The Synthesis of Bicyclo[2.2.2]octan-2,6-dione Revisited

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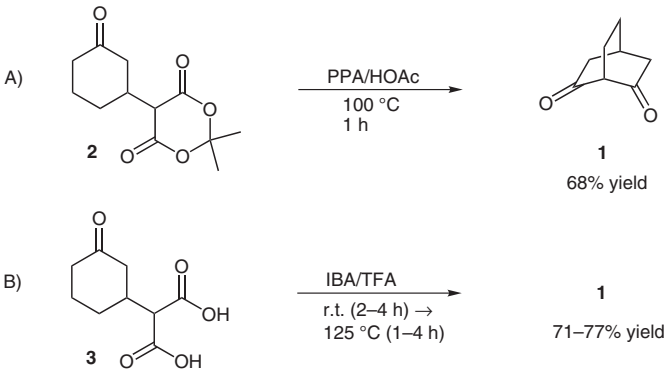
Abstract: The cyclisation conditions for the formation of bicyclo[2.2.2]octan-2,6-dione (**1**) from 3-substituted cyclohexanones **2** and **3** have been re-investigated. Use of a medium consisting of isobutyric anhydride and trifluoroacetic acid resulted in a simplified and reproducible method for large-scale synthesis of this compound.

Key words: bicyclic compounds, cyclisations, diketones, carboxylic acids, anhydrides



Scheme 1

Bicyclo[2.2.2]octane derivatives are frequently used in total synthesis and as ligands for asymmetric catalysis, and they are also found in many natural products.[1] One of the simpler derivatives for synthesis among the bicyclo[2.2.2]octanes is bicyclo[2.2.2]octane-2,6-dione (**1**). Synthetic procedures for this dione have been presented in the literature,[2,3] none of which are entirely satisfactory. Our need for larger amounts of **1** could not be met by these procedures. This problem was partially solved by the cyclisation of **2** (Scheme 1, A).[4]

Keeping the output scale below 5 g, the yields were reproducible around 60%, sometimes even higher. However, a very serious limitation was that the yields dropped drastically when the scale was increased, e.g. at 10 g scale the yields seldom exceeded 40% and at larger scales the yields were even lower.

A further impracticality was the use of polyphosphoric acid (PPA). Its viscosity is perhaps tolerable a few times but not repetitively and since the scale-up of the cyclisation in PPA/AcOH using **2** was hampered by low yields at larger scales, synthesis of **1** had to be performed repeatedly. The neutralisation of rather large amounts of PPA/AcOH was also inconvenient. We present here a more convenient large-scale method for the synthesis of **1**.

The reasons for the scale-up problems with **2** are not clear. We noticed that higher proportions of acetic acid in the medium to make it less viscous adversely influenced the yields of **1** despite consumption of **2**.[4] An important factor to consider was the 'anhydridic' medium. It is likely that acetic anhydride or mixed acetic-PPA anhydrides are formed to some extent when acetic acid and PPA are mixed.[5] This indicated that it would be reasonable to perform the reaction of **2** in acetic anhydride in the presence of an acidic catalyst. The best results were achieved using trifluoroacetic acid (TFA) (35% yield) or PPA (36% yield). Alternative acids were tested and the results are given in Table 1 (see also experimental). Further experimentation with **2** as starting material was abandoned at this point since the yields were not satisfactory.

Earlier experiments with the malonic acid **3** in PPA/AcOH were not rewarding, but since **3** is very easy to synthesise in large amounts it is indeed an attractive starting

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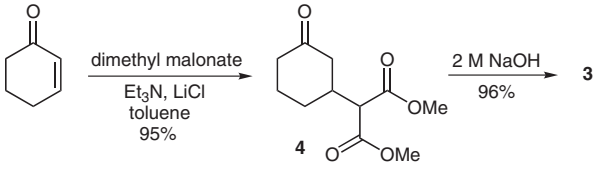
Table 1 Cyclisation Experiments of **2** in Acetic Anhydride[a]

