temperature of the water bath was controlled by the addition or removal of circulated water.

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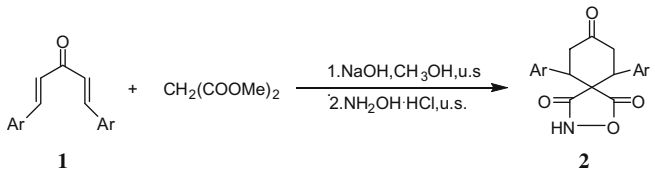

Scheme 1. One-pot synthesis of 3-aza-6,10-diaryl-2-oxa-spiro[4.5]decane-1,4,8-trione.

2.2. General procedure for the synthesis of 3-aza-6,10-diaryl-2-oxa-spiro[4.5]decane-1,4,8-trione

Dimethyl malonate (132 mg, 1 mmol), 1,5-diaryl-1,4-pentadien-3-one (**1,** 1 mmol), sodium hydroxide (12 mg, 0.3 mmol), methanol (2 mL) were added into a 25 mL round bottomed flask. The reaction mixture was irradiated in the water bath of the ultrasonic cleaner at 50 °C for a appropriate period (the reaction was monitored by TLC). Hydroxylamine hydrochloride (69 mg, 1 mmol) was then added in the above mixture and continued to irradiate. After the completion of the reaction (the reaction was followed by TLC), the solvent was evaporated under reduced pressure. The further purification was accomplished by column chromatography on silica on (200–300 mesh), eluted with petroleum ether or a mixture of petroleum ether and ethyl acetate (10:1–5:1). The authenticity of compounds **2a**–**d** was established by comparing their melting points with data reported in literatures. The others (**2e**–**i**) were established by their ^{1}H NMR, ^{13}C NMR and MS.

2.2.1. Compound *2e*

White solid, m.p. 237–239 °C; ^{1}H NMR (DMSO), δ: 3.31–3.34 (d, J = 14.2 Hz, 2H, $COCH_2$), 3.34–3.39 (d, 2H, $COCH_2$), 3.53–3.86 (m, 2H, 2PhCH), 7.13–7.45 (m, 8H, Ph-H), 10.62 (s, 1H, N–H); m/z (ESI): 492 $[M-1]^+$; ^{13}C NMR (DMSO): 27.4, 33.9, 43.5, 44.1, 52.7, 63.9, 121.2, 131.5, 131.9, 141.0, 154.8, 170.0, 170.1 ppm.

2.2.2. Compound *2f*

White solid, m.p. 186–188 °C; ^{1}H NMR (DMSO), δ: 3.31–3.34 (d, J = 10.5 Hz, 2H, $COCH_2$), 3.42–3.45 (d, J = 10.0 Hz, 2H, $COCH_2$), 3.54–3.58 (t, J = 14.0 Hz, 1H, PhCH), 3.86–3.89 (t, J = 12.5 Hz, 1H, PhCH), 7.19–7.45 (m, 8H, Ph-H), 7.62 (s, 1H, N-H); m/z (ESI): 493 M^+; ^{13}C NMR (DMSO): 27.2, 33.9, 43.6, 44.4, 52.6, 64.1, 121.8, 128.8, 130.9, 132.7, 143.6, 154.6, 169.0, 170.1 ppm.

2.2.3. Compound *2g*

White solid, m.p. 212–214 °C; ^{1}H NMR (DMSO), δ: 3.24–3.31 (m, 4H, $2COCH_2$), 3.89–3.93 (t, J = 13.6 Hz, 2H, PhCH), 4.03–4.06 (t, J = 17.5 Hz, 2H, PhCH), 7.18–7.45 (m, 8H, Ph-H), 10.66 (s, 1H, N-H); m/z (ESI): 404 $[M+1]^+$; ^{13}C NMR (DMSO): 22.0, 36.6, 44.8, 45.6, 53.0, 55.9, 127.9128.5, 129.2, 129.5, 134.0, 157.2, 168.3, 168.7 ppm.

