Direct 4-Alkylation of 1,3-Cyclohexanediones via Dianionic Species

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1,3-Cyclohexanediones are directly alkylated at the 4 position via dianionic species generated at −78 °C using lithium diisopropylamide/hexamethylphosphoric triamide. Acetylation of the reaction products at room temperature yields the 3-acetoxy-6-alkylcyclohex-2-enones selectively.

During the course of recent studies, we required direct access to a series of 4-alkyl-1,3-cyclohexanediones. Such compounds are accessible via the procedure of Stork and

Danheiser[1] in which the monoanion of the monoenol ether, derived from the diketone, is successively alkylated and hydrolysed. Except for the instances of the more reactive benzylic and allylic halides, good yields in the alkylation step of this three step sequence were only obtained using alkyl iodides. Mellor and Pattenden have reported instances of direct alkylation of 1,3-cyclopentanedione via the dianion generated using *n*-butyllithium/hexamethylphosphoric triamide[2].

A similar process with 1,3-cyclohexanediones would be expected to furnish the required derivatives in a single step. Examination of the literature revealed that this conversion had been investigated previously, solely in the case of 1,3-cyclohexanedione[3]. The dianion, generated with potassium amide, was reported to react only with methyl, allyl, and benzyl halides (i.e. reactive halides) in low yields (15–45%). In particular, no work has been published to date concerning the direct 4-alkylation of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and, as the presence of the *gem*-dimethyl groups precludes an approach from aromatic precursors, we have investigated this reaction and report our results herein.

The dianions of 5,5-dimethyl-1,3-cyclohexanedione (**1**; $R^1 = CH_3$) or 1,3-cyclohexanedione (**1**; $R^1 = H$) were smoothly generated with 2 equivalents of lithium diisoprop-

Table 1. Compounds **2** prepared

Product-[a]	Yield [%] X=Br	Yield [%] X=J	Ref.[3]	b.p. [°C]/torr or m.p. [°C]	Molecular Formula[b] or Lit. Data	M.S. *m/e* (rel.int.%)	^{1}H-N.M.R. ($CDCl_3$)[c] δ [ppm]
2a	–	41	16.5	109°/1.2	97–99°/0.2[3]	126 (M^+, 22); 83 (24)	1.21 (d, 3H, J = 6 Hz, CH_3); 1.56 (qd, 1H, J = 13 Hz, J = 5 Hz, 1H of $CH_2C\underline{H}_2CH$); 2.11–2.21 (m, 1H, 1H of $CH_2C\underline{H}_2CH$); 2.54–2.76 (m, 3H, $CH_2C{=}O$, $CHC{=}O$); 3.40 (d, 1H, J = 18 Hz, 1H of $O{=}CCH_2C{=}O$); 3.46 (d, 1H, J = 18 Hz, 1H of $O{=}CCH_2C{=}O$)
2b	56	–	21	142°/2.0	113–114°/0.5[3]	152 (M^+, 21); 110 (30); 95 (34); 82 (44)	1.50–1.66 (m, 0.5H); 1.72–1.86 (m, 0.5H); 2.12–2.26 (m, 2H, $C{=}CCH_2{-}$); 2.32–2.47 (m, 1H); 2.51–2.76 (m, 3H); 3.42 (d, 0.5H, J = 17 Hz, $O{=}CCH_2C{=}O$); 3.48 (d, 0.5H, J = 17 Hz, $O{=}CCH_2C{=}O$); 5.04–5.15 (m, 2H, $C{=}CH_2$); 5.47 (s, 0.5H, $O{=}C\underline{C}\underline{H}{=}COH$); 5.71–5.88 (m, 1H, $-CH{=}C$); 6.70 (br. s, 0.5H, removable with D_2O, OH)
2c	67	–	45	109–112°	109–110°[3]	202 (M^+, 40); 131 (41); 117 (40); 91 (100)	1.55 (qd, 1H, J = 13 Hz, J = 5 Hz, 1H of $CH_2C\underline{H}_2CH$); 2.03–2.14 (m, 1H, 1H of $CH_2C\underline{H}_2CH$); 2.34–2.66 (m, 3H); 2.68–2.84 (m, 1H); 3.34 (dd, 1H, J = 14 Hz, J = 5 Hz, 1H of $C_6H_5C\underline{H}_2$); 3.44 (d, 0.8H, J = 16 Hz, $O{=}CCH_2C{=}O$); 3.51 (d, 0.8H, J = 16 Hz, $O{=}CCH_2C{=}O$); 5.53 (s, 0.2H, $C{=}CH$); 7.19–7.35 (m, $5H_{arom}$)
2d	–	42	–	100–102°	$C_9H_{14}O_2$ (154.2)	154 (M^+, 17); 97 (74); 83 (54); 70 (100)	0.78 (s, 3H, CH_3); 1.13 (s, 3H, CH_3); 1.15 (d, 3H, J = 7 Hz, $C\underline{H}_3CH$); 2.55 (d, 1H, J = 15 Hz, 1H of $CH_2C{=}O$); 2.63 (q, 1H, J = 7 Hz, $CHC{=}O$); 2.65 (d, 1H, J = 15 Hz, 1H of $CH_2C{=}O$); 3.36 (d, 1H, J = 15 Hz, 1H of $O{=}CCH_2C{=}O$); 3.43 (d, 1H, J = 15 Hz, 1H of $O{=}CCH_2C{=}O$)
2e	57	–	–	176°/1.2	$C_{11}H_{16}O_2$ (180.2)	96 (100); 81 (42)	0.86 (s, 3H, CH_3); 1.13 (s, 3H, CH_3); 2.32 (t, 1H, J = 8 Hz, $CHC{=}O$); 2.53 (t, 2H, J = 8 Hz, $C{=}CCH_2{-}$); 2.58 (d, 2H, J = 3 Hz, $CH_2C{=}O$); 3.35 (d, 1H, J = 15 Hz, 1H of $O{=}CCH_2C{=}O$); 3.42 (d, 1H, J = 15 Hz, 1H of $O{=}CCH_2C{=}O$); 5.07 (m, 2H, $CH_2{=}C$); 5.78–5.93 (m, 1H, $C{=}CH$)

