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Direct Synthesis of Dithioketals from *N,N*-Dialkylhydrazones

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Abstract: Direct dithioketalisation of *N,N*-dialkylhydrazones promoted by $BF_3 \cdot Et_2O$ or *p*-TsOH and 1,2-ethanedithiol in dry medium affords the corresponding dithiolanes in nearly quantitative yields. A variety of hydrazones derived from several kinds of aldehydes (aliphatic, aromatic, and α,β-unsaturated) and hydrazines [*N,N*-dimethylhydrazine, 1-aminopyrrolidine, and (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)] were reacted, indicating the generality of the method. The reaction was demonstrated to proceed without racemization of a particularly sensitive chiral substrate.

N,N-Dialkylhydrazones are an important class of compounds involved in a number of synthetic routes. In addition to the classical *S*AMP/*R*AMP methodology[1] for the stereocontrolled α-functionalization of their aza-enolates, a growing number of synthetic applications have been recently reported.[2] Our particular contribution to this field during the last few years has centered on the use of formaldehyde *N,N*-dialkylhydrazones as neutral formyl anion and cyanide equivalents in their additions to Michael acceptors[3] and carbonyl compounds.[4] Many of the products obtained by these routes retain the hydrazone moiety and, therefore, their synthetic potential depends not only on the many possibilities available for further C-C bond forming processes at their azomethine carbon (i.e. as a target for the addition of nucleophilic radicals,[2b] the addition of organometallics to their C=N bond,[5] etc.), but also on the palette of functional group transformations available, most commonly the deprotection reaction to aldehydes (ozonolysis, hydrolysis) and the oxidative cleavage to nitriles.[6]

In this paper, we report the unprecedented direct transformation of a variety of aldehyde *N,N*-dialkylhydrazones into their corresponding dithioketals. The main interest of this transformation arises from the fact that the chemistry of these compounds is complementary to that of hydrazones themselves, and also to that of the deprotected products (aldehydes and nitriles) usually obtained from them. Except for the rather limited aza-enamine reactivity of the former,[7] the synthetic usefulness of all these compounds are essentially based on their electrophilic character. On the contrary, dithioketals can be used as umpoled acyl equivalents for further *nucleophilic* C-C bond forming reactions *via* their corresponding lithium derivatives,[8] in addition to other interesting possibilities (desulfurisation, etc.) offered by this class of compounds. Additionally, this

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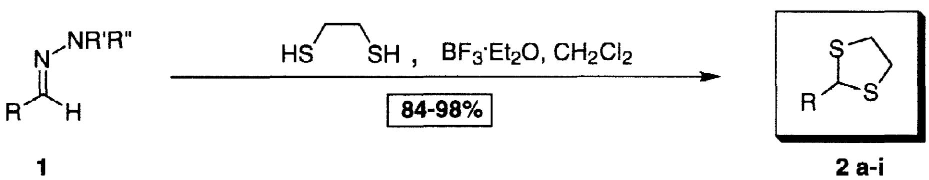
transformation can be particularly useful in those frequent cases in which the corresponding aldehyde cannot be isolated because of instability.

The activation of nitrogen-containing compounds by Lewis acids is claimed to be troublesome[9] because of the irreversible formation of strong complexes followed, in most cases, by decomposition of the substrate and/or the acidic reagent. However, during previous investigations we found that dialkylhydrazones could survive the presence of the relatively strong $BF_3 \cdot Et_2O$ and could be recovered almost quantitatively after neutralization. Considering the mentioned interest for the expected products, we decided to investigate the addition of ethanedithiol as nucleophile to $BF_3 \cdot Et_2O$-activated hydrazones (Scheme 1). The dithioketalisation reaction was found to proceed smoothly under very simple experimental conditions,[10] affording the expected products in excellent yields (84-98%) in all cases.



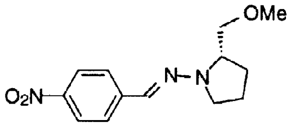
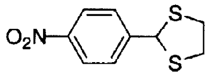
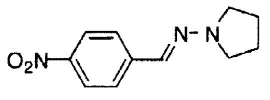
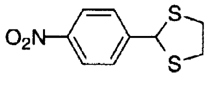
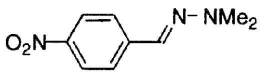
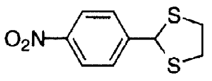
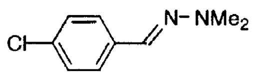
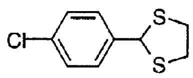
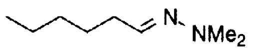
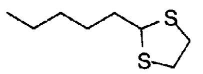
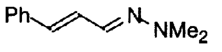
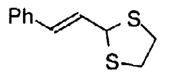
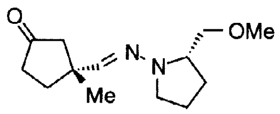
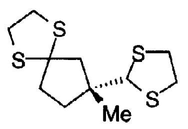
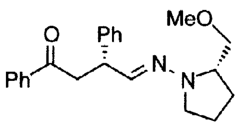
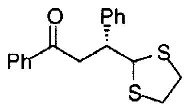
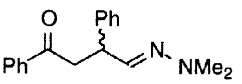
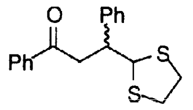
Scheme 1

