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Metallic chalcogenolates mediated modular Michael-aldol cascade reaction: an easy route to multi-functionalized chalcogenides and Morita–Baylis–Hillman adducts

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ABSTRACT

Chalcogenolate mediated Michael-aldol cascade reactions consists of a very efficient route to multi-functionalized γ-hydroxichalcogenides. Although, when selenolates are employed, these γ-hydroxichalcogenides can be readily converted into the corresponding Morita–Baylis–Hillman adducts by oxidative elimination of the selenium moiety. In this context, herein we present a complete study on the scope and limitations of this reaction.

1. Introduction

The Michael and the aldol reactions have always been amongst the most important and widely employed reactions in organic synthesis.[1] Another relevant feature of these two reactions is the fact that both transformations can be performed in a cascade fashion.[2–8] For this purpose, metallic organochalcogenolates consists on a key class of nucleophiles due to its high nucleophilicity and low basicity.[9] In special, when metallic selenolates are employed as initial nucleophiles, the resulting adduct can be easily converted into the corresponding Morita–Baylis–Hillman (MBH) adduct by *syn*-selenoxide elimination, as previously described by the group.[10] Since these kinds of nucleophiles can be generated in situ by the reductive cleavage of the elemental chalcogen by the corresponding organometallic, it is worth noting that this methodology completely avoids the manipulation of chalcogen nucleophiles with unpleasant odors and can be applied in many different situations.[11–15]

In this study we decided to evaluate the scope and the limitations of this protocol and its complementarity to the MBH reaction. Focusing in possible synthetic applications of this methodology, we have evaluated the behavior of different chalcogenolates, aldehydes, and Michael acceptors.

2. Results and discussion

Willing to investigate the cascade reaction, we proposed a systematic study in order to evaluate each of the three components involved in this protocol and the most important effects that might drive the reactivity (Fig. 1).

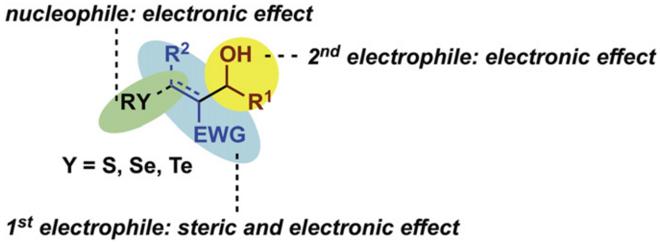

Fig. 1. The possible driving effects of each component of the cascade reaction.

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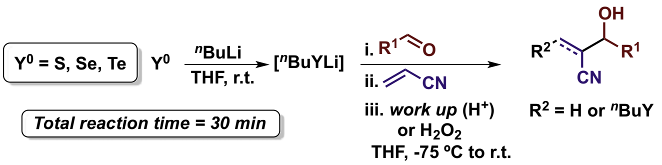
One of the most serious drawbacks of the MBH reaction is the fact that the reaction with electron rich aldehydes, such as alkyl- and electron-donating substituted aryl-aldehydes is quite slow in comparison to electron-poor aldehydes, such as nitro-aromatic ones.[16] Our initial study focused on the evaluation of the behavior of different aldehydes and chalcogenolates. In these initial experiments we have chosen acrylonitrile as the standard Michael acceptor. In order to verify the influence of the electronic effect on the secondary electrophile, some aromatic aldehydes were tested, in which the substituents were varied from electron donating- to electron withdrawing groups.