Table 1. (Continued)

Product-[a]	Yield [%] X=Br	Yield [%] X=J	Ref.[3]	b.p. [°C]/torr or m.p. [°C]	Molecular Formula[b] or Lit. Data	M.S. *m/e* (rel.int.%)	^{1}H-N.M.R. ($CDCl_3$)[c] δ [ppm]
2f	32	62	–	115°/0.6	$C_{11}H_{18}O_2$ (182.3)	182 (M^+, 1); 140 (34); 125 (100)	0.87 (s, 3H, CH_3); 0.96 (t, 3H, J = 8 Hz, $C\underline{H}_3CH_2$); 1.08 (s, 3H, CH_3); 1.37–1.55 (m, 2H, $CH_3C\underline{H}_2$); 1.65–1.81 (m, 2H, CCH_2C); 2.36 (dd, 1H, J = 10 Hz, J = 2 Hz, $C\underline{C}HC{=}O$); 2.49 (d, 1H, J = 15 Hz, 1H of $CH_2C{=}O$); 2.59 (d, 1H, J = 15 Hz, 1H of $CH_2C{=}O$); 3.38 (s, 2H, $O{=}CCH_2C{=}O$)
2g	75	78	–	140°/0.6	$C_{11}H_{18}O_2$ (182.3)	182 (M^+, 6); 125 (100); 83 (73)	0.92 (d, 0.6H, J = 7 Hz, CH_3CH); 1.00 (s, 3H, CH_3); 1.05 (d, 2.4H, J = 7 Hz, CH_3CH); 1.11 (d, 0.6H, J = 7 Hz, $C\underline{H}_3CH$); 1.13 (s, 3H, CH_3); 1.16 (d, 2.4H, J = 7 Hz, CH_3CH); 2.05 (d, 0.2H, J = 21 Hz, $CH_2C{=}O$); 2.13–2.25 [m, 1H, $(CH_3)_2C\underline{H}$)]; 2.22 (d, 1H, J = 1 Hz, $CHC{=}O$); 2.37 (d, 0.8H, J = 15 Hz, $CH_2C{=}O$); 2.49 (d, 0.2H, J = 21 Hz, $CH_2C{=}O$); 2.69 (d, 0.8H, J = 15 Hz, $CH_2C{=}O$); 3.30 (s, 1.6H, $O{=}CCH_2C{=}O$); 5.52 (s, 0.2H, $CH{=}OH$)
2h	16	54	–	129–132°	$C_{14}H_{22}O_2$ (222.3)	140 (35); 125 (100)	0.96 (s, 3H, CH_3); 1.14 (s, 3H, CH_3); 1.06–1.41, 1.58–1.86 (m, $11H_{cyclohexyl}$); 2.18 (d, 1H, J = 6 Hz, $CHC{=}O$); 2.33 (d, 1H, J = 15 Hz, 1H of $CH_2C{=}O$); 2.71 (d, 1H, J = 15 Hz, 1H of $CH_2C{=}O$); 3.28 (s, 2H, $O{=}CCH_2C{=}O$)
2i	70	–	–	190–200°/0.8	$C_{15}H_{18}O_2$ (230.3)	230 (M^+, 44); 146 (100); 145 (44); 131 (30); 91 (54)	0.89 (s, 3H, CH_3); 1.29 (s, 3H, CH_3); 2.58 (d, 1H, J = 18 Hz, 1H of CH_2CO); 2.69 (d, 1H, J = 18 Hz, 1H of CH_2CO); 2.79–2.86 (m, 2H, 1H of $CHC{=}O$, 1H of $C_6H_5C\underline{H}_2$); 3.17 (dd, 1H, J = 13 Hz, J = 5 Hz, 1H of $C_6H_5CH_2$); 3.37 (d, 1H, J = 21 Hz, 1H of $O{=}CCH_2C{=}O$); 3.43 (d, 1H, J = 21 Hz, 1H of $O{=}CCH_2C{=}O$); 7.14–7.34 (m, $5H_{arom}$)
2j	67	0	–	90–93°	$C_{12}H_{18}O_3$ (210.3)	C.I. 228 (21, M + NH_4^+); 21 (100, M + H^+); 210 (12, M^+)	0.85 (s, 3H, CH_3); 1.15 (s, 3H, CH_3); 1.88–1.95 (m, 2H, $O{=}CCH_2C\underline{H}_2$); 2.16 (s, 3H, $CH_3C{=}O$); 2.41–2.56 (m, 2H, $O{=}C\underline{C}H_2CH_2$); 2.58 (br. s, 2H, $O{=}CCH_2$); 2.63–2.76 (m, 1H, $CHC{=}O$); 3.40 (s, 2H, $O{=}CCH_2C{=}O$)