Entry	**2** (g)	Ac_2O (mL)	Acid	Yield (%)
1	1	5	TFA, 5 mL	35
2	5	15	TFA, 15 mL	21
3	10	50	TFA, 50 mL	9
4	1	7.5	TFA, 7.5 mL	–[b]
5	1	11	PPA, 11 g	36
6	3	14	PPA, 14 g	33
7	10	45	PPA, 50 g	17
8	5	35	$MgCl_2$, 2 g	–[c]
9	1	5	TFA, 5 mL/$MgCl_2$, 0.4 g	17
10	5	35	BF_3·AcOH, 0.05 mL	18
11	5	–	PPA, 43 g/AcOH, 40 mL[d]	23

[a] Conditions: Compound **2** was added in one portion to the reaction medium at r.t. and then the temperature was increased to 100 °C, reaction time, 1 h.
[b] The addition of **2** was made over 1 h, but **1** could not be detected by TLC.
[c] No product could be isolated.
[d] PPA and AcOH were stirred at 100 °C for 24 h before addition of **2**.

material. The synthesis of **3** was carried out by the Michael reaction of cyclohex-2-ene-1-one with dimethyl malonate followed by hydrolysis of the ester groups in the addition product **4** (Scheme 2).

The best results in the cyclisation of **3** were achieved with isobutyric anhydride (IBA) in combination with TFA (Scheme 1, B and Table 2). Using this reaction medium the yields were reproducible and in the range of 70–80%, and the scaling-up of the reaction was possible without a drop in yield. The highest yields were obtained using a 1:1.1 molar ratio of IBA/TFA, in slight excess with respect to **3**. At scales ≤50 g, stirring at room temperature for two hours before increasing the temperature to 125 °C was necessary to obtain good yields. During this period, formation of **1** was not detected. However, a slightly exothermic process was observed. As decarboxylation gently began at a temperature just above 100 °C, formation of **1** was observed. The reaction was performed in up to 500 g scale with standard laboratory equipment. However, at this scale a longer reaction time was required (see experimental part). Isolation of the product was accomplished



Scheme 2

by removing the excess of the reaction medium directly from the reaction vessel by low-pressure distillation, which left a residue that could be purified by crystallisation from heptane–EtOAc to give a high quality of **1**, directly useful for further transformations, e.g. stereoselective baker's yeast reduction.[4,6] Thus, the procedure does not require column chromatography.

Table 2 Cyclisation of **3** in the IBA/TFA Medium

Entry	**3** (g)	IBA (mL)	TFA (mL)	Yield (%)
1	1	1	0.1	10[a,b]
2	1	1	0.5	68[a,b]
3	50	50	25	72[b,c]
4	500	500	250	77[c,d]

[a] Isolated by aqueous work-up followed by column chromatography.
[b] Reaction time: 2 h at r.t., then 1 h at 125 °C.
[c] Isolated by removal of excess reagent by distillation followed by recrystallisation.
[d] Reaction time: 4 h at r.t., then 4 h at 125 °C.

Since small amounts of **1** are lost due to sublimation at reduced pressure, the yields are noticeably affected when the reaction is run at smaller scales. Therefore, the low-pressure distillation is best suited for large-scale operations (≥50 g). For small-scale reactions an aqueous work-up followed by column chromatography is recommended.

Other reaction media can also be used. The reaction was run using trifluoroacetic anhydride (TFAA) with a catalytic amount (5 mol%) of TFA (Table 3). A slight excess (1.1 equiv) of TFAA was required to obtain yields comparable to those obtained in the IBA-mediated cyclisations. However, using two equivalents of TFAA was detrimental for the reaction, resulting in a significantly lower yield and large amounts of labile by-products, which decomposed during column chromatography.

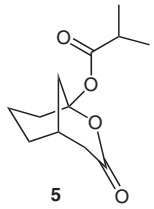
Table 3 Cyclisation Experiments of **3** in TFAA in the Presence of TFA (5 mol%)

Entry	**3** (g)	TFAA (equiv)	Yield (%)[a]
1	1	1	49
2	1	2	19
3	5	1.1	69

[a] Isolated yield.

