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Formaldehyde SAMP-Hydrazone – a Neutral Chiral Formyl Anion and Cyanide Equivalent

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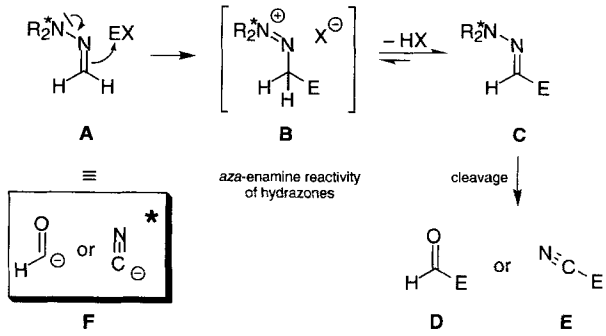
The formyl group is one of the most important functional groups in synthetic chemistry. Besides the classical electrophilic formylations to introduce this C_1-unit, nucleophilic acylation techniques have been investigated extensively (concept of Umpolung) [1], among them reagents which are synthetic equivalents of the formyl anion [2].

In 1968 Brehme and Nikolajewski recognized that formaldehyde *N,N*-dialkylhydrazones **A** can be regarded as azaenamines and reported electrophilic substitutions at the aldehyde hydrazone carbon with reactive electrophiles (**A**→**B**→**C**), such as the Vilsmeier reagent, the Mannich reagent and sulfonylisocyanates [3]. After transformation of the hydrazone group to the aldehyde (**C**→**D**) or the nitrile function (**C**→**E**) a nucleophilic formylation or cyanation under neutral conditions is the overall result. Thus, formaldehyde hydrazones **A** are indeed synthetic equivalents of the formyl anion and cyanide anion synthons **F** (Scheme 1).

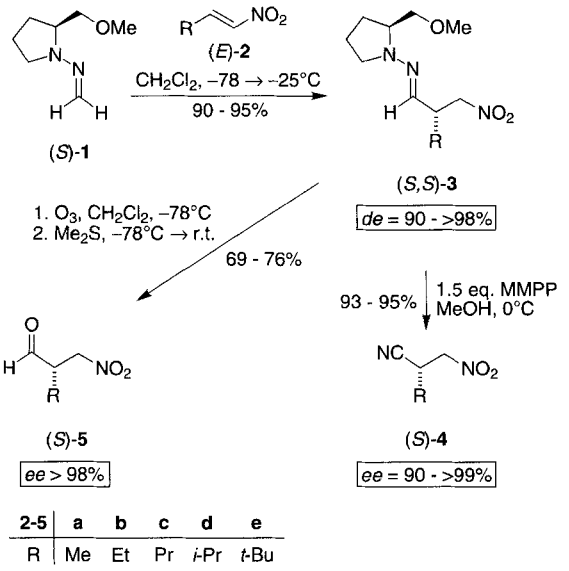
In their work on lithiated aldehyde *tert*-butylhydrazones as acyl anion equivalents Baldwin *et al.* showed that such nucleophilic acylations are also possible under nonbasic conditions in a thermal ene-type process with methyl acrylates and acrylonitrile as Michael acceptors [4]. Later Hojo *et al.* extended the palette of electrophiles by trifluoroacetic anhydride in their reactions using aldehyde dimethylhydrazones [5]. Reactions with less reactive electrophiles such as carbonyl compounds [6] remained unsuccessful. Recently, one of our groups [7] reported that formaldehyde dimethylhydrazone undergoes 1,4-additions with nitroalkenes as Michael acceptors, a further important extension of the method.