[a] I.R. ($CDCl_3$) for all compounds ν = 1740–1745, 1710–1715 cm^{-1} (1,3-dicarbonyl).

[b] Satisfactory microanalyses obtained C ±0.3, H ±0.3.

[c] Typical spectra quoted; keto-enol ratios variable.

ylamide at −78 °C in the presence of three equivalents of hexamethylphosphoric triamide. Reaction of these with various alkyl halides by addition at −78 °C, warming to room temperature, quenching and work-up afforded the required 4-alkylated derivatives **2** in moderate to good yields after chromatography on silica.

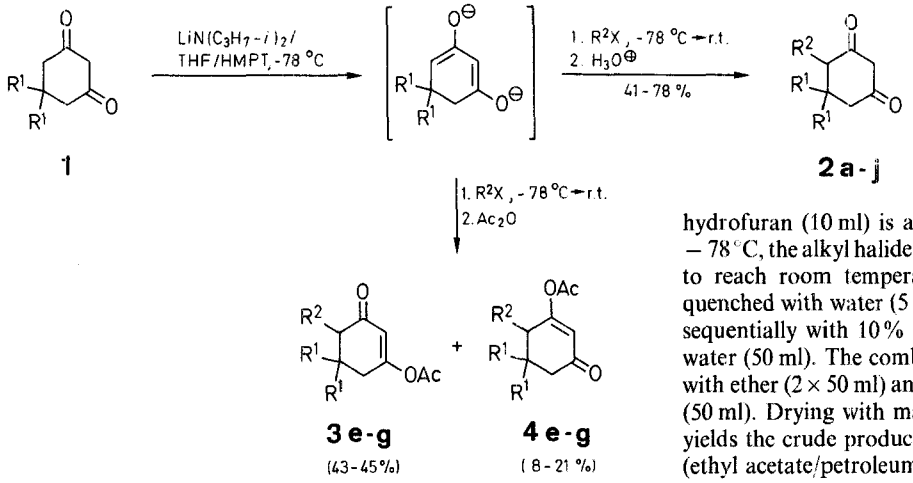
The only impurities detectable in the crude products were unreacted starting material and, in a few instances, traces of *O*-alkylated material. Omission of the hexamethylphosphoric triamide from the sequence resulted in the formation of monoenol ethers only and none of the desired products, indicating absence of dianion formation under these con-