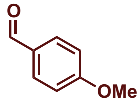
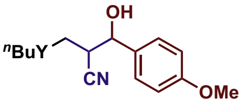
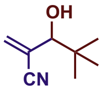
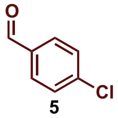
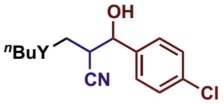
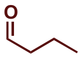
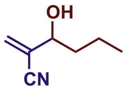
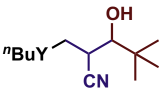
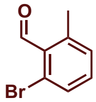
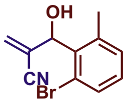
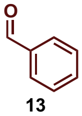
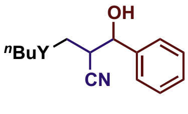
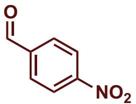
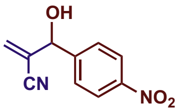
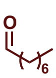
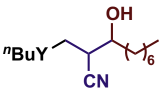
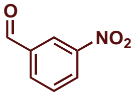
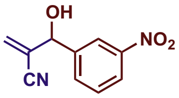
Amongst these examples, some selenides were converted into the corresponding MBH adducts by in situ oxidative elimination, by quenching the reaction with hydrogen peroxide solution (30%). The following Table 1 summarizes the obtained results.

A fair reactivity comparison can be made with aromatic aldehydes with different substituents and an alkyl aldehyde (Table 1, entries 1–4). In comparison to entry 4 (benzaldehyde), the presence of an electron donating group (methoxy, entry 1) or a weak electron-withdrawing group (chlorine, entry 2) does not strongly affect the conversion into the expected aldol product. However, a trend to lowest conversions can be observed when employing more electron deficient aldehydes, such as in entry 2. In this case, this is particularly important to the applicability of this protocol, since no aldehyde activation is necessary and common alkyl aldehydes can be readily employed, leading to the expected aldol products in good yields (Table 1, entries 3 and 5). As can be seen in Table 1 (entries 1–4), the average yield of the sulfides and the selenides produced by this protocol is the same, both leading to the aldol products in good yields. On the other hand, the corresponding tellurides were obtained in lower yields in all the cases. It is important to note that this observation on the tellurides yields is not only related to the reactivity of the intermediate lithium-tellurolate, but also on the stability of the product. In all cases, the cyano-tellurides have shown to be very unstable under various conditions.[17] It is possible to observe the decomposition of these compounds when in solution, during the chromatography and even when stored in low temperatures after purification. In this case, unfortunately it is not possible to affirm that the lower yields are due to a different reactivity without considering the pronounced decomposition during the extraction and isolation procedures.

We have also optimized this protocol for the one-pot preparation of the corresponding MBH adducts, by quenching the reaction with hydrogen peroxide solution. Some examples of MBH adducts have been produced (Table 1, entries 6–10) and as can be seen, alkyl and aromatics aldehydes are tolerated. It is also worth noting that when nitro aldehydes were employed (Table 1, entries 9 and 10) the lowest yields were observed. As depicted in the general reaction scheme in Table 1, the aldehyde is added first into the reaction media, since no reaction between the lithium chalcogenolate and the aldehyde is expected. In the case of the nitro aldehydes, a reaction between the aldehyde and the chalcogenolate clearly takes place. As well as being visually distinct, these reactions furnish the

Table 1
Evaluation of different aldehydes and lithium chalcogenolates



Entry	Aldehyde	Aldol product	Chalcogen yield	Entry	Aldehyde	MBH adduct	Yield
1	 **1**		a **2**, Y=S, 98% b **3**, Y=Se, 97% c **4**, Y=Te, 65%	6	 **9**		**19**, 87%
2	 **5**		a **6**, Y=S, 80% b **7**, Y=Se, 88% c **8**, Y=Te, 60%	7	 **20**		**21**, 79%
3	 **9**		a **10**, Y=S, 83% b **11**, Y=Se, 83% c **12**, Y=Te, 60%	8	 **22**		**23**, 87%
4	 **13**		a **14**, Y=S, 91% b **15**, Y=Se, 95% c **16**, Y=Te, 60%	9	 **24**		**25**, 40%
5	 **17**		**18**, Y=Se, 85%	10	 **26**		**27**, 32%

All the reactions were conducted under nitrogen atmosphere and in a 3 mmol scale.
In all the cases in which a diastereomeric mixture was obtained, *anti*:*syn*=3:2 d.r., calculated by ^{1}H and ^{77}Se NMR.