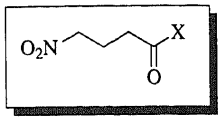
Methyl 4-Nitrobutanoate[1]



(1; X = OMe)
[13013-02-0] $C_5H_9NO_4$ (MW 147.15)
(2; X = OH)
[16488-43-0] $C_4H_7NO_4$ (MW 133.12)
(3; X = OEt)
[2832-16-8] $C_6H_{11}NO_4$ (MW 161.18)
(4; X = Cl)
[75938-95-3] $C_4H_6ClNO_3$ (MW 151.56)

(bifunctional C_4 synthetic building blocks with d^4 reactivity; preparation of functionalized carbo-[2,3] and heterocyclic[4] compounds; undergoes nitroaldol,[5] Michael addition, and ketone acylation reactions[6]; the α-NO_2 position has also been acylated;[7] the mononitrile oxide can be trapped by alkene and alkyne groups to give isoxazoline and isoxazole derivatives[8,9])

Physical Data: (1) bp 106–110 °C/9 mmHg. (2) bp 120 °C/0.04 mmHg. (3) bp 97–98 °C/1 mmHg. (4) bp 70 °C/0.03 mmHg.

Solubility: sol most common organic solvents.

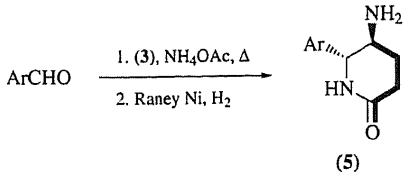
Form Supplied in: the methyl ester (1) is commercially available.

Preparative Methods: the esters (1) and (3) are prepared by Michael addition of ***Nitromethane*** to the corresponding acrylates[10] (higher primary and secondary nitroalkanes can be added likewise); (2) is obtained by acid-catalyzed hydrolysis of the ester; the acid chloride (4) is prepared from the acid (2) and ***Thionyl Chloride***.[6]

Handling, Storage, and Precautions: as for the 3-nitropropanoic acid derivatives (see ***Methyl 3-Nitropropanoate***).

Ring Forming Reactions of 4-Nitrobutanoic Acid Derivatives. The nucleophilic reactivity of the α-NO_2 position in the esters (1) and (3) or the electrophilicity of the acid chloride carbonyl group in (4) may be used to form the first bond of a new ring. In the second step, an intramolecular acylation or Henry reaction leads to ring formation.

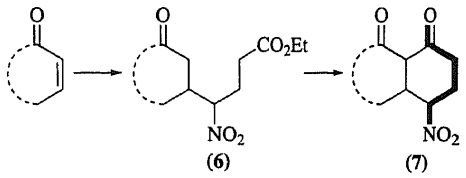
Thus a Mannich-type variation of the nitroaldol addition of (3) to aromatic aldehydes produces a *trans*-substituted aryl-nitro-valerolactam, the nitro group of which can be reduced to give the lactam (5), a 4,5-diamino acid derivative (eq 1).[4]



(1)

(5)

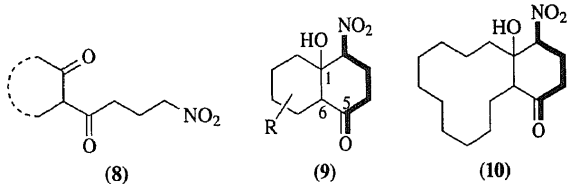
Michael addition of the ethyl ester (3) to enones to afford (6) and Dieckmann condensation produces nitro diketones (7) with a bicyclo[4.3.0]nonane, -[4.4.0]decane, or -[5.4.0]undecane skeleton in ca. 20% overall yield (eq 2).[3]



(2)

(6) (7)

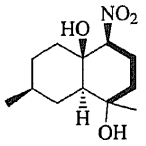
Ketone lithium enolate acylation with the acid chloride (4) under conditions as specified in the article ***Methyl 3-Nitropropanoate*** furnishes 6-nitro 1,3-diketones (8), as demonstrated with numerous examples (yields 40–85%).[6,11] Those products of type (8) containing no ring or a six- or a twelve-membered ring, but not the cyclopentanone, -heptanone, and -octanone derivatives, undergo cyclization ($NaHCO_3$)/THF/H_2O) to give hydroxy-nitro ketones such as (9) and (10).[2] The 8-methyl-substituted decalin (9), isolated as a single diastereoisomer in 50% yield, reacts with ***Methyltitanium Triisopropoxide*** to give the nitrodiol (11) containing five stereogenic centers also as a single diastereoisomer.[12,13] Acetalization and ***Raney Nickel*** catalyzed hydrogenation of the nitro group of (9) (R = H) lead to the amino alcohol (12) (77% overall), the oxalate salt of which undergoes Tieffeneau–Demjanov rearrangement upon treatment with $NaNO_2/H_2O$; after acetal cleavage, the *trans*-fused bicyclic diketone (13) is isolated in 80% yield.