Scheme 1

But there was still the necessity for enantioselective variants using chiral carbonyl-d^1-reagents in order to obtain optically active products [2a, 8–10]. Therefore, the commercially available (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP) was used as chiral auxiliary to synthesize the formaldehyde SAMP-hydrazone [(*S*)-**1**] [11] and to test its application as a chiral equivalent of the formyl anion and the cyanide anion. As is depicted in Scheme 2, formaldehyde SAMP-hydrazone [(*S*)-**1**] reacts with aliphatic nitroalkenes (*E*)-**2** under neutral conditions by simply mixing both components at low temperature [12]. Michael addition occurs almost quantitatively and the resulting, exclusively (*E*)-configured, α-substituted β-nitroaldehyde SAMP-hydrazones (*S,S*)-**3** could be

obtained, after purification by chromatography, in excellent yields (90–95%) and with high diastereoisomeric excesses (*de* = 90–>98%). These compounds are particularly attractive, as they have two differently masked carbonyl groups which can be transformed selectively into alternate functional groups.



Scheme 2

Oxidative transformation of the hydrazones (*S,S*)-**3** with magnesium monoperoxyphthalate (MMPP) led, *via* an *aza*-Cope type elimination, to the corresponding α-substituted β-nitronitriles (*S*)-**4** in excellent yields (93–95%) and enantiomeric excesses (*ee* = 90–>99%) [13]. Ozonolysis of the SAMP hydrazones (*S,S*)-**3** gave the relatively unstable α-substituted β-nitroaldehydes (*S*)-**5** in acceptable yields (69, 76%) and high enantiomeric excesses (*ee* > 98%) without detectable racemisation [14]. The auxiliary may be recycled in a well-known procedure [15]. The (*S*)-configuration of the new stereogenic centre was determined by X-ray structure analysis carried out on the crystalline compound (*S,S*)-**3e**. The absolute configuration is in agreement with a proposed six-membered chair-like transition state shown in Figure 1.

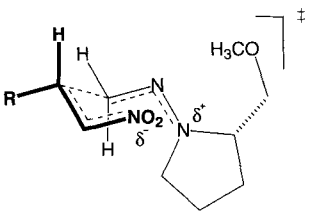
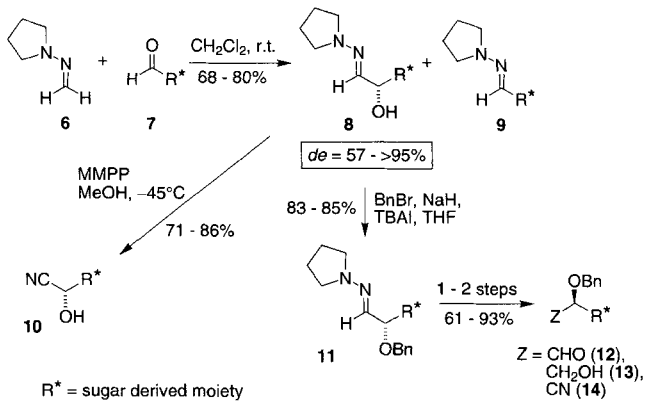


Fig. 1

The diastereoselective synthesis of sugar derived β-nitrodialkylhydrazones was also achieved using enantiopure sugar nitroalkenes [16]. The double asymmetric induction with formaldehyde SAMP- and RAMP-hydrazone led to the desired products in very good yields (71–95%) and in the "matched" case with nearly complete asymmetric induction (*de* ≥96%). Oxidative cleavage with MMPP afforded the corresponding sugar β-nitronitriles in excellent yields (81–96%) without epimerisation.