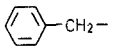
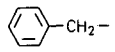
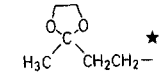
Table 2. Compounds **3** and **4** prepared

Product[a,b]	X in R^2—X	Yield [%]	b.p. [°C]/torr	Molecular Formula[c]	M.S. *m/e* (rel.int.%)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3e	Br	45	190°/4.5	$C_{13}H_{18}O_3$ (222.3)	222 (2, M^+); 180 (35); 165 (55)	1.02 (s, 3H, CH_3); 1.12 (s, 3H, CH_3); 2.16 (m, 1H, CHC=O); 2.22 (s, 3H, CH_3C=O); 2.32 (m, 2H, $\underline{C}H_2CH$=C); 2.41 [m, 2H, C=C(OAc)CH_2]; 5.00 (m, 2H, C=CH_2); 5.83 [m, 2H, CH=C, CH=C(OAc)]
4e	Br	8	190°/4.5	$C_{13}H_{18}O_3$ (222.3)	222 (2, M^+); 180 (15); 165 (40)	1.07 (s, 3H, CH_3); 1.14 (s, 3H, CH_3); 2.14–2.53 [m, 5H, CH—C(OAc)=C, $\underline{C}H_2CH$=C, CH_2C=O]; 2.20 (s, 3H, CH_3C=O); 5.05 (m, 2H, CH_2=C); 5.83 (m, 1H, CH=C); 5.93 [s, 1H, CH=C(OAc)]
3f	J	44	99°/1.1	$C_{13}H_{20}O_3$ (224.3)	182 (22); 140 (100); 125 (93)	0.91 (t, 3H, J = 15 Hz, $CH_2\underline{C}H_3$); 1.02 (s, 3H, CH_3); 1.10 (s, 3H, CH_3); 1.21–1.31 (m, 1H, 1H of $CH\underline{C}H_2CH_2$); 1.36–1.47 (m, 3H, 1H of $CH\underline{C}H_2CH_2$, $CH_2\underline{C}H_2CH_3$); 2.00 (dd, 1H, J = 10 Hz, J = 2 Hz, CHC=O); 2.20 (s, 3H, CH_3C=O); 2.28 (d, 1H, J = 19 Hz, 1H of CH_2C=C); 2.48 (dd, 1H, J = 19 Hz, J = 2 Hz, 1H of CH_2C=C); 5.82 (d, 1H, J = 2 Hz, C=CH)
4f	J	21	99°/1.1	$C_{13}H_{20}O_3$ (224.3)	140 (53); 125 (50)	0.94 (t, 3H, J = 15 Hz, $CH_2\underline{C}H_3$); 1.05 (s, 3H, CH_3); 1.15 (s, 3H, CH_3); 1.47 (m, 3H, $CH_3\underline{C}H_2$ and 1H of $CH_2\underline{C}H_2CH$); 1.69 (m, 1H, 1H of $CH_2\underline{C}H_2CH$); 2.13 (d, 1H, J = 19 Hz, 1H of CH_2C=O); 2.42 (d, 1H, J = 19 Hz, 1H of CH_2C=O); 2.20 (m, 1H, $CH_2\underline{C}H$); 2.31 (s, 3H, CH_3C=O); 5.92 (s, 1H, CH=C)
3g	J	43	94°/0.8	$C_{13}H_{20}O_3$ (224.3)	C.I. 225 (100, M + H^+)	0.92 [d, 3H, J = 7 Hz, 1CH_3 of $CH(\underline{C}H_3)_2$]; 1.06 [d, 3H, J = 7 Hz, 1CH_3 of $CH(\underline{C}H_3)_2$]; 1.08 (s, 3H, CH_3); 1.15 (s, 3H, CH_3); 1.92 (d, 1H, J = 4 Hz, CHC=O); 2.07 [m, 1H, $\underline{C}H(CH_3)_2$]; 2.10 (d, 1H, J = 18 Hz, 1H of CH_2C=C); 2.21 (s, 3H, CH_3C=O); 2.74 (dd, 1H, J = 18 Hz, J = 2 Hz, 1H of CH_2C=C); 5.86 (d, 1H, J = 2 Hz, CH=C)
4g	J	21	95°/0.7	$C_{13}H_{20}O_3$ (224.3)	C.I. 225 (100, M + H^+); 183 (80)	0.95 [d, 3H, J = 6 Hz, 1CH_3 of $CH(\underline{C}H_3)_2$]; 1.10 [d, 3H, J = 6 Hz, 1CH_3 of $CH(\underline{C}H_3)_2$]; 1.13 (s, 3H, CH_3); 1.17 (s, 3H, CH_3); 2.11 (d, 1H, J = 19 Hz, 1H of CH_2C=O); 2.22 (s, 3H, CH_3C=O); 2.23 [d, 1H, J = 5 Hz, $\underline{C}HCH(CH_3)_2$]; 2.48 (d, 1H, J = 19 Hz, 1H of CH_2C=O); 2.45–2.51 [m, 1H, $\underline{C}H(CH_3)_2$]; 6.02 (s, 1H, C=CH)

