Acta Chemica Scandinavica B 33 (1979) 710—714

Acylation of Enamines. II. Formation of Enaminones by Condensation of Methyl Alkyl Ketone Enamines with α-Hydrogen Possessing Acid Chlorides and Benzoyl Chloride

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In the acylation reaction of methyl alkyl ketone enamines (alkyl = isobutyl and neopentyl) with benzoyl chloride and some α-hydrogen possessing acid chlorides (acetyl chloride, isobutyryl chloride and cyclohexanoyl chloride) it was found that only in one case was it possible to detect any trace of a cyclobutanone intermediate. The isolated products were the enaminones regiospecifically formed, and to some extent diacylated products. The reaction proceeds smoothly for the morpholine enamines whereas the diethylamine enamines in addition to the enaminones yield self-condensation products. Structures of enaminones formed are briefly discussed and general considerations concerning formation and use of enaminones are evaluated.

The acylation reaction of aldehyde and cyclic ketone enamines have been thoroughly investigated.[1] In a recent report the possibility of a regiospecific transformation of unsymmetrical methyl alkyl ketone enamines to β-diketones *via* a benzoylation reaction was outlined.[2] The reaction involves the formation of stable intermediate enaminones. The enaminones possess three different sites for an electrophile to attack (Fig. 1) and have been subjected to recent reviews.[3,4] To evaluate if these potentially pharmacologically interesting enaminones are obtainable also from the reaction between α-hydrogen possessing acid chlorides and unsymmetrical methyl alkyl ketone enamines, an investigation was undertaken.

RESULTS AND DISCUSSION

Benzoyl chloride was found to act well in the enaminone formation, and after hydrolysis gave good yields of β-diketones.[2] Acid chlorides capable of ketene formation have been postulated[5] to react with enamines, *via* a zwitterionic intermediate, to yield a cyclobutanone derivative which is ring-opened more or less easily depending on factors such as temperature and substituents (Fig. 2). When the enamines used in this investigation were subjected to reaction with α-hydrogen possessing acid chlorides the products isolated were mono-, diacylated and self-condensation products. The only indication of cyclobutanone formation was in the reaction of the morpholine enamine obtained from methyl isobutyl ketone and isobutyryl chloride, which showed IR absorption at 1770 cm^{-1} directly after addition of the acid chloride. By warming the sample for a few minutes with a hair-drier, the absorption at 1770 cm^{-1} disappeared with increase in the enaminone absorption band.

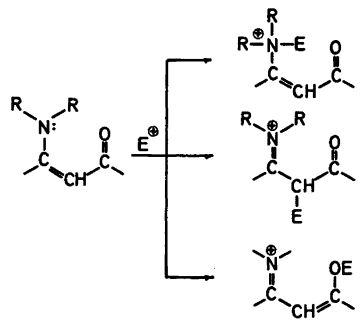

Fig. 1. Possible sites for electrophilic attack on enaminones.

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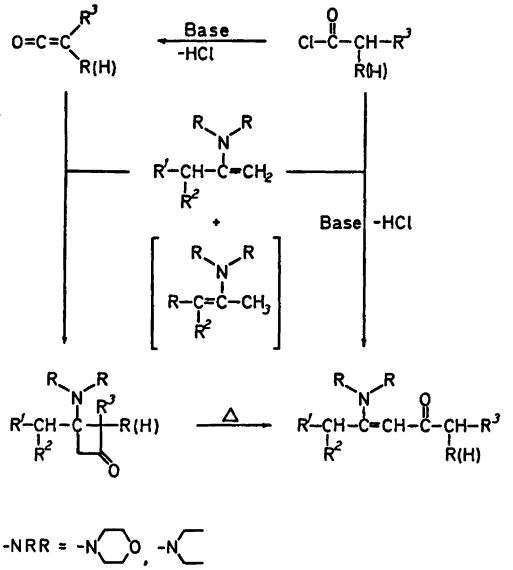

Fig. 2. Acylation of enamines with α-hydrogen possessing acid chlorides can take place either directly on β-carbon or *via* the generated ketene.

The pure least substituted isomer of the morpholine enamine of methyl isobutyl ketone, however, did not show any indication of a cyclobutanone formation when subjected to acylation with isobutyryl chloride under the same conditions. In the acylation reactions of cyclic ketone enamines [5] the use of two-fold excess of enamine in place of an auxiliary base was sufficient to avoid the formation of cyclobutanone derivatives and subsequent ring enlargement under the following ring-opening reactions.

