Acta Chemica Scandinavica B 33 (1979) 547—550

Acylation of Enamines. III. Reduction of Protonated Enaminones with Sodium Borohydride. Synthesis of α,β-Unsaturated Ketones

LARS NILSSON

Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

Enamines obtained from methyl alkyl ketones (alkyl = propyl, isobutyl, neopentyl) and secondary amines (morpholine, diethylamine) were converted to enaminones *via* acylation with acid chlorides (benzoyl chloride, isobutyryl, chloride, cyclohexanoyl chloride). Protonation of the enaminones with trifluoroacetic acid in isopropanol followed by addition of sodium borohydride suspended in isopropanol gave, after the usual work-up, good yields of α,β-unsaturated ketones. Structures of products formed are briefly discussed.

Protonation of enaminones is reported to take place preferentially on oxygen.[1] This results indicates a possibility of a regiocontrolled reduction of the protonated enaminone system since a resulting enol-immonium structure would protect the carbonyl carbon from attack, leaving the nitrogen bonding carbon to be attacked by the reducing agent. Previous attempts by others to reduce the enaminone system as such has been reported[2–4] (if employing lithium aluminiumhydride the result is β-aminoketones,[2] whereas hydrogenation using platinum catalyst [3] leads to cleavage of the molecule and subsequent formation of an amine and a saturated ketone, and hydrogenation using rhodium (or ruthenium) catalysts [4] results in the formation of β-amino alcohols). However, other and more selectively reducing agents such as sodium cyanoborohydride in acidic solution fail to reduce the enaminone system resulting only in good recovery of starting material.[5]

RESULTS AND DISCUSSION

To evaluate the possibility of a selective reduction at the nitrogen bonding carbon, the enaminone *1a* dissolved in isopropanol was protonated with one equivalent of trifluoroacetic acid. The generated enol-immonium salt was not isolated, although a recorded ^{1}H NMR spectrum showed that the normally sharp vinylic hydrogen signal was considerably broadened and the two multiplets from the morpholine moiety had coincided to the characteristic broad immonium multiplet at *ca.* 4 ppm with an integral corresponding to eight protons.[6] Subsequent addition of sodium borohydride suspended in isopropanol to the protonated enaminone solution, externally cooled in an ice-water bath, caused an immediate evolution of gases. The product was the corresponding α,β-unsaturated ketone thus revealing deamination of an initially formed β-aminoketone (Fig. 1). However when the reduction of *1a* was performed using a slurry of the sodium borohydride in methanol, besides the expected α,β-unsaturated ketone, an α,β-unsaturated alcohol was formed in various amounts, probably through a further reduction of the initially formed α,β-unsaturated ketone in accordance with previous reports [7] concerning reduction of α,β-unsaturated ketones. When enaminones *1b*, *2* and *3* (Fig.2) were treated with a slurry of sodium borohydride in isopropanol they were all found to yield α,β-unsaturated ketones in ranges 60–80 %, and the corresponding α,β-unsaturated alcohols to an extent < 5 % thus indicating a strong solvent influence in a further reduction of a previously formed α,β-unsaturated ketone which is in agreement with previous reports.[7]

The reduction was applicable also to enaminones derived from the benzoylation of methyl alkyl ketone enamines, *viz* the enaminones *4*, *5* and *6* gave yields of α,β-unsat-

0302-4369/79/080547-04$02.50

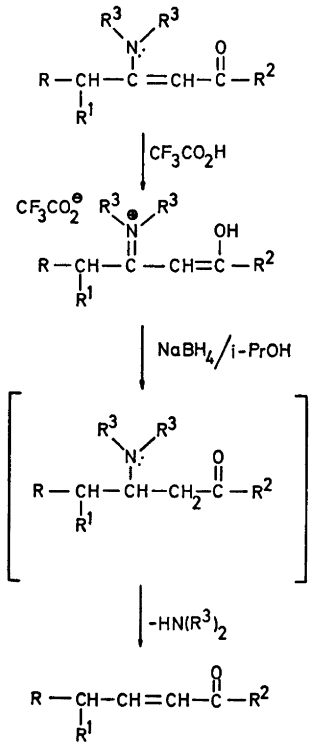


Fig. 1. Reaction procedure for the formation of α,β-unsaturated ketones.

