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A NEW SYNTHESIS OF α-METHYLENE CARBONYL COMPOUNDS

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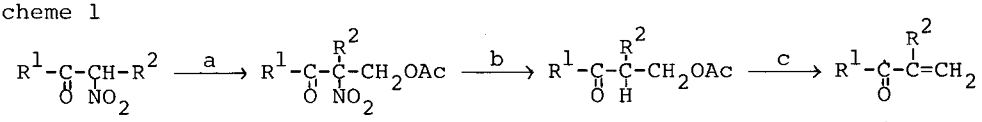
Summary: α-Methylene carbonyl compounds are regioselectively prepared by the reaction of α-nitroketones or α-nitroesters with 37% formaldehyde in the presence of a catalytic amount of weak bases followed by acetylation, denitration with Bu_3SnH, and elimination of acetic acid.

In a preceding paper we described a useful method for the preparation of ketones via denitration of α-nitroketones (1) with Bu_3SnH.[1] We describe herein a new reaction of 1 or α-nitroesters (5) with 37%-formaldehyde in the presence of a catalytic amount of Ph_3P or 10%-NaOH showing novel methods of regioselective synthesis of α-methylene carbonyl compounds. Preparation of α-methylene ketones (4) was accomplished according to Scheme 1.

Scheme 1



$$R^1\text{-}\underset{\overset{\|}{O}}{C}\text{-}\underset{NO_2}{CH}\text{-}R^2 \xrightarrow{a} R^1\text{-}\underset{\overset{\|}{O}}{C}\text{-}\overset{R^2}{\underset{NO_2}{C}}\text{-}CH_2OAc \xrightarrow{b} R^1\text{-}\underset{\overset{\|}{O}}{C}\text{-}\overset{R^2}{\underset{H}{C}}\text{-}CH_2OAc \xrightarrow{c} R^1\text{-}\underset{\overset{\|}{O}}{C}\text{-}\overset{R^2}{C}=CH_2$$

1 2 3 4

(a) 37%-HCHO, Ph_3P (0.1 eq)/i-PrOH, rt, 24 h; Ac_2O/pyridine
(b) Bu_3SnH, AIBN/benzene, 80 °C, 2 h
(c) DBU/benzene, rt, 3 h

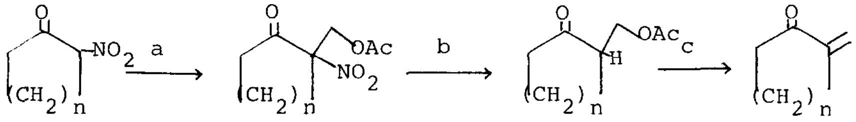
A mixture of 1 (10 mmol) prepared from nitroparaffins and N-acylimidazoles,[2] 37%-HCHO and Ph_3P (1 mmol) in i-PrOH (10 ml) was stirred at room temperature for 24 h to give the hydroxymethylated compounds which was acetylated with acetic anhydride in pyridine giving the compound 2.[3] Subsequent treatment of 2 with Bu_3SnH in the presence of a catalytic amount of AIBN in benzene at 80 °C for 2 h resulted in clean denitration to give 3 which was converted to α-methylene ketones (4) on treatment with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in benzene in good yields.[4] Yields of 2, 3, 4 are summarized in Table 1.

Table 1 Preparation of α-methylene ketones (4)

	R^1	R^2	2, yield %	3, yield %	4, yield %
a	$n\text{-}C_3H_7$	C_2H_5	76	74	90
b	$i\text{-}C_3H_7$	C_2H_5	75	75	82
c	$n\text{-}C_5H_{11}$	CH_3	73	83	85
d	$n\text{-}C_6H_{13}$	CH_3	80	84	85
e	C_2H_5	$n\text{-}C_5H_{11}$	91	83	83

Yields refer to pure and isolated products

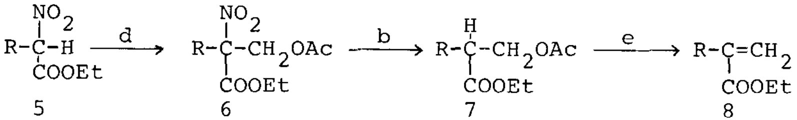
Cyclic α-methylene ketones were also prepared in a similar way.



n = 3	83%	73%	75%
n = 4	90%	85%	85%

Preparation of α-methylenecarboxylic esters (8) was accomplished according to Scheme 2.

