Acta Chemica Scandinavica B 39 (1985) 187–190

Formic Acid Reduction of Enamines. Scope of the Reaction

ÅSA NILSSON and ROLF CARLSON

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

The scope of enamine reduction with formic acid has been investigated. The compounds studied include enamines from aldehydes, aliphatic ketones, aryl alkyl ketones and functionalized ketones. The procedure is simple and allows the reaction to be conducted without solvent. The method gives short reaction times and generally good yields of saturated amines.

Formic acid can be used as a reducing agent for enamines, and the reaction has been studied in detail with heterocyclic enamines and with enamines from aldehydes.[1] With other types of enamines the literature on formic acid reduction is rather meager and does not allow any conslusions on the general scope of the reaction to be drawn. It has been stated that enamines derived from bridged bicyclic ketones, e.g. norcamphor, are not readily reduced by formic acid.[2] However, we have found that enamines obtained from camphor are rapidly reduced by formic acid to give excellent yield of saturated bornylamines.[3] These results which are in disagrement with those results reported in Ref. 2, prompted us to study the general scope of the formic acid reduction of enamines.

The enamines studied were derived from aliphatic ketones, aryl alkyl ketones and functionalized ketones. The test substrates were selected to allow for a variation in steric hindrance as well as in electronic effects that might influence the reaction. The other groups in the functionalized ketones were selected with regard to the chemoselectivity of the reduction.

RESULTS

The results summarized in Tables 1–3 show the isolated yields of saturated amines obtained by formic acid reduction of different types of enamines.

To check the material balance of the reaction two substrates *11* and *12* (See Table 2), were studied. When the reaction was ready (CO_2-evolution ceased), water was added to hydrolyse the remaining enamine. The parent ketone and the saturated amine were isolated. The amounts correspond to a recovery of 90–96 % of the initial amount of enamine.

The reduction was also carried out on 1-methylpiperazine enamine from deoxybenzoin. The yield of amine was only 24 % (72 % of the deoxybenzoin was recovered).

DISCUSSION

Enamines are ambident bases and can be protonated either on the nitrogen to give an enammonium ion or on the β-carbon to give an iminium ion.[1]

0302-4369/85 $2.50

Table 1. Yield and physical properties of amines obtained by reduction of enamines from aliphatic carbonyl compounds.

Enamine (A)		Saturated amine (B) Yield[a] %	B.p. °C/mmHg	^{1}H NMR[b]	MS[c]
1	1-(4-morpholinyl)-cyclohexene	85	100–101/10	2.12–2.25 (m)	169(16), 126(100)
2	2-(4-morpholinyl)-3,3-dimethylbutene	70	95–97/10	2.12 (q, J=7Hz)	171(1), 156(5), 114(100)
3	4-(4-morpholinyl)-2,6-dimethylhept-3-ene	74	106–107/10	2.46–2.49 (m)[d]	213(4), 156(100)
4	2-(4-morpholinyl)-3-methylbutene[e]	80	65–66/10	2.03–2.09 (p)	157(5), 142(6), 114(100)
5	2-(4-morpholinyl)-4-methylpent-1-ene[e]	75	81–82/10	2.56–2.63 (m)[d]	171(4), 156(9), 114(100)
6	1-(1-pyrrolidinyl)-cyclohexene	86	95–97/10	1.90–2.04 (m)[d]	153(11), 110(100)
7	1-(1-pyrrolidinyl)-2-methylpropene	71	84–86/120	2.21 (d, J=7.3 Hz)	127(8), 84(100)

[a] Yield of isolated distilled products. [b] ^{1}H NMR signal from RRCH-NR_2. [c] m/z (relative abundance). [d] Partially hidden by the amine signal. [e] Equilibrium mixture of both regio-isomers.

Table 2. Yield and physical properties of amines obtained by reduction of enamines from aryl-alkyl ketones.

Enamine (A)		Saturated amine (B) Yield[a] %	B.p. (m.p.) °C/mmHg	^{1}H NMR[b]	MS[c]
8	1-(4-morpholinyl)-1-phenylethene	63	76–78/0.05	3.40 (q, J=7.5Hz)	191(13), 176(100), 105(69)
9	1-(4-morpholinyl-1-phenyl-2-methylpropene	85	99–100/0.1	2.99 (d, J=8Hz)	219(0.6), 176(100)
10	1-(4-morpholinyl)-1-(4-nitrophenyl)-ethene	56	(46–47)	3.42 (q, J=6.6Hz)	236(11), 221(100), 150(28)
11	1-(4-morpholinyl)-1-(4-methoxyphenyl)-ethene	70	104–105/0.01	3.27 (q, J=6.7Hz)	221(19), 206(65), 135(100)
12	1-(1-pyrropidinyl)-1-phenylethene	52	62–64/0.08	3.17 (q, J=6.6Hz)	175(13), 160(100), 98(47)
13	1-(1-pyrrolidinyl)-1-phenyl-2-methylpropene	88	94–95/0.005	2.99 (d, J=5.2Hz)	203(0.4), 160(100), 91(24)

[a] Yield of isolated products. [b] ^{1}H NMR signal from RRCH-NR_2. [c] *m/z* (relative abundance).

