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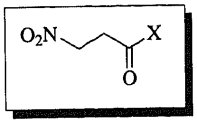
Methyl 3-Nitropropanoate[1]



(**1**; X = OMe)
[20497-95-4] $C_4H_7NO_4$ (MW 133.12)
(**2**; X = OH)
[504-88-1] $C_3H_5NO_4$ (MW 119.09)
(**3**; X = OEt)
[3590-37-2] $C_5H_9NO_4$ (MW 147.15)
(**4**; X = Cl)
[51834-15-2] $C_3H_4ClNO_3$ (MW 137.53)

(nitroaldol additions,[2,3] condensation[4] reactions, and Michael additions[5] involving the NO_2-substituted carbon; the α-carbonyl carbon in dilithionitronate enolates of the esters undergoes alkylations,[6–9] double alkylations,[6,8] and aldol[6,8] and Michael additions;[6,8] elimination of HNO_2 from the products gives α,β-unsaturated esters with substituents in either the β-[2,3a,5b] or the α-position,[8,9] thus making the reagent a synthetic equivalent of acrylate anions with d^3 or d^2 reactivity;[8,10] precursor to nitrile oxide for [3 + 2] cycloadditions;[11] 3-nitropropanoyl chloride can be used for enolate acylation[12–15] and five-membered ring annulation[14])

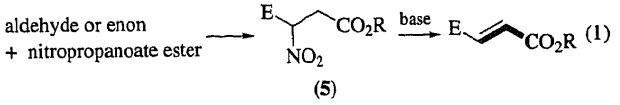
Physical Data: (**1**) bp 63 °C/0.5 mmHg. (**2**) mp 65–68 °C. (**3**) bp 146 °C/760 mmHg. (**4**) bp 123 °C/10 mmHg.

Solubility: sol most organic solvents.

Preparative Methods: the acid (**2**) and its esters (**1**) and (**3**) are prepared from the corresponding 3-halopropanoic acid derivatives with nitrite. (**2**) is a commercial product and can be esterified[8] and converted to the acid chloride (**4**)[15,18] and anhydride[15] by conventional methods.

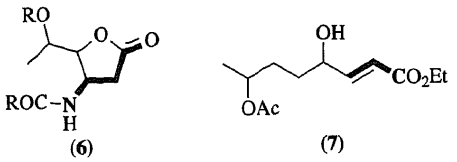
Handling, Storage, and Precautions: the acid (**2**) is a natural, toxic metabolite of aspartic acid in plants[16] and in fungi.[17] The nitropropanoic acid derivatives should be handled with caution, as should all nitro compounds of low molecular weight. They are stable when stored in dark bottles in a refrigerator. Acid chloride (**4**) should be stored with exclusion of air and moisture.

Reactions of the Esters (1) and (3) at C-3. Although the 3-nitropropanoate esters readily undergo HNO_2 elimination to acrylates, it is possible to carry out typical nitronate transformations such as the Henry reaction and the Michael addition to enones. The resulting chain-elongated β-nitro esters (**5**) can then be subjected to β-elimination, so that the carbon skeleton of the compound introduced as an electrophile has been elongated by a β-acrylate unit (eq 1).

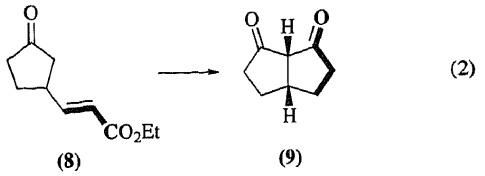


(**5**)

Alternatively, the original adducts can be converted without loss of the nitrogen functionality; for example, reduction of NO_2 to NH_2 leads to β-amino acid derivatives. Thus, nitropropanoate esters (**1**) and (**3**) have been used for the synthesis of amino sugars, e.g. (**6**),[3b,3c] of macrolides such as brefeldin,[2b] of macrodiolides such as pyrenophorin via the intermediate (**7**),[2a] and of bicyclo[3.3.0]octane-2,8-dione (**9**) (by Michael addition of (**3**) with cyclopentenone, HNO_2 elimination to (**8**), hydrogenation, and Dieckmann condensation) (eq 2).[5b]



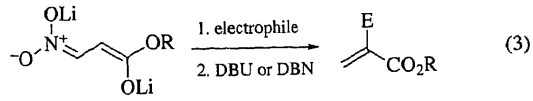
(**6**) (**7**)



(2)

(**8**) (**9**)

