

# Acylation of Enamines. Regiospecific Transformation of Unsymmetrical Methyl Ketones to 1,3-Diketones via Benzoylation of Enamines

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The morpholine enamines obtained from methyl alkyl ketones (alkyl = propyl, isopropyl, isobutyl, neopentyl, 2-phenylethyl and cyclopropyl) and the dimethylamine enamine obtained from methyl isopropyl ketone were readily converted to 1,3-diketones by condensation with benzoyl chloride in hydrocarbon solvent under conditions leading to regiospecific reactions. A great difference in reactivity between enamine isomers was found. The structures of intermediates are discussed and directions for synthetic procedures are given.

(1-isomer). This method initiated the investigation of regiospecific functionalization of methyl alkyl ketones *via* the corresponding enamine. It was also found that, in some instances, it was possible to separate isomeric mixtures by means of regioselective protonation,<sup>11</sup> which shows a difference in reactivity between the two isomers.

## RESULTS AND DISCUSSION

1,3-Dicarbonyl compounds serve as key intermediates in organic synthesis. Numerous methods for synthesizing these compounds are available.<sup>1–3</sup> One which employs the acylation of enamines has been investigated by several authors.<sup>4</sup> These studies were performed on enamines derived from cyclic ketones, symmetrical alkyl ketones and aldehydes. Methyl ketone enamines were long considered to be unstable and susceptible to self-condensation reactions.<sup>5–8</sup> Some years ago a method was reported for preparing these enamines in synthetic amounts, using titanium tetrachloride as water scavenger and catalyst.<sup>9</sup> In most cases unsymmetrical methyl ketones having  $\alpha$  and  $\alpha'$  hydrogens give rise to isomeric enamines,<sup>9</sup> although in a few cases it has been possible to obtain the kinetically controlled isomer as the main product.<sup>9,10</sup>

In order to evaluate the possibility of regiospecific functionalization of morpholine enamines derived from methyl alkyl ketones a preliminary study was undertaken, using benzoyl chloride and the morpholine enamine obtained from methyl isobutyl ketone (I). This enamine has a 1-isomer/2-isomer distribution of 1:1 at equilibrium in a hydrocarbon solvent.<sup>12</sup> Chloroform proposed in a previous report on the acylation of cyclic ketone enamines as being more suitable,<sup>13</sup> was replaced by hexane. The reason for changing the solvent was that the protonation-deprotonation sequence did not yield pure 1-isomer in chloroform at temperatures  $\geq 0^\circ\text{C}$ , probably owing to rapid isomerization<sup>11,12</sup> (Fig. 1). This observation may be attributed to the fact that the intermediate immonium salt is completely soluble in chloroform whereas it precipitates in hexane. Benzoyl chloride was selected as being suitably sterically hindered and moderately aggressive in its action as an electrophile.

The acylation reactions of enamines are considered to yield primarily an acylated

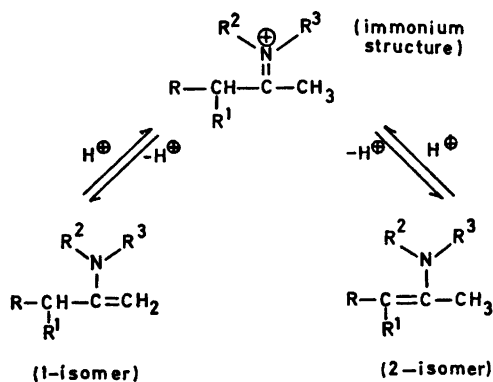


Fig. 1. Isomerization of enamines via the immonium structure.

immonium salt, which deprotonates very easily to the more stable enaminone <sup>4,13</sup> (Fig. 2). This necessitates the use of an auxiliary base, triethylamine, so as to prevent half the amount of enamine from acting as a base and thus being deprived of its ability to take part in the acylation reaction. Enaminones have  $pK_a$  values reported to lie in the range of 2.8–3.1.<sup>14</sup> Acylation of enamines can take place at the  $\beta$ -carbon or at the nitrogen atom. *N*-Acylated

compounds are either not stable, or acylating agents, so that products arising from *C*-acylation are normally obtained.

