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Solvent and substituent effects on conjugated eliminations in propargylic systems

Frédéric Le Strat and Jacques Maddaluno*

Laboratoire des Fonctions Azotées & Oxygénées Complexes de l'IRCOF, UMR 6014 CNRS, Université de Rouen, 76821 Mont St Aignan Cedex, France

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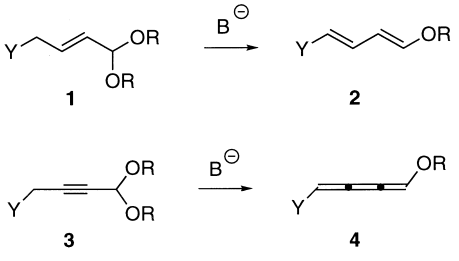
Abstract

The deprotonation of 4-methoxy-but-2-ynal diethyl acetal by *n*-butyllithium induces an acetylenic–allenic isomerization (in diethylether) or a conjugated elimination reaction (in THF), providing the corresponding 1,4-dialkoxycumulene. An allenyllithium, that has been trapped as an allenylstannane, is proposed to be a common intermediate to both pathways. Also, the deprotonation of 4-dialkylamino-but-2-ynal diethyl acetals in the same conditions affords a mixture of (*E*) and (*Z*) aminocrotonates of which formation can be explained by a chemioselective removal of the acetalic proton leading to an intermediate allenyllithium that has equally been trapped by stannylation.

The base-triggered conjugated elimination reaction on ethylenic acetals **1** provides a short-cut to 1,4-disubstituted butadienes[1] **2** that are good partners for cycloadditions.[2] Correspondingly, propargylic acetals lead to dialkoxycumulenes, as described by Brandsma and colleagues as early as 1970.[3] These authors observed that the action of 2 equiv. of *n*-BuLi in diethyl ether on 4-methoxy-but-2-ynal diethyl acetal **3** (Y = EtO and R = Et) provides the corresponding 1,4-diethoxy-1,2,3-butatriene **4** in excellent yield and with a 2:1 selectivity in favor of the *E*-isomer (Scheme 1).



Scheme 1. Conjugated elimination on functionalized allylic and propargylic acetals

* Corresponding author: Fax: 33 (0) 235 522 971; e-mail: jmaddalu@crihan.fr

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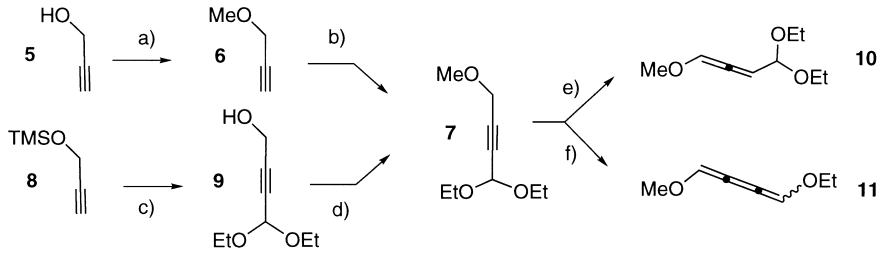
Albeit these cumulenes have been cleanly isolated and are described as relatively robust species, their synthetic potential has drawn relatively little attention[4] despite an exceptionally high density of functionalities on such small synthons. Brandsma's procedure, based on acetal **7**, is extremely convenient for preparing these compounds. Two methods can be employed to access **7**. The first one[5] is based on the condensation of the Grignard derivative of propargyl ether **6** on phenyl diethyl orthoformate[6] (Scheme 2). The second one relies on the same steps from propargyloxytrimethylsilane **8**, providing alcohol **9** that is alkylated by dimethylsulfate to afford **7** in slightly better yields (65% versus 52%).



Scheme 2. (a) Me_2SO_4, NaOH, H_2O; (b) EtMgBr then $PhOCH(OEt)_2$; (c) EtMgBr, $PhOCH(OEt)_2$ then K_2CO_3, MeOH, 0°C; (d) NaH, THF then Me_2SO_4; (e) *n*-BuLi, Et_2O, –40°C; (f) *n*-BuLi, THF, –40°C

To our surprise, reacting *n*-BuLi with **7** (≈0.25 M) in ether did not prompt the expected elimination step but the quantitative isomerization of **7** into allene **10**. By contrast, performing the same reaction in THF completely reversed the selectivity in favor of cumulene **11** (in an *E*:*Z* ratio identical to that reported by Brandsma[3]), at the condition that a sufficient excess of base is used (Scheme 2 and Table 1).