In the IBA-mediated cyclisation, a by-product was formed in up to 20% yield, which we failed to isolate in the pure state due to partial decomposition in solution and on silica gel. The by-product did not originate from further reaction of **1** with the medium, since a pure sample of **1** on heating for three hours in the IBA/TFA mixture was indifferent as checked by TLC analysis. IR and NMR spectroscopic evidence of an impure sample of the by-product gave indications that pointed to structure **5** (Figure 1). A similar

ester-acetal-lactone formed under similar conditions was reported by Mori.[7]



5

Figure 1 Structure of the by-product **5**

Since the large-scale operations also required larger amounts of **4** (Scheme 2), it was desirable to avoid chlorinated solvents (dichloromethane), which had been used earlier in the conjugate addition of dimethyl malonate to cyclohexenone. From an environmental point of view toluene is more tolerable, and it is also superior to dichloromethane. A close to quantitative yield of **4** was obtained in toluene as compared to less than 80% in dichloromethane or THF (see experimental part). Alternatively, **4** can be prepared by an electrochemically promoted Michael addition reaction of cyclohex-2-ene-1-one and dimethyl malonate under solvent-free conditions in high yield.[8]

In conclusion, a convenient method has been worked out for the synthesis of **1** by the use of IBA/TFA as reaction medium for the ring closure of **3**. It is now possible to produce large amounts (>100 g) of **1** in less than two days without the use of chromatography, starting from cyclohex-2-ene-1-one. It is also possible to recover the solvents and reagents for recycling.

All chemicals were purified by standard methods, unless otherwise stated. Dimethyl malonate (97%, Merck), LiCl (99%, Riedel-de-Haen), cyclohex-2-ene-1-one (98.5%, Fluka), isobutyric anhydride (97%, Acros), TFA (99%, Acros) and trifluoroacetic anhydride (≥99%, Aldrich) were used as delivered. Column chromatography was performed on Matrex (25–70 μm) silica gel. TLC was performed on silica gel covered glass plates (60 F_{254}, Merck) and the plates were impregnated with a solution of *p*-methoxybenzaldehyde (10 mL), conc. H_2SO_4 (50 mL) and EtOH (95%, 950 mL). The compounds were visualized by heating. NMR data were recorded on a Bruker DRX 400 MHz or Bruker ARX 300 MHz spectrometer, and the chemical shifts were measured using the solvent peaks as internal references. Melting points were taken on a Sanyo Gallenkamp melting point apparatus (MPD.350.BM3.5) and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer.

Cyclisation of 2 in Acetic Anhydride; General Procedure

The Meldrum's acid derivative **2** was added to a mixture of Ac_2O and co-reagent (Table 1) under argon at r.t. The temperature was increased to 100 °C and held there for 1 h. The mixture was cooled to r.t., then sat. $NaHCO_3$ (50 mL) was added followed by further addition of sat. $NaHCO_3$ until neutral pH. It was then saturated with NaCl and extracted with toluene (5 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was removed at reduced pressure. The residue was purified by column chromatography [SiO_2, heptane–EtOAc (1:1); R_f 0.3] to give **1** as a white solid, which was analysed by IR and ^{1}H NMR spectroscopy.

Dimethyl (3-Oxocyclohexyl)malonate (4)

Et_3N (8 mL) and LiCl (24.6 g, 0.582 mol) were added to a solution of dimethyl malonate (100 mL, 0.872 mol) in toluene (100 mL). The mixture was stirred at r.t. under argon for 10 min and a solution of cyclohex-2-ene-1-one (58.8 mL, 0.582 mol) in toluene (100 mL) was then added. The resulting mixture was stirred at r.t. overnight, then H_2O (50 mL) was added followed by conc. HCl (~20 mL) until neutral pH. The phases were separated and the H_2O phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed at reduced pressure. The resulting yellow oil was purified by distillation to give **4** (126 g, 95%) as a colourless liquid; bp 140 °C/1 Torr (Lit.[9] bp 124–130 °C/0.4 Torr). The ^{1}H NMR data of **4** were in accord with literature values.[9]

(3-Oxocyclohexyl)malonic Acid (3)

Dimethyl (3-oxocyclohexyl)malonate (**4**; 227 g, 1.00 mol) was dissolved in aq 2 M NaOH (1.8 L) and stirred at r.t. for 2 h. The mixture was then acidified with conc. HCl (~360 mL), saturated with NaCl and extracted with EtOAc (4 × 600 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed at reduced pressure to give **3** (191 g, 96%) as a white solid powder, which was used in the next step without further purification; mp 146–147 °C (melt and dec.) (Lit.[2] mp 166–168 °C).

