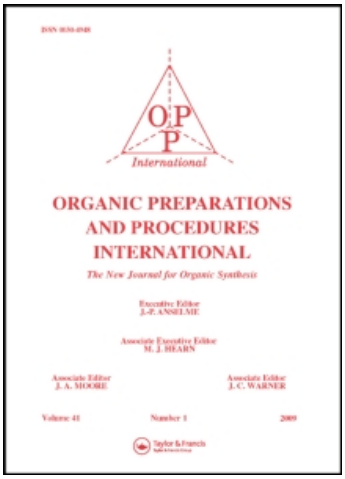

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A FACILE PREPARATION OF *E*-ALKYL ENAMINONES

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A FACILE PREPARATION OF E-ALKYL ENAMINONES

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Enaminones are versatile synthetic intermediates, particularly in the construction of heterocyclic compounds.[1-6] They are also valuable intermediates for the synthesis of α,β-unsaturated ketones by action of organometallic reagents.[7-9] Enaminones of physiologically active amines are attractive synthons for medicinal chemists.[1]

Our investigation of the synthesis of heterocyclic compounds required a large quantity of 4-dialkylamino-3-butene-ones. The desired enaminones can be prepared from acetone using N,N-dimethylformamide dimethylacetal (DMF-acetal), which is however, expensive and the yield is low even with prolonged heating.[10] Other methods such as addition of an amine to an acetylenic moiety,[11] substitution of the chlorine in 2-chlorovinyl ketones by an amine[6,12] and acetylation of aliphatic enamines[13] and palladium assisted amination of methyl vinyl ketone[14] are known in the literature. However, these methods are not considered to be convenient large scale procedures because of the low accessibility of starting materials. We now report that 4,4-dimethoxy-2-butanone,[15] a readily available and less costly starting material, provides a facile preparation of alkyl enaminones in excellent yield.

1 2 3

An important feature of this preparation is that it is remarkably simple to perform. The synthesis proceeds smoothly in refluxing methanol in a short time, and affords the desired enaminone in excellent yield. The reaction is so clean that the quality of the crude enaminone obtained in most cases is suitable for use in the next step without further purification. Vacuum distillation gives a good to excellent yield of pure product.

TABLE 1. Yields and Physical Constants of Enaminones

Entry	R^1	R^2	% Yield[a]	bp (mmHg) (°C)	n_D^{20}
1	C_2H_5	C_2H_5	90.3	143(11)	1.5375[6]
2	CH_3	CH_3	85.7[b]	123(11)	1.5566[6]
3	$-(CH_2)_4-$		80.5	167-168(14)	1.5790
4	$-(CH_2)_5-$		89.2	167(12)	1.5720[6]
5	$-(CH_2)_2O(CH_2)_2-$		83.0	174-175(10)	1.5705[16]
6	$PhCH_2$	CH_3	85.0	205(12)	1.6009
7	Ph	CH_3[c]	14[d]	(e)	
8	Ph	CH_3[f]	60[g]	(e)	
9	H	H	15[h]	71-72(3)[12]	1.5666

(a) Yields of distilled product. These are the average yields of several runs of 1 mole scale with reproducibility of 2-3% (b) The reaction was carried out at room temperature overnight because of the low boiling point of dimethylamine (c) Without CH_3ONa (d) Percentage estimated by proton NMR (e) Isolated by chromatography (f) With one equivalent of CH_3ONa (g) See Experimental Section (h) Excess of anhydrous ammonia was used.

As illustrated by the entries 1-6, this method can be readily extended to various dialkyl and cyclic amines. The reaction is quite dependent upon the nature of the amines. The listed yields obtained are very satisfactory with the use of strong bases. A weak base such as N-methylaniline (entry 7) afforded only 14% of the expected enaminone after overnight reflux in methanol. However, when one equivalent of sodium methoxide was

added, the same reaction gave 60% of the desired product (entry 8). It is suggested that, by action of a base (amine or sodium methoxide), the reaction proceeds by initial formation of vinyl ethers 4, which are converted into enaminones.[17]

$$\underset{1}{CH_3COCH_2CH(OCH_3)_2} + \text{Base} \longrightarrow \underset{4}{CH_3COCH{=}CH{-}OCH_3} \xrightarrow{R'NMR} 3$$

The conversion of 4,4-dimethoxy-2-butanone with anhydrous ammonia was incomplete (entry 9), the low yield with ammonia might be caused by the low concentration of ammonia dissolved in methanol because the reaction was carried out at room temperature.

The most striking finding is that the reaction is stereospecific. Enaminones obtained in all the cases are of E configuration.[18] The temperature has no influence on the composition of the geometric isomers. In fact, the reaction gives only the E isomer at room temperature or at methanol reflux (68°). Proton NMR shows, in all the cases, the large coupling constants J =13 Hz)[12,14] of the two trans vinylic protons. We have no evidence for the presence of the Z isomer in the final reaction mixture.

Thus, widely used E-alkyl enaminones can be prepared in high yield from a commercially available starting material in a one-pot procedure.

EXPERIMENTAL SECTION

Boiling points are uncorrected. All products appeared as single spot on TLC and gave confirmatory NMR and IR spectra and refraction indices. For the new compounds, satisfactory elemental analysis and/or high resolution mass spectra are obtained. We thank the staff of Kodak Industrial Laboratory for analytical assistance.

General Procedure. 4-Diethylamino-3-butene-2-one (Entry 1). - To 132.16 g (1 mol) of 4,4-dimethoxy-2-butanone in 240 mL of methanol was added, under nitrogen, 76.8 g (1.05 mols) of diethylamine. The reaction mixture was heated at reflux for 15 min. Thin layer chromatography ($CHCl_3/CH_3OH$ = 9/1) showed the reaction to be complete; R_f = 0.55 (one spot).

Methanol was removed by distillation and the oily residue was vacuum distilled to yield 127.5 g (90.3%) of pure product, bp 143°/11 mm, lit.[6] bp 125°/6 mm, n_D^{20} 1.5373, lit.[6] 1.5378. IR (film): 1650, 1595, 1555 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.20 (t, 6H, CH_2-CH_3, J=7.2 Hz), 2.10 (s, 3H, CH_3CO), 3.25 (q, 4H, CH_2-CH_3, J=7.2 Hz), 5.13 (d, 1H, H_α, J=13 Hz), 7.53 (d, 1H, H_β, J=13 Hz).

4-Methylphenylamino)-3-butene-2-one (Entry 8). - To 132.16 g (1 mol) of 4,4-dimethoxy-2-butanone in 240 mL of methanol was added, portionwise under nitrogen, 54.1 g (1 mol) of sodium methoxide and 107.2 g (1 mol) of N-methylaniline. The reaction mixture was refluxed overnight. To the cooled mixture was added dichloromethane and a cold aqueous solution of 10% hydrochloric acid. After stirring for 15 min., the organic layer was separated, washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent by distillation gave 131.4 g (75%) of the desired crude enaminone. Proton NMR showed that the crude product was essentially pure. Neither the Z isomer nor other impurities were present. The 4-(methylphenylamino)-3-butene-2-one obtained in this way exhibited spectroscopic data identical with those described in reference 14.

Column chromatography on silica gel of a part of the product gave an analytical sample. The yield based on the starting material was 60% after chromatography.

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