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Michael Addition of Formaldehyde Dimethylhydrazone to Nitroolefins. A New Formyl Anion Equivalent[1]

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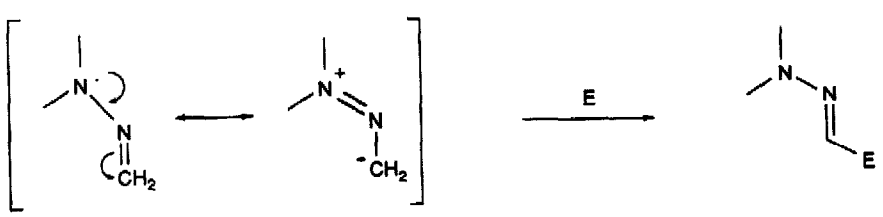
Key Words: Formyl anion equivalent, *N,N*-Dialkylhydrazones, Nitroolefins, Michael Reaction, β-Nitroaldehydes.

Abstract: Formaldehyde dimethylhydrazone readily adds to simple nitro-olefins in the absence of base giving β-nitrodimethylhydrazones in very high yields. The corresponding β-nitroaldehydes can be obtained by ozonolysis.

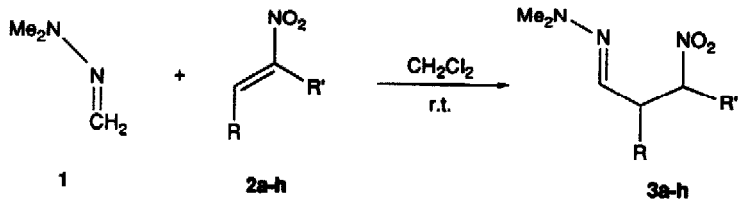
Carbon-carbon bond forming reactions are of the greatest importance in synthesis, an additional challenge being the simultaneous introduction of versatile functional groups with stereocontrol of each newly created chiral centre. Among the methods for the introduction of a functionalized carbon fragment into a carbon skeleton, those employing operational equivalents of formyl and acyl anions [X-$^-$CR-Y, X and Y being anion stabilizing auxiliary groups] have been widely used.[2] These methods present two inconveniences: the need of a strong base to generate the nucleophile and, in many cases, the difficulty to eliminate X and Y to release the carbonyl function. Hydrazones are ambident nucleophiles, which can react with electrophiles either at the amine nitrogen or at the azomethine carbon, the former being usually the most nucleophilic. It seems reasonable to suppose that in *N,N*-dialkylhydrazones, in which the nitrogen is blocked, the nucleophilicity of this centre would be decreased. Moreover, theoretical calculations[3] predict that an increase of the electron-donating capacity of the nitrogen increases the nucleophilicity of the azomethine carbon towards different electron acceptors, the *N,N*-dialkylhydrazone behaving as a sort of low-energy carbanion (Scheme 1). The use of *N,N*-dialkylhydrazones



Scheme 1.

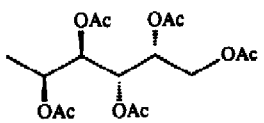
in this context has been scarcely investigated, the only antecedent being the use of aldehyde dialkylhydrazones as nucleophiles in trifluoroacetylation reactions,[4,5] and acylations using the Vielsmeier reagent[6] or isocyanates.[7] Related azo anions derived from t-butyl- or tritylhydrazones have been reported to undergo additions to electrophiles,[8] but there is no precedent for Michael additions of *N,N*-dialkylhydrazones.

We report here on the utility of formaldehyde *N,N*-dialkylhydrazones as synthetic equivalents of the formyl anion. We have investigated the reaction of formaldehyde dimethylhydrazone (FDMH,1)[4] with nitroolefins **2a-h**, which leads to β-nitrodimethylhydrazones **3a-h** (Scheme 2). These compounds, which are formed in some cases almost quantitatively and can be isolated in very good yields,[9] seem to us particularly attractive, since they posses two differentially masked carbonyl groups which could be transformed in different ways and at different steps of a synthetic sequence. The formation of compounds **3** proceeds at room temperature without any need of base or catalyst, just by mixing the reagents. Results of the reactivity and stereoselectivity of 1 towards nitro-olefins **2a-h** are collected in the Table.



Scheme 2.

Table. Formation of compounds 3.

