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Short and tandem syntheses of spiro[2.5]octane-5,7-dione and spiro[3.5]nonane-6,8-dione via diethyl acetonedicarboxylate

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ABSTRACT

A general synthetic route to spiro[2.5]octane-5,7-dione and spiro[3.5]nonane-6,8-dione that involves cyclization of the related acrylates and diethyl acetonedicarboxylate, followed by decarboxylation, has been developed. Compared with previous synthetic methods, the developed protocol avoids the use of column chromatography in each of the synthetic steps. Therefore, it can be readily scaled-up. The use of diethyl acetonedicarboxylate under mild conditions to build the skeleton of 1,3-cyclohexanedione has proved to be very efficient.

Compounds spiro[2.5]octane-5,7-dione (**1**) and spiro[3.5]nonane-6,8-dione (**2**, Fig. 1) are very useful and key intermediates of pharmaceutical development products.[1–3] Several routes to them are known, although they are all quite challenging. Moreover, they all suffer from severe drawbacks from a chemical synthetic point of view.[1–4] Therefore, there is a demand for developing efficient and robust methods to synthesize **1** and **2** in order to circumvent these problems.

One example is a four-step synthesis of spiro[2.5]octane-5,7-dione (**1**) through Wittig reaction, Michael/Claisen reaction, followed by hydrolysis and decarboxylation using (1-ethoxycyclopropoxy)trimethylsilane (**3**) as the starting material (Scheme 1), as described in patent literature.[1,2] However, this approach requires flash chromatography for the purification of intermediates and the final product. In addition, the overall yield was in the range 30–35% and needed improvement.

One published Letter described the synthesis of spiro[3.5]nonane-6,8-dione (**2**) by a similar protocol as above.[3] Due to the high volatility of the starting material cyclobutanone (**5**), the first step could only be carried out in silicon oil to avoid the loss of cyclobutanone from the reaction system. After the reaction, the resulting enone (**6**) had to be distilled out from the silicon oil in order to proceed to the next step (Scheme 2).

Therefore, there is a strong demand for developing a novel and practical protocol to synthesize both **1** and **2**.

For short and practical preparations of **1** and **2**, it was decided to use the same starting materials (**3** and **5**) as in Schemes 1 and 2 for the new syntheses. For the first steps of both syntheses, it was also decided that the corresponding acrylate esters should be prepared instead of the enones (**4** and **6**), because we realized that **4** and **6** could further react with the Wittig reagent ($MeC(O)CH{=}PPh_3$), thereby decreasing the yields of the desired products.[5]

For the Wittig reaction between (1-ethoxycyclopropoxy) trimethylsilane (**3**) and (2-ethoxy-2-oxoethylidene)triphenylphosphorane (**7**), a high-boiling-point solvent (tetraethylene glycol dimethyl ether) was used. Therefore, the product (**8**) could be easily distilled out from the reaction mixture in 76% yield.[6] For the reaction with cyclobutanone (**5**), the corresponding Horner–Wadsworth–Emmons protocol was developed, which allowed the process to be completed at lower temperature in 79% yield. Hence, the problem of the high volatility of cyclobutanone was overcome (Scheme 3).[7]

For the next step, our initial plan was to let the produced acrylates (**8** or **9**) react with ethyl acetoacetate. Based on the proposed mechanism, the in situ generated dianion of ethyl acetoacetate was

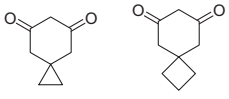

Figure 1. The structures of **1** and **2**.

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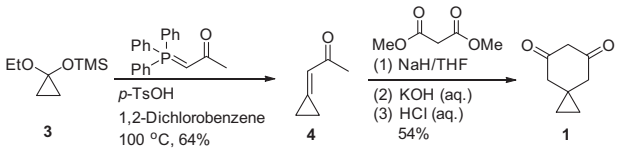
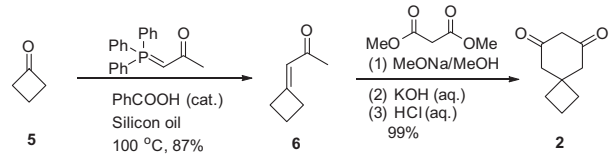
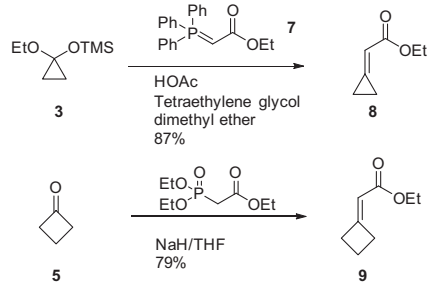