Table 3. Yield and physical properties of amines obtained by reduction of enamines from functionalized ketones.

Enamine (A)		Saturated amine (B) Yield[a] %	B.p. (m.p.) °C/mmHg	^{1}H NMR[b]	MS[c]
14	2-(4-morpholinyl)-1,5-hexadiene[d]	65	90–91/10	3.39–3.52 (m)	154(12), 114(100)
15	4-(4-morpholinyl)-3,3-dimethylpent-4-ene-2-one	35	71–72/0.005 (dec.)	2.87 (q, J=7Hz)	114(100)
16	*2H*-1-Thia-4-(4-morpholinyl)-napthalene	78	(83.5–85)	3.55 (dd, J=7.7Hz, J=2.3Hz)	235(51), 149(100)
17	2-(4-morpholinyl-1-pentenoicacid methylester[d]	43	[e]	2.31–2.41 (m)[f]	201(5), 114(100)
18	1-(4-morpholinyl)-2-(2-cyanoethyl)-cyclohexene[d]	83[g]	120–122/0.2	2.36 (m)[f]	222(12), 182(45),[h] 126(100)
19	1-acetyl-4-(4-morpholinyl)-azacyclohex-3-ene	54	[e]	2.24–2.37 (m)	212(11), 169(35), 126(100)

[a] Isolated yield. [b] ^{1}H NMR signal from RRCH-NR_2. [c] *m/z* (relative abundance). [d] Equilibrium mixture of both regio-isomers. [e] See experimental section. [f] Partially hidden by the morpholine signal. [g] Mixture of *cis*- and *trans*-product. [h] Identical mass spectrum for both *cis*- and *trans*-product.

Competition between N and C protonation of the enamine may explain the presence of parent ketone in the hydrolysed reaction mixture and that a complete transformation to the iminium ion does not occur under these reaction conditions. This is also supported by the observation that the reduction of the 1-methyl-piperazine enamine from deoxybenzoin gave only 24 % of the saturated amine and 72 % of parent carbonyl compound. In this case, the enamine has two basic nitrogen sites which can compete with the carbon protonation.

When dissymmetric ketones are transformed to enamines, mixtures of regio-isomeric enamines are usually formed. The reduction of substrates *4,5,14,17* and *18* (Tables 1 and 3) was actually performed on the equilibrium mixture of enamine tautomers. In view of the reaction mechanism, this does not matter since the iminium ion is formed by protonation of either isomer.

Conclusions. The results reported in this paper show that the scope of formic acid reduction of enamines is general. It can be applied to enamines obtained from aliphatic ketones and aryl alkyl ketones. Substrates containing functional groups which are reduced by hydride reagents, as well as substrates that poison the catalyst or are reduced by catalytic hydrogenation can also be reduced by this method.

EXPERIMENTAL

General techniques. GLC-analyses; A PYE M 64 Gas chromatograph with FID was used with 6 % QF 1 (2.1 m, 2 mm ID) on Chromosorb W AW DMC (100–120 mesh) glass columns. *^{1}H NMR*: Spectra were recorded on a Bruker WM-250, and chemical shifts were

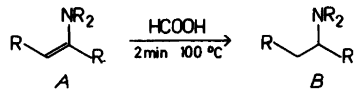

Fig. 1.

measured at 25 °C using TMS as internal reference. *GLC-MS*: Spectra were recorded on a Finnigan 4500 with INCOS data system (EI, 70 eV).

Chemicals: All enamines were obtained by a modified titanium tetrachloride procedure.[4] Formic acid, *puriss* 98 % from Riedel de Haen was used.

Reduction of enamines:[3] A 100 ml Erlenmeyer flask equipped with a Liebig condenser and a magnetic stirrer was charged with 50 mmol of enamine and heated to 100 °C. Formic acid 98 %, (2.0 ml, 52 mmol) was added dropwise through the condenser at such a rate that the resulting foaming could be kept under control. When carbon dioxide evolution ceased (*ca* 2 min), 50 ml of water and 5 ml of concentrated HCl were added. After 0.5 h, the mixture was cooled and washed with ether. The aqueous layer was made alkaline with 5 M NaOH, extracted with ether and dried (KOH) over night. After removal of solvent, the crude product was distilled under reduced pressure. Some amines decompose during distillation (see Table 1–3). Amine *17* and *19* was purified by flash chromatography.[5] Potassium carbonate was added to the reaction mixture after the carbon dioxide evolution ceased. Ethyl acetate (5 ml) was added and the solution was purified by flash chromatography on Silica-60. EtOAc/hexane was used as eluent for amine *17* and ethanol for amine *19*.

Acknowledgement. Financial support from the Swedish Natural Science Research Council, the National Swedish Board for Technical Development and from *Stiftelsen Bengt Lundqvists Minne* is gratefully acknowledged. The authors are indebted to Doc. Robert E. Carter for linguistic revision.

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Received June 6, 1984.