



Lithium butylchalcogenolate induced Michael-aldol tandem sequence: easy and rapid access to highly functionalized organochalcogenides and unsaturated compounds

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ABSTRACT

Lithium ⁿbutylchalcogenolates are generated in situ by reacting the elements (S, Se, and Te) with ⁿbutyllithium at 0 °C. Reaction of the lithium alkylchalcogenolates with activated alkenes and aldehydes gives the corresponding aldol adducts. The selenium-containing products give Morita–Baylis–Hillman adducts after the oxidation/elimination of the selenoxide. The whole sequence can be performed in a one-pot procedure.

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The addition of chalcogenols or metal alkyl chalcogenolates to activated alkenes is a useful method to prepare functionalized alkylchalcogenides.¹ A serious drawback of this methodology is the use of alkylchalcogenols or dialkylchalcogenides as starting materials, since these compounds are volatile and very bad smelling. Recently we demonstrated that alkylchalcogenols, generated in situ by reacting commercial alkyllithiums and elemental sulfur, selenium and tellurium, react with activated alkenes to give functionalized dialkylchalcogenides in good yields.¹ This protocol constitutes an important advance in preparative organochalcogen chemistry, since it allows the preparation of non-volatile products starting from easily available and friendly precursors. It is especially important in the context of the sulfur chemistry, since lithium alkylthiolates, which are widely used in synthesis, surprisingly continue to be generated by deprotonation of foul smelling alkylthiols.²

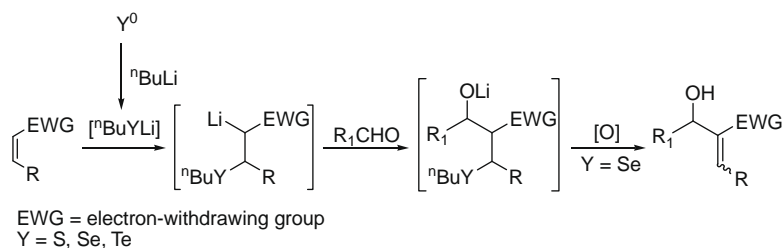
Application of our protocol to activated alkenes and capture of the intermediate enolate with an aldehyde, followed by sulfoxide or selenoxide elimination would constitute a simple and efficient one-pot access to Baylis–Hillman adducts (Scheme 1).³ In addition, the tellurium containing products are precursors of functionalized reactive organometallics, as recently demonstrated by our group.⁴ In this Letter we disclose our preliminary results on the reaction sequence shown in Scheme 1 and in Table 1.

Initially we investigated the best experimental conditions to perform the chalcogenation/condensation sequence. Several reaction conditions and sequence of addition of the components were tested. The best experimental protocol found was to generate the lithium alkylchalcogenolate by adding an equimolar amount of

ⁿBuLi to a suspension of the chalcogen in THF under nitrogen at 0 °C. The limpid solution was cooled to –70 °C and then equimolar amounts of freshly distilled benzaldehyde, and after 5 min, the activated alkene were added. The mixture was then allowed to reach room temperature to give the adducts in the isolated yields as shown in Table 1.⁵ No additive was needed to promote the condensation reaction.³ As can be observed, the reaction works well with the three chalcogens. In one case (Table 1, entry 3) a two-substituted olefin was used, with a good yield being obtained. The products are almost odorless oils, stable to the light and air, and can be purified by column chromatography. When stored under refrigeration the sulfides and selenides do not degrade to an observable extent. The tellurides are less stable and after some days some degree of decomposition can be detected by the darkening of the samples. However, by taking the proper care, evaporating the solvent immediately after the work-up, even the tellurides can be safely manipulated in the presence of the light and the air. It is worth mentioning that during the reaction course, no bad smell typical of butylthiol, -selenol, or dibutyltelluride was detected.

