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**Preliminary communication**

# COMPARATIVE STUDY FOR THE INTRODUCTION OF A MASKED NUCLEOPHILIC ACYL MOIETY AT THE C(3) SITE OF α,β-UNSATURATED ALDEHYDES AND ESTERS

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## Summary

Bis(methylthio)- and bis(methylseleno)-alkyllithiums in THF/HMPT (1.1 eq) and bis(phenylthio)alkyllithiums in DME were found to be the best reagents out of several examined for formally introducing an acyl moiety at the C(3) site of α,β-unsaturated aldehydes and esters.

## Introduction

The control of the reactivity of α-heterosubstituted organometallics has been the subject of several reports [1—3]. It was first found that in many cases, the C(1) adduct of organometallics to enones is transferred to the C(3) site on raising the temperature or by increasing the polarity of the medium [1]. Recently, the groups of Brown [4], Seyden-Penne and ourselves [5] found simultaneously and independently that the presence in the medium of hexamethylphosphotriamide (HMPT), prior to the addition of the enone greatly changes the course of the reaction, allowing the "kinetic" introduction of the organometallics at the C(3) site. Following this, several reports appeared [7—11] * which substantiate these observations.

We present in this communication preliminary findings concerning the introduction of masked acyl groups at the C(3) sites of α,β-unsaturated aldehydes and esters (Scheme 1).

These two classes of derivatives are particularly interesting since α,β-unsaturated aldehydes usually have a higher propensity [1] than enones to react at

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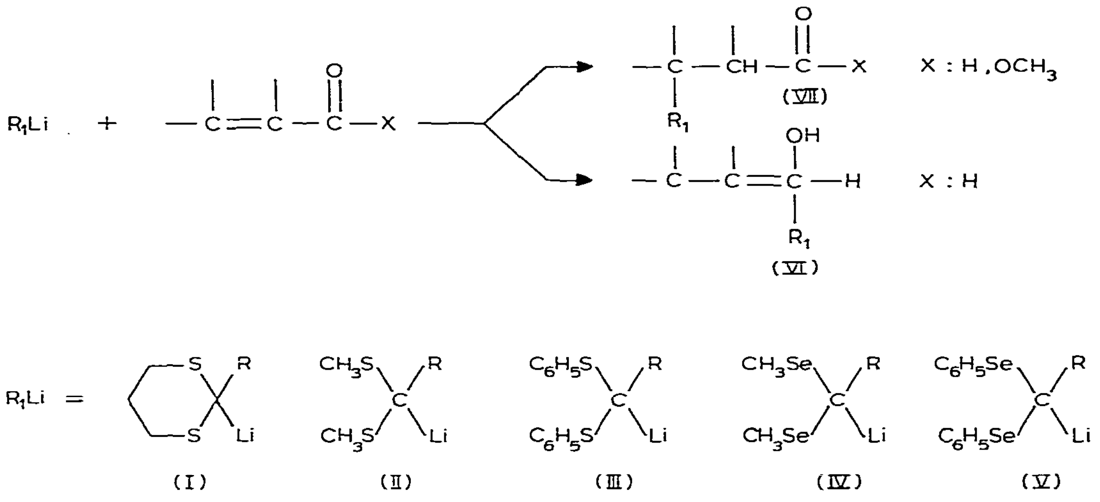
*Hünig et al. [11] observed that HMPT favours the C(1) instead of the C(3) attack of enones. The results which seem contradictory to our predictions can be explained in terms of further reaction of the first formed alcoholate (resulting from the C(1) attack) favoured by addition of HMPT. However, this explanation has to be experimentally verified. We thank Dr. Hünig for a valuable discussion during his visit to Namur.



SCHEME 1

C(1), and in the case of esters the C(1) adduct if formed cannot be transformed into the C(3) adduct.

## Results and discussion

We used α-lithio-1,3-dithianes (I) [12], α-lithiobis(methylthio)alkanes (II) [13], α-lithiobis(phenylthio)alkanes (III) [14], α-lithiobis(methylseleno)alkanes (IV) [15] and α-lithiobis(phenylseleno)alkanes (V) [15,16] as acyl anion equivalents [1—3] and we performed the reactions under a variety of experimental conditions, using solvents of different polarity and complexing ability such as ether, tetrahydrofuran (THF), dimethoxyethane (DME), in the absence or in the presence of additives such as HMPT, tripyridinophosphoramide (TPPT) and cryptand.

In general, yields of products resulting from the C(3) attack are negligible in the case of 2-hexanal when ether or THF is used (conditions: −78°C, 0.2 h, then $NH_4Cl/H_2O$ at −78°C). Under similar conditions only a few percent (<25%) of the C(3) adduct is observed together with a large amount of unidentified products* when α,β-unsaturated esters are substituted for the aldehydes.

In all the cases studied, the presence of HMPT (1.1 eq) favours the formation of the C(3) adduct as expected. However, when hexenal is used (Table 1), we were unable to avoid the concomitant formation of the C(1) adduct, and in the case of esters the yields of the C(3) adducts are modest (24—48%) due to enolate formation.

Various solvents were examined in order to improve the C(3) addition reaction. The results are presented in Tables 1 and 2. In summary, the best procedure for the introduction of the acyl moieties at the C(3) site of α,β-unsaturated esters is to use bis(phenylthio)alkyllithiums in DME**, whereas for α,β-un-

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*In some cases, such as bis(methylseleno)alkyllithiums, the C(1) adduct undergoes a subsequent reaction which allows the recovery of a unique adduct. These results will be reported later.

