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NEW SYNTHESIS OF β-KETO ACETALS

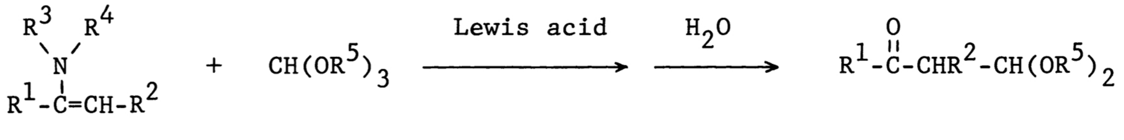
Osamu TAKAZAWA* and Teruaki MUKAIYAMA**
Kawasaki Research Laboratories, T. Hasegawa Co. Ltd.,
335 Kariyado, Nakahara-ku, Kawasaki 211
**Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Enamines derived from ketones or aldehydes react smoothly with trialkyl orthoformates in the presence of Lewis acids to give β-keto acetals in good yields.

In the preceding paper, it was shown that β-keto acetals are obtained by the reaction of silyl enol ethers with trimethyl orthoformate in the presence of $TiCl_4$.$^{1)}$ In the present investigation, we wish to report that enamines, instead of silyl enol ethers, react with trialkyl orthoformates in the presence of Lewis acids to give the corresponding β-keto acetals, useful synthetic intermediates, in good yields.

The typical procedure is described for the reaction of 1-(N-morpholino)-1-cyclohexene with triethyl orthoformate: To a mixture of 1-(N-morpholino)-1-cyclohexene (50 mmol), triethyl orthoformate (65 mmol), and dichloromethane (50 ml) was added $BF_3 \cdot OEt_2$ (65 mmol) at -40 °C under argon atmosphere. Then the reaction mixture was stirred for 1 h at 0 °C. The mixture was quenched with water and stirred for 1 h at room temperature. After hydrolysis, the organic layer was washed with a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was distilled under reduced pressure. The reaction product, 2-diethoxymethylcyclohexanone, was isolated in 85% yield.

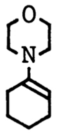
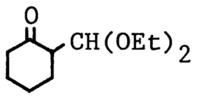
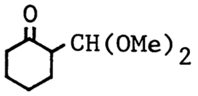
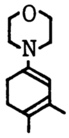
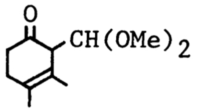
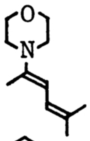
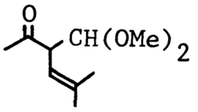
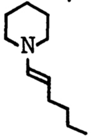
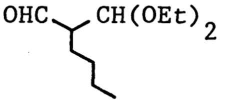
In a similar manner, the reactions of enamines derived from various ketones or aldehydes with trialkyl orthoformates afforded the corresponding β-keto acetals as listed in the table.



$$\underset{R^1\text{-}\overset{|}{C}\text{=CH-}R^2}{\overset{R^3\ \ R^4}{\diagdown N \diagup}} + CH(OR^5)_3 \xrightarrow{\text{Lewis acid}} \xrightarrow{H_2O} R^1\text{-}\overset{\overset{O}{\|}}{C}\text{-CHR}^2\text{-CH(OR}^5)_2$$

It is known that the reaction of enamines with mixed anhydride of formic acid and acetic acid2) or Vilsmeier reagent ($POCl_3$-DMF)3) affords 2-formyl ketones. In comparison with the above methods, the present reaction has an advantage point in exclusive formation of β-keto acetals having the protected formyl and keto groups in the same molecule, by one-step procedure. Different from the result that the reaction of dienoxysilanes with trialkyl orthoformates gave γ-dialkoxymethyl-α,β-unsaturated ketones, the present reaction of dienamines with trialkyl orthoformates afforded α-dialkoxymethyl-β,γ-unsaturated ketones, useful synthetic intermediates.

Table. The reactions of enamines with methyl or ethyl orthoformate

Enamines	Methyl or ethyl orthoformate	Lewis acids	Reaction conditions		Products$^{a)}$	Yields$^{b)}$ (%)
			Temp.(°C)	Time(h)		
	$CH(OEt)_3$	$BF_3 \cdot OEt_2$	0	1		85
		$SnCl_4$	0	1		90
		$ZnCl_2$	r.t.	14		54
	$CH(OMe)_3$	$BF_3 \cdot OEt_2$	0	1		74
		$TiCl_4$	-40	1		64
	$CH(OMe)_3$	$TiCl_4$	-78	0.5		70
	$CH(OMe)_3$	$BF_3 \cdot OEt_2$	0	1		75
		$SnCl_4$	0	1		68
		$TiCl_4$	0	1		63
	$CH(OEt)_3$	$BF_3 \cdot OEt_2$	-40	1		71
		$SnCl_4$	-40	1		70

a) All of the products gave satisfactory NMR and IR data in accord with the assigned structures. b) Isolated yields.

References

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