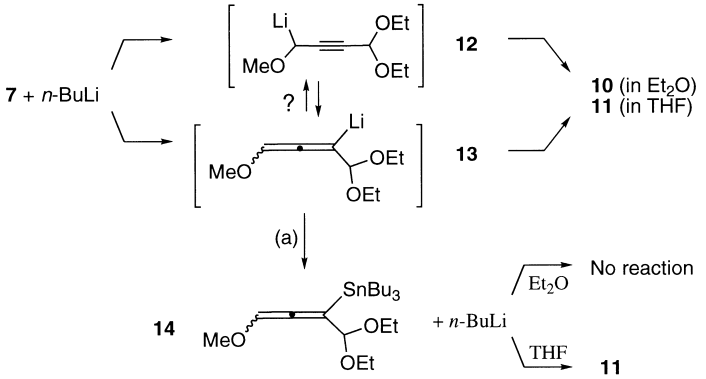
Table 1
Elimination/isomerisation selectivity on propargylic acetal **7** as a function of the base

Entry	Base (eq)	Solvent	T°C	Conv. (%)	**11/10**
1	*n*-BuLi (2.3)	Et_2O	-45°C	64	0 : 100
2	*n*-BuLi (1.5)	THF	-45°C		70 : 30
3	*n*-BuLi (2.3)	THF	-45°C	81	100 : 0
4	*n*-Buli/LiBr (2.3)	Et_2O	-45°C	82	66 : 33
5	KHMDS	THF	-45°C	0	-
6	KHMDS	THF	0°C	88	0 : 100

Considering that this discrepancy with Brandsma's observations could stem from the quality of the *n*-BuLi, and especially from the well-known influence of lithium halides on the behavior of the organolithium compound,[7] we decided to resort, in ether, to a 1:1 mixture of LiBr and commercial *n*-BuLi. This restored the selectivity in favor of **11** (entry 4). But the allene **10** can also be prepared in THF, replacing butyllithium by potassium hexamethyldisilazane (KHMDS). Slightly warming up the medium leads indeed, in an almost quantitative yield, to **10** (entry 6).

On a mechanistic point of view, the deprotonation of **7** can yield to either a propargyllithium derivative such as **12** or to an allenyllithium **13** and these species can equilibrate in solution.[8] In

our case, the conversion is total and the two products recovered (**10** and/or **11**) seem to derive from **13**, which is either protonated to give the allene **10** or undergoes a β-elimination to provide cumulene **11** (Scheme 3). We have checked that **10** thus obtained cannot be converted into **11** upon treatment with *n*-BuLi in THF. Trapping of the intermediate **13** has also been achieved. The treatment of **7** with 2.3 equiv. of *n*-BuLi in ether at –40°C has been followed by the addition of 2.3 equiv. of neat Bu_3SnCl and warming up to 0°C (Scheme 3). After 1 h and hydrolysis, the corresponding tin-substituted allenic acetal **14** was obtained in ≈40% yield after purification by flash-chromatography on silica gel. The predominance of the allenyllithium form **13** is in fine agreement with Reich's thorough NMR studies[8] that have clearly established that oxygen substituents on the propargylic position favor this isomer, even with strongly chelating groups such as MOM, MEM or β-(dimethylamino)ethoxy.[8a] Regenerating **13** from **14** in THF by action with *n*-BuLi at –40°C triggers the β-elimination and leads to cumulene **11** in quantitative yields. By contrast, **14** remains inert towards butyllithium in ether in the same conditions.†

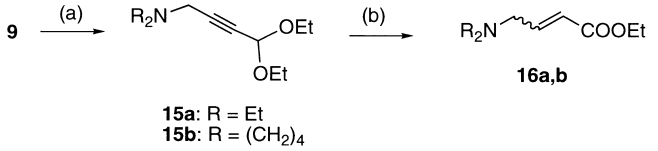


Scheme 3. (a) Bu_3SnCl, Et_2O, 0°C, 1 h

Therefore, the solvent effect we observe could be due to differences in the structure/aggregation of **13** in solution. At least two reasons can be invoked to explain these differences: (i) NMR indicates lithiomethoxyallene to be dimeric in THF and tetrameric in diethyl ether;[9] (ii) it has been shown that when the allenyl structure bears a chelating group, it can act as a supplementary ligand in the lithium coordination sphere in place of a solvent molecule.[10] If we assume that one of the oxygens of the acetal in **13** plays this role, it could endow this group with a leaving character. Thus, only in THF would the lithium act as an intramolecular Lewis acid for **13**.

