Synthesis of *N*-Substituted 2-Alkyl-3-amino-2-cyclopenten-1-ones

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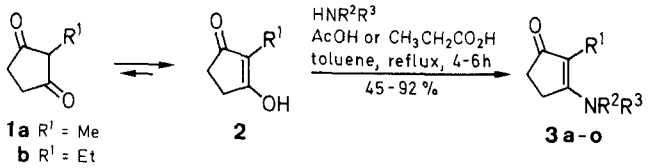
Several 2-alkyl-3-amino-2-cyclopenten-1-ones are prepared in 45–92% yield from 2-alkyl-1,3-cyclopentanediones and a slight excess of an equimolar mixture of various primary and secondary amines and acetic or propionic acid in boiling toluene.

Originally developed as D-ring precursors for the total synthesis of estron and related 19-norsteroids 2-alkyl-1,3-cyclopentanediones **1** became versatile intermediates also for the synthesis of many other cyclopentanoid natural products, such as prostaglandins, jasmonoids, mitomycins, trichothecanes, indolizidines, pseudoguaianolides and pentalenolactones.[1] These cyclic diketones are strongly enolized and exist as 2-alkyl-3-hydroxy-2-cyclopenten-1-ones **2**. When the enolic hydroxy group is converted into an alkoxy group[1-3] or into a substituted amino group[4,5] the resulting enol ethers or enamines may be deprotonated by lithium bis(trimethylsilyl)amide at C-4[1,6,7] or lithium diisopropylamide at C-5[1,6,8] forming anions capable of reacting with electrophiles in the corresponding position. Although the preparation of several enamines of type **3** by heating **1** with a primary or secondary amine and a catalytic amount of acid in boiling benzene has previously been described,[4,5] we have not been able to successfully employ this procedure in the preparation of **3d**, a compound we were especially interested in for the alkylation at C-4 and/or C-5.



3	R^1	R^2	R^3
a	Me	H	Me
b	Me	H	*n*-C_8H_{17}
c	Me	H	CH_2Ph
d	Me	$(CH_2)_4$	
e	Me	$(CH_2)_2O(CH_2)_2$	
f	Et	H	*i*-Bu
g	Et	H	*n*-C_8H_{17}
h	Et	H	*n*-C_9H_{19}
i	Et	H	*n*-$C_{10}H_{21}$
j	Et	H	*n*-$C_{11}H_{23}$
k	Et	H	CH_2Ph
l	Et	Me	Me
m	Et	$(CH_2)_4$	
n	Et	$(CH_2)_5$	
o	Et	$(CH_2)O(CH_2)_2$	

We found, however, that **3d** can be conveniently obtained in a yield of 87%, when the dione **1a** is refluxed in toluene with a slight excess of an equimolar mixture of pyrrolidine and propanoic acid. This method could be used with equal success to gain the enamine **3m** from **1b**. The examples in Table 1 demonstrate that the diones **1a, b** afford good yields also with equimolar mixtures of propanoic acid and piperidine, morpholine, or dimethylamine. Other secondary amines, such as diethylamine, diisopropylamine or *N*-methylaniline in combination with propanoic acid, however, failed. The corresponding enamines **3** were also obtained using equimolar mixtures of propanoic acid with primary aliphatic amines, but not with cyclohexylamine and aniline. Finally, we observed that the outcome of the reaction was not significantly influenced if acetic acid was used instead of propanoic acid under the same conditions.

Table 1. *N*-Monosubstituted and *N,N*-Disubstituted 2-Alkyl-3-amino-2-cyclopenten-1-ones **3** Prepared

Product	Yield (%)	mp (°C) (solvent)	bp[a] (°C)/ mbar	Molecular Formula[b] or Lit. mp (°C)
3a	90	197–198 (EtOAc)[c]	–	$C_7H_{11}NO$ (125.2)
3b	60	46–48 (hexane/ benzene)	180–200/ 0.008	$C_{14}H_{25}NO$ (223.4)
3c	67	135–137 (EtOAc)	170–220/ 0.004	$C_{13}H_{15}NO$ (201.3)
3d	87	96–98 (hexane)	170/ 0.0065	96–97[4]
3e	90	45–47	180/ 0.0065	$C_{10}H_{15}NO_2$ (181.2)
3f	90	108–109 (benzene)	160–185/ 1.3	$C_{11}H_{19}NO$ (181.3)
3g	55	75–77 (hexane/ benzene)	210–230/ 1.3	$C_{15}H_{27}NO$ (237.4)
3h	45	77–78 (hexane)[c]	–	$C_{16}H_{29}NO$ (251.4)
3i	88	85–86 (hexane/ benzene)[c]	–	$C_{17}H_{31}NO$ (265.4)
3j	60	87–89 (heptane)[c]	–	$C_{18}H_{33}NO$ (279.5)
3k	58	104–105 (EtOAc)[c]	–	$C_{14}H_{17}NO$ (215.3)
3l	77	–	165–185/ 1.3	$C_9H_{15}NO$ (153.2)
3m	92	59–61 (pentane/ benzene)	180–195/ 1.3	$C_{11}H_{17}NO$ (179.3)
3n	84	–	160–185/ 1.3	$C_{12}H_{19}NO$ (193.3)
3o	71	–	180–200/ 1.3	$C_{11}H_{17}NO_2$ (195.3)

[a] Bath temperature.

