Use of Boron Trifluoride Etherate in the Preparation of 2-Amino-1-alkenyl Ketones from β-Diketones and Low-Boiling Amines

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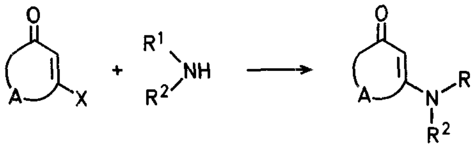
Recently, potential uses of enamino ketones or β-amino-α,β-unsaturated ketones have been demonstrated in synthetic and medicinal chemistry[1,2,3]. Enaminones in general and particularly cyclohexane-1,3-dione derivatives, have therapeutic qualities due to their analeptic properties combined with low toxicity[1]. The most usual preparation of **3** involves the direct reaction of a dione **1a** with the amine **2** in an aromatic solvent with azeotropic removal of the water formed[2-6].



1a X = OH
b X = OCH_3, OC_2H_5
c X = Cl, Br

2 R^1,R^2 = H, alkyl, aryl

3

Sometimes, the diketone is first converted into a vinylogous ester **1b** or a vinylogous acid halide **1c** and then condensed with the amine[7]. However, in any case, there are problems associated with the use of low boiling amines: it is necessary either to pass a rapid stream of gaseous amine through the refluxing dione solution[8], or to operate in an autoclave[1] at 130-150 °C, or in a glass pressure bottle containing anhydrous calcium chloride[9]. The first procedure requires a large excess of amine. With the latter methods, the reaction cannot be easily followed, the yields are not quantitative, and polymerization occurs. In any case, the utilization of these methods is not easy, as we have experienced in the course of our physicochemical studies on the enaminone derivative of 5,5-dimethylcyclohexane-1,3-dione[10].

The good results obtained in enamine synthesis with titanium(IV) chloride[11,12] and with boron trifluoride in the amidation of carboxylic acids[13], incited us to try a new synthetic route of these enaminones using a Lewis acid/amine complex. We have selected the boron trifluoride diethyl etherate because of easier handling as compared with titanium(IV) chlo-

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Table. 1-Amino-5,5-dimethyl-3-oxocyclohexenes from 5,5-Dimethylcyclohexane-1,3-dione and Low Boiling Amines

Product R^1	R^2	Yield[a] [%]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]	I.R. (CH_2Cl_2)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$)[d] δ [ppm]	M.S.[e] m/e
CH_3	H	82	153-154°	152-153°[14]	3435, 3250, 1613, 1587, 1520, 1365, 1150, 1050	1.08 (s, 6H); 2.17 (s, 2H); 2.27 (s, 2H); 2.80 (d, 3H, $J=5$ Hz); 5.05 (s, 1H); 6.4 (m, 1H)	153 (59%); 69 (100%)
CH_3	CH_3	96	93-94°	—[9]	1606, 1560, 1385, 1368, 1172, 1150	1.11 (s, 6H); 2.13 (s, 2H); 2.30 (s, 2H); 3.01 (s, 6H); 5.13 (s, 1H)	167 (74%); 55 (100%)
C_2H_5	H	90	104-105°	$C_{10}H_{17}NO$ (167.3)	3420, 3250, 1611, 1583, 1517, 1375, 1368, 1172, 1150	1.08 (s, 6H); 1.23 (t, 3H, $J=7$ Hz); 2.17 (s, 2H); 2.25 (s, 2H); 3.17 (dq, 2H, $J=7$ Hz, 6 Hz); 5.13 (s, 1H); 6.0 (m, 1H)	167 (48%); 83 (100%)
i-C_3H_7	H	91	143-144°	$C_{11}H_{19}NO$ (181.3)	3410, 3255, 1609, 1581, 1514, 1385, 1368, 1335, 1172, 1148	1.08 (s, 6H); 1.23 (d, 6H, $J=6$ Hz); 2.17 (s, 2H); 2.26 (s, 2H); 3.62 (dq, 1H, $J=6$ Hz); 5.10 (s, 1H); 6.28 (d, 1H, $J=6$ Hz)	181 (12%); 43 (100%)
n-C_4H_9	H	96	121-122°	$C_{12}H_{21}NO$ (195.3)	3420, 3250, 1611, 1583, 1520, 1368, 1150	0.98 (d, 3H, $J=6$ Hz); 1.08 (s, 6H); 1.0-1.8 (m, 4H); 2.21 (s, 2H); 2.31 (s, 2H); 2.9-3.3 (m, 2H); 5.23 (s, 1H); 6.36 (m, 1H)	195 (25%); 97 (100%)

[a] Yield of pure, recrystallized, isolated product.