The morpholine enamine (1) exhibited quantitative transformation of the least substituted isomer to the enaminone (7). The <sup>1</sup>H NMR, IR and mass spectra were consistent with the proposed general structure of enaminones (see experimental section). It seems plausible to assume that, of the four possible conformers (Fig. 3), the *trans-s-trans* is the major one. This assumption is supported by the IR spectral data, which show absorption at 1620  $cm^{-1}$ . *trans-s-trans* conformers are reported to show absorption<sup>18</sup> at 1600–1630  $cm^{-1}$ , *cis-s-trans* at ca. 1640  $cm^{-1}$ , *trans-s-cis* at ca. 1655  $cm^{-1}$  and *cis-s-cis* at 1580–1600  $cm^{-1}$ .

There are two possible positions at which a second acylation can take place, either at the oxygen atom (forming an enol ester), or at the  $\beta$ -carbon (yielding a triketone after hydrolysis). When the second acylation occurred – as could be detected by <sup>1</sup>H NMR (vinylic peak at lower field than the enaminone –C=CH–) and by GLC-MS (molecular ion, proper fragments) – it obviously took place solely at the oxygen atom since this diacylated product

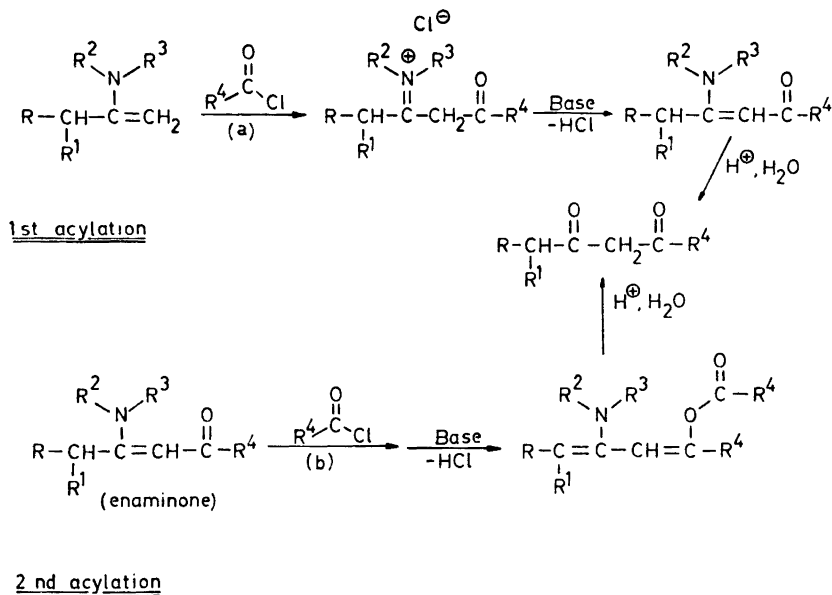


Fig. 2. Reaction between enamine and acid chloride (1st acylation) and reaction between enaminone and acid chloride (2nd acylation). (a) *N*-Acylated compound not stable, or acylating agent. (b) Second acylation generally on oxygen, see Ref. 4.

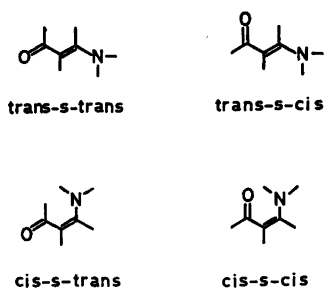


Fig. 3. Possible conformers of enaminones.

as well as the monoacylated one were readily hydrolysed by HCl solution to yield the 1,3-diketone. No triketone products were found. The observed course of the second acylation is in agreement with previous reports on cyclic ketone enamines.<sup>4</sup> Formation of diacylated products could mostly be avoided by careful dosage and by dropwise addition of the acid chloride to the well-stirred enamine solution. After hydrolysis of the enamionone this regio-specific acylation afforded the diketone (13) in 91 % yield.

