Synthesis of 1,4-Diketones by Reaction of Bicyclic Lactams Derived from 4-Oxoalkanoic Acids with Organolithium Compounds

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Dedicated to Prof. Dr. habil. Roland Mayer on the occasion of his 65th birthday

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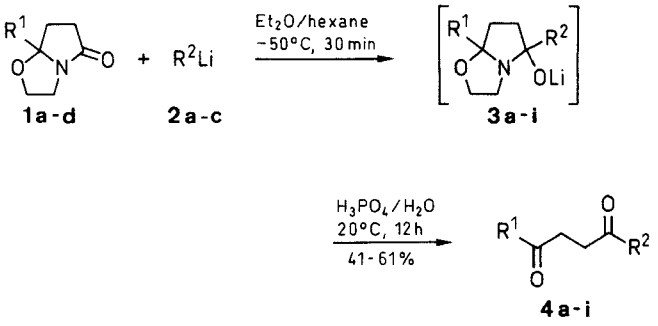
Bicyclic lactams obtained from ethyl 4-oxoalkanoates and 2-aminoethanol add saturated and unsaturated aliphatic lithium compounds forming the corresponding 1,4-diketones in 41–61% yield after acidic hydrolysis.

1,4-Diketones are versatile intermediates for the synthesis of many heterocyclic[1–3] and carbocyclic compounds.[4] Hence, there is a permanent interest in the development of new strategies for the preparation of these synthetically useful compounds. Due to their functionality, derivatives of 4-oxoalkanoic acids have proved to be well-suited starting materials for the conversion into 1,4-diketones.[5] These conversions comprise the transformation of the modified carboxylic group into a ketone by monoaddition of a suitable organometallic reagent without attacking the 4-oxo group. This requires a proper activation of the carboxylic group[6–11] and, in general, the protection of the 4-oxo group.[6–8,12] Only in few cases this protection can be omitted.[10,11]

Recently we have prepared the bicyclic lactams **1** in nearly quantitative yield by reaction of ethyl 4-oxoalkanoates with 2-aminoethanol as conveniently accessible derivatives of 4-oxoalkanoic acids meeting the above-mentioned requirements.[13] Now we report on the conversion of these lactams into 1,4-diketones.

The reaction of the bicyclic lactam **1a** with two equivalents of butyllithium in diethyl ether/hexane at −50 °C afforded the diketone **4a** in an isolated yield of nearly 60% after hydrolysis of the intermediate adduct **3a** with dilute phosphoric acid. With one equivalent of **2a** the yield dropped to about 20%. Performing the reaction at 0 °C or even at ambient temperature also resulted in a lower yield. Attempts to use butylmagnesium bromide instead of **2a** did not improve the outcome of the reaction either. The yield reached under optimal conditions seems to be the consequence of a competition between the desired addition of **2a** to the carbonyl group of **1a** and the enolization caused by a deprotonation of the α-methylene group of **1a**. This assumption is supported by the fact that the addition of hexamethylphosphoramide further lowers the yield. The educt **1a** which had not been converted into **4a** could be isolated in the form of 4-oxopentanoic acid, the hydrolysis product of **1a**. No attempts were made to isolate the intermediate addition product **3a**.

Under optimal reaction conditions the homologous lactams **1b–d** react with **2a** forming the 1,4-diketones **4b–d** in 50–60% yield. Hexyllithium (**2b**), prepared from 1-chlorohexane and lithium in diethyl ether supported by sonication, added to **1a–d** affording the diketones **4e–h** in a comparable yield. Finally, the unsaturated diketone **4i**, the precursor for the synthesis of *cis*-jasmone,[4] was obtained in 60% yield by addition of (*Z*)-hex-3-enyllithium (**2c**) to **1a**.



1	R^1	2	R^2	3,4	R^1	R^2
a	Me	**a**	Bu	**a**	Me	Bu
b	Et	**b**	C_6H_{13}	**b**	Et	Bu
c	Pr	**c**	(*Z*)-$(CH_2)_2CH$=CHEt	**c**	Pr	Bu
d	Bu			**d**	Bu	Bu
				e	Me	C_6H_{13}
				f	Et	C_6H_{13}
				g	Pr	C_6H_{13}
				h	Bu	C_6H_{13}
				i	Me	(*Z*)-$(CH_2)_2CH$=CHEt

In conclusion, the bicyclic lactams **1**, easily available derivatives of 4-oxoalkanoic acids, have proved to be suitable intermediates for an efficient one-pot conversion into various 1,4-diketones. The described procedure represents a cheap access especially to alkane-2,5-diones, such as **4a, 4e**, and **4i**, because 4-oxopentanoic acid, the precursor of **1a**, is an inexpensive commercially available starting material.

Melting points were determined on a Boëtius micro melting point apparatus and are corrected. Microanalyses were obtained using a Carlo Erba autoanalyzer 1106. IR spectra were measured on a Bruker spectrometer IFS 66. ^{13}C NMR spectra were recorded at 75 MHz on a Varian Gemini 300 spectrometer. Mass spectra were obtained on a GC/MS Datensystem HP 5985 B. For sonication a Sonopuls HD 60 ultrasound disintegrator (Bandelin) was used.

