N-Acyl Imidazoles: Excellent Acyl Electrophiles for 1,3-Dithiane Oxide Anions

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Abstract: 1,3-Dithiane 1-oxide anions are efficiently acylated by treatment with N-acyl imidazoles; the optimum procedure involves use of sodium hexamethyl disilazide/butyl lithium base mixtures.

In connection with our development of dithiane oxides as asymmetric building blocks we required an efficient method for acylation of 1,3-dithiane 1-oxide 2-anions.[1] 1,3-Dithianes have proved to be of great synthetic utility due to ease of handling and wide applicability, and a great deal of their chemistry has been discovered.[2] Methods of preparation of acyl dithianes commonly fall into one of two categories: direct acylation of dithiane anions or their reaction with aldehydes and subsequent oxidation.[3] However, direct acylation of 1,3-dithiane anions with carboxylic acid derivatives, while feasible, is fraught with limitations;[4-8] for example, double addition of the nucleophile has been reported as a source of byproducts unless a large excess of ester is used, and enolization rather than nucleophilic addition may also occur.[5] Yields are commonly limited by product deprotonation.[5,9] While 1,3-dithiane anions in general react well with aldehydes,[10] substitution at the 2-position can result in a much poorer or capricious reaction. For example, the enolate derived from ethyl 1,3-dithiane 2-carboxylate is reported to undergo efficient reaction with aldehydes,[11] while aldol reaction of the corresponding methyl ester apparently fails without trapping of the intermediate aldolate.[12] Anions derived from the analogous 1,3-oxathianes display a similar pattern of reactivity but can be successfully acylated using acid chlorides via the less basic cuprate reagents.[13]

In our hands dithiane oxide anions have proved even less successful as nucleophiles in reactions with aliphatic aldehydes and especially esters, orthoesters and anhydrides, perhaps due to inherently poorer nucleophilicity as a result of increased stability of the anion, although the lithio anion of 1,3-dithiane 1-oxide is known to react in fair yields with benzaldehyde (54%) and ethyl benzoate (52%).[14] Fang has reported that the allylic anion derived from 2-prop-1-enyl-1,3-dithiane 1-oxide reacts with aldehydes and ketones in high yields,[15] and a recent report describes reliable reaction of trans 1,3-dithiane 1,3-dioxide anions with aldehydes.[16] However we have been unable to obtain efficient reaction of anions derived from 1,3-dithiane 1-oxide with aliphatic aldehydes or esters using a variety of reaction conditions. Indeed, the reactions appear to be extraordinarily sensitive both to the type of base and the counter-ion used. It is interesting to note that, of all counter-ions

tested, sodium was by far the most effective, producing a dramatic improvement for aliphatic aldehyde and ester electrophiles (Tables I & II). In a series of experiments using ethyl propionate as electrophile and NHMDS as base THF proved to be a much better solvent than either DME (40% yield) or ether (0%). Use of two equivalents of NHMDS did not improve the yields of the reactions. Lewis acid additives including $TiCl_4$, $ZnCl_2$, $SnCl_4$, $BF_3.Et_2O$, and $MgBr_2$ uniformly produced only mixtures of starting material and a decomposition product, perhaps resulting from a Pummerer rearrangement process, known to us to be facile in these systems.[17] Exceptionally, use of LiCl did provide a modest increase in the yield of acylated product from 46 to 57%.

Table I. 1,3-Dithiane 1-Oxide Anions: Aldehyde Electrophiles
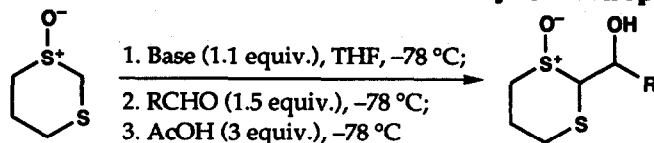
Base[‡]	Ester	Yield/%
LDA	Benzaldehyde	36
NHMDS	Acetaldehyde	64
NHMDS	Propionaldehyde	59
NHMDS	Butyraldehyde	55
NHMDS	Benzaldehyde	54

‡ Use of BuLi, LDA, KHMDS, or ^{i}BuMgCl as base led to poor or zero isolated yields of product in all reactions with aliphatic aldehydes