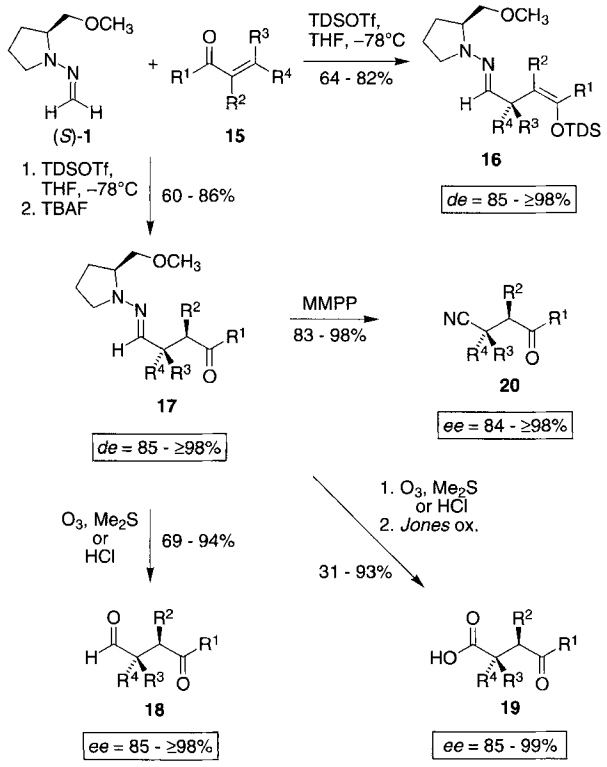
This methodology was later extended to sugar derived aldehydes to allow the one-carbon homologation of aldoses and dialdoses [17]. The addition of formaldehyde dialkylhydrazones such as **6** to sugar derived aldehydes **7** gave α-hydroxy hydrazones **8** with fair to good yields (68–80%) and stereoselectivites in a range of *de* = 57–>95% ("matched or mismatched case"). All efforts to improve the yields or to shorten the reaction times by changing the solvent or by adding catalysts favoured the formation of hydrazones **9**, also isolated as by-product in the non-catalysed addition reaction (Scheme 3). The use of the enantiopure formaldehyde SAMP or RAMP hydrazone to form the α-hydroxy hydrazones of type **8** did not give better diastereoselectivities or different stereochemical results than the achiral dimethyl- and pyrrolidine hydrazones. This indicates that the diastereofacial selectivity of the addition to sugar aldehydes is determined by the α-substituent and the chiral reagent has limited influence [18]. Therefore, only the α-hydroxy pyrrolidine-hydrazones **8** were converted to cyanohydrins **10** in high yields [19]. The reactivity exhibited by the formaldehyde pyrrolidine hydrazone was clearly higher than that of the acyclic dimethylhydrazone. This indicates a more effective delocalisation of the pyrrolidine nitrogen lone-pair electrons into the π-system, which implies an increased nucleophilic character of the azomethine carbon, in accordance with observations in the case of related enamines [20]. In addition, α-benzyloxy hydrazones **11** were cleaved, leading in one or two steps to α-hydroxy aldehydes **12**, monoprotected diols **13**, and cyanohydrins **14**.



Scheme 3

Recently, the thexyldimethylsilyl triflate (TDSOTf)-promoted regio- and stereoselective 1,4-addition of formaldehyde dimethylhydrazone and SAMP-hydrazone to α,β-unsaturated ketones was reported [21] (Scheme 4). The aza-enamine reactivity was not high enough to allow spontaneous conjugate addition to the enones **15** in contrast to the more electrophilic nitroalkenes **2** or sugar aldehydes **7**. Thus, it was necessary to use trialkylsilyltriflates as promoters giving rise to the Michael adducts as their corresponding silyl enol ethers **16**. The rich