1,4-Diketones 4a–h; General Procedure:

A 1 N solution of BuLi (**2a**; 20 mL, 20 mmol) in hexane or a 0.5 N solution of hexyllithium (**2b**; 40 mL, 20 mmol) in Et_2O was cooled to −50 °C. Then a solution of a bicyclic lactam **1** (10 mmol) in Et_2O (10 mL) was added dropwise under stirring at −50 °C within 30 min. After complete addition, the mixture was stirred for further 30 min at this temperature and then allowed to warm up to r.t. For hydrolysis, the mixture was poured carefully into dilute H_3PO_4 (20 mL, 20%) and stirred at 20 °C for 12 h. After separation the aqueous layer was extracted with Et_2O (3 × 20 mL). The extracts were combined with the organic phase, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the resulting oil on silica gel (80 g) with hexane/EtOAc (2:1) as eluent afforded the corresponding diketone **4**. (Table).

Table. 1,4-Diketones **4a–i** Prepared

Product	Yield (%)	bp (°C/mbar)[a] or mp (°C) (solvent)	Molecular Formula[b] or Lit. bp (°C/mbar) or mp (°C)	IR (film/KBr) ν (cm^{-1})	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (%)
4a	58	50–60/0.13	113/20[14]	1705	13.79, 22.33, 25.99, 29.89, 36.08, 36.94, 42.55, 207.08, 209.49	156 (M^+, 2), 114 (100)
4b	50	50–60/0.13	150/3–4[15]	1712	7.82, 13.82, 22.38, 26.05, 35.67, 35.92, 36.14, 42.55, 209.52, 209.83	170 (M^+, 1), 57 (100)
4c	56	23–24 (hexane)	110–112/13.3[16]	1713	13.71, 13.81, 17.34, 22.34, 26.00, 36.03, 42.58, 44.79, 209.56, 209.67	185 [$(M+1)^+$, 100][c]
4d	61	46–47 ($CHCl_3$/hexane)	48–50[17]	1708	13.84, 22.32, 25.96, 36.00, 42.57, 209.75	199 [$(M+1)^+$, 100)[c]
4e	60	31–32 (hexane)	33–34[18]	1704	14.02, 22.48, 23.81, 28.87, 29.93, 31.59, 36.04, 36.89, 42.83, 207.22, 209.62	185 [$(M+1)^+$, 100][c]
4f	54	35–37 (hexane)	41[14]	1708	7.78, 14.01, 22.47, 23.80, 28.87, 31.58, 35.05, 35.59, 35.94, 42.87, 209.80, 210.07	198 (M^+, 1.5), 57 (100)
4g	41	36–38 (hexane)	$C_{13}H_{24}O_2$ (212.2)	1703	13.70, 14.01, 17.30, 22.48, 23.80, 28.88, 31.59, 36.02, 42.88, 44.75, 209.62, 209.76	212 (M^+, 3), 169 (100)
4h	48	44–46 ($CHCl_3$/hexane)	$C_{14}H_{26}O_2$ (226.2)	1703	13.84, 14.02, 22.32, 22.48, 23.80, 25.95, 28.88, 31.59, 35.99, 42.56, 42.87, 209.76	226 (M^+, 3), 57 (100)
4i	60	70/0.07	138–141/4[18]	1715, 1655 (sh)	14.25, 20.47, 21.57, 29.92, 36.16, 36.89, 42.71, 127.11, 132.86, 207.19, 208.93	182 (M^+, 4), 99 (100)

[a] Bath temperature.
[b] Satisfactory microanalyses obtained: C ±0.09, H ±0.37.
[c] Obtained by chemical ionization using isobutane.

(*Z*)-Undec-8-ene-2,5-dione (4i); Typical Procedure (for Large-scale Preparation):

Lithium (3.8 g, 0.55 mol) cut into small pieces and submersed with Et_2O (400 mL) was sonicated for 30 min. Then (*Z*)-1-chlorohex-3-ene (30 g, 0.25 mol) in Et_2O (100 mL) was added under continuous sonication during 1 h maintaining a gentle reflux of the solvent. To complete the reaction sonication was continued for further 3 h at reflux temperature. After separation of the supernatant solution from the remaining solid by pipetting, a 0.25 N solution of **2c** was obtained. To this solution (400 mL, 0.1 mol) cooled to −78 °C the lactam **1a** (7 g, 0.05 mol) dissolved in Et_2O (50 mL) was admixed dropwise under stirring. The mixture was kept at this temperature for 15 min, and allowed to warm up to room temperature. Then the mixture was poured into diluted H_3PO_4 (200 mL, 20%) and stirred for 5 h. After separation of the organic phase the aqueous phase was extracted with Et_2O (3 × 50 mL). Organic phase and the extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the remaining yellow oil on silica gel (250 g) using hexane/EtOAc as eluent afforded pure **4i** as an oil; yield: 5.5 g (60%) (Table).

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