IR (KBr): 2955, 1724, 1684, 1302, 1219 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.82 (v br s, 2 H), 3.19 (m, 1 H), 2.35–2.06 (m, 5 H), 2.01–1.88 (m, 1 H), 1.81 (br d, *J* = 12.6 Hz, 1 H), 1.64–1.34 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 209.6, 169.6, 169.5, 56.9, 44.8, 40.5, 37.5, 28.1, 24.2.

Note that complicated NMR patterns were obtained with MeOH as solvent. Depending on concentration, partial acetal formation was observed.

Bicyclo[2.2.2]octane-2,6-dione (1)

Method 1: Isobutyric anhydride (500 mL, 3.02 mol) and TFA (250 mL, 3.37 mol) were added under stirring to finely powdered **3** (500 g, 2.51 mol). The mixture was stirred at r.t. for 4 h and then the temperature was slowly increased to 125 °C. After 4 h at 125 °C, evolution of CO_2 ceased and the mixture was cooled to r.t. A colourless liquid (mostly excess IBA and TFA) was distilled off (bp 70 °C/1 Torr) and the remaining crude brown residue was crystallised from EtOAc–heptane (1:1). On cooling with on solid CO_2, diketone **1** (211 g, 61%) precipitated as colourless needles. From the mother liquor a second crop of **1** was obtained (56 g, 16%); mp 194–197 °C (Lit.[2] mp 190–191 °C). The total yield was 267 g (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (t, *J* = 2.9 Hz, 1 H), 2.66 (heptet, *J* = 3.0 Hz, 1 H), 2.52 (doublet of multiplets, *J* = 20.4 Hz, 1 H), 2.51–2.47 (m, 1 H), 2.38 (doublet of multiplets, *J* = 19.3 Hz, 1 H), 9.37–9.34 (m, 1 H), 2.16–2.09 (m, 2 H), 1.91–1.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.7, 63.8, 44.0, 28.0, 23.7, 22.1.

HRMS-FAB+: *m/z* $[M + H]^+$ calcd for $C_8H_{11}O_2$: 139.0759; found: 139.0755.

By-Product 5

A by-product was formed in up to 20% yield. Attempted purification of an analytical sample, obtained from the mother liquor after recrystallization of **1**, by column chromatography (SiO_2, heptane–EtOAc, 1:1) gave the following spectroscopic data:

IR (film): 2937, 1751, 1215, 1142, 1099, 1074, 1042, 1003, 972 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.77 (dd, *J* = 18.8, 6.9 Hz, 1 H), 2.64–2.36 (m, 4 H), 2.17–2.09 (m, 2 H), 2.00–1.88 (m, 1 H), 1.85–1.74 (m, 1 H), 1.69–1.55 (m, 3 H), 1.16 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.7, 170.1, 105.8, 35.6, 35.1, 34.9, 33.7, 30.2, 27.5, 18.9, 18.5.

For small-scale synthesis, it is recommended that an aqueous work-up is applied as for the general procedure for the cyclisation of **2** in Ac_2O (see above).

Method 2: TFAA (3.84 mL, 27.6 mmol) and TFA (93 μL, 1.3 mmol) were added under stirring to finely powdered **3** (5.00 g, 25.1 mmol). The mixture was stirred at r.t. for 2 h and then the temperature was increased to 125 °C and held there for 1 h. After cooling the mixture to r.t., aq sat. $NaHCO_3$ (150 mL) was added and the resulting H_2O phase was extracted with EtOAc (3 × 70 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed at reduced pressure. The residue was purified by column chromatography (SiO_2, heptane–EtOAc, 3:1 to 1:1) to give **1** (2.41 g, 69%) as a white solid; mp 192–195 °C (Lit.[2] mp 190–191 °C); R_f 0.3 (heptane–EtOAc, 1:1). The ^{1}H NMR data were in accord with those reported for **1** above.