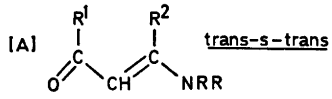
urated ketones in the range 60–80 %, when subjected to the described procedure. No α,β-unsaturated alcohols were detected, thus implicating that the further reduction to α,β-unsaturated alcohols is probably hindered by the introduced conjugation with the phenyl group.

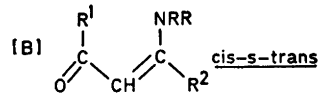
When methanol was used as solvent, and the sodium borohydride completely dissolved before addition, no reaction occurred. Only partially dissolved sodium borohydride was capable of reducing the enaminones *1*, *2* and *3*, which indicates that the complex sodium trimethoxyborohydride that is formed,[8] when sodium borohydride is dissolved in methanol, is a too weak hydride donor to perform the desired reaction. Only good recovery (92–96 %) of starting material was obtained. This result is in agreement with previously reported attempts to reduce enaminones with selectively reducing agents such as sodium cyanoborohydride.[5]

The ease with which the deamination took place may be explained by the presence of the equivalent of trifluoroacetic acid. It was postulated that the reverse reaction, that is the addition of arylamines to vinyl ketones, involves the participation of a catalyst (acetic acid, phosphoric acid) in the transition state.[9] However, in contrast to previous reports concerning deamination of Mannich bases [10] where modest yields and rather long reaction times are required, the α,β-unsaturated ketones in this investigation were formed smoothly and could be isolated in fair yields (60–80 %) requiring no drastic conditions (see Experimental).

STRUCTURES OF COMPOUNDS FORMED

The α,β-unsaturated benzoyl ketones *10*, *11* and *12* were all found to exhibit a doublet with strong absorption at *ca.* 1000 and 980 cm^{-1},





Enaminone	R^1	R^2	NRR	Structure
1a	Isopropyl	Isobutyl	Morpholine	|B|
1b	Isopropyl	Isobutyl	Diethylamine	|B|
2	Isopropyl	Neopentyl	Morpholine	|B|
3	Cyclohexyl	Neopentyl	Morpholine	|B|
4	Phenyl	Propyl	Morpholine	|A|
5	Phenyl	Isobutyl	Morpholine	|A|
6	Phenyl	Neopentyl	Morpholine	|A|

Fig. 2. Enaminones used in this investigation.

respectively, which is typical for *trans* olefinic carbon-hydrogen out-of-plane vibrations. Samples of the α,β-unsaturated ketones *10*, *11* and *12* when run on GC, all showed a small peak at the base of the major peak, which may be the corresponding *cis* isomers. The mass spectra of these small peaks furnished the same molecular ion but a partially different fragmentation pattern. Somewhat surprisingly, the IR spectra of the α,β-unsaturated ketones *10*, *11* and *12* showed only two strong absorption bands in the region between 1600 and 1700 cm^{-1}, namely at *ca.* 1670 and 1620 cm^{-1}, respectively. The absence of an additional strong absorption at *ca.* 1695 cm^{-1} indicates a preponderance of the *s-trans* rotational isomer, since the *s-cis* is designated [11] to show absorption at 1690–1700 cm^{-1}. This was not the case for the α,β-unsaturated ketones *7*, *8* and *9* which all showed two carbonyl absorption bands at *ca.* 1695 and 1670 cm^{-1} and one common olefinic band at *ca.* 1620 cm^{-1}. The α,β-unsaturated ketones *7*, *8* and *9* were all found to be exclusively the *trans* olefinic isomers (IR: doublet at *ca.* 1000 and 980 cm^{-1}; ^1H NMR: *J* 16 Hz), whereas a definite quantification of the relation between *cis*- and *trans*-olefinic isomers for the α,β-unsaturated ketones *10*, *11* and *12* is complicated due to overlap of the olefinic protons and the phenylic protons in the ^1H NMR spectra of these ketones. The ^1H NMR spectra of *10*, *11* and *12* show typical ABX_2 patterns, and the only information which is obtainable without a computer action is J_{AB}, which was found in all three cases to be 16 Hz.