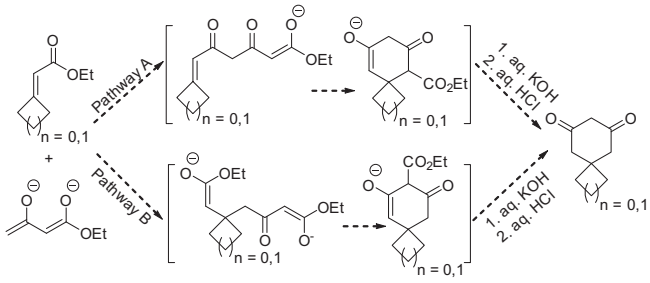
Scheme 1. Synthesis of **1** via the enone intermediate **4**.



Scheme 2. Synthesis of **2** via the enone intermediate **6**.



Scheme 3. Synthesis of the acrylate intermediates **8** and **9**.

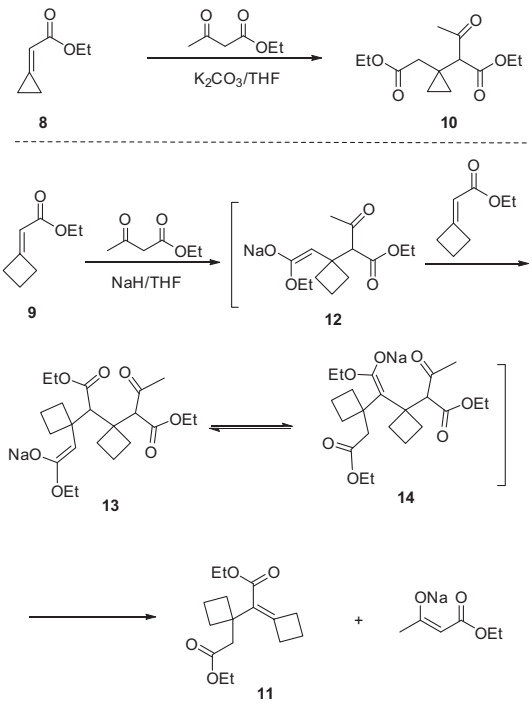


Scheme 4. Proposed synthetic pathways to **1** and **2** via ethyl acetoacetate.

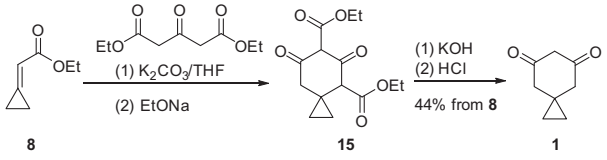
envisaged as building the 1,3-cyclohexanedione skeleton directly via either one of two plausible pathways (Scheme 4).

To our surprise, neither of the above two substrates (**8** and **9**) afforded the desired product with the dianion of ethyl acetoacetate, giving only complex mixtures. It was further realized that cyclopropylidene carboxylic acid ethyl ester (**8**) only produced **10** in 60% yield under milder Michael addition conditions (Scheme 5). Even more surprisingly, cyclobutylidene carboxylic acid ethyl ester (**9**) could only produce **11** with ethyl acetoacetate under basic conditions. It was assumed that the Michael addition intermediates **12** and **13** underwent a process akin to a Baylis–Hillman-type reaction via **14** to generate the product **11** (Scheme 5).

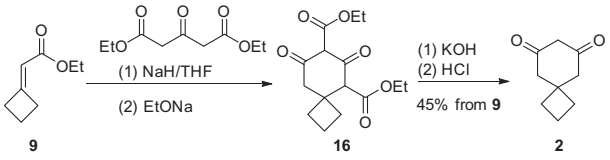
Gratifyingly, it was quickly found that by replacing ethyl acetoacetate with diethyl acetonedicarboxylate, the original goals could be achieved. As shown in Scheme 6, the cyclization to form the six-membered ring could be accomplished by treating cyclopropylidene carboxylic acid ethyl ester (**8**) and diethyl 1,3-acetonedicarboxylate with potassium carbonate (K_2CO_3) in



Scheme 5. Products formed by reaction of acrylates (**8** and **9**) and ethyl acetoacetate.