[b] Satisfactory microanalyses obtained: C ±0.34, H ±0.36, N ±0.35.

[c] The compound was purified by recrystallization of the crude product obtained by removal of the solvent.

Table 2. Spectral Data of Compounds **3a–o**

Compound	^{1}H-NMR ($CDCl_3$/HMDS) δ, J (Hz)	MS (70 eV) m/z (%)
3a	1.55 (s, 3H, 2-CH_3), 2.44 (m, 4H, CH_2CH_2), 3.02 (d, 3H, J = 5, NCH_3), 5.23 (m, 1H, NH)	
3b	0.82 (t, 3H, J = 6, CH_2CH_3), 1.24 (m, 12H (CH_2)$_{chain}$), 1.54 (s, 3H, 2-CH_3), 2.40 (m, 4H, (CH_2)$_{ring}$), 3.26 (q, 2H, J = 7, NCH_2), 5.48 (t, 1H, J = 7, NH)	223 (M^+, 29), 208 (3), 194 (7), 180 (15), 166 (13), 152 (7), 138 (33), 124 (100), 111 (10), 96 (17), 82 (10), 67 (21), 55 (19), 41 (41)
3c	1.56 (s, 3H, 2-CH_3), 2.36 (m, 4H, CH_2CH_2), 4.44 (d, 2H, J = 6, NCH_2), 6.00 (t, 1H, J = 6, NH), 7.24 (s, 5H$_{arom.}$)	201 (M^+, 37), 186 (1), 172 (9), 158 (2), 144 (2), 130 (1), 91 (100), 77 (3), 65 (32), 51 (14), 41 (19)
3d	1.86 (s, 3H, 2-CH_3), 1.88 (m, 4H, 2(CH_2)$_{carbocycl.}$), 2.36 (m, 4H, (CH_2)$_{carbocycl.}$), 3.56 (m, 4H, CH_2NCH_2)	165 (M^+, 26), 148 (3), 136 (24), 122 (21), 110 (15), 96 (44), 81 (11), 67 (27), 53 (4), 41 (100)
3e	1.81 (s, 3H, 2-CH_3), 2.38 (m, 4H, 2 (CH_2)$_{carbocycl.}$), 3.64 (m, 8H, 4 (CH_2)$_{heterocycl.}$)	181 (M^+, 100), 166 (4), 150 (50), 136 (38), 124 (49), 108 (25), 95 (82), 80 (9), 67 (55), 53 (28), 41 (50)
3f	0.91 (t, 3H, J = 8, CH_2CH_3), 0.94 (d, 6H, J = 8, $C(CH_3)_2$), 2.10 (q, 2H, J = 8, CH_2Me), 2.42 (m, 4H, CH_2CH_2), 3.08 (t, 2H, J = 7, NCH_2), 5.40 (m, 1H, NH)	181 (M^+, 58), 166 (86), 138 (100), 124 (12), 105 (21), 94 (11), 77 (21), 67 (8), 53 (10), 41 (98)
3g	0.92 (t, 6H, J = 8, 2 CH_3), 1.23 (m, 12H, 6(CH_2)$_{chain}$), 2.08 (q, 2H, J = 8, CH_2Me), 2.44 (m, 4H, 2 (CH_2)$_{carbocycl.}$), 3.30 (q, 2H, J = 7, NCH_2), 5.00 (m, 1H, NH)	237 (M^+, 24), 222 (24), 208 (14), 194 (26), 180 (10), 166 (12), 152 (100), 138 (66), 124 (32), 110 (24), 96 (10), 91 (14), 79 (12), 69 (16), 55 (32), 41 (66)
3h	0.90 (t, 6H, J = 8, 2 CH_3), 1.23 (m, 14H, 7(CH_2)$_{chain}$), 2.08 (q, 2H, J = 8, CH_2Me), 2.38 (m, 4H, 2 (CH_2)$_{carbocycl.}$), 3.24 (q, 2H, J = 7, NCH_2), 5.72 (t, 1H, J = 7, NH)	251 (M^+, 40), 236 (40), 222 (15), 208 (24), 194 (28), 180 (14), 166 (14), 152 (100), 139 (66), 124 (32), 110 (20), 96 (9), 79 (8), 67 (7), 55 (24), 41 (56)
3i	0.90 (t, 6H, J = 8, 2 CH_3), 1.22 (m, 16H, 8(CH_2)$_{chain}$), 2.06 (q, 2H, J = 8, CH_2Me), 2.38 (m, 4H, 2 (CH_2)$_{carbocycl.}$), 3.23 (q, 2H, J = 7, NCH_2), 4.96 (m, 1H, NH)	265 (M^+, 36), 250 (34), 236 (8), 222 (14), 208 (17), 194 (24), 180 (12), 166 (14), 152 (100), 139 (80), 124 (32), 110 (16), 96 (8), 79 (8), 67 (6), 55 (24), 41 (27)
3j	0.90 (t, 6H, J = 8, 2 CH_3), 1.21 (m, 18H, 9(CH_2)$_{chain}$), 2.10 (q, 2H, J = 8, CH_2Me), 2.42 (m, 4H, 2 (CH_2)$_{carbocycl.}$), 3.26 (q, 2H, J = 7, NCH_2), 5.05 (m, 1H, NH)	279 (M^+, 34), 264 (34), 250 (10), 236 (10), 222 (24), 208 (38), 194 (26), 180 (14), 166 (14), 152 (100), 139 (95), 124 (30), 110 (16), 96 (8), 79 (8), 67 (6), 55 (22), 41 (52)
3k	0.94 (t, 3H, J = 8, CH_3), 2.10 (q, 2H, J = 8, CH_2Me), 2.37 (m, 4H, CH_2CH_2), 4.47 (d, 2H, J = 7, NCH_2), 5.72 (m, 1H, NH), 7.30 (m, 5H$_{arom.}$)	215 (M^+, 12), 200 (9), 172 (3), 124 (10), 91 (100), 77 (6), 65 (27), 53 (14), 41 (26)
3l	0.94 (t, 3H, J = 8, CH_2CH_3), 2.32 (m, 6H, 3 CH_2), 3.09 (s, 6H, $N(CH_3)_2$)	153 (M^+, 38), 138 (100), 124 (3), 110 (18), 94 (11), 82 (22), 67 (27), 53 (20), 42 (79)
3m	0.94 (t, 3H, J = 8, CH_3), 2.38 (m, 4H, 2(CH_2)$_{carbocycl.}$), 3.57 (m, 4H, CH_2NCH_2)	179 (M^+, 65), 164 (81), 150 (15), 136 (52), 122 (12), 108 (14), 94 (20), 79 (18), 67 (37), 53 (37), 41 (100)
3n	0.93 (t, 3H, J = 8, CH_3), 1.63 (m, 6H, 3(CH_2)$_{heterocycl.}$), 2.32 (m, 6H, 2 (CH_2)$_{carbocycl.}$, CH_2Me), 3.44 (m, 4H, CH_2NCH_2)	193 (M^+, 40), 178 (92), 164 (15), 150 (14), 136 (8), 122 (4), 110 (7), 95 (3), 82 (3), 67 (4), 55 (3), 41 (6)
3o	0.90 (t, 3H, J = 8, CH_3), 2.35 (m, 6H, 2(CH_2)$_{carbocycl.}$, CH_2Me), 3.58 (m, 8H, 4 (CH_2)$_{heterocycl.}$)	195 (M^+, 30), 180 (16), 166 (3), 150 (21), 136 (9), 122 (5), 108 (7), 94 (7), 79 (12), 67 (18), 55 (45), 42 (100)