The results collected in Table 1 indicate a quite uniform behaviour of the reaction, as similar yields of product were obtained for different kind of hydrazones such as *N,N*-dimethylhydrazine, 1-aminopyrrolidine, and (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (*S*AMP) derivatives from a variety of aldehydes including aromatic (**1a-d**), aliphatic (**1e, g-i**),[11] and α,β-unsaturated (**1f**)[12] substrates. The selective dithioketalisation of compound **1h** is a good index of relative reactivity, as the unreactive carbonyl group of the aromatic ketone remained untouched under the reaction conditions. In the case of compound **1g**, however, the reactive cyclopentanone carbonyl was obviously converted at once. The absence of racemization during the reaction was demonstrated for a particularly sensitive substrate (entry **h**), in which the chiral centre in position α to the hydrazone is benzylic.[13] To this aim shift experiments were performed using europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [$Eu(hfc)_3$] as the reagent and the racemic compound **2i** as reference. A single set of peaks was observed, indicating an ee ≥95%. This is a particularly important point for compounds in which the corresponding aldehyde cannot be isolated or handled due to a high tendency to racemize.

In addition to the $BF_3 \cdot Et_2O$-promoted reaction, we have also found that *p*-TsOH can also be used to promote the dithioketalisation reaction (entry **h**), affording the same products in similar yield, the only difference being a slower reaction rate. Finally, it is important to stress that the chiral hydrazine SAMP obtained as by-product in this reaction can be recovered from the aqueous layer and transformed into its valuable formaldehyde hydrazone[14] (83 %) by reaction with trioxane.

In our opinion, the high chemical efficiency and generality of this new racemization-free direct transformation from *N,N*-dialkylhydrazones into dithiolanes should find further applications, in particular from those chiral substrates formed when SAMP and related auxiliaries are used as the source of chirality in asymmetric synthesis.

Table 1. Synthesis of dithiolanes **2** from aldehyde *N,N*-dialkylhydrazones **1a-i**

Entry	Hydrazone 1	Product 2	Yield of 2 (%)[a]	Reaction time
a			96	4d
b			84	9d
c			90	10d
d			93	2d
e			85	24h
f			84	5d
g			98[b]	3d
h			90[c] 97[c,d]	16h 3d
i			85	18h

a) Promoted by $BF_3 \cdot Et_2O$. b) ee ≥98%, given as de of the starting hydrazone **1g**; see Ref. 3e; $[\alpha]^{22}_D$ +5.5 (*c* 1.0, $CHCl_3$). c) ee ≥95%, determined by ^1H-nmr shift experiments using $Eu(hfc)_3$ as reagent; $[\alpha]^{22}_D$ -19.0 (*c* 1.0, $CHCl_3$). d) Promoted by *p*-TsOH.

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10. Typical procedure: To a cooled (0 °C) solution of the hydrazone **1** (1 mmol) in dry CH_2Cl_2 (5 mL) was added 1,2 ethanedithiol (126 μL, 1.5 mmol) and then $BF_3 \cdot Et_2O$ (256 mL, 2 mmol) under an argon atmosphere. The mixture was allowed to warm to room temperature and stirred until t.l.c indicated total consumption of the starting material. The mixture was then washed with saturated $NaHCO_3$ solution (2 × 10 mL), dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography (petroleum ether-diethyl ether) to yield pure dithioketals **2**. Compound **1g** was reacted with 3.0 mmol of ethanedithiol and 4.0 mmol of $BF_3 \cdot Et_2O$. All compounds were fully characterized by ^{1}H- and ^{13}C-nmr spectroscopy and by combustion analysis. Compound **1h** (1 mmol) was alternatively dissolved in dry CH_2Cl_2 (15 mL) and treated with *p*-TsOH (1.1 mmol). Work-up was performed as described above.
11. Hydrazones **1g-i** were synthesized as previously described before: see Ref. 3f.
12. No 1,4-addition by-products were detected in the reaction mixture.
13. The corresponding free aldehyde resulting from ozonolysis of the same starting hydrazone proved to be extremely prone to racemization: See Ref. 3e.
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