The overall result reveals a regiocontrolled transformation of the enaminones *1*, *2* and *3*, which were all assigned to be the *cis-s-trans* conformers,[12a] to the *trans*-olefinic α,β-unsaturated ketones *7*, *8* and *9* whereas the enaminones *4*, *5* and *6*, which were all assigned [12b] to be the *trans-s-trans* conformers, were predominantely transformed to the *trans*-olefinic α,β-unsatuted ketones *10*, *11* and *12*.

EXPERIMENTAL

The IR spectra were obtained on neat samples of liquid film or crystals suspended in paraffin, using a Perkin Elmer 257 spectrometer. The ^1H NMR spectra were recorded on a JEOL C60-HL spectrometer on neat samples, and the ^{13}C NMR spectra were recorded on a JEOL PFT-60 HL spectrometer on neat samples using a deuterium oxide capillary, the temperature being *ca.* 25°C. GC-MS: an LKB 9000 mass spectrometer, equipped with a PYE M 64 gas chromatograph with a 1 % OV-17 on Chromosorb W-AW 60-80 mesh column (1.5 m, 4 mm i.d., glass) was used. Enamines were prepared according to reported methods,[13,14] and the enaminones were prepared by acylation of the methyl alkyl ketone enamines with benzoyl chloride,[12b] isobutyryl chloride or cyclohexanoyl chloride.[12a] Benzoyl and isobutyryl chloride were commercially obtainable, whereas cyclohexanoyl chloride was obtained from cyclohexanecarboxylic acid and thionyl chloride according to known methods.[15]

Preparation of α,β-unsaturated ketones – general procedure, To 0.1 mol of the enaminone dissolved in 50 ml of isopropanol, in a 250 ml three-necked flask (equipped with a Hershberg stirrer, reflux condenser and a dropping funnel), was added with stirring 0.1 mol (11.5 g) of trifluoroacetic acid dissolved in 20 ml of isopropanol. The reaction flask was externally cooled in an ice-water bath. Stirring was continued for an additional 15 min. To the stirred solution was added in small portions a slurry of the fine-powdered 0.05 mol (1.9 g) of sodium borohydride suspended in 50 ml of isopropanol over a period of 10 min, the ice-water bath was removed and the reaction mixture was stirred for an additional 4 h (or overnight) at room temperature. The colourless to pale yellow mixture was freed from solvent on an evaporating dish, and the remaining oily residue was treated with 20 ml of 5 % NaOH solution and extracted with 3 × 20 ml of ether. The ether layers were combined, washed with water and dried with anhydrous Na_2SO_4. Removal of the ether and fractionated distillation afforded the α,β-unsaturated ketones in yields of 60-80 %. The α,β-unsaturated ketones *7* and *8* exhibited an intensive fruity odour.

2,7-Dimethyl-4-octen-3-one, 7. Yield: 65 %, b.p. 83–85 °C/ 10 mmHg. ^1H NMR (60 MHz, neat): δ 0.90 (6 H, d), 1.05 (6 H, d), 1.7 (1 H, m), 2.1 (2 H, t, *J* 8 Hz), 2.85 (1 H, sept), 6.2 (1 H, d, *J* 16 Hz), 6.9 (1H,ABX_2,J_{BX} 8 Hz,J_{AB} 16 Hz). (Note: The spectrum is "nearly" first order AMX).

2,7,7-Trimethyl-4-octen-3-one, 8. Yield: 57 %, b.p. 40 °C/0.1 mmHg. ^1H NMR (60 MHz,neat): δ 0.96 (9 H, s), 1.1 (6 H, d), 2.1 (2 H, d,J 8 Hz), 2.9 (1 H, sept), 6.2 (1 H, ABX_2, J_{BX} 8 Hz, J_{AB} 16 Hz).
(Note: The spectrum is "nearly" first order AMX).