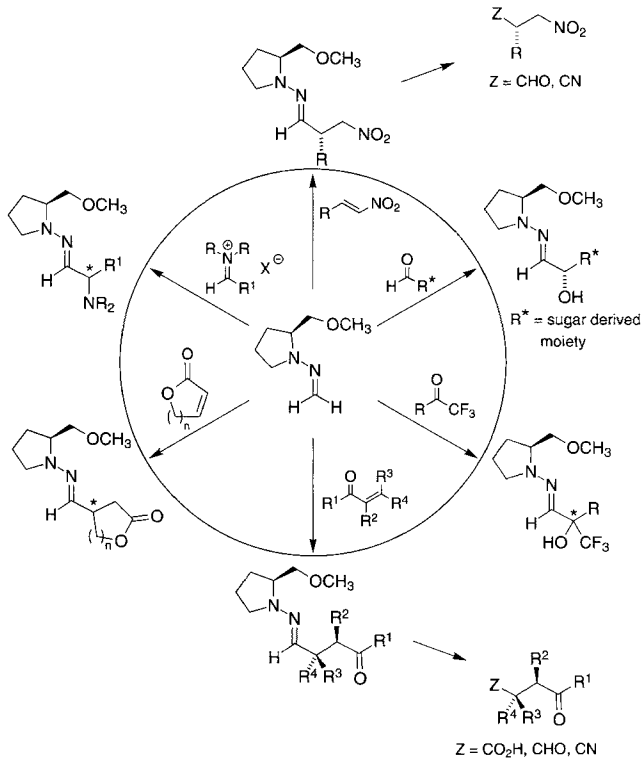
chemistry of the latter makes the primary adducts promising synthetic intermediates that not only represent protected forms of the corresponding ketones, but should also allow further regioselective electrophilic α-substitutions typical for silyl enol ethers. The reaction proceeded cleanly in all cases and 1,2-adducts could not be detected. After having established the optimum conditions for the novel Michael additions using the achiral dimethylhydrazone, an asymmetric version was developed employing the title reagent.



Scheme 4

Both, the silyl enol ethers **16**, the primary products of the reaction, and the corresponding deprotected ketones **17** could be isolated in good yields (60–86%) and with excellent diastereomeric excesses (*de* = 85–>98%). It should be emphasized that quarternary stereogenic centres [22] are easily created in this way with the highest diasteroselectivity (de ≥ 98%) within the series. The reactions proceeded with similar results in the presence of equimolar amounts of triethylamine, which may allow the 1,4-reaction to proceed in the presence of acid sensitive groups. Racemisation free cleavage of **17** to yield the desired 4-oxoaldehydes **18** has been performed in good yields (69–94%) and stereoselectivities (*ee* = 85–≥ 98%) either by ozonolysis or by acidic hydrolysis. Few possibilities can be found for asymmetric acylations (1,4-diketones), a good approach being the addition of metalated aminonitriles [8c–f]. It is also possible to obtain the 4-oxo carboxylic acids **19** by treatment of the corresponding crude aldehyde with the Jones reagent. Oxidative cleavage of **17** to 4-oxonitriles **20** has also been readily achieved with MMPP. The absolute configuration of the newly created stereogenic center was determined using different methods (X-ray structure analysis, polarimetry and the empirical rule developed by Lemière *et al.* [23]). The relative topicity turned out to be the same in all cases indicating a uniform reaction mechanism.

Current investigations have shown that formaldehyde SAMP-hydrazone reacts with other reactive electrophiles. Addition reactions to trifluoroketones, α,β-unsaturated lactones and Mannich salts are currently under investigation in our laboratories and will be reported in due course. Scheme 5 gives a survey of the synthetic potential of (*S*)-**1** at present.



Scheme 5

In summary, the title compound formaldehyde SAMP-hydrazone [24], easily prepared by reaction of paraformaldehyde with the commercially available hydrazine auxiliary SAMP, smoothly adds to various electrophilic reagents, such as nitroalkenes, sugar-aldehydes, iminium salts, trifluoromethyl ketones, α,β-unsaturated ketones and lactones, under neutral conditions. By employing the enantiomeric auxiliary RAMP, both enantiomers of the target molecules are available at will, respectively. The novel asymmetric nucleophilic formylation and cyanation methodology opens an efficient and simple route to a variety of polyfunctional aldehydes and nitriles of high enantiomeric purity. Although the protocol is stoichiometric in nature, the simplicity and mildness of the procedure avoiding strong bases usually necessary for these C–C bond formations, should stimulate further applications in synthetic chemistry.

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[24] Formaldehyde SAMP-hydrazone will be commercially available from Merck-Schuchardt, 85662 Hohenbrunn, Germany, in due course.

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