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NEW AND EFFICIENT SYNTHESIS OF γ-KETO ESTERS FROM NITRO OLEFINS

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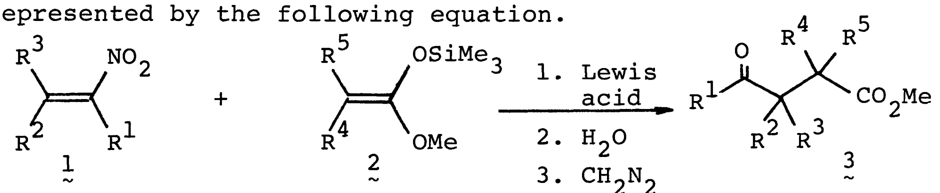
The Lewis acid-catalyzed reaction of nitro olefins and ketene methyl trimethylsilyl acetals afforded methyl 4-oxo-carboxylates on hydrolysis of the resulting adducts followed by treatment with diazomethane.

γ-Keto esters (acids) are useful synthetic intermediates for γ-lactones, butenolides, 1,3-cyclopentanediones, cyclopentenones, and heterocyclic compounds such as thiophenes, pyrrolidines, 1,2-pyrazines, etc. Available synthetic methods[1] have some methodological limitations in the synthesis of α- and/or β-alkyl-γ-keto esters.

In this paper we report the reaction of nitro olefins[2] (**1**) and ketene methyl trimethylsilyl acetals[3] (**2**), both of which are readily accessible by conventional methods, giving γ-keto esters (**3**) by a simple manipulation in high yields. The reaction is represented by the following equation.



The reaction of **1** and **2** was conducted in dichloromethane at low temperature (-78 °C) for 1 h using a mixture of $TiCl_4$ and $Ti(i\text{-}PrO)_4$ (1:1 in a molar ratio) as catalyst,[4,5] and the crude reaction product was then hydrolyzed in refluxing 70% aqueous 1,2-dimethoxyethane to afford γ-keto ester (**3**) containing a small amount of the corresponding free acid which resulted from partial hydrolysis of **3**. The intermingled free acid was esterified with diazomethane, and the desired product was isolated by preparative silica gel layer chromatography.

Selected examples are listed in the Table. As seen, yields of **3** largely depend on the degree of substitution at the reaction site of ketene silyl acetal (**2**). The reaction proceeded smoothly with all types of nitro olefins used to yield γ-keto esters in high yields (entries 1∿6), unless **2** was fully substituted. In the reaction of 2-methyl-1-nitro-1-cyclohexene and methylketene acetal, lactol (**4**), mp 110∿116°C, was obtained as an epimeric mixture along with the expected γ-keto ester in good combined yield (entry 6). With fully substituted ketene silyl acetals, on the other hand, β-substituted nitro olefins reacted sluggishly as seen in the reaction of dimethylketene acetal with 1-nitrocyclohexene (entry 7) or with 2-methyl-1-nitro-1-cyclohexene (entry 8). It is worthy to note that vinyl(methyl)ketene acetal gave the α-acetonylated product selectively (entry 9).

This synthetic method of γ-keto esters is convenient and efficient, and its wide application in organic synthesis is promising and currently under investigation.