1-Cyclohexyl-5,5-dimethyl-2-hexen-1-one, 9.
Yield: 75%, b.p. 132–134 °C/9 mmHg. ^1H NMR (60 MHz,neat): δ 0.95 (9H,s), 1.8-1.0 (11H,m), 2.1 (2H,d, *J* 8 Hz), 6.1 (1H,d, *J* 16 Hz), 6.8 (1H,ABX_2, J_{BX} 8 Hz, J_{AB} 16 Hz).
(Note: The spectrum is "nearly" first order AMX).

1-Phenyl-2-hexen-1-one, 10. Yield: 70 %, b.p. 78–79 °C/0.1 mmHg. ^{1}H NMR (60 MHz,neat): δ 0.9 (3H,t), 1.4 (2H,m), 2.1 (2H,m), 8.2–7.9, 7.5–7.25, 7.1–6.9 (m, total 7H, J_{AB} 16 Hz).

5-Methyl-1-phenyl-2-hexen-1-one, 11. Yield: 56 %, b.p. 80 °C/0.1 mmHg. ^{1}H NMR (60 MHz,neat): δ 0.9 (6H,d), 1.7 (1H,sept), 2.1 (2H,m), 8.1–7.8, 7.5–7.3, 7.1–6.9 (m, total 7H, J_{AB} 16 Hz).

5,5-Dimethyl-1-phenyl-2-hexen-1-one, 12. Yield: 82 %, b.p. 81–82 °C/0.08 mmHg. ^{1}H NMR (60 MHz,neat): δ 0.90 (9H,s), 2.1 (2H,d), 8.2–8.0, 7.55–7.35, 7.15–7.0 (m, total 7H, J_{AB} 16 Hz).

Note to all α,β-unsaturated ketones formed: The IR, ^{13}C NMR and mass spectra were in accordance with proposed structures.

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

REFERENCES

1. Greenhill, J. V. *Chem. Soc. Rev. 6* (1977) 277.
2. Walker, G. N. *J. Org. Chem. 27* (1962) 4227.
3. Baker, R. H. and Schlesinger, A. H. *J. Am. Chem. Soc. 68* (1946) 2009.
4. Martin, J. C., Barton, K. R., Gott, P. G. and Meen, R. H. *J. Org. Chem. 31* (1966) 943.
5. Borch, R. F., Bernstein, M. D. and Durst, H. D. *J. Am. Chem. Soc. 93* (1971) 2897.
6. Nilsson, L., Carlson, R. and Rappe, C. *Acta Chem. Scand. B 30* (1976) 271.
7. House, H. O. *Modern Synthetic Reactions*, Benjamin Menlo Park, California 1972, 2nd Ed., pp 91–94 and references therein.
8. *Organikum*, 15 Aufl., VEB Deutscher Verlag der Wissenschaften, Berlin 1977, p. 616.
9. Ogata, Y., Kawasaki, A. and Kishi, I. *J. Chem. Soc. B* (1968) 703.
10. Tramontini, M. *Synthesis* (1973) 703 and references therein.
11. Dimmock, J. R., Carter, P. L. and Ralph, P. D. *J. Chem. Soc. B* (1968) 698.
12. a. Nilsson, L. *Acta Chem. Scand. B 33* (1979). *In press*:; b. Nilsson, L. *Acta Chem. Scand. B 33* (1979) 203.
13. White, W. A. and Weingarten, H. *J. Org. Chem. 32* (1967) 213.
14. Carlson, R., Phan-Tan-Luu, R., Mathieu, D., Ahouande, F. S., Babadjamian, A. and Metzger, J. *Acta Chem. Scand. B 32* (1978) 452.
15. *Organikum* 15 Aufl., VEB Deutscher Verlag der Wissenschaften, Berlin 1977, p. 529.

Received May 8, 1979.