The investigation was extended with two methyl *prim.* alkyl ketone enamines, *viz.* the morpholine enamines of methyl neopentyl ketone (2) and methyl 2-phenylethyl ketone (3), and two methyl *sec.* alkyl ketone enamines, *viz.* the morpholine enamines of methyl isopropyl ketone (4) and methyl cyclopropyl ketone (5). Of these enamines, 1, 3 and 4 give rise to structural isomers; 2 and 5, as previously reported by us,<sup>12</sup> seem to exist only as the least substituted isomers (1-isomer). In none of the benzoylation reactions was it possible to detect any conversion of isomers from the least substituted to the most substituted, leading after hydrolysis to a product mixture of 1,3-diketones. Isolated yields were found to lie in the range 40–90 %. The 1,3-diketones synthesized in this investigation were found preferentially to exist in the enolic state (<sup>1</sup>H NMR).

The same reaction conditions as used in the regio-specific transformation were used in the attempted selective functionalization of the 1-isomer from an isomeric mixture of enamines. Triethylamine was excluded as auxiliary base, leaving the 2-isomer to serve as base. This,

however, necessitated the use of two equivalents of enamine compared with the acid chloride. In all the cases studied — benzoylation of the morpholine enamines obtained from methyl propyl ketone (6), and the enamines 1, 3 and 4 — selectivity was found to be absolute in the sense that only the 1-isomers reacted and formed 1,3-diketones after hydrolysis. The 2-isomers acted as a base and thereby obviated the use of triethylamine. In contrast to previous reports by us<sup>11</sup> and others,<sup>17</sup> the precipitated salt, after being filtered off and isolated, was found to be exclusively the immonium chloride, and no *N*-protonated species could be detected. This finding can be attributed to the fact that the salt was isolated after refluxing the reaction mixture for 3 h, and any *N*-protonated species formed would have rearranged to the *C*-protonated species. The physical and chemical properties of these immonium chlorides were in agreement with previous reports.<sup>11,12</sup> This opens up a possible alternative to the regio-specific reaction described above. By recycling the enamine, *i.e.* regioselective deprotonation of the immonium chloride to the least substituted isomer and thus continually repeating the procedure, one can obtain the 1,3-diketones in fair yields. Since no special effort is needed in the synthesis of the enamines, besides optimization of the yield, it is possible to exclude one reaction step in order to obtain the diketone. An investigation of factors affecting optimal synthesis of morpholine enamines from methyl ketones was recently reported.<sup>15</sup> The decrease of yield in these isomer selective reactions compared with the regio-specific ones may be attributed to the dual role the 1-isomer has, acting both as base and nucleophile thereby being partially deprived of its ability to react with the acid chloride. Isolated yields were found to be in the range 40–70 %.

In order to evaluate whether this selectivity is applicable to other enamines apart from morpholine enamines, an isomeric mixture at equilibrium (1-isomer/2-isomer, 1:1) of the dimethylamine enamine obtained from methyl isopropyl ketone (8) was employed. This enamine did not react selectively under the reaction conditions sufficient for regioselective protonation and deprotonation of the morpholine enamines to occur.<sup>11</sup> However, when an isomeric mixture of the enamine 8 was

subjected to the action of benzoyl chloride, complete selectivity was found to be present, and the isolated yield of the diketone *11* was 35 %. This observed difference, compared with the protonation case, may be attributed mainly to the increased steric bulk of the electrophile. Estimations of the yield of diketones in all the selective reactions were based on the amount of 1-isomer present in the starting isomeric mixture.

Finally, it should be mentioned that the benzoylation reactions are accompanied by competitive reactions leading to miscellaneous products. The most unstable enamine used in this investigation, *viz.* the morpholine enamine *6*, was found to yield some self-condensation products as detected by  $^1\text{H}$  NMR, where vinylic peaks at  $\delta$  ca. 6.0–5.5 were found, and by GC-MS, which detected mass fragments appropriate to dienamine species. Mass spectral data also indicated that the compound benzoylmorpholine ( $M = 191$ ,  $105(\text{C}_6\text{H}_5\text{CO})$ ,  $86(\text{C}_4\text{H}_8\text{NO})$ ) was present. These self-condensation products were significantly scarcer, or not present at all, in the reactions of the more stable enamines. It must also be mentioned that unbranched methyl alkyl ketone enamines, like enamine *6*, are quite unstable and exhibit self-condensation reactions even when stored in the cold under nitrogen.