Scheme 6. Synthesis of **1** from **8** via diethyl 1,3-acetonedicarboxylate.



Scheme 7. Synthesis of **2** from **9** via diethyl 1,3-acetonedicarboxylate.

tetrahydrofuran (THF), followed by addition of sodium ethoxide (EtONa). Without any isolation, compound **15** was directly hydrolyzed by potassium hydroxide (KOH) and the product was subjected to decarboxylation under acidic conditions. The obtained crude spiro[2.5]octane-5,7-dione (**1**) was further purified by crystallization from methyl *tert*-butyl ether (MTBE), which afforded the desired product with 99% purity. The overall yield from cyclopropylidene carboxylic acid ethyl ester (**8**) was 44%.[8]

The above protocol could also be used for the synthesis of spiro[3.5]nonane-6,8-dione (**2**). For the cyclization step, sodium hydride (NaH) was used instead of K_2CO_3. For this, cyclobutylidene carboxylic acid ethyl ester (**9**) was added to a solution of diethyl 1,3-acetonedicarboxylate in THF containing NaH and then EtONa was added, which led to the formation of compound **16**. As above, without any isolation, compound **16** was directly hydrolyzed with KOH and the product was decarboxylated under acidic conditions.

The obtained crude spiro[3.5]nonane-6,8-dione (**2**) was further purified by crystallization from MTBE, which afforded the desired product with 98% purity. The overall yield from cyclobutylidene carboxylic acid ethyl ester (**9**) was 45% (Scheme 7).[9]

In conclusion, it has been demonstrated that both spiro[2.5]octane-5,7-dione (**1**) and spiro[3.5]nonane-6,8-dione (**2**) could be synthesized by using diethyl 1,3-acetonedicarboxylate as the key material to build up the skeleton of the 1,3-cyclohexanedione. This developed protocol is superior to the previously reported syntheses of spiro[2.5]octane-5,7-dione (**1**) and spiro[3.5]nonane-6,8-dione (**2**) in terms of the reaction conditions and the corresponding purification methods. Application of the same methodology to other substrates to generate spiro 1,3-cyclohexanediones is being investigated, and the corresponding experimental results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.132.