[a] Ratios – **3e** : **4e** = 5.6 : 1.0; **3f** : **4f** = 2.1 : 1.0; **3g** : **4g** = 2.1 : 1.0.
[b] I.R. ($CDCl_3$) for all compounds ν = 1780–1770 cm^{-1} (enol acetate carbonyl), 1685–1670 cm^{-1} (α,β-unsaturated carbonyl).
[c] Satisfactory microanalyses obtained C ±0.3, H ±0.3.

ditions. Primary and secondary bromides frequently gave good yields of purified products in contrast with the work of Stork and Danheiser[1]. In the case of **2j**, the desired alkylation occurred only when the requisite bromide was used, as the corresponding iodide presumably was not stable under the reaction conditions.



2,3,4	R^1	R^2
a	H	CH_3
b	H	$H_2C{=}CH{-}CH_2{-}$
c	H	
d	CH_3	CH_3
e	CH_3	$H_2C{=}CH{-}CH_2{-}$
f	CH_3	$n\text{-}C_3H_7$
g	CH_3	$i\text{-}C_3H_7$
h	CH_3	
i	CH_3	
j	CH_3	 ★

★ Isolated as the deprotected material

We have also investigated the ratio of enol acetates **3** and **4** obtained by quenching the reaction mixtures with acetic anhydride. (Table 2). Differentiation between the two isomers was possible by observation of the allylic coupling patterns of the vinylic protons in each isomer which showed a 2 Hz allylic coupling in **3e, f, g** and appeared as singlets in **4e, f, g**.

In the cases studied, the major isomer was always **3**, presumably due to the lower steric interactions present in **3** compared with **4**.

In conclusion, this procedure enables 1,3-cyclohexanediones to be alkylated in a convenient and efficient one-pot process to give the corresponding 4-alkylated derivatives in generally good yields. All of the procedures herein described are amenable to medium scale work (20–50 mmol).

Starting materials were obtained commercially except for 2-(2-bromoethyl)-2-methyldioxolane and 2-(2-iodoethyl)-2-methyldioxolane which were prepared according to literature procedures[4]. All manipulations were carried out under a slight positive pressure of nitrogen. All products gave spectroscopic and microanalytical data in accord with their assigned structures. (Table 1, Table 2).

4-Alkylation of Cyclic 1,3-Diketones 1; General Procedure:
n-Butyllithium (2.4 ml, 9.5 molar in hexane, 22 mmol) is added dropwise to a solution of dry diisopropylamine (3.1 ml, 22 mmol) in dry tetrahydrofuran (30 ml) with stirring at 0 °C. After 30 min, the mixture is cooled to − 78 °C and a solution of the cyclic 1,3-dione **1** (10 mmol) and hexamethylphosphoric triamide (6 ml) in dry tetrahydrofuran (10 ml) is added over 5 min. After stirring for 1 h at − 78 °C, the alkyl halide (11 mmol) is added and the mixture allowed to reach room temperature over 15 h. The reaction mixture is quenched with water (5 ml), diluted with ether (50 ml), and washed sequentially with 10% aqueous hydrochloric acid (3 × 50 ml) and water (50 ml). The combined aqueous phases are extracted further with ether (2 × 50 ml) and the total organic phase washed with brine (50 ml). Drying with magnesium sulphate and removal of solvent yields the crude product **2** which is chromatographed on silica gel (ethyl acetate/petroleum ether 30/40).

Enol Acetates 3 and 4; General Procedure:
The general alkylation procedure detailed above is followed except that the reaction mixture is quenched with acetic anhydride (15 ml) at room temperature. The isomeric enol acetates **3** and **4** are separated by chromatography on silica (ethyl acetate/petroleum ether 30/40).

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