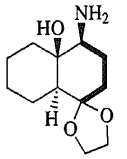
(8)

(9)

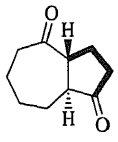
(10)



(11)



(12)



(13)

The 1,2-, 1,4-, and 1,6-distances between functional groups in the products (5)–(13) show that 4-nitrobutanoic acid is a reagent with reactivity umpolung (d^1),[14] which is itself prepared by a reaction involving reactivity umpolung (d^1 reactivity when nitromethane is added to acrylate).

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1. Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *C* **1979**, *33*, 1.
2. Weller, T.; Seebach, D; Davis, R. E.; Laird, B. B. *HCA* **1981**, *64*, 736 (*CA* **1981**, *95*, 219 793f).
3. Schank, K.; Lorig, W. *LA* **1983**, 112 (*CA* **1983**, *98*, 106 853u).
4. Mühlstädt, M.; Schulze, B. *JPR* **1975**, *317*, 919 (*CA* **1976**, *84*, 89 768m). Bhagwatheeswaran, H.; Gaur, S. P.; Jain, P. C. *S* **1976**, 615.
5. Barrett, A. G. M.; Robyr, C.; Spilling, C. D. *JOC* **1989**, *54*, 1233. Ono, N.; Kawamura, H.; Bougauchi, M.; Maruyama, K. *T* **1990**, *46*, 7483.

6. Seebach, D.; Weller, T.; Protschuk, G.; Beck, A. K.; Hoekstra, M. S. *HCA* **1981**, *64*, 716 (*CA* **1981**, *95*, 186 681n).
7. Ono, N.; Fujii, M.; Kaji, A. *S* **1987**, 532.
8. Kawakami, H.; Hirokawa, S.; Asaoka, M.; Takei, H. *CL* **1987**, 85. Padwa, A.; Dean, D. C. *JOC* **1990**, *55*, 405. Madsen, U.; Wong, E. H. F. *JMC* **1992**, *35*, 107.
9. Reactions not involving C–C bond formation such as (a) $CH_2NO_2 \rightarrow CHO$, (b) $CH_2NO_2 \rightarrow CH{=}NOH$, (c) $CH_2NO_2 \rightarrow CN$, and (d) $CH_2NO_2 \rightarrow CSNHOH$ can only be alluded to here: (a) Simoneau, B.; Brassard, P. *T* **1988**, *44*, 1015. (b) Kende, A. S.; Mendoza, J. S. *TL* **1991**, *32*, 1699. (c) Wehrli, P. A.; Schaer, P. *JOC* **1977**, *42*, 3956. (d) Hwu, J. R.; Tsay, S.-C. *T* **1990**, *46*, 7413.
10. Colonge, J.; Pouchol, J. M. *BSF* **1962**, 596 (*CA* **1962**, *57*, 4534a). Chasar, D. W. *S* **1982**, 841. Bergbreiter, D. E.; Lalonde, J. J. *JOC* **1987**, *52*, 1601. Padeken, H. G.; Schickh, O. von; Segnitz, A. In *MOC* **1971**, *10/1*, 182.
11. The same nitro diketones (**8**) can also be prepared by Michael addition of doubly deprotonated 1,3-diketones to nitroethylene: Ehrig, V.; Seebach, D. *CB* **1975**, *108*, 1961 (*CA* **1975**, *83*, 96 645b).
12. Weidmann, B.; Maycock, C. D.; Seebach, D. *HCA* **1981**, *64*, 1552 (*CA* **1982**, *96*, 5735k). Seebach, D.; Weidmann, B.; Widler, D. In *Modern Synthetic Methods 1983*, Scheffold, R., Ed.; Wiley: New York, 1983; Vol. 3, pp 217.
13. Since the enantiomeric Li enolates of 4-methylcyclohexanone can now be generated selectively (review: Koga, K. In *Organic Synthesis in Japan: Past, Present, and Future*, Noyori, R., Ed.; Tokyo Kagaku Dozin: Tokyo, 1992; p 195), the corresponding products (**9**) and (**11**) become available in enantiomerically pure form.
14. Seebach, D. *AG(E)* **1979**, *18*, 239.