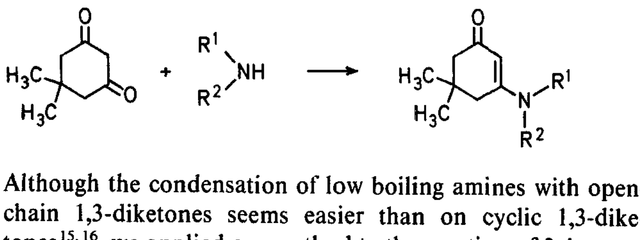
[b] Satisfactory microanalyses obtained: C ±0.15, H ±0.25, N ±0.28.

[c] Measured on a Perkin-Elmer Model 457 infrared spectrometer.

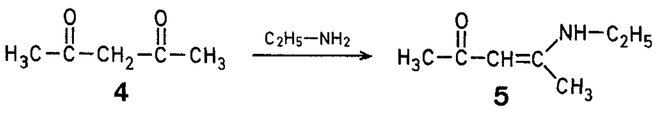
[d] Recorded at 60 MHz on a Varian A60A NMR spectrometer.

[e] Recorded with R. 10-10 Nermag Mass Spectrometer.

ride. The excellent results that we have obtained with five gaseous or low boiling amines **2** and 5,5-dimethylcyclohexane-1,3-dione [**1a**; A = —CH_2—$C(CH_3)_2$—CH_2—] are summarized in the Table.



Although the condensation of low boiling amines with open-chain 1,3-diketones seems easier than on cyclic 1,3-diketones[15,16], we applied our method to the reaction of 2,4-pentanedione (**4**) with ethylamine and obtained the expected 4-(N-ethylamino)-pent-3-en-2-one (**5**) in 92% yield.



$$H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{C_2H_5-NH_2} H_3C-\overset{O}{\overset{\|}{C}}-CH=C\begin{smallmatrix}NH-C_2H_5\\ CH_3\end{smallmatrix}$$

4 **5**

The use of a Lewis acid in these preparations brings three advantages: the complexation of low boiling amines, the acid catalysis of the reaction, and the equilibrium shift towards the enaminone formation by complexation of the water formed. It is necessary to use a 1:1 amine/boron trifluoride complex with a small excess of complex with regard to the 1,3-dione. Indeed, use of an excess of free boron trifluoride ethyl etherate results in a mixture of enaminone **3** and the vinylogous ester **1b**. Attention must be drawn to the fact that the use of boron trifluoride dialkyl etherate with the 1,3-dione is a facile route for vinylogous ester preparations[18].

2-Amino-1-alkenyl Ketones from Low Boiling Amines and 5,5-Dimethylcyclohexane-1,3-dione; General Procedure:

To freshly distilled boron trifluoride ethyl etherate (Fluka; 8 ml, 9 g, 0.063 mol) in dry benzene (10 ml) is slowly added the appropriate amine (0.063 mol; from pressure bottle for gaseous amines). To the clear solution is added 5,5-dimethylcyclohexane-1,3-dione (8 g, 0.057 mol) and dry benzene (80 ml) and the mixture is refluxed for 4-6 h with stirring. After cooling the yellow solution is washed with 5% sodium hydroxide solution (50 ml). The benzene phase is separated. After saturation with sodium chloride, the aqueous solution is extracted with several portions of chloroform. The combined benzene and chloroform extracts are dried with magnesium sulfate. The solvent is removed in a rotavapor and the residual matter is recrystallized from benzene/hexane to give solely the expected enaminone. The purity of product is verified by T.L.C. (silica gel, eluent: benzene/acetone, 8:2), by comparison of its melting point with an authentic sample, or by microanalysis for new compounds.

4-(N-Ethylamino)-pent-3-en-2-one (5):

Prepared as described above from 2,4-pentanedione (**4**; 5.0 g, 0.05 mol) and ethylamine (2.48 g, 0.055 mol); yield: 92%; b.p. 75-76°C/5 torr (Lit.[15], b.p. 210-215°C/760 torr).

M.S.: $m/e = 127$ (M^+, 88%); 112 (100%).

I.R. (CH_2Cl_2): $\nu = 1610$, 1570, 1517, 1300, 1155 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 1.15$ (t, 3H, $J=6$ Hz); 1.82 (s, 3H); 1.85 (s, 3H); 3.22 (quint, 2H, $J=6$ Hz); 4.78 (s, 1H); 10.6 ppm (m, 1H). These chemical shifts are in agreement with the literature data[17].

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