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NEW SYNTHESIS OF γ-KETO ACIDS FROM NITROOLEFINS AND CARBOXYLIC ACID DIANIONS

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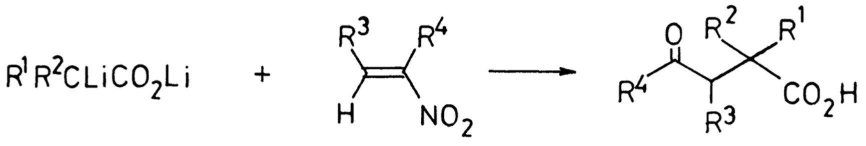
As a convenient synthetic method of γ-keto acids, oxoalkylation of carboxylic acids with nitroolefins was examined. Carboxylic acid dianions reacted with conjugated nitroolefins at low temperature (-100°C) and a variety of γ-keto acids were obtained on acidic workup in moderate to good yields.

Previously it was reported from this laboratory that the Lewis acid-catalyzed reaction of aliphatic and alicyclic conjugated nitroolefins with ketene methyl trimethylsilyl acetals yielded γ-keto acid methyl esters in good yields.[1] The choice of the combination of the silyl acetals and the Lewis acid was made by taking it into consideration that conjugated nitroolefins were in general highly unstable in basic circumstances. Nevertheless, direct oxoalkylation of carboxylic acids with nitroolefins would be attractive as a more convenient method for γ-keto acid synthesis, and we found, as described herein, appropriate reaction conditions which provided satisfactory results.

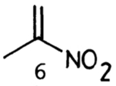
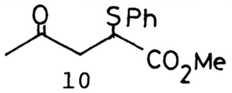
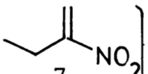
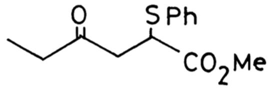
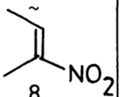
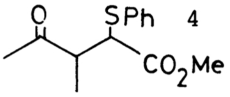
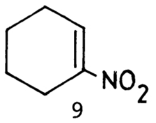
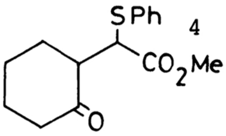
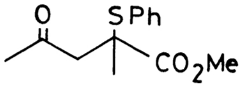
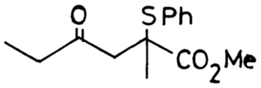
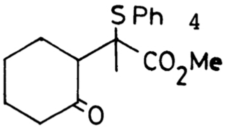
Although aliphatic nitroolefins are extremely sensitive to bases, the dianion 1 of a carboxylic acid was found to react smoothly with a nitroolefin 2 at low temperature,[2] and the expected γ-keto acid 3 was obtained on acidic workup in one-pot operation.



1 2 3

In order to find out suitable reaction conditions, we commenced the reaction of (phenylthio)acetic acid (4) and 2-nitropropene (6). (Phenylthio)acetic acid was selected for the further advantage of obtaining α,β-unsaturated carbonyl compounds from the oxoalkylation product, as will be mentioned later. Results are summarized in Table 1. Thus the expected product was obtained in moderate yields when LDA was used as base under conventional conditions (entry 1), while LDA could be replaced with n-BuLi to generate the dianion of the acid[3] which gave the same product in rather better yield (entry 2). At a lower temperature (-100°C), the dianion generated by the latter base afforded the product in high yield (entry 3). Under the optimum conditions we also obtained oxoalkylation products from some other nitroolefins and 4 (entries 4~6) or α-(phenylthio)propionic acid (5) (entries 7~9) respectively,

Table 1. Oxoalkylation of (Phenylthio)acetic and α-(Phenylthio)propionic Acids with Nitroolefins

Entry	Carboxylic acid	Nitro- olefin	Base	Temp. (°C)	Product[2]	Isolated yield (%)[3]
1	$PhSCH_2CO_2H$ **4**	 **6**	LDA	-78~0	 **10**	50~55
2	**4**	**6**	n-BuLi	-78~0	**10**	69
3	**4**	**6**	n-BuLi	-100~0	**10**	80
4	**4**	 **7**	n-BuLi	-100~0		76
5	**4**	 **8**			 [4]	64
6	**4**	 **9**			 [4]	76
7	$PhSCHMeCO_2H$ **5**	**6**				55
8	**5**	**7**				39
9	**5**	**9**			 [4]	37

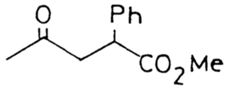
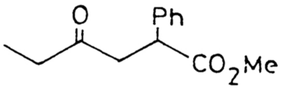
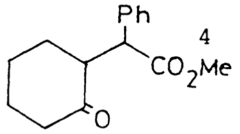
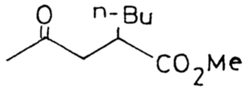
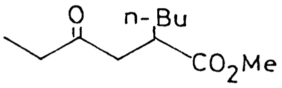
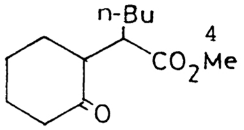
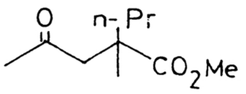
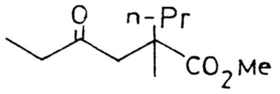
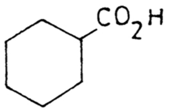
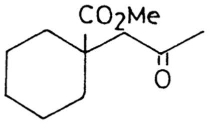
1) THF was used as solvent. 2) Product esterified with diazomethane.
3) Based on carboxylic acid. 4) Diastereomeric mixture.

although α-branching in the latter acid lowered the yields in comparison with those of the former acid.

