Acta Chemica Scandinavica B 38 (1984) 523–531

Short Communications

Enamine Synthesis from Functionalized Carbonyl Compounds

ÅSA NILSSON and ROLF CARLSON

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

Over the years a number of methods for enamine preparation have been presented.[1] Even though many of these methods are likely to be useful in enamine synthesis from functionalized carbonyl compounds such examples are, however rarely found in the literature.

In our study of enamine reactions we needed enamines with different functional groups present. We have earlier reported an improved titanium tetrachloride procedure for enamine formation.[2] In this procedure the carbonyl compound is added to a preformed complex between amine and titanium tetrachloride. The method is general for enamine formation from different types of nonfunctionalized carbonyl compounds *viz.* cyclic and acyclic ketones, aryl alkyl ketones as well as aldehydes.[2,3]

We here report that the titanium tetrachloride procedure can be used to prepare enamines from ketones functionalized with various groups *viz.* cyano, ester, allyl, carboxamine, thioether or ketone.

Results. The results given in Table 1 show isolated yields of enamines from functionalized ketones.

The crude yields before purification were in all cases >90 %. The purity was >95 % and the enamine products can be used in subsequent synthetic manipulations without purification. There are considerable losses due to decomposition during purification by distillation and the yields given in Table 1 are lower than the crude yields.

The enamine from acetoacetanilide (VI) is obtained in poor isolated yield. The main reason for this is that the product is only slightly soluble in hydrocarbon solvents. Extraction of the precipitated TiO_2 with a more polar solvent also dissolves the unreacted titanium-amine complex and this interfere with the enamine product.

Conclusion. The modified titanium tetrachloride procedure for enamine synthesis which is of general scope when applied to aldehydes, cyclic and acyclic aliphatic ketones and aryl alkyl ketones[2,3] can now be extended to include enamine synthesis from functionalized ketones as well.

Spectral data of the enamines. The ^1H NMR spectra are all in accordance with the expected

Table 1. Morpholine enamines from functionalized carbonyl compounds.

Enamine	Yield %[a]	Reaction time min	Reaction temp. °C	Solvent
1	83	60	r.t.[b]	Benzene
2	70	15	reflux	Pentane
3	46	60	50	Benzene
4	49	5	reflux	Hexane
5	68	10	reflux	Hexane
6	29	45	0	Hexane
7	74	15	reflux	Light petroleum (30–50 °C)

[a] Isolated yields of purified products. [b] r.t.=room temperature (20 °C).

0302-4369/84 $2.50

spectra. For brevity, only chemical shifts for the vinylic protons are given below.

Morpholine enamine from thiochroman-4-one (I); ^{1}H NMR (250 MHz, benzene): δ 5.31 (1H, t, J=5.7 Hz). MS *m/e* (relative abundance) ⟨assignment⟩: 233 (94) ⟨M^+⟩ and 147 (100) ⟨M^+-morpholino⟩. IR (KBr) (cm^{-1}): 1630 ($\nu_{C=C-N}$).

Morpholine enamine from 2-oxa-1-cyclohexanepropionitrile (II): ^{1}H NMR (250 MHz, $CDCl_3$): Two regioisomers are formed, trisubstituted isomer (50 %), δ 4.84 (1H, t, J=4.0 Hz). MS *m/e* (relative abundance) ⟨assignment⟩: Tetrasubstituted isomer, 220 (10.8) ⟨M^+⟩ and 180 (100) ⟨M^+-CH_2CN⟩. Trisubstituted isomer 220 (36.3) ⟨M^+⟩, 180 (80.7) ⟨M^+-CH_2CN⟩ and 167 (100) ⟨$M^+-CH_2CH_2CN$⟩. IR (neat) (cm^{-1}) 2250 ($\nu_{C\equiv N}$), 1650 and 1665 ($\nu_{C=C-N}$).

Morpholine enamine from N-acetyl-4-piperidone (III): ^{1}H NMR (250 MHz, $CDCl_3$): Two isomers are detected due to *syn/anti* configuration of the amide group, ratio 50/50, δ 4.63 (1H, t, J=3.9 Hz) respectively 4.54 (1 H, t, J=3.9 Hz). MS *m/e* (relative abundance) ⟨assignment⟩: 210 (96.4) ⟨M^+⟩ and 167 (100) ⟨M^+−acetyl⟩. IR (neat) (cm^{-1}): 1640−1679 ($\nu_{C=O}$).