Scheme 2



$$\underset{\substack{|\\ \text{COOEt}}}{\overset{\substack{NO_2\\ |}}{R\text{-}C\text{-}H}} \xrightarrow{d} \underset{\substack{|\\ \text{COOEt}}}{\overset{\substack{NO_2\\ |}}{R\text{-}C\text{-}CH_2OAc}} \xrightarrow{b} \underset{\substack{|\\ \text{COOEt}}}{\overset{\substack{H\\ |}}{R\text{-}C\text{-}CH_2OAc}} \xrightarrow{e} \underset{\substack{|\\ \text{COOEt}}}{R\text{-}C{=}CH_2}$$

5 6 7 8

(d) 37%-HCHO, 10%-NaOH (0.1 eq)/i-PrOH, rt, 2 h; Ac_2O/pyridine
(e) DBU/benzene, 80 °C, 5 h

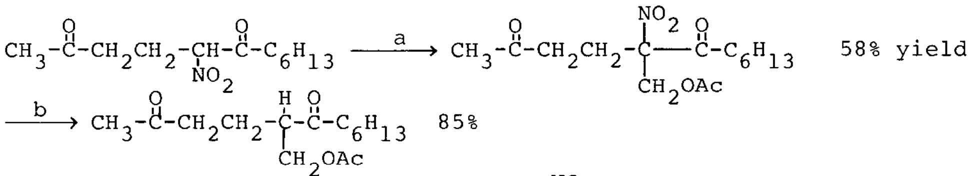
Condensation of α-nitroesters (5)[5] with formaldehyde was carried out in the presence of 10%-NaOH which was more effective than Ph_3P. Elimination of acetic acid from 7 required more drastic conditions than elimination from 3. The results are summarized in Table 2.

Importance of α-methylene carbonyl compounds in organic synthesis is now well understood, and numerous methods to prepare them have been reported.[6] Although our new method is not direct and consists of four steps, it offers several advantages over the known methods. First, various kinds of R^1 and R^2

can be easily introduced into 4, because R^1 derives from R^1COOH or R^1CHO and R^2 from $R^2CH_2NO_2$. Secondly, condensation of 1 or 5 with formaldehyde is catalyzed by very weak bases such as Ph_3P. Thirdly, denitration with Bu_3SnH proceeds with very high functional selectivity.[7] Thus, methylene group can be introduced at only one center sepecifically without the necessity of recourse to protecting group techniques. Typical examples are shown below. This novel and selective method for the preparation of α-methylene carbonyl compounds makes α-nitroketones and α-nitroesters useful intermediates in organic synthesis

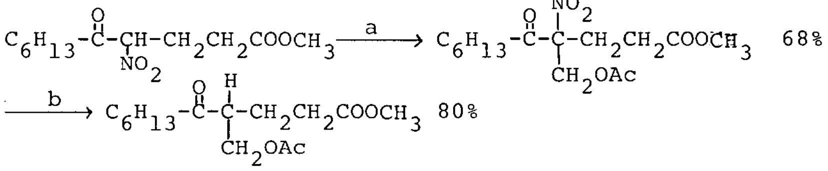
Table 2 Preparation of α-methylenecarboxylic esters (8)

	R	6, yield %	7, yield %	8, yield
a	CH_3	60	66	60
b	C_2H_5	67	71	75
c	n-C_3H_7	67	88	85
d	i-C_3H_7	79	83	94
e	n-C_4H_9	82	78	90



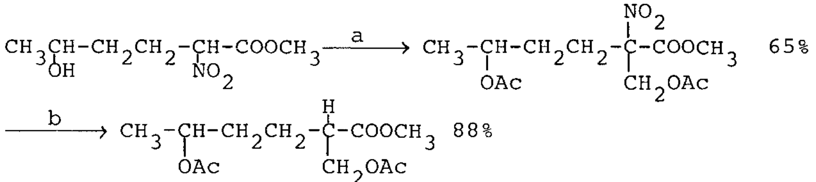
$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_2-\underset{NO_2}{CH}-\overset{O}{\overset{\|}{C}}-C_6H_{13} \xrightarrow{a} CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_2-\overset{NO_2}{\underset{CH_2OAc}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_{13} \quad \text{58\% yield}$$

$$\xrightarrow{b} CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_2-\overset{H}{\underset{CH_2OAc}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_{13} \quad 85\%$$