## EXPERIMENTAL

The IR spectra were obtained on samples dissolved in deuteriochloroform, using a Perkin Elmer 257 spectrometer. The  $^1\text{H}$  NMR spectra were recorded on a JEOL C60-HL spectrometer, using deuteriochloroform as solvent. Sample concentrations ca. 1 M, recording temperature ca. 25 °C. For the 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. Benzoyl chloride (Merck *zur Synth.*) was used without further purification. Enamines were prepared according to reported methods.<sup>9,15</sup>

**Regiospecific acylation. General procedure.** A 250 ml three-necked flask was fitted with a Hershberg stirrer, a dropping funnel and a drying tube. To an equilibrium mixture of morpholine enamine (0.1 mol) in hexane (50 ml) was added, with vigorous stirring, 11.5 g (0.1 mol) of trifluoroacetic acid over a period of ca. 15 min. The mixture was stirred for an additional 20 min. The temperature must at

all times be kept at 0 °C. *tert*-Butylamine, 8.0 g (0.11 mol), was then introduced as a single addition with vigorous stirring. Stirring was continued for 10 min, after which the precipitated *tert*-butylammonium trifluoroacetate was removed by filtration using a sintered glass funnel. The filtrate was transferred to a 250 ml three-necked flask fitted with a Hershberg stirrer, a dropping funnel, and a reflux condenser equipped with a drying tube. To the filtrate was added 13.2 g (0.13 mol) of triethylamine, and to this reaction mixture was added 15.4 (0.11 mol) of benzoyl chloride in 50 ml of hexane over a period of 30 min. The addition was carried out under external cooling with an ice-water bath. When the addition was complete, the reaction mixture was refluxed for 3 h with continuous stirring. The precipitated triethylammonium hydrochloride was filtered off and washed with  $3 \times 10$  ml of dry ether. Evaporation at reduced pressure of the hexane-ether afforded the enamionone, which was hydrolysed under reflux for 90 min with 30 ml of 6 M HCl. Extraction with dichloromethane, drying with  $\text{Na}_2\text{SO}_4$  and evaporation of solvent, furnished after distillation at reduced pressure, yields of 1,3-diketones in the range 40–90 %.

**Selective acylation of an isomeric mixture.** The acylation procedure was performed with the same equipment and under similar reaction conditions as used in the regiospecific reactions. However, the isomeric mixture was not transferred to the 1-isomer, but the enamine served both as base and reagent. No auxiliary base was used. The following points need to be emphasized: (a) the molar amount of benzoyl chloride added should not exceed the molar amount of the 1-isomer present in the isomeric mixture, (b) the total amount of enamine present must be at least twice the molar amount of benzoyl chloride added, so as to ensure all the added acid chloride the possibility to react, (c) the precipitated immonium salt is hygroscopic and must be protected from moisture; isolation under nitrogen is necessary so as to avoid considerable hydrolysis of the salt.

## Data on compounds formed

**5-Methyl-3-morpholinyl-1-phenyl-2-hexene-1-one (7).** Yield: quantitative.  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.9–7.63 (2 H, m), 7.43–7.17 (3 H, m), 5.8 (1 H, s), 3.83–3.6 (4 H, m), 3.47–3.23 (4 H, m), 3.1 (2 H, d), 1.9 (1 H, m), 1.0 (6 H, d). IR ( $\text{CDCl}_3$ ): 1530 (s), 1572 (m), 1620 (m),  $\text{cm}^{-1}$ . MS (IP 20eV:  $m/e$  (% $^{\text{rel.int.}}$ , fragment)): 273 (38,  $\text{M}^+$ ), 258 (88,  $\text{M}-\text{CH}_3$ ), 230 (62,  $\text{M}-\text{C}_6\text{H}_7$ ), 168 (100,  $\text{M}-\text{C}_6\text{H}_5\text{CO}$ ), 105 (68,  $\text{C}_6\text{H}_5\text{CO}$ ).