Table **2** shows that similar reaction conditions can be successfully applied to phenylacetic acid (**11**), giving satisfactory yields of the expected oxoalkylation products (entries 1~3).

The typical procedure is illustrated by the reaction of **4** with **6**; n-BuLi (1.65 M in hexane, 0.75 ml (1.2 mmol)) was added dropwise at -78°C to a solution of **4** (84 mg, 0.5 mmol) in dry THF (3.5 ml) under Ar. After being stirred for 45 min at

Table 2. Oxoalkylation of Phenylacetic and Some Aliphatic Acids with Nitroolefins[1]

Entry	Carboxylic acid	Nitroolefin	Base	Product[2]	Isolated yield (%)[3]
1	$PhCH_2CO_2H$ **11**	**6**	n-BuLi		88
2		**7**			73
3		**9**		 4	72
4	$Me(CH_2)_4CO_2H$	**6**	LDA[5]		65
5		**7**			55
6		**9**		 4	24
7	$Me(CH_2)_2CHMeCO_2H$	**6**	LDA[6]		46
8		**7**			38
9		**6**	LDA[6]		37

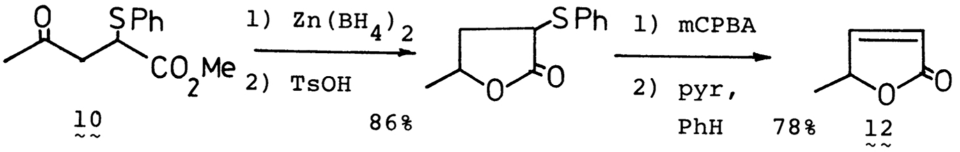
1) Solvent, THF; reaction temperature with nitroolefin, -100~10°C. 2) Product esterified with diazomethane. 3) Based on carboxylic acid. 4) Diastereomeric mixture. 5) HMPA (1 equiv to carboxylic acid) was added. 6) To complete the dianion formation, a mixture of the carboxylic acid and LDA prepared at -20°C was warmed and kept at 50°C for 2 h.[4]

the same temperature, the mixture was cooled to -100°C in a liquid nitrogen-methanol bath and **6** (57 mg, 0.66 mmol) was added by a microsyringe. The mixture was then gradually warmed to 0°C over 5 h with stirring. Hydrochloric acid (17%, 3 ml) was added at 0°C, and the resulting heterogeneous mixture was stirred at 0~10°C overnight and then poured into cold water. The product was extracted with CH_2Cl_2 and the extract was washed with water and saturated brine. An ethereal solution of the crude keto acid thus obtained was treated with ethereal diazomethane and the methylation product was purified by preparative TLC (CH_2Cl_2-n-hexane, 7:1) to give methyl 4-oxo-2-(phenylthio)pentanoate (95 mg, 80%).

Since n-BuLi cannot be applied as base to aliphatic primary and secondary acids, LDA was employed in the reaction of these acids with nitroolefins (Table 2, entries 4~9). The yields were somewhat lower than those in the corresponding reactions of 4 or 11.

As the sole precedent of the reaction of ester enolates with nitroolefins, Seebach reported the formation of a Michael adduct (nitro compound) in the reaction of the lithium enolate of ethyl acetate with a base-insensitive aryl-conjugated nitroolefin.[5] Our procedure was also applicable to some esters (i, LDA; ii, nitroolefin; iii, aqueous HCl) which gave γ-keto esters as expected, e.g. methyl 2-phenylpentanoate was obtained from methyl phenylacetate and 6 in 79% yield.[6]

Transformation of α-phenylthio-γ-keto esters into α,β-unsaturated carbonyl compounds was exemplified by the following synthesis of β-angelica lactone (12).



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References

1) M. Miyashita, T. Kumazawa, and A. Yoshikoshi, Chem. Lett., 1980, 1043.

2) Reactions of nitroolefins with the di- and trianions derived from secondary acetamides and some 1,3-dicarbonyl compounds were previously reported by Seebach, resulting in the formation of Michael adducts. V. Ehrig and D. Seebach, Chem. Ber., 108, 1961 (1975).

3) This is not the first case of the dianion formation with n-BuLi from 4. We (M. M. and A. Y.) experienced that in the preparation of nitro(phenylthio)methane from 4, n-BuLi gave much better results than did LDA. See M. Miyashita, T. Kumazawa, and A. Yoshikoshi, J. Org. Chem., 45, 2945 (1980).

4) P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr., J. Org. Chem., 37, 451 (1971).

5) D. Seebach, H. F. Leitz, and V. Ehrig, Chem. Ber., 108, 1924 (1975).

6) γ-Keto ester synthesis using ester enolates and nitroolefins is currently under investigation in our laboratory.

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