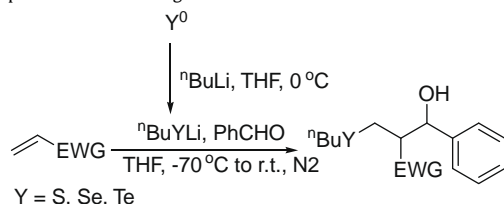
The best yield was achieved when lithium butylselenolate and acrylonitrile were reacted (Table 1, entry 5). It is well known that the selenoxide *syn*-elimination reaction occurs under much milder conditions than the sulfoxide *syn*-elimination,⁶ while the sulfoxide *syn*-elimination requires reflux at about 120 °C to occur,⁷ the selenoxide *syn*-elimination proceeds at room temperature or below.⁸ This fact is especially important if we intend to apply this protocol in the synthesis of more complex and sensitive substrates. In view of this we concentrated our efforts in the reaction involving the lithium butylselenolate to test the influence of the aldehyde in the reaction yield and to obtain the butyl selenides for further selenoxide elimination.

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Scheme 1. Morita–Baylis–Hillman adducts formation.

Table 1
Three-component electrochalcogenation reactions^a



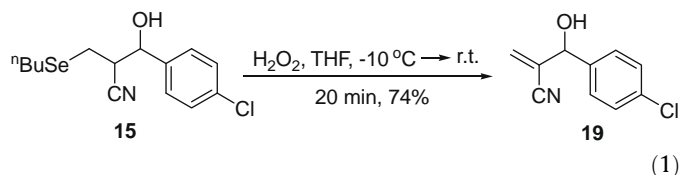
Entry	Chalcogen (Y ⁰)	Alkene	Aldol product	Yield ^b (%)
1	Te			73
2	Se			78
3	Se			81
4	S			68
5	Te			79
6	Se			95
7	S			79

^a All the reactions were performed in THF using stoichiometric amounts of the alkene, aldehyde, and the lithium butylchalcogenolate in a 3 mmol scale.

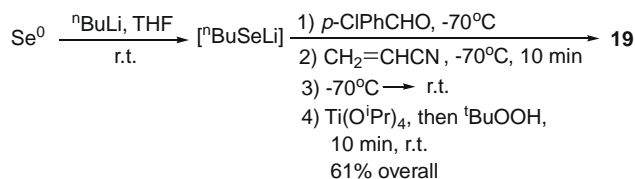
^b The yields refer to the isolated products purified by column chromatography.

In Table 2 we can see the result of the reaction sequence using aromatic aldehydes bearing electron-withdrawing and electron-donating groups, as well as aliphatic aldehydes. In all cases the yields were high except for the nitrobenzaldehydes (Table 2, entries 2 and 3). In these cases a darkening of the reaction mixture was observed. However, it is well known that reaction of compounds bearing the nitro group with carbanionic substrates is troublesome. Entry 4 shows that the reaction is sensitive to steric factors.

As mentioned before, the selenoxide *syn*-elimination reaction is milder than the analogous sulfoxide *syn*-elimination. Normally the selenoxide elimination is performed with substrates bearing aryl groups linked to the selenium atom, electron-withdrawing substituents enhancing the elimination rate.^{6,9} However, the presence of an acidic proton α to the organoselenium moiety of the aldol adducts (Table 2, entries 8–18) facilitates the elimination, which occurred in 74% isolated yield when compound **15** was subjected to the oxidation reaction with H₂O₂ in THF at 0 °C for 10 min (Eq. 1), while the oxidation of the same compound with ^tBuOOH, Ti(OⁱPr)₄, and DHP¹⁰ for 10 min at room temperature gave **19** in 93% isolated yield (Eq. 2).