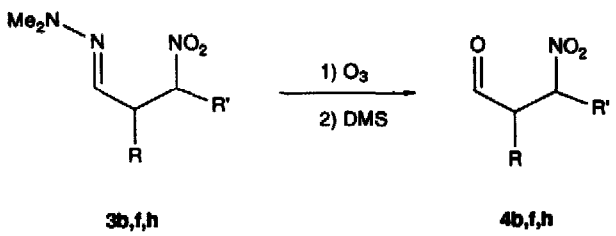
Compounds 2,3	R	R'	Reaction time	Yield of 3 %[a]	Diastereoisomeric ratio
a	Me	H	15m	90[b]	
b	^{i}Pr	H	8h	92[b]	
c	Ph	H	24h	75[c]	
d	*p*-C_6H_4-Me	H	18h	70[c]	
e	*p*-C_6H_4-OMe	H	4d	40[c]	
f	Ph	Me	48h	80[c]	1,7:1[d]
g	-$(CH_2)_4$-		30h	80[c]	[e]
h		H	18h	91[c]	3,6:1[f]

a) Of isolated pure 3. b) By fractional distillation. c) After column chromatography. d) Of pure erythro *and* threo *isomers. e) Only the* trans *isomer isolated. f) Of pure epimers* (2R) *and* (2S).

The lowest yield obtained, corresponding to the reaction of nitroolefin **3e**, can be explained considering its *push-pull* character, that makes it a poorer electrophile.

The diastereoselectivity observed for the reaction of **2h** is explained by 1,2-asymmetric induction. The *R*-configuration at C-2 of the major isomer of compound **3h** is tentatively assigned assuming prefential approach of the FDMH to the less sterically hindered *si* face of the nitroolefin in its preferred conformation, in agreement with earlier observations on similar systems.[10]

Selective cleavage of the dimethylhydrazone (DMH) group in some of compounds **3** to obtain the β-nitroaldehydes **4** has been performed (Scheme 3). The best results, which allow the retention of the configuration, were obtained by ozonolysis.[11,12] Under these conditions, both epimers (2*R*) and (2*S*) of the β-nitrodimethylhydrazone **3h**, previously separated by column chromatography, were transformed in very good yields into the corresponding β-nitroaldehydes **4h** without isomerization.



3b,f,h **4b,f,h**

3,4	Isomer	Yield of 4 (%)
b		82
f		80
h	2*R*	90
h	2*S*	85

Scheme 3.

In conclusion, through the sequence a) Michael addition to nitroolefins and b) cleavage of the DMH group, FDMH appears to be a convenient alternative to other precursors for the formyl group. The advantages of **1** are:

i) it can be easily and economically prepared,

ii) it can be stored for long periods without particular care,

iii) it is a very efficient reagent for the Michael addition to good carbon electrophiles, and

iv) the DMH group can release the formyl group under conditions that do not affect many functional groups and chiral centers.

The extension of the reaction of FDMH and other *N,N*-disubstituted formaldehyde hydrazones with different electrophiles and the application to natural product synthesis are under study in our laboratory.

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References and Notes

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3. Calculations were carried out using GAUSSIAN90™ program (Gaussian Inc., Pittsburgh PA, 1990) and the 3-21G basis set.
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9. As an illustration of the procedure, reaction of FDMH with 3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy- 1-nitro-D-*galacto*-hept-1-enitol (**2h**) is described: To a solution of the nitroolefin **2h** (2.17g, 5 mmol) in CH_2Cl_2 (20 mL) is added FDMH (**1**) (0.64mL, 7.5 mmol). The mixture is kept 18h at room temperature, until which time the nitroolefin has reacted completely (TLC control). Evaporation of the solvent and the excess of **1** and column chromatography of the residue (ether-hexane 1:1) afford (2*R*)-**3h** (1.79g, 71%), m.p. 54-55°C, $[\alpha]_D^{25}$-6.2° (c 1, $CHCl_3$) and (2*S*)-**3h** (0.51g, 20%), m.p. 121-122°C, $[\alpha]_D^{25}$+0.9° (c 1, $CHCl_3$)
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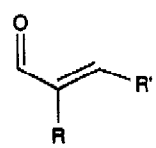
12. General procedure: Dry ozone is passed through a solution of **3** (1 mmol) in CH_2Cl_2 (30 mL) cooled at -78°C, until a slight blue colour appears. A solution of Me_2S (1 mL) in CH_2Cl_2, also cooled at -78°C is then added and the mixture is allowed to come to room temperature. After washing with brine and water and drying ($MgSO_4$), the solvent is evaporated and the residue purified by column cromathography to yield pure **4**. Ozonolysis has to be performed very carefully because an excess of ozone give mixtures of compounds **4** and compounds **5**, the latter being formed by the loss of the elements of nitrous acid in **4**.



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13. All new compounds were fully characterized by ^{1}H nmr, ^{13}C nmr, ir and high resolution mass spectroscopy and/or combustion analysis.

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