2.2.4. Compound *2h*

White solid, m.p. 236–238 °C;^{1}H NMR (DMSO), δ: 3.22–3.23 (d, J = 4.84 Hz, 2H, $COCH_2$), 3.31–3.33 (d, J = 9.12 Hz, 2H,$COCH_2$), 3.84–3.88 (dd, J = 13.2, 3.48 Hz, 1H, PhCH), 3.97–4.00 (dd, J = 13.2, 3.72 Hz, 1H, PhCH), 7.19–7.61 (m, 6H, Ph-H), 10.71 (s, 1H, N-H); m/z (ESI): 473 M^+; ^{13}C NMR (DMSO): 26.8, 33.6, 44.0, 45.4, 58.3, 65.0, 124.8, 126.9, 128.3, 129.6, 132.5, 178.6, 209.7, 209.9 ppm.

2.2.5. Compound *2i*

White solid, m.p.196–198 °C; ^{1}H NMR ($CDCl_3$), δ: 3.38–3.54 (m, 4H, $2COCH_2$), 3.56–4.04 (m, 2H, 2PhCH), 7.08–7.25 (m, 8H, Ph-H), 7.69 (s, 1H, N–H); m/z (EI): 402 $[M-1]^+$; ^{13}C NMR (DMSO): 27.2, 33.9, 43.6, 44.4, 52.4, 64.1, 125.8, 128.2, 129.8, 143.3, 154.3, 168.9, 170.0 ppm.

3. Results and discussion

The effect of the reaction conditions on the condensation of 1,5-diphenyl-1,4-pentadien-3-one, dimethyl malonate and hydroxylamine hydrochloride under ultrasound was shown in Table 1. From the results in Table 1, we can see that the amount of sodium hydroxide had a significant effect on the yield of 3-aza-6,10-diphenyl-2-oxa-spiro[4.5]decane-1,4,8-trione (**2a**). When the amount of sodium hydroxide was 10% mmol, 15% mmol, 30% mmol and 50% mmol, the yield of **2a** was 22% (Entry 1), 43% (Entry 2), 68% (Entry 3) and 61% (Entry 4) respectively.

As shown in Table 1, when increasing the temperature, the yield also increased. For example, when the molar ratio of 1,5-diphenyl-1,4-pentadien-3-one and sodium hydroxide was 1:0.15, the 3-aza-6,10-diphenyl-2-oxa-spiro[4.5]decane-1,4,8-trione (**2a**) was obtained in 43% yield at 30 °C for 6 h (Entry 2). When increasing the temperature to 40 °C or 50 °C, the yield of **2a** was 52% and 73%, respectively (Entries 5, 6).

We also observed the effect of frequency of ultrasound irradiation on the reaction. The yield with 25 kHz irradiation for 6 h (Entry 6) was better than that with 40 kHz irradiation for 6 h (Entry 7) when the molar ratio of 1,5-diphenyl-1,4-pentadien-3-one and sodium hydroxide was 1:0.15 at 50 °C. It is shown that lower frequency of ultrasound irradiation improved the yield. The reason may be that the lower frequency irradiation produces the better cavitations [5,13]. We also did the experiments in the absence of ultrasound, the condensation of 1,5-diphenyl-1,4-pentadien-3-one with dimethyl malonate and hydroxylamine hydrochloride was carried out in 36% yield (Entry 9) using refluxing for 6 h at the same conditions. It is apparent that the reaction can be finished in shorter reaction time to give better yield under ultrasound irradiation.

From the results above, the reaction conditions we chose were as follows: 1,5-diphenyl-1,4-pentadien-3-one (1 mmol), sodium hydroxide (0.30 mmol), CH_3OH (2 mL), dimethyl malonate (1 mmol), hydroxylamine hydrochloride (1 mmol). Using this reaction system, we did a series of experiments for one-pot synthesis of 3-aza-6,10-diaryl-2-oxa-spiro[4.5]decane-1,4,8-trione under 25 kHz ultrasound irradiation. The results are summarized in Table 2.