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References

(1) (a) Sarvary, I.; Almqvist, F.; Frejd, T. *Chem. Eur. J.* **2001**, *7*, 2158. (b) Sarvary, I.; Wan, Y.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 645. (c) Almqvist, F.; Manner, S.; Thornqvist, V.; Berg, U.; Wallin, M.; Frejd, T. *Org. Biomol. Chem.* **2004**, *2*, 3085. (d) Butkus, E.; Stoncius, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1885. (e) Martin, S. F.; Assercq, J. M.; Austin, R. E.; Dantanarayana, A. P.; Fishpaugh, J. R.; Gluchowski, C.; Guinn, D. E.; Hartmann, M.; Tanaka, T.; Wagner, R.; White, J. B. *Tetrahedron* **1995**, *51*, 3455. (f) Paquette, L. A.; Poupart, M. A. *J. Org. Chem.* **1993**, *58*, 4245. (g) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2431. (h) Coons, S.; Javanmard, S.; Collard, D. M.; Kuhar, M. J.; Schweri, M. M.; Deutsch, H. M. *Med. Chem. Res.* **2002**, *11*, 24. (i) Thoison, O.; Cuong, D. D.; Gramain, A.; Chiaroni, A.; Hung, N. V.; Sevenet, T. *Tetrahedron* **2005**, *61*, 8529. (j) Hong, R.; Chen, Y.; Deng, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 3478. (k) Liu, W.; Gu, Q.; Zhu, W.; Cui, C.; Fan, G.; Zhu, T.; Liu, H.; Fang, Y. *Tetrahedron Lett.* **2005**, *46*, 4993. (l) Bringmann, G.; Lang, G.; Gulder, T. A. M.; Tsuruta, H.; Muhlbacher, J.; Maksimenka, K.; Steffens, S.; Schaumann, K.; Stohr, R.; Wiese, J.; Imhoff, J. F.; Perovic-Ottstadt, S.; Boreiko, O.; Muller, W. E. G. *Tetrahedron* **2005**, *61*, 7252. (m) Majetich, G.; Wang, Y.; Li, Y.; Vohs, J. K.; Robinson, G. H. *Org. Lett.* **2003**, *5*, 3847. (n) Pitsinos, E. N.; Vidali, V. P.; Couladouros, E. A. *Arkivoc* **2002**, *(xiii)*, 105; www.arkat-usa.org. (o) Tanaka, T.; Mine, C.; Kouno, I. *Tetrahedron* **2002**, *58*, 8851. (p) Abad, A.; Agullo, C.; Cunat, A. C.; Navarro, I. *Tetrahedron Lett.* **2001**, *42*, 8965. (q) Srikrishna, A.; Ravi Kumar, P.; Gharpure, S. J. *Tetrahedron Lett.* **2001**, *42*, 3929. (r) Mori, K.; Matsushima, Y. *Synthesis* **1993**, 406.

(2) Bartlett, P. D.; Woods, G. F. *J. Am. Chem. Soc.* **1940**, *62*, 2933.

(3) (a) Gerlach, H.; Mueller, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1030. (b) Mori, K.; Nakahara, Y.; Matsui, M. *Tetrahedron* **1972**, *28*, 3217.

(4) Almqvist, F.; Eklund, L.; Frejd, T. *Synth. Commun.* **1993**, *23*, 1499.

(5) Kazlauskas, R. J.; Whitesides, G. M. *J. Org. Chem.* **1985**, *50*, 1069.

(6) Botes, A. L.; Harvig, D.; van Dyk, M. S.; Sarvary, I.; Frejd, T.; Katz, M.; Hahn-Haegerdal, B.; Gorwa-Grauslund, M. F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1111.

(7) Mori, K. *Tetrahedron* **1971**, *27*, 4907.

(8) Palombi, L.; Feroci, M.; Orsini, M.; Inesi, A. *Chem. Commun.* **2004**, 1846.

(9) Marshall, J. A.; Belletire, J. L. *Synth. Commun.* **1971**, *1*, 93.