Morpholine enamine from levulinic acid methylester (IV): ^{1}H NMR (250 MHz, $CDCl_3$): Two regioisomers are formed, the major product (68 %), is the enamine isomer with the non-terminal double bond, δ 4.55 (1H, t, J=7.1 Hz). The minor product (32 %), is the isomer with the terminal double bond, δ 3.96 (1H, s) and 3.88 (1H, s). MS *m/e* (relative abundance) ⟨assignment⟩: 199 (19.3) ⟨M^+⟩, 140 (100) ⟨M^+−COOMe⟩ and 125 (28.9) ⟨M^+-CH_2COOMe⟩. The isomer mixture was not separated by GLC. IR (neat) (cm^{-1}): 1740 ($\nu_{C=O}$), 1650 ($\nu_{C=C-N}$).

Morpholine enamine from 3,3-dimethyl-2,4-pentandione (V): ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.22 (1H, d, J=1.2 Hz) and 4.40 (1H, d, J=1.2 Hz). MS *m/e* (relative abundance) ⟨assignment⟩: 197 (20.4) ⟨M^+⟩ and 154 (100) ⟨M^+-acetyl⟩. IR (KBr) (cm^{-1}): 1710 ($\nu_{C=O}$), 1605 ($\nu_{C=C-N}$).

Morpholine enamine from acetoacetanilide (VI): ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.80 (1H, s). MS *m/e* (relative abundance) ⟨assignment⟩: 210 (96.4) ⟨M^+⟩ and 167 (100) ⟨M^+−acetyl⟩. IR (KBr) (cm^{-1}): 1600−1650 (three absorptions bands, $\nu_{C=C-C=O}$).[4]

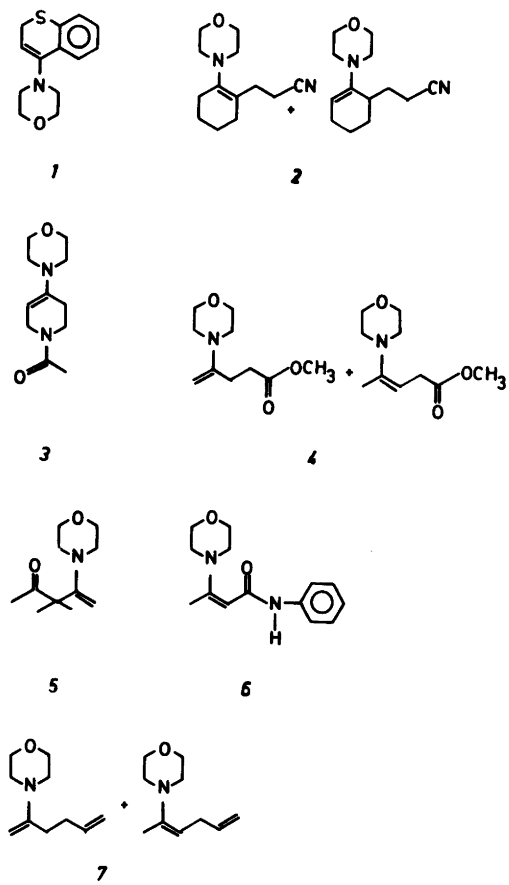
Morpholine enamine from allylacetone (VII): ^{1}H NMR (250 MHz, $CDCl_3$): Two regioisomers are formed, the major product (67 %), is the enamine isomer with the non-terminal double bond, δ 4.43 (1 H, t, J=7.2 Hz). The minor product (33 %), is the isomer with the terminal double bond (33 %), δ 3.85 (1 H, s) and 3.94 (1 H, s). MS *m/e* (relative abundance) ⟨assignment⟩: 167 (71.7) ⟨M^+⟩ and 126 (100) ⟨$M^+-CH_2CH=CH_2$⟩. Isomer mixture was not separated by GC. *IR* (neat) (cm^{-1}): 3110 and 3070 ($\nu_{CH=C-N}$), 3080 ($\nu_{CH_2=CH-R}$), 1655, 1640 and 1610 ($\nu_{C=C-N}$), 1645 ($\nu_{R-CH=CH}$).