These somewhat unexpected results reveal a considerable difference compared to the results obtained from the acylation reactions of aldehyde and cyclic ketone enamines, where the cyclobutanone derivatives were quite stable and could, depending on the substituents in the α positions to the carbonyl, in some cases be isolated by distillation.[5]

No acylation products from reaction of the most substituted enamine isomers could be detected, thus emphasizing previous observations [6,7,8] of a substantial difference in reactivity between the methyl alkyl ketone enamine isomers towards electrophilic species. This means that the use of two equivalents of enamine or the pure least substituted enamine isomer (released *via* a protonation-deprotonation sequence [6,7]) are possible alternatives in the acylation reactions of these unsymmetrical methyl alkyl ketone enamines.

Ring-opening by *path(b)* would yield a different enaminone, if R^2 or $R^3 = H$, from the enaminone obtained by ring-opening by *path(a)*, whereas the situation where neither R^2 nor $R^3 = H$ would lead to a nonconjugated enaminoketone (Fig. 3). The absence of such products implies that either ring-opening of a cyclobutanone derivative is regiospecific (*i.e.* only *path(a)* is applicable) and/or direct acylation of the enamine is at hand. However, the result shows to be a regiospecific transformation of the methyl alkyl ketone enamine to the conjugated acylenamine – enaminone –.

In contrast to benzoylation of some methyl alkyl ketone enamines where diacylation mostly could be avoided by a careful addition of the acid chloride to the well-stirred solution of the enamine,[2] it was found that the reaction with the α-hydrogen possessing acid chlorides always yielded some diacylated products (MS: molecular ion, IR absorption at 1740 – 1760 cm^{-1} and ^1H NMR: vinylic peak at lower field than the corresponding enaminone; see Tables 1 – 2). The enaminones are freed from diacylated products by filtration or fractionated distillation at reduced pressure.

STRUCTURES OF ENAMINONES

As previously noticed [2] the enaminones with a benzoyl moiety, as noticed from their IR spectra, show characteristic absorption band in the range of 1600 – 1630 cm^{-1}.

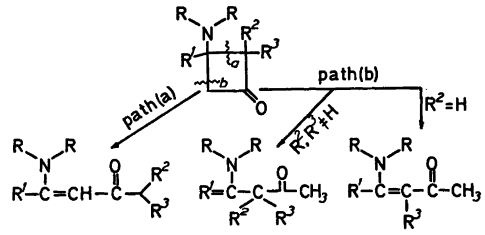

Fig. 3. Possible ring-opening paths for a cyclobutanone intermediate.

Table 1. Distribution of acylated products in the reaction between enamines and acid chlorides.

Enamine $R^1(R_2N)C=CH_2$/mol		Acid chloride	R^2COCl/mol	Yielded products	Enaminone/mol	Enamino-enolester/mol
R^1 = neopentyl NRR = morpholinyl	0.127	R^2 = methyl	0.127	*1*	0.069	0.02
R^1 = isobutyl NRR = morpholinyl	0.15	R^2 = isopropyl	0.15	*3*	0.11	0.01
R^1 = isobutyl NRR = diethylamino	0.075	R^2 = isopropyl	0.075	*2*	0.06	0.007
R^1 = neopentyl NRR = morpholinyl	0.10	R^2 = isopropyl	0.10	*4*	0.073	0.013
R^1 = neopentyl NRR = morpholinyl	0.10	R^2 = cyclohexyl	0.10	*5*	0.07	0.011

The differences between enaminones with benzoyl moities and enaminones with isobutyryl or cyclohexanoyl moities were found to be independent of the amine part (Table 2). The UV spectra of enaminones *2*, *3*, *4* and *5* were almost superimposable and the absorption peaks were quite narrow. The UV spectrum of enaminone *1* emphasizes a difference between this enaminone and the enaminones *2*, *3*, *4* and *5*.

GENERAL CONCLUSIONS AND SUMMARY OF ENAMINONE FORMATION

The results of the acylation reactions as noticed during this investigation and the previously reported publication concerning formation of β-diketones reveal that:

(a) If an isomeric mixture of the enamine is subjected to the action of acid chloride all cases studied showed that out of the isomeric enamines only the least substituted isomers reacted with the electrophilic species, whereas the most substituted isomers, if present, acted only as hydrogen chloride scavenger.

(b) Only one monoacylated enamine (enaminone) is formed. This indicates that if acylation by a ketene is present, the subsequently formed cyclobutanone derivative is ring-opened in a regiospecific manner leading to the same product as by direct acylation on the least substituted enaminic β-carbon.

(c) The reaction between benzoyl chloride and an isomeric mixture of the morpholine enamine obtained from methyl isobutyl ketone was found to be more or less solvent independent, giving after hydrolysis the β-diketones in yields: (%/solvent) 68/hexane, 70/ether, 68/chloroform, 66/dichlormethane, 76/benzene. All other variables were kept constant.[9]

(d) The unbranched morpholine enamine obtained from methyl propyl ketone gave the enaminone almost quantitatively when benzoyl chloride was added at −15 °C, and the self-condensation products formed at higher temperature [2] were almost undetectable.