**1-Cyclopropyl-3-phenyl-1,3-propanedione (9).** Yield: 49 %, b.p. 126–128 °C/0.8 mmHg.  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.9–7.7 (2 H, m), 7.47–7.27 (3 H, m), 6.23 (1 H, s), 1.8 (1 H, m),

1.33–0.67 (4 H,  $A_2B_2$  pattern), 15.5 (1 H, enolic OH, broad). MS (IP 20 eV:  $m/e$  (% rel.int., fragment)): 188 (63,  $M^+$ ), 173 (13,  $M-CH_3$ ), 160 (100,  $M-C_2H_4$ ), 147 (41,  $M-C_3H_5$ ), 118 (38,  $M-C_4H_6O$ ), 105 (73,  $C_6H_5CO$ ), 77 (11,  $C_6H_5$ ), 69 (73,  $C_6H_5CO$ ), 41 (9,  $C_3H_5$ ).

*1,5-Diphenyl-1,3-pentanedione* (10). Yield: 40 % (regiospecific), b.p. 181 °C/0.8 mmHg. 40 % (selective).  $^1H$  NMR (60 MHz,  $CDCl_3$ ):  $\delta$  7.81–7.5 (2 H, m), 7.38–7.17 (3 H, m), 7.08 (5 H, s), 6.0 (1 H, s), 3.23–2.25 (4 H,  $A_2B_2$  pattern), 15.2 (1 H, enolic OH, broad). MS (IP 20 eV:  $m/e$  (% rel.int., fragment)): 252 (3,  $M^+$ ), 210 (17,  $M-CH_3CO$ ), 209 (100,  $M-CH_3CO$ ), 147 (40,  $M-C_6H_5C_2H_4$ ), 105 (56,  $C_6H_5CO$ ), 91 (3,  $C_6H_5CH$ ), 77 (3,  $C_6H_5$ ).

*4-Methyl-1-phenyl-1,3-pentanedione* (11). Yield: 60 % (regiospecific), b.p. 110–113 °C/1 mmHg. 57 % (selective, morph. enamine) (lit.<sup>2</sup> 186 °C/45 mmHg. 35 % (selective, dimethylam. enamine).  $^1H$  NMR (60 MHz,  $CDCl_3$ ):  $\delta$  7.91–7.68 (2 H, m), 7.45–7.25 (3 H, m), 6.1 (1 H, s), 2.6 (1 H, sept), 1.21 (6 H, d), 15.8 (1 H, enolic OH, broad). MS (IP 20 eV:  $m/e$  (% rel.int., fragment)): 190 (23,  $M^+$ ), 147 (100,  $M-C_3H_7$ ), 105 (23,  $C_6H_5CO$ ), 69 (24,  $C_6H_5CO$ ).

*5,5-Dimethyl-1-phenyl-1,3-hexanedione* (12). Yield: 65 % (regiospecific), b.p. 114 °C/0.5 mmHg.  $^1H$  NMR (60 MHz,  $CDCl_3$ ):  $\delta$  7.86–7.67 (2 H, m), 7.38–7.18 (3 H, m), 6.05 (1 H, s), 2.23 (2 H, s), 1.07 (9 H, s), 16.2 (1 H, enolic OH broad). MS (IP 20 eV:  $m/e$  (% rel.int., fragment)): 218 (15,  $M^+$ ), 203 (6,  $M-CH_3$ ), 163 (10,  $M-C_4H_7$ ), 162 (100,  $M-C_4H_8$ ), 161 ((39,  $M-C_4H_8$ ), 147 (83,  $M-C_5H_{11}$ ), 120 (7,  $M-C_5H_{10}CO$ ), 105 (43,  $C_6H_5CO$ ), 69 (10,  $C_6H_5$ ).