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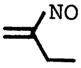
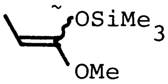
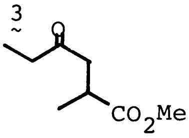
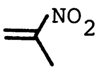
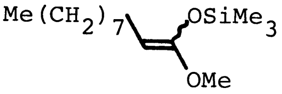
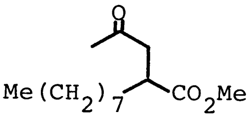
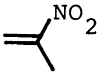
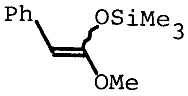
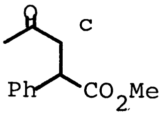
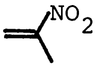
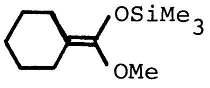
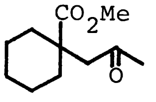
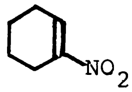
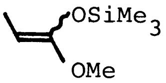
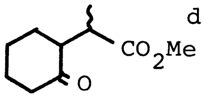
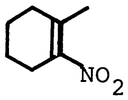
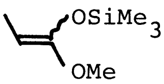
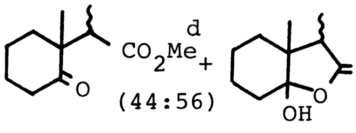
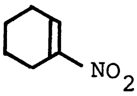
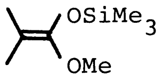
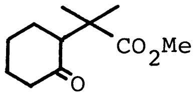
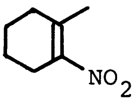
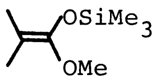
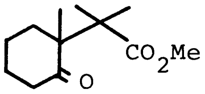
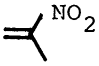
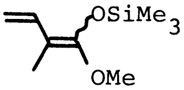
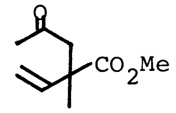
Table

Entry	Nitro olefin (1)	Ketene acetal[a] (2)	Molar ratio of 1 and 2	Product[a] 3	Isolated yield (%)[b]
1			1.5:1		63
2			1.5:1		84
3			1.5:1	 c	82
4			1.5:1		79
5			1:1.5	 d	70
6			1:3[e]	 d (44:56) d 4	73
7			1:1.5		25
8			1:3		0
9			1.5:1		47

a) All new compounds gave satisfactory microanalytical and spectroscopic data.
b) The yield refers to the reactant used in minor mole ratio (1 mmol). c) Mp 69∿70 °C. d) Diastereomeric mixture. e) The optimum yield was secured using the ketene acetal in excess.

References and Notes: 1) (Recent synthetic methods of γ-keto esters) R. Lukeš and A. Zobáčová, Coll. Czech. Chem. Commun., 24, 3189 (1959); W. H. Puterbaugh and R. L. Readshaw, Chem. Ind. (London), 1959, 255; A. A. Ponomarev and V. A. Sedavkina, Zh. Obshch. Khim., 31, 984 (1961) [Chem. Abstr., 55, 25905b (1961)]' G. P. Chiusoli, S. Merzoni, and G. Mondelli, Tetrahedron Lett., 1964, 2777; H. Reinheckel, K. Haage, and R. Gensike, Angew. Chem., 77, 810 (1965); A. Takeda, K. Takahashi, S. Torii, and T. Moriwake, J. Org. Chem., 31, 616 (1966); P. A. Wehrli and V. Chu, ibid., 38, 3436 (1973); C. G. Chavdarian and C. H. Heathcock, J. Am. Chem. Soc., 97, 3822 (1975); A.-R. B. Manas and R. A. J. Smith, J. Chem. Soc., Chem. Commun., 1975, 216; H. Stetter, M. Schreckenberg, and K. Wiemann, Chem. Ber., 109, 541 (1976); E. Nakamura, K. Hashimoto, and I. Kuwajima, J. Org. Chem., 42, 4166 (1977). 2) For the preparation of nitro olefins used here, see M. Miyashita, T. Yanami, and A. Yoshikoshi, J. Am. Chem. Soc., 98, 4679 (1976); E. J. Corey and H. Estreicher, ibid., 100, 6294 (1978). 3) C. Ainsworth, F. Chen, and Y.-N. Kuo, J. Organomet. Chem., 46, 59 (1972). 4) K. Narasaka, K. Soai, and T. Mukaiyama, Chem. Lett., 1974, 1223; K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 49, 779 (1976). 5) This mixed catalyst was used in one mole equivalent to the minor reactant (refer to the Table).

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