(e) The acylation reactions of methyl alkyl ketone enamines are applicable to enamines with morpholine, dimethylamine and diethylamine parts, although from a practical point of view morpholine enamines are preferable, unless the amine part is essential. These enamines rarely give rise to self-condensation products, whereas dimethylamine, diethylamine and especially pyrrolidine enamines undergo self-condensation reactions even when stored in the cold under nitrogen.

EXPERIMENTAL

The IR spectra were recorded on neat samples (liquid film) or crystals suspended in paraffin. The UV spectra were recorded on samples in methanolic solutions. ^1H NMR spectra were recorded on a 60 MHz spectrometer on samples dissolved in deuteriochloroform, sample concentration *ca.* 1 M. For the GC–MS: A 1 % OV–17 on Chromosorb W–AW 60–80 mesh column (1.5m, 4mm i.d., glass, or a 25 meter SP 2100 capillary column in the GC part, was used. Enamines were prepared according to reported methods.[10,11] Benzoyl chloride, acetyl chloride and isobutyryl chloride were commerci-

Table 2. Physical data on enaminones: $R^1COCH=C(NR_2)R^2$.

Compound	IR/cm^{-1}	UV λ_{max}/nm [c]	^{1}H NMR [d]	B.p./(°C/mmHg) M.p./°C	Yield/%
1 R^1=methyl R^2=neopentyl NRR=morpholinyl	1652 (C=O) 1545 (C=C) [a]	350,228	5.3(−CH=C−)	103/0.1	55
2 R^1=isopropyl R^2=isobutyl NRR=diethylamino	1637 (C=O) 1531 (C=C) [a]	314,201	5.1(−CH=C−)	84/0.15	80
3 R^1=isopropyl R^2=isobutyl NRR=morpholinyl	1646 (C=O) 1545 (C=C) [a]	312,200	5.2(−CH=C−)	112−114/0.06	73
4 R^1=isopropyl R^2=neopentyl NRR=morpholinyl	1641 (C=O) 1552 (C=C) [b]	310,202	5.3(−CH=C−)	66−67	73
5 R^1=cyclohexyl R^2=neopentyl NRR=morpholinyl	1638 (C=O) 1535 (C=C) [b]	312,204	5.3(−CH=C−)	77	70
6 R^1=phenyl R^2=propyl NRR=morpholinyl	1626 (C=O) 1530 (C=C) [a]	341,243,204	5.7(−CH=C−)	135/0.5	95
7 R^1=phenyl R^2=isobutyl NRR=diethylamino	1615 (C=O) 1525 (C=C) [a]	343,244,202	5.7(−CH=C−)	107−109	90
8 R^1=phenyl R^2=isobutyl NRR=morpholinyl	1620 (C=O) 1530 (C=C) [a]	342,244,202	5.8(−CH=C−)	72−73	100
9 R^1=phenyl R^2=neopentyl NRR=morpholinyl	1626 (C=O) 1532 (C=C) [a]	345,247,203	5.8(−CH=C−)	59−61	100

[a] Neat film. [b] In paraffin. [c] In methanol. [d] In deuteriochloroform.

ally available whereas cyclohexanoyl chloride was prepared from cyclohexanecarboxylic acid.[12]

Formation of enaminones – general procedure. The least substituted isomer of the enamine (0.1 mol) was placed in a 250 ml three-necked flask (equipped with a Hershberg stirrer, reflux condenser with a drying tube and a dropping funnel), dissolved in 75 ml of hexane, and 0.11 mol of triethylamine was added as hydrogen chloride scavenger (when using an isomeric mixture of the enamine, it needs to be checked that the amount of least substituted isomer is > 0.1 mol, and triethylamine added in order to fill up the need for base). The acid chloride (0.1 mol) dissolved in 75 ml of hexane was added dropwise to the vigorously stirred enamine solution, externally cooled on an ice-water bath. After completed addition, the reaction mixture was refluxed for an additional 2 h and stirred at room temperature overnight.

The precipitated triethylamine hydrochloride was filtered off (or when using the most substituted isomer as base, the immonium chloride was filtered off under nitrogen) and washed with 3 x 20 ml of dry ether. Evaporation of ether–hexane and fractionated distillation at reduced pressure afforded the enaminone in a pure state, yields 55–100 % (in the case of a crystalline enaminone, washing with cold hexane was sufficient to obtain ^{1}H NMR pure enaminone).

Note. The reaction can be scaled up to 1 mol scale. However, in such cases it is preferred to first convert the mixture of enamine isomers to the least substituted isomer, since the otherwise precipitated immonium chloride, which is quite hygroscopic, tends to absorb some of the formed enaminone.

Acknowledgement. The author is indebted to Professor Christoffer Rappe for valuable discussions and for his kind interest in this project.

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Received June 18, 1979.