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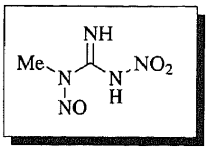
1-Methyl-3-nitro-1-nitrosoguanidine



[70-25-7] $C_2H_5N_5O_3$ (MW 147.12)

(precursor to diazomethane[1])

Alternate Names: MNNG; *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.

Physical Data: mp 118 °C (dec).

Solubility: sol alcohol, chloroform, acetone.

Form Supplied in: orange-yellow powder; commercially available.

Handling, Storage, and Precautions: shelf life of several years (somewhat longer than that of ***N-Methyl-N-nitroso-p-toluenesulfonamide***); store in brown bottle, refrigerated; severe irritant, carcinogen, potent mutagen;[2] contact may lead to sensitization, so contact by all routes must be avoided; handle in a fume hood.

General Discussion. This reagent reacts to generate ***Diazomethane*** upon treatment with aqueous sodium hydroxide at rt. For the generation of small quantities of diazomethane (e.g. less than 1 mmol), this compound is probably the reagent of choice. A convenient apparatus (Figure 1) has been reported by Fales et al;[3,4] the following procedure is representative.

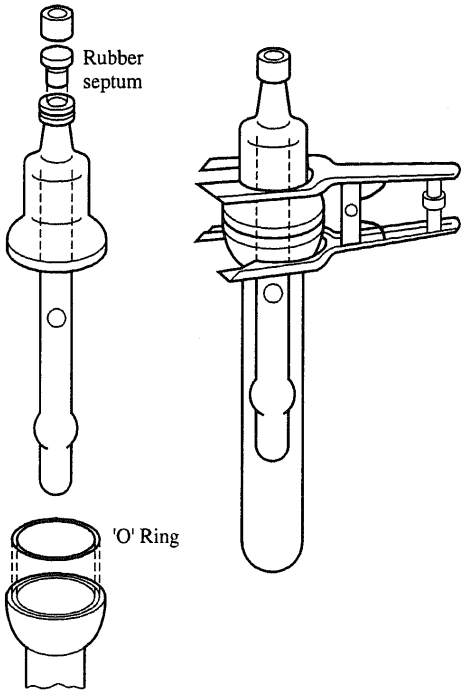


Figure 1 Apparatus for preparing diazomethane (reproduced by permission of the American Chemical Society from *Anal. Chem.* **1973**, *45*, 2302).

1 mmol (133 mg) of the reagent is placed in the inside tube through its screw-cap opening along with 0.5 mL of water to dissipate any heat generated. 3 mL of ether is placed in the outside tube and the two parts are assembled with a butyl O-ring and held with a pinch-type clamp. The lower part is immersed in an ice bath and about 0.6 mL of 5 N sodium hydroxide is injected through the silicone rubber septum via a syringe with a narrow-gauge (No. 22) needle to prevent leakage around the shank.[1,3] Diazomethane is collected in ether.

The alkali injection must be dropwise and very slow to control the volume of gas produced. At least 45 min are required for acceptable yields (over 50%). Solvents other than ether can be used for the collection of diazomethane. It is generally desirable to dissolve the substrate for reaction with diazomethane in the solvent in the outer tube prior to the generation, so that the reagent is consumed as it is produced.

1. McKay, A. F.; Wright, L. F. *JACS* **1948**, *70*, 1974.
2. A large number of papers have also reported biological use of this reagent as mutagen and carcinogen. For example: (a) Druckrey, H.; Preussmann, R.; Ivankovic, S.; Schmahl, D. *Z. Krebsforsch.* **1967**, *69*, 103. (b) Sugimura, T.; Fujimura S.; Baba, T. *Cancer Res.* **1970**, *30*, 455. (c) Fujimura, S.; Kogure, K.; Oboshi, S.;