*5-Methyl-1-phenyl-1,3-hexanedione* (13). Yield: 91 % (regiospecific), b.p. 115–117 °C/0.7 mmHg; 67 % (selective) (lit.<sup>2</sup> 110–113 °C/1 mmHg).  $^1H$  NMR (60 MHz,  $CDCl_3$ ):  $\delta$  7.96–7.73 (2 H, m), 7.5–7.3 (3 H, m), 6.13 (1 H, s), 2.26 (2 H, d), 2.17 (1 H, m), 1.15 (6 H, d), 16.2 (1 H, enolic OH, broad). MS (IP 20 eV:  $m/e$  (% rel.int., fragment)): 204 (32,  $M^+$ ), 189 (14,  $M-CH_3$ ), 162 (46,  $M-C_3H_6$ ), 161 (17,  $M-C_3H_7$ ), 147 (100,  $M-C_4H_8$ ), 120 (29,  $M-C_4H_8CO$ ), 105 (61,  $C_6H_5CO$ ), 85 (16,  $C_6H_5CO$ ), 69 (35,  $C_6H_5CO$ ).

*1-Phenyl-1,3-hexanedione* (14). Yield: 55 % (selective), b.p. 88–92 °C/0.5 mmHg (lit.<sup>2</sup> 166–171 °C/20 mmHg).  $^1H$  NMR (60 MHz,  $CDCl_3$ ):  $\delta$  7.88–7.72 (2 H, m), 7.44–7.25 (3 H, m), 6.1 (1 H, s), 2.37 (2 H, t), 1.63 (2 H, sext), 0.95 (3 H, t), 16.0 (1 H, enolic OH, broad). MS (IP 20 eV:  $m/e$  (% rel.int., fragment)): 190 (39,  $M^+$ ), 162 (19,  $M-C_2H_4$ ), 147 (100,  $M-C_3H_5$ ), 120 (16,  $M-C_3H_6CO$ ), 105 (62,  $C_6H_5CO$ ), 71 (19,  $C_6H_7CO$ ), 69 (40,  $C_3H_5CO$ ).

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## REFERENCES

- House, H. O. *Modern Synthetic Reactions*, 2nd Ed., Benjamin, Menlo Park, California 1972, Chapter 11.
- Enders, D. and Weuster, P. *Tetrahedron Lett.* (1978) 2853.
- Beck, A. K., Hoekstra, M. S. and Seebach, D. *Tetrahedron Lett.* (1977) 1187.
- Kuehne, M. E. In Cook, A. G., Ed., *Enamines: Synthesis, Structure and Reactions*, Dekker, N. Y. 1969, pp. 384–393, and references therein.
- Jacquier, R., Petrus, C. and Petrus, F. *Bull. Soc. Chim. Fr.* (1966) 2845.
- Madsen, P. and Laweson, S.-O. *Recl. Trav. Chim. Pays-Bas* 85 (1966) 753.
- Hickmott, P. W., Hopkins, B. J. and Yoxall, C. T. *J. Chem. Soc. B* (1971) 205.
- Bianchetti, G., Croce, P. D. and Pocar, D. *Tetrahedron Lett.* (1965) 2039.
- White, W. A. and Weingarten, H. *J. Org. Chem.* 32 (1967) 213.
- Edlund, U. and Bergson, G. *Acta Chem. Scand.* 25 (1971) 3625.
- Nilsson, L., Carlson, R. and Rappe, C. *Acta Chem. Scand. B* 30 (1976) 271.
- Carlson, R., Nilsson, L., Rappe, C., Babadjamian, A. and Metzger, J. *Acta Chem. Scand. B* 32 (1978) 85.
- Hünig, S., Benzing, E. and Lücke, E. *Chem. Ber.* 90 (1957) 2833.
- Greenhill, J. V. *Chem. Soc. Rev.* 6 (1977) 277.
- Carlson, R., Phan-Tan-Luu, R., Mathieu, D., Ahouande, F. S., Babadjamian, A. and Metzger, J. *Acta Chem. Scand. B* 32 (1978) 452.
- Hünig, S. and Hoch, H. *Fortschr. Chem. Forsch.* 14 (1970) 235.
- Opitz, G. and Griesinger, A. *Justus Liebigs Ann. Chem.* 665 (1963) 101.

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