**In the case of enones, DME was found to largely favour the C(3) introduction of α-lithio(methylseleno)-alkanes [6].

TABLE 1[a]

REACTIONS OF COMPOUNDS I—V WITH $\alpha,\beta$-UNSATURATED $C_3H_7CH{=}CHCHO$

| Entry | Organometallics | | Conditions | VI + VII (%) | VI/(VI + VII) (%) | VII/(VI + VII) (%) |
|---|---|---|---|---|---|---|
| | Number | R | | | | |
| 1 | I | $CH_3$ | THF/HMPT (1.1 eq) | 57 | 58 | 42 |
| 2 | II | $CH_3$ | THF/HMPT (1.1 eq) | 68 | 18 | 82 |
| 3 | III | $CH_3$ | THF/HMPT (1.1 eq) | 33 | 82 | 18 |
| 4 | IV | $CH_3$ | THF/HMPT (1.1 eq) | 63 | 28 | 72 |
| 5 | V | $CH_3$ | THF/HMPT (1.1 eq) | — | 100 | 0 |
| 6 | IV | $CH_3$ | THF | 74 | 100 | 0 |
| 7 | II | $CH_3$ | THF/HMPT (2.2 eq) | 40 | 16 | 84 |
| 8 | IV | $CH_3$ | THF/HMPT (2.2 eq) | 51 | 21 | 79 |
| 9 | IV | $CH_3$ | THF/TPPT (1.1 eq) | 58 | 24 | 76 |
| 10 | IV | $CH_3$ | THF/(2.2.1)[b] | — | 68 | 32 |
| 11 | IV | $CH_3$ | THF/(2.2.2)[b] | — | 86 | 14 |
| 12 | IV | $CH_3$ | DME | — | 83 | 17 |
| 13 | IV | $CH_3$ | DME/HMPT (1.1 eq) | — | 24 | 76 |

[a] All the reactions were performed at −78°C and quenched, after 0.2 h, by addition at −78°C of an aqueous solution of $NH_4Cl$. [b] Kryptofix-2.2.1 and -2.2.2 were purchased from Merck.

TABLE 2[a]

REACTIONS OF COMPOUNDS I, III and IV WITH $\alpha,\beta$-UNSATURATED ESTERS

| Entry | Organometallics | | $\alpha,\beta$-Unsaturated esters | Conditions | VII (%) |
|---|---|---|---|---|---|
| | Number | R | | | |
| 1 | I | H | $C_5H_{11}CH{=}CHCOOCH_3$ | THF/HMPT (1.1 eq) | 35 |
| 2 | I | $CH_3$ | $C_5H_{11}CH{=}CHCOOCH_3$ | THF/HMPT (1.1 eq) | 42 |
| 3 | III | $CH_3$ | $C_5H_{11}CH{=}CHCOOCH_3$ | THF/HMPT (1.1 eq) | 45 |
| 4 | IV | $CH_3$ | $C_5H_{11}CH{=}CHCOOCH_3$ | THF/HMPT (1.1 eq) | 48 |
| 5 | III | $CH_3$ | $(CH_3)_2CHCH{=}CHCOOCH_3$ | THF/HMPT (1.1 eq) | 24 |
| 6 | III | $CH_3$ | $C_6H_5CH{=}CHCOOCH_3$ | THF/HMPT (1.1 eq) | 54 |
| 7 | III | $CH_3$ | $C_6H_5CH{=}CHCOOCH_3$ | THF/(2.2.1)[b] | 66 |
| 8 | III | $CH_3$ | $C_5H_{11}CH{=}CHCOOCH_3$ | DME | 68 |
| 9 | III | $CH_3$ | $(CH_3)_2CHCH{=}CHCOOCH_3$ | DME | 43 |
| 10 | III | $CH_3$ | $C_6H_5CH{=}CHCOOCH_3$ | DME | 68 |
| 11 | III | $CH_3$ | $CH_2{=}CHCOOCH_3$ | DME | 52 |
| 12 | III | H | $CH_2{=}CHCOOCH_3$ | DME | 45 |
| 13 | III | H | $C_5H_{11}CH{=}CHCOOCH_3$ | DME | 55 |

[a] All the reactions were performed at −78°C and quenched, after 0.2 h, by addition at −78°C of an aqueous solution of $NH_4Cl$. [b] Kryptofix-2.2.1 and -2.2.2 were purchased from Merck.

saturated aldehydes, the preferred reagents are bis(methylthio)- and bis(methylseleno)-alkyllithiums (II, IV) in THF/HMPT (1.1 eq.). Thus, the choice of the correct combination of reagents and solvents is important in achieving the best yield.

We also observed that DME does not favour the C(3) addition of organometallics I—V to $\alpha,\beta$-unsaturated aldehydes. This sharply contrasts with the case of $\alpha$-enones, which react in the C(3) fashion with IV in this solvent [6].

Finally, we were surprised to find that bis(phenylthio) and bis(phenylseleno) derivatives III and V (R = $CH_3$), in which the phenylthio and phenylseleno groups are thought to be bulkier and to stabilize the carbanionic centre better than the methyl analogues II and IV, respectively, do not react to a large extent at the C(3) site of aldehydes. These results contrast with the usual observations [1]*.

In several instances (Table 1 entries 1, 3 and 4) we have confirmed that the C(3) addition occurs under "kinetic control" and we were not able to change the ratio of VI/VII by allowing the reaction mixture to warm up to 20°C prior to hydrolysis.

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*This observation was also verified in this work: compare Table 2, entries 8—13 and 11—12.