As shown in Table 2**,** the reaction of bischalcone with dimethyl malonate and hydroxylamine hydrochloride catalyzed by sodium hydroxide was carried out in good yields under ultrasound irradiation. The dramatic improvement observed was with regard to a short reaction time. According to the method reported in the liter-

Table 1
The effect of reaction conditions on one-pot synthesis of 3-aza-6,10-diphenyl-2-oxa-spiro[4.5]decane-1,4,8-trione under ultrasound irradiation.*

Entry	Amount of NaOH, mmol	Frequency, kHz	Temperature, °C	Isolated yield, %
1	0.10	25	30	22
2	0.15	25	30	43
3	0.30	25	30	68
4	0.50	25	50	61
5	0.15	25	40	52
6	0.15	25	50	73
7	0.15	40	50	69
8	0.30	25	50	91
9	0.30	–	Reflux	36

* Substrate: 1,5-diphenyl-1,4-pentadien-3-one, 1 mmol; CH_3OH, 2 mL; dimethyl malonate, 1 mmol; hydroxylamine hydrochloride, 1 mmol. Reaction time: addition: 2 h, cyclocondensation: 4 h.

Table 2
One-pot synthesis of 3-aza-6,10-diaryl-2-oxa-spiro[4.5]decane-1,4,8-trione at 50 °C under ultrasound irradiation.

Entry	Ar	Time (reflux), h	Products	Isolated yield (reflux), %	M.p., °C	M.p., °C [Lit]
a	C_6H_5	6(6)	2a	91(36)	172–174	172–174 [3]
b	4-ClC_6H_4	5(5)	2b	88(26)	222–224	223–224 [3]
c	4-$CH_3C_6H_4$	7(7)	2c	86(49)	214–216	213–214 [3]
d	4-$CH_3OC_6H_4$	8(8)	2d	79(42)	215–217	218–219 [3]
e	4-BrC_6H_4	6	2e	73	237–239	–
f	3-BrC_6H_4	6	2f	55	186–188	–
g	2-ClC_6H_4	6	2g	68	212–214	–
h	2,4-$Cl_2C_6H_3$	6	2h	49	236–238	–
i	3-ClC_6H_4	6(6)	2i	76(24)	196–198	–

ature [3], the reaction time was 14–22 h, whereas under ultrasonication, the reaction time was reduced to half or more. For example, compound **2a** was previously prepared in 74% yield under refluxing as reported in the literature [3], while under ultrasound irradiation, **2a** was obtained in 91% yield (Table 2, Entry a) within 6 h catalyzed by sodium hydroxide. Compound **2b** was obtained in 76% yield, whereas present procedure resulted in 88% yield within 5 h (Table 2, Entry b). In the absence of ultrasound under refluxing alone, **2a**–**d, 2i** were obtained in 36% (Table 2, Entry a), 26% (Table 2, Entry b), 49% (Table 2, Entry c), 42% (Table 2, Entry d), 24% (Table 2, Entry i) yield at the other reaction conditions consistent respectively, while under ultrasound irradiation, the yields of **2a**–**d**, **2i** were 91%, 88%, 86%, 79%, 76% respectively. It is apparent that the ultrasound can accelerate the reaction significantly.

Sonochemistry can be defined as chemistry in a liquid medium in presence of pressure waves. The increasing interest for sonochemistry is due to the positive chemical and mechanical effects when ultrasonic waves propagate in a liquid medium. Cavitation is the origin of sonochemistry. Liquids irradiated with ultrasound can produce bubbles. Under the proper conditions these bubbles can undergo a violent collapse, which generates localized "hot spots" with a transient high temperature and pressures, inducing molecular fragmentation, and highly reactive species are locally produced, which are responsible for the chemical effects of ultrasound on homogeneous solutions. In the some case, sonication can probably provide more efficient stirring [5a,14]. All of these can cause the reaction to take place rapidly.

4. Conclusion

An efficient one-pot synthesis of some 3-aza-6,10-diaryl-2-oxa-spiro[4.5]decane-1,4,8-trione from 1,5-diaryl-1,4-pentadien-3-one has been developed under ultrasound irradiation. Compared with reported method, this method provided several advantages such as simple work-up procedure, shorter reaction time and higher yield.

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