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ALKYLATION OF STABILIZED ACETYLIDES IN DMSO. PREPARATION OF α,β-ACETYLENIC ALCOHOLS AND ACETALS.

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Summary: Stabilized terminal acetylenes **1** [e.g. R=CH_2OTHP, Ph, $CH(OEt)_2$] may be converted into lithioacetylides and readily alkylated with 1° alkyl halides in DMSO to afford functionalized disubstituted acetylenes.

The alkylation of terminal acetylenes has traditionally been carried out using sodium amide in liquid ammonia[1] or n-butyllithium in HMPA.[2] Other alkylation methods may be desirable for convenience or for health reasons. The alkylation of metal (M=Li, Na) acetylides in DMSO has also been reported.[3] However, the reaction in DMSO seems to be restricted by competing metalation of the solvent (eq. 1).[4] For example, propynyllithium was alkylated with iodobutane to afford a moderate (48%) yield of 2-heptyne only when the reaction mixture was saturated with propyne.[3c]

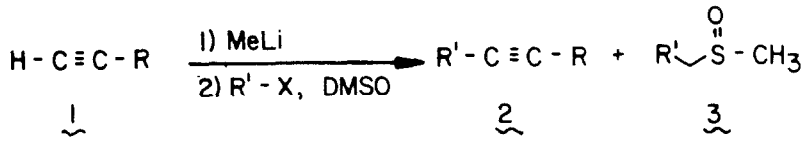
$$R-C\equiv C-M + CH_3SOCH_3 \rightleftharpoons R-C\equiv C-H + MCH_2SOCH_3 \qquad (1)$$

We now wish to report that whereas deprotonation of DMSO is a major problem in the alkylation of simple (R=alkyl) acetylides, those possessing an inductively stabilizing group may be conveniently alkylated in good yields using DMSO as solvent.

A series of terminal acetylenes (1) were treated with n-BuLi or MeLi (THF, 0°C, 15 min) followed by an alkyl halide and DMSO (0°C → RT, 3h) to afford a mixture of alkylation products 2 and 3. The much more polar sulfoxide 3 was conveniently removed by filtration through silica gel (petroleum ether:ethyl ether, 20:1); distillation of the eluate afforded the desired alkylated acetylene 2. Results are summarized in the Table. For example, with the tetrahydropyranyl ether of propargyl alcohol (entry 1), a 93:7 mixture of 2 and 3 was obtained which, upon purification, furnished an 84% yield of 2. Similar ratios and yields were obtained with other protected propargyl alcohols investigated (entries 2, 3). Not unexpectedly, a protected homopropargyl alcohol (entry 4) gave a much lower yield of 2, and a simple terminal acetylene (entry 5) afforded an even lower yield of the desired product. In these two cases, the major

product was the alkylated sulfoxide 3. In contrast, with phenylacetylene (entry 6) and 3,3-diethoxypropyne[5] (entry 7), the alkylated sulfoxide 3 was not detected (by 250 MHz ^{1}H NMR spectroscopy).

TABLE Alkylation of Terminal Alkynes in DMSO[a]



1 2 3

Entry	R	R'-X	Ratio 2:3[b]	Yield of 2 (%)[c]
1	CH_2OTHP	$nC_{10}H_{21}Br$	93:7	84
2	$C(CH_3)_2OBn$	$nC_{10}H_{21}Br$	90:10	76
3	CH_2OBn	$nC_{10}H_{21}Br$	94:6	77
4	$(CH_2)_2OTHP$	$nC_{10}H_{21}Br$	35:65	28
5	$(CH_2)_5CH_3$	$nC_{10}H_{21}Br$	9:91	7
6	Ph	$nC_{10}H_{21}Br$	>99:<1	85
7	$CH(OEt)_2$	$nC_{10}H_{21}Br$	>99:<1	87
8	CH_2OTHP	$nC_{10}H_{21}Cl$	94:6	66[d]
9	CH_2OTHP	$nC_{10}H_{21}I$	92:8	84
10	CH_2OTHP	$nC_6H_{13}Br$	94:6	82
11	CH_2OTHP	$(CH_3)_2CHCH_2Br$	e	42
12	CH_2OTHP	$nC_6H_{13}(CH_3)CHBr$	e	6

[a] See typical experimental procedure given. [b] Determined by ^{1}H NMR (250 MHz) spectroscopy on the crude reaction product. [c] Isolated yield of chromatographed and distilled (Kugelrohr) product. [d] Reaction was allowed to proceed at room temperature for 15 h. [e] Not determined.

If the above results are indicative of the position of the equlibrium represented by equation 1, then the following order of acidities is suggested:

$$Ph-C\equiv CH \approx (EtO)_2CH-C\equiv CH > ROCH_2C\equiv CH > ROCH_2CH_2C\equiv CH > R-C\equiv CH$$

This order presumably reflects the ability of the substituents to stabilize the resulting anions.

We have also briefly investigated the effect of the alkyl halide on the alkylation of 1 ($R=CH_2OTHP$). With a primaryl alkyl chloride (entry 8), a reasonable yield (66%) of alkylated product was obtained but only after a prolonged (15h) reaction time. Reaction with a primary iodide (entry 9) gave results comparable to primary bromides (entries 1, 10). Only a modest (42%) yield of 2 was obtained with a branched (e.g. 2-methyl-1-bromopropane, entry 11) alkyl halide, presumably due to competing elimination.[2c] (The crude reaction product contained a 44:56 mixture of 1 and 2, respectively.) Even more dismal results were observed with a 2° bromide (entry 12). Hence it appears that this method is best suited for 1° bromides and iodides not branched at the 2-position.

The alkylation products 2 ($R=CH_2OTHP$) are potentially useful precursors to α,β-acetylenic alcohols which may be converted into (E)-[6] or (Z)[7]-allylic alcohols, substrates for the enormously popular Sharpless asymmetric epoxidation.[8] For example, when the THP ether 2 ($R=CH_2OTHP$, $R'=nC_{10}H_{21}$) was stirred with DOWEX 50X8 (MeOH, RT, 12h),[9] 2-tridecyn-1-ol[10] was obtained in 96% yield. Reduction with $LiAlH_4$ (THF, reflux, 2h) afforded the corresponding (E)-allylic alcohol (91%) while semihydrogenation (Pd-$BaSO_4$, hexanes) gave the (Z)-allylic alcohol (96%).

α,β-Acetylenic acetals are also useful synthetic intermediates.[11]

A typical experimental procedure follows:

Alkylation of 1-Tetrahydropyranyloxy-2-propyne with 1-bromodecane

To a cold (0°C), stirred solution of 1 (R = CH_2OTHP, 2.3 mmol) in dry THF (1 mL) was added a solution of MeLi•LiBr in ether (1.28M, 2.0 mmol). The resulting pale yellow solution was stirred at 0°C for 15 minutes. 1-Bromodecane (2.0 mmol) was then added followed by dry DMSO (5 mL). The tan slurry was allowed to warm to room temperature and was stirred at ambient temperature for 3h. The mixture was cooled in a cold water bath and quenched by the dropwise addition of water. Ether (30 mL) was added and the organic layer was washed with 4 x 20 mL of half-saturated brine. Drying ($MgSO_4$) and concentration afforded a yellow oil. Filtration through silica gel (7g, pet ether:ether, 20:1) gave a colourless oil free of sulfoxide 3. Kugelrohr distillation (air-bath temperature 110-120°C/0.2 Torr) then afforded the desired product as a clear colourless liquid (84%). Spectral data (IR, 250 MHz ^1H NMR) was consistent with the expected product.

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