Reactions of the Esters (1) and (3) at C-2. Double deprotonation of 3-nitropropanoate esters to nitronate enolates (**10**) enables alkylation (by alkyl halides and enones) and hydroxyalkylation (by aldehydes and ketones) at the 2-position, to give α-substituted acrylates (**11**) (eq 3).[8,9]

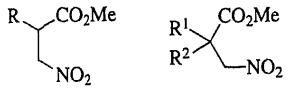


(3)

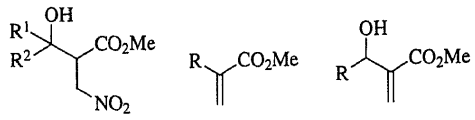
(**10**) (**11**)

(from (**1**) + 2 LDA)

The reaction with alkyl iodides and bromides to give monoalkylated products (**12**) is so efficient that an in situ double alkylation is possible; for instance, a 71% yield of (**13**) (R^1 = Me, R^2 = Bn) is obtained.[8] Addition to aldehydes to give (**14**) (R^2 = H) gives better yields (50–85%) than addition to ketones (<30%). The products (**15**) and (**16**) of HNO_2 elimination are formed in high yields when Eiter bases[19] are employed. The overall yield for the preparation of (**15**) (R = $CH_2CH{=}CH_2$) from methyl 3-nitropropanoate (**1**) and allyl bromide is 64%, and that for the preparation of the hydroxy methylene ester (**16**) (R = C_5H_{11}) from (**1**) and hexanal is 71%.

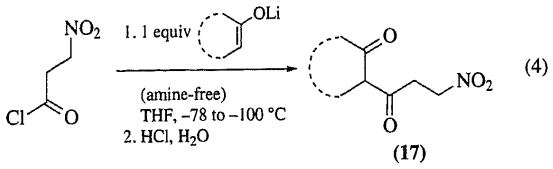


(12) (13)



(14) (15) (16)

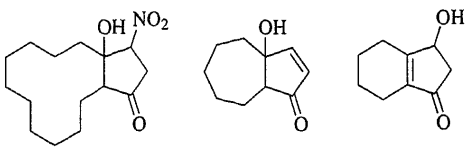
Lithium Enolate Acylation and Five-Membered Ring Annulation. Direct 1:1 acylation of amine-free solutions of ketone lithium enolates by addition to a 3-nitropropanoyl chloride (**4**) solution in THF (both cooled to temperatures between –78 and –100 °C) gives 5-nitro 1,3-diketones (**17**) in yields of 40–80% (eq 4). The enolates may be derived from open-chain ketones such as diethyl ketone, or from cyclic ketones with, for instance, six-, seven-, eight-, and twelve-membered rings.[12–15]



(4)

(17)

Meerwein acylation of ketones with the anhydride of 3-nitropropanoic acid/BF_3 is also feasible.[15,20] The products of type (**17**) undergo nitroaldol cyclization with formation of a hydroxynitrocyclopentanone ring which, depending upon the particular structure and upon the conditions used, may lose HNO_2 to give a hydroxycyclopentenone derivative. Examples are the annulation products (**18**) (mp 155–156 °C) and (**19**) (mp 68–70 °C) of cyclododecanone and cycloheptanone. The hydroxy enone with a tertiary hydroxy group may rearrange to the isomer with a secondary hydroxy group, e.g. (**20**) obtained from cyclohexanone. Pure products (as single diastereoisomers, where applicable) can be isolated in yields of 15–90%.[14]



(18) (19) (20)

Related Reagents. Lithium α-Lithiomethanenitronate; *O,O*-Dilithio-1-nitropropene; Methyl 4-Nitrobutanoate; Nitroethane; Nitromethane.

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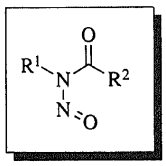
N-Methyl-*N*-nitrosoacetamide[1]



(**1**; R^1 = Me, R^2 = Me) *[7417-67-6]*	$C_3H_6N_2O_2$	(MW 102.11)
(**2**; R^1 = Me, R^2 = Pr) *[16395-81-6]*	$C_5H_{10}N_2O_2$	(MW 130.17)
(**3**; R^1 = Bu, R^2 = Me) *[14300-06-2]*	$C_6H_{12}N_2O_2$	(MW 144.20)
(**4**; R^1 = Bu, R^2 = Et) *[99389-05-6]*	$C_7H_{14}N_2O_2$	(MW 158.23)

(alkylating agent;[2] source of diazomethane;[3] useful as activated acylating agent;[4] precursor to esters and alkenes[1a,5,6])