Experimental. GLC analyses. A PYE UNICAM GCD with FID was used with 6 % QF 1 (2.1 m, 2 mm ID) on Chromosorb W AW DMCS (100−120 mesh) glass columns.

^{1}H NMR. Spectra were recorded on a Bruker WM-250 or on a JEOL C-60 HL. Chemical shifts were measured at 26 °C using TMS as internal reference.

GLC-MS. Analyses were performed on a Finnigan 4500 quadropole instrument equipped with an INCOS data system. Electron impact, 70 eV, was used for ionization and a 25 m BP-5 fused silica capillary column was used for sample introduction *via* the GLC−MS inlet system.

IR. Spectra were recorded on a Perkin Elmer 681 infrared spectrophotometer.



Chemicals. 3,3-dimethyl-2,4-pentanedione was prepared by a published method.[5] The other ketones were commercial *puriss* or *p.a.* products. Morpholine and titanium tetrachloride were technical grade and were used without purification.

Solvents. Pentane, hexane and petroleum ether of technical grade were dried over $CaCl_2$ and benzene *puriss* was distilled prior to use.

General procedure for enamine synthesis. A 250 ml three-necked flask equipped with a dropping funnel, reflux condenser and a stirrer (Hershberg) was purged with dry nitrogen prior to use and protected from moisture. The reaction flask was charged with morpholine 5.22 g (60 mmol) and about 80 ml of solvent according to Table 1. $TiCl_4$ 1 ml (9 mmol) was dissolved in about 10 ml of solvent and added dropwise to the cold (0 °C) amine solution. After the addition was complete 10 mmol of the carbonyl compound was added in one portion. The reaction was allowed to proceede at the temperature and for the time given in Table 1. After cooling, the reaction mixture was filtered through a sintered glass filter (pore size 3) and the solvent was removed under reduced pressure.[a] The crude product was freed from solvent and unreacted amine by prolonged evaporation at 0.1 mmHg. *Note:* [a] A different purification procedure was used for enamine VI, see below.

Isolation of the products. Enamine I. Yield of crude product, 2.28 g (98 %) m.p. 84–89 °C, purity 95 % (GLC, NMR). Recrystallisation from hexane, yield 1.93 g, 83 %, m.p. 90–91 °C.

Enamine II. Distillation at reduced pressure, yield 1.54 g (70 %), b.p. 125–130 °C/0.01 mmHg.

Enamine III. The purity of the crude product (GLC) was 95 %, yield 2.0 g (95 %). Distillation at reduced presure yielded 0.98 g (46 %), b.p. 149–153 °C/0.01 mmHg. The product decomposes during distillation.

Enamine IV. Yield of crude product 1.91 g (96 %), purity 95 % (GLC). Distillation of the product yielded 0.98 g (49 %), b.p. 86–88 °C/ 0.01 mmHg. The product decomposes on distillation.

Enamine V. Yield 1.74 g (88 %), purity 95 % (NMR). Distillation gave 1.34 g (68 %), b.p. 140–145 °C/2 mmHg, m.p. 37.5–38.5 °C.

Enamine VI. The reaction mixture was filtered and the precipitate was washed several times with methylene chloride (the solution turns red). The combined hexane and methylene chloride solutions were treated with 2 ml of dry acetone to remove dissolved $TiCl_4$-amine complex, filtered through a sintered glass filter (pore size 4), yield 2.4 g (97 %) of a yellow product. Recrystallization from benzene, yield 0.70 g (29 %), m.p. 166–167 °C (decomposes).

Enamine VII. Distillation at reduced pressure yielded 1.24 g (74 %) b.p. 93–94 °C/10 mmHg.

Acknowledgements. 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.

1. Cook, A. G. *Enamines: Synthesis, Structure and Reactions,* Dekker, New York 1969.
2. Carlson, R., Nilsson, Å. and Strömqvist, M. *Acta Chem. Scand. B 37* (1983) 7.
3. Carlson, R. and Nilsson, Å. *Acta Chem. Scand. B 38* (1984) 49.
4. Greenhill, J. V. *Chem. Soc. Rev. 6* (1977) 277.
5. Perfetti, B. M. and Levine, R. *J. Am. Chem. Soc. 75* (1953) 626.

Received April 5, 1984.