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5. Our internal experimental observations.
6. *Synthesis of acrylate* **8**: A solution of (2-ethoxy-2-oxoethylidene) triphenylphosphorane in dichloromethane (270 mL) was added dropwise to a solution of 1-ethoxy-1-(trimethylsiloxy)cyclopropane (**3**) (100 g) and AcOH (17.1 g) in tetraethylene glycol dimethyl ether (400 mL) at 90–100 °C over a period of 3 h under stirring. During the addition, dichloromethane was removed by distillation to keep the process temperature at 90–100 °C. The mixture was stirred at 90–100 °C for a further 1 h, which allowed complete removal of the dichloromethane by distillation. The product was then purified by fractional distillation at 10 mbar in the range 90–100 °C (cooling temperature of fluid in condenser should not be above −10 °C; all distillate collected under these conditions consisted of the product). A total of 50–55 g (yield: 69–76%) of compound **8** was obtained as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (m, 1H), 4.13 (q, 2H, J = 7.1 Hz), 1.40–1.35 (m, 2H), 1.23 (t, 3H, J = 7.1 Hz), 1.18–1.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 144.8, 110.8, 60.0, 14.2, 4.4, 1.8; MS: (m/z) [M−28] 98.1.
7. *Synthesis of acrylate* **9**: A solution of triethyl phosphonoacetate (44.8 g) in THF (25 mL) was added dropwise to a slurry of NaH (8.0 g, 60% in oil) in THF (150 mL) at 0–10 °C over a period of 40 min. The reaction mixture was stirred at 0–10 °C for a further 0.5 h. A solution of cyclobutanone (14.0 g) in THF (25 mL) was then added dropwise at 0–10 °C over a period of 30 min. The reaction mixture was stirred at 0–10 °C for 2 h. Water (50 mL) was then slowly added at 20–30 °C. The organic solvent was removed under reduced pressure and then further water (150 mL) was added. The aqueous solution was extracted with MTBE (3 × 100 mL). The combined organic phases were washed with water (100 mL) and then dried over anhydrous $MgSO_4$. Filtration followed by evaporation of the solvent gave the crude product, which was purified by fractional distillation at 81–82 °C/19 mbar to give 22.2 g (79% yield) of compound **9** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.58 (m, 1H), 4.13 (q, 2H, J = 7.1 Hz), 3.14 (m, 2H), 2.84 (m, 2H), 2.09 (m, 2H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 166.6, 112.4, 59.5, 33.8, 32.3, 17.7, 14.4; MS: (m/z) 140.1.
8. *Synthesis of* ***1****:* Diethyl 1,3-acetonedicarboxylate (76.9 g) and compound **8** (40.0 g) were each added dropwise to a slurry of K_2CO_3 (43.8 g) in THF (200 mL) at 20–30 °C, and the mixture was stirred for 1 h. NaOEt solution (20% in EtOH; 215.7 g) was added dropwise at below 40 °C over a period of 30 min. The mixture was then heated under reflux for 3 h. KOH solution (20% in water; 354.7 g) was slowly added to keep the reaction mixture under slight reflux, and reflux conditions were maintained for a further 5 h. The organic solvent in the mixture was then removed under reduced pressure. The resulting aqueous phase was washed with MTBE (2 × 100 mL). The aqueous phase was then heated at 50–60 °C. At this temperature, concd aq HCl was added dropwise until pH 2.5–3.0 was attained. The mixture was stirred for a further 1 h and then cooled to 20–30 °C. Water (200 mL) was added and the resulting aqueous solution was extracted with MTBE (3 × 300 mL). The combined organic phases were concentrated under reduced pressure. A further portion of MTBE (30 mL) was then added to the residue, and the slurry was stirred for 30 min at 0–10 °C. A first portion of the product was collected by filtration. The filtrate was concentrated under reduced pressure once more and then MTBE (20 mL) was added. After the slurry had been stirred at 0–10 °C for 0.5 h, a second portion of the product was also collected by filtration. The combined product was washed with MTBE (5 mL), and then dried under vacuum. A total of 19.5 g (44% yield) of **1** was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (br s, 1H), 5.27 (s, 1H), 2.13 (br s, 4H), 0.37 (br s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.4, 178.6, 104.0, 41.7, 15.0, 10.8; MS: (m/z) 138.1.
9. *Synthesis of* ***2****:* Diethyl 1,3-acetonedicarboxylate (2.4 g) was slowly added to a slurry of NaH (0.96 g, 60% in oil) in THF (5.0 mL) at 0–15 °C. After the mixture had been stirred for 0.5 h, compound **9** (1.4 g) was slowly added at 0–15 °C. The mixture was stirred at 20–30 °C for 1 h and then heated to reflux. EtOH (5 mL) and NaOEt solution (20% in EtOH; 2.4 g) were then added. The resulting mixture was heated under reflux for 5 h. Thereafter, KOH solution (20% in water; 11.2 g) was slowly added, and the reaction mixture was heated under reflux for a further 5 h. The organic solvent in the reaction mixture was removed under reduced pressure. The aqueous solution was extracted with MTBE (2 × 10 mL) and then heated to 50–60 °C with the addition of concd HCl until pH 2.5–3.5 was attained. The resulting mixture was stirred at 50–60 °C for 2 h and then cooled to 20–30 °C. It was then extracted with dichloromethane (3 × 25 mL). The combined organic phases were concentrated under reduced pressure. MTBE (5.0 mL) was then added to the residue and the resulting slurry was stirred for 0.5 h at 0–10 °C. The solid was collected by filtration, washed with MTBE (5.0 mL), and dried under vacuum. A total of 0.68 g (45% yield) of **2** was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (br s, 1H), 5.17 (s, 1H), 2.36 (br s, 4H), 1.87–1.82 (m, 2H), 1.78–1.74 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.2, 103.6, 44.7, 38.4, 31.5, 14.6; MS: (m/z) 152.1.