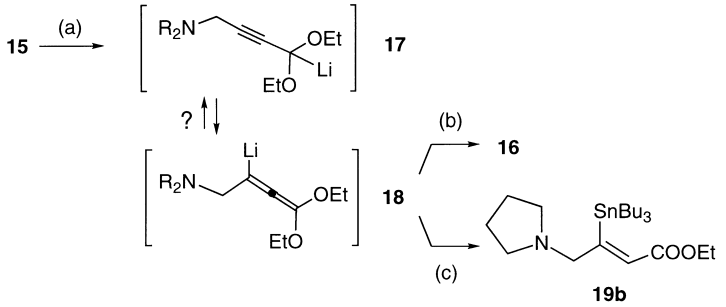
To extend the scope of this reaction, we then studied the case of propargylic aminoacetals. The two compounds **15** can be readily prepared by tosylation of **9** and substitution by diethylamine or pyrrolidine in THF (Scheme 4).[11] Their deprotonation with 2.2 equiv. of *n*-BuLi at –40°C affords, after 30 min in THF (no reaction was observed in ether), a mixture of *E*/*Z* aminocrotonate **16** (*E*:*Z* = 1:1 for R = NEt_2, 1:2 for R = pyrrolidine) in ≈35% yield after distillation in a bulb-to-bulb oven.

† Warming up the medium would probably make this reaction possible in ether as well as in THF, as described in a related situation by: Beaudet, I.; Launay, V.; Parrain, J. L.; Quintard, J. P. *Tetrahedron Lett*. **1995**, *36*, 389–392. However, this would not mimic our reaction conditions. See also in relation: (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841–869. (b) Beaudet, I.; Parrain, J. L.; Quintard, J. P. *Tetrahedron Lett*. **1991**, *32*, 6333–6336.



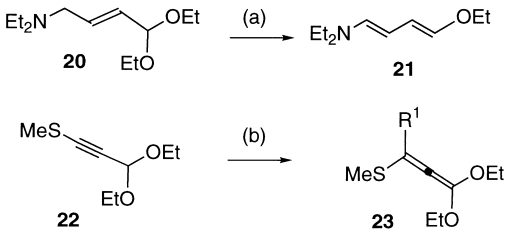
Scheme 4. (a) (i) TsCl, KOH, THF, –10°C, 1 h; (ii) 3 equiv. amine, THF, rt, overnight; (b) *n*-BuLi, THF, –40°C, 30 min

This change in the reaction pathway can be due to the chemioselective deprotonation of the acetalic position, leading again to a propargyl (**17**) and/or allenyl (**18**) lithium intermediate (Scheme 5). Since the conversion of **15** is total again, it seems that upon hydrolysis, only the allenyl form **18** is protonated to yield an intermediate ketene ketal, that is hydrolized during the work-up to provide the aminocrotonates **16**. The allenyl **18b** can be trapped by Bu_3SnCl in conditions similar to those described above, leading to the pure (*Z*)-β-stannyl crotonate **19b** in 22% yield after flash-chromatography.



Scheme 5. (a) *n*-BuLi, THF, –40°C, 30 min; (b) H_2O; (c) Bu_3SnCl, THF, 0°C, 40 min

This result is relatively unexpected since the deprotonation in extremely similar conditions of allylic aminoacetals such as **20** provides in high yields the corresponding elimination product, viz. dienamine **21** (Scheme 6).[2b,12] On the other hand, a comparable deprotonation of the propargylic acetal **22** has been described[13] and gives access to the corresponding ketene ketal **23**, following a reaction pathway identical to that we report here. This swap of the regioselectivity of the deprotonation is difficult to rationalize but is probably to be considered in relation to the likely complexation occurring between the amino appendage of the propargylic acetal **15** and butylllithium prior to the reaction.



Scheme 6. (a) 3 equiv. *t*-BuOK+3 equiv. *n*-BuLi, THF, –70°C, 30 min; (b) Ref. 13

In conclusion, we have shown that the deprotonation of propargylic acetals can lead at will to the isomerization into the corresponding allenes or to the conjugated elimination reaction on a simple solvent swap. We have also observed that aminopropargylic acetals undergo a regioselective deprotonation of the acetalic position, at the origin of the formation of a ketene ketal that is hydrolized upon work-up into the corresponding aminocrotonates.

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