The 2-alkyl-1,3-cyclopentanediones **1a,b** were produced by Jenapharm according to Ref. 9. Toluene and the amines, commercial products of reagent quality, were used without further purification. Melting points were determined on a Boëtius micro melting point apparatus and are corrected. Microanalyses were obtained using a Carlo Erba autoanalyzer 1106. Mass spectra were recorded using a GC/MS-Datensystem HP 5985 B. ^{1}H-NMR spectra were measured at 100 MHz on a Tesla BS 567 spectrometer in $CDCl_3$ with hexamethyldisiloxane as internal standard. Chemical shifts are given in δ values related to TMS.

***N*-Monosubstituted and *N,N*-Disubstituted 2-Alkyl-3-amino-2-cyclopenten-1-ones 3; General Procedure:**

The 2-alkyl-1,3-cyclopentanedione **1a** or **b** (0.1 mol) is added to a mixture of the corresponding amine (0.11 mol) and propanoic acid (8.15 g, 0.11 mol) or AcOH (6.60 g, 0.11 mol) in toluene (100 mL) and heated in a Dean–Stark water separator for 4–6 h. After cooling, the dark reaction mixture is concentrated at reduced pressure slowly raising the bath temperature up to 130 °C. The remaining crude enaminone **3** is purified by Kugelrohr distillation and/or recrystallization. Yields and analytical data of the compounds prepared are given in Tables 1 and 2.

Received: 27 June 1990; revised: 24 September 1990

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