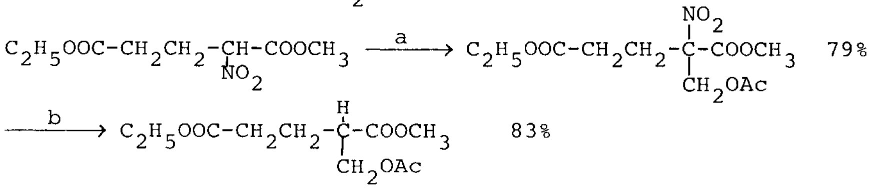
$$C_6H_{13}-\overset{O}{\overset{\|}{C}}-\underset{NO_2}{CH}-CH_2CH_2COOCH_3 \xrightarrow{a} C_6H_{13}-\overset{O}{\overset{\|}{C}}-\overset{NO_2}{\underset{CH_2OAc}{C}}-CH_2CH_2COOCH_3 \quad 68\%$$

$$\xrightarrow{b} C_6H_{13}-\overset{O}{\overset{\|}{C}}-\overset{H}{\underset{CH_2OAc}{C}}-CH_2CH_2COOCH_3 \quad 80\%$$



$$CH_3\underset{OH}{CH}-CH_2CH_2-\underset{NO_2}{CH}-COOCH_3 \xrightarrow{a} CH_3-\underset{OAc}{CH}-CH_2CH_2-\overset{NO_2}{\underset{CH_2OAc}{C}}-COOCH_3 \quad 65\%$$

$$\xrightarrow{b} CH_3-\underset{OAc}{CH}-CH_2CH_2-\overset{H}{\underset{CH_2OAc}{C}}-COOCH_3 \quad 88\%$$



$$C_2H_5OOC-CH_2CH_2-\underset{NO_2}{CH}-COOCH_3 \xrightarrow{a} C_2H_5OOC-CH_2CH_2-\overset{NO_2}{\underset{CH_2OAc}{C}}-COOCH_3 \quad 79\%$$

$$\xrightarrow{b} C_2H_5OOC-CH_2CH_2-\overset{H}{\underset{CH_2OAc}{C}}-COOCH_3 \quad 83\%$$

These final products can be regarded as the protected forms of α-methylene carbonyl compounds, for they are readily converted to α-methylene carbonyl compounds when they are necessary.

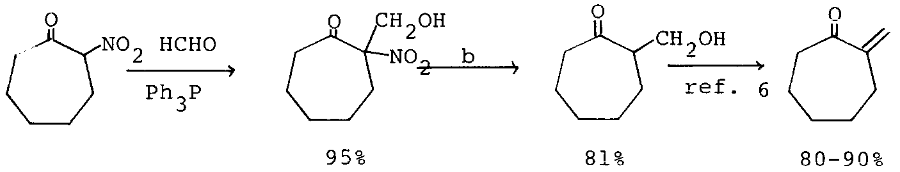
References and notes

(1) N. Ono, I. Hamamoto, H. Miyake, and A. Kaji, Chem. Lett., 1079 (1982).

(2) α-Nitroketones were prepared in about 80-90% yields by acylation of nitroparaffins. [R. L. Crumbie, J. S. Nimitz, and H. S. Mosher, J. Org. Chem., 47, 4040 (1982)]. Cyclic α-nitroketones were prepared by the reaction of enol acetates with nitric acid. [R. H. Fisher and H. M. Weitz, Synthesis, 261 (1980)].

(3) Triphenylphosphine gave the best results among the bases which were frequently used for nitro-aldol reactions. Stronger bases such as NaOH or triethylamine were not only necessary for this transformation but also caused some decomposition of 1.

(4) α-Methylene ketones (4) were also prepared by denitration with Bu_3SnH before acetylation and followed by dehydration.



(5) N. Kornblum, R. K. Blackwood, and J. W. Poweres, J. Am. Chem. Soc., 79, 2507 (1957); H. L. Finkbeiner anf G. W. Wagner, J. Org. Chem., 28, 215 (1963); M. L. Prostenik and I. Butula, Angew. Chem. Suppl., 225 (1982).

(6) Reviews, P. A. Grieco, Synthesis, 67 (1975); S. S. Newaz, Aldochim. Acta., 10, 64 (1977); T. Shono and Y. Matsumura, Yukigosei Kagaku Kyokaishi, 39, 358 (1981).

(7) Most common functional groups such as keto, alkoxycarbonyl, formyl, cyano, sulfinyl and sulfonyl groups are not affected by the conditions of denitration with Bu_3SnH, see following papaers. N. Ono, H. Miyake, R. Tamura, and A. Kaji, Tetrahedron Lett., 1705 (1981); N. Ono, H. Miyake, A. Kamimura, N. Tsukui, and A. Kaji, Tetrahedron Lett., 2957 (1982); N. Ono, H, Miyake, and A. Kaji, J. Chem. Soc. Chem. Commun., 33 (1982).

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