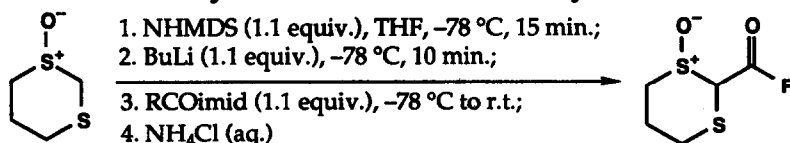**Table II. 1,3-Dithiane 1-Oxide Anions: Ester Electrophiles**
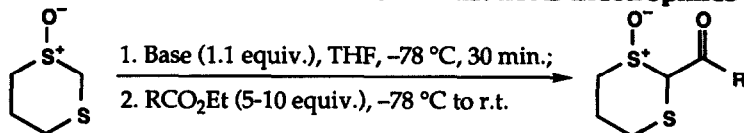
Base[§]	Ester	Yield/%
BuLi	Ethyl butyrate	32
LHMDS	Ethyl benzoate	61
KHMDS	Ethyl propionate	26
NHMDS	Ethyl acetate	68
NHMDS	Ethyl propionate	46
NHMDS	Ethyl butyrate	40
NHMDS	Ethyl benzoate	56
NHMDS/BuLi	Ethyl benzoate	61

§ Use of BuLi, LHMDS, or KHMDS as base generally led to poor or zero isolated yields of product in reactions with aliphatic esters

We reasoned that use of an acyl electrophile possessing a suitable balance of reactivity should resolve these problems.

N-Acyl imidazoles were reported by Staab in 1962 to be excellent acylating agents for Grignard reagents, no double addition to produce carbinol being observed.[18] Other suitable carbon nucleophiles include anions derived from α-keto esters,[19,20] phosphorus ylids,[20] and α-silyl esters.[21] *N*-Acyl imidazoles have even been used as electrophiles in Friedel–Crafts reactions[20,22] and as formyl transfer agents for the preparation of formyl transition metal complexes;[23] but seem now to be used routinely only for heteroatom acylation rather than carbon–carbon bond formation.[24] Interestingly, Solladié has observed two cases of successful acylation of a sulphoxide anion using an α,β-unsaturated acyl imidazole.[25] We were therefore pleased to find that treatment of dithiane oxide anions under the correct conditions with various *N*-acyl imidazoles led smoothly and cleanly to the corresponding acylated products in high yields (Table III).

Table III. Acyl Dithiane Oxides from *N*-Acyl Imidazoles

1. NHMDS (1.1 equiv.), THF, –78 °C, 15 min.;
2. BuLi (1.1 equiv.), –78 °C, 10 min.;
3. RCOimid (1.1 equiv.), –78 °C to r.t.;
4. NH$_4$Cl (aq.)

N-Acyl Imidazole	Yield/%
CH$_3$COimid	85
CH$_3$CH$_2$COimid	85
CH$_3$CH$_2$CH$_2$COimid	79
CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$COimid	88
(CH$_3$)$_3$COimid	80
PhCH$_2$COimid	83
CH$_2$=CHCH$_2$CH$_2$COimid	69
PhCOimid	77
4-^{t}BuPhCOimid	90
4-CF$_3$PhCOimid	80

Generation of the *N*-acyl imidazoles was readily accomplished as reported by Staab either from carboxylic acid by treatment with CDI (1 equiv.) in THF solution at 0 °C or, more satisfactorily, from acid chloride by treatment with two equivalents of imidazole in THF solution at room temperature.

The optimum procedure for acyl dithiane oxide production involves generation of the metallated species from 1,3-dithiane 1-oxide by deprotonation at –78 °C with a solution of sodium hexamethyl disilazide (1.1 equiv.) over 15 minutes followed by addition of a solution of butyl lithium (1.1 equiv.) at –78 °C to prevent yields being compromised by reprotonation of the dithiane oxide anion by the more acidic acyl dithiane oxide product. After a further 10 minutes the resulting anion mixture is treated with *N*-acyl imidazole (1.1 equiv.) at –78 °C and the reaction allowed to reach room temperature over about one hour before quenching with aqueous ammonium chloride solution. The acyl dithiane oxide may then be isolated after normal work up in excellent yields. *N*-Acyl imidazoles themselves apparently do not undergo deprotonation faster than nucleophilic attack under these conditions.

Although this procedure appears to be quite general for simple substrates, there are a number of limitations. For example, α,β-unsaturated and α-keto acyl imidazoles are unsatisfactory electrophiles; in this context it is interesting to recall the successful use of α,β-unsaturated acyl imidazoles in acylation of a simpler sulphoxide anion by Solladié.[25] In addition, anions derived from 1,3-dithiane oxides substituted at the C-2 position and, curiously, from 1,3-dithiane itself are unsuccessful nucleophiles. Our reactions appear to be among the first examples of acylation of relatively unreactive carbon nucleophiles using N-acyl imidazoles, perhaps because of this very unpredictability.

Acknowledgment

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