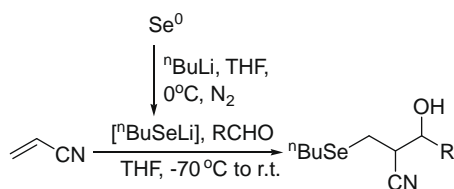


The oxidation/elimination sequences described in Eqs. 1 and 2 were performed in a 3 mmol scale and the isolated yields are in the range expected for the selenoxide *syn*-elimination reaction.¹¹ A number of reaction conditions are available to perform this classical transformation.⁶ In this way, the proper choice of reagents and reaction conditions can be made, depending on the substrate structure. The whole reaction sequence, that is, lithium butylselenolate generation, Michael addition to the activated alkene, aldol condensation, and selenide oxidation/elimination can be performed in one-pot operation as shown in Eq. (3), when compound **15** was transformed into **19** in 61% overall yield.¹²



(3)

Table 2
Three-component electroseenylation reaction of acrylonitrile^a



Entry	Aldehyde	Aldol products ^c	Yield ^b (%)
1			95
2			40
3			32
4			57
5			87
6			81
7			81
8			88
9			72
10			70
11			83

^a All the reactions were performed in THF using stoichiometric amounts of alkene, aldehyde, and the lithium butylchalcogenolate in a 3 mmol scale. Compound **15** was prepared in a 10 mmol scale.

^b The yields refer to the isolated products purified by column chromatography.

^c All prepared compounds were subjected to the selenoxide *syn*-elimination to eliminate a stereogenic center facilitating the product analysis. No attempts were made to improve the yields of this step, except for the oxidation–elimination reaction of compounds **2** and **15**.

In conclusion, a three-component sequence leading to highly functionalized alkyl chalcogenides was developed. The reactions were performed under friendly conditions, which avoid the manipulation of bad smelling alkyl thiols, selenols, and dialkylditellurides. In the case of the selenides, the oxidation/elimination occurs under very mild conditions and the whole reaction sequence can be performed in a one-pot operation, leading to a Morita–Baylis–Hillman adduct.

Acknowledgments

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- Lithium phenylselenolate, generated by reacting methylolithium with diphenyldiselenide, promoted the condensation of butylacrylamide with benzaldehyde. The reaction took 15 h to occur. The selenoxide *syn*-elimination was performed by oxidation of the selenide with H₂O₂, taking 12 h to complete. The overall yield of the sequence was 72%: Kamimura, A.; Omata, Y.; Mitsudera, H.; Kakehi, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4499–4504; A similar sequence was published recently, which described the transformation of acryloyl chloride into the corresponding phenylthio esters aldol adducts, by reaction with 3 equiv of lithium phenylthiolate in the presence of benzaldehyde, assisted by MgBr₂·Et₂O. Oxidation of the resulting sulfide with MCPBA, followed by pyrolysis of the selenoxide in refluxing toluene gave the corresponding Baylis–Hillman adduct: Tarsis, E.; Gromova, A.; Lim, D.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2008**, *10*, 4819–4822. To our knowledge, similar aldol condensations with activated alkenes, promoted by metal alkyltelluroates, were not yet described.
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- Typical procedure for the electrochalcogenation of activated alkenes: 2-(butylselenanylmethyl)-3-(4-chlorophenyl)-3-hydroxypropanenitrile (**15**). A 250 mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer and a rubber septum and charged with elemental selenium (0.78 g, 10 mmol), flame-dried twice under a positive Ar⁰ stream, and then cooled to room temperature. Freshly distilled THF (150 mL) was transferred to the reaction flask. Butyllithium (5 mL of a 2 M solution in hexane, 10 mmol) was added dropwise to the vigorously stirred Se⁰/THF mixture at room temperature. After the addition the powder was completely consumed and then the reaction mixture was cooled to –70 °C. *p*-Chlorobenzaldehyde (1.4 g, 10 mmol) in dry THF (10 mL) was added to the reaction flask. After 5 min, freshly distilled acrylonitrile (0.69 mL, 10 mmol) was added dropwise. The reaction mixture was stirred for 10 min at –70 °C and then it was gradually warmed to room temperature (c.a. 20 min), after which time the reaction was quenched with NaHSO₃ saturated aqueous solution (200 mL). The product was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Column chromatography (3:1 hexane/AcOEt) of the crude oil on silica gel afforded **15** as a pale yellow oil. Yield 2.91 g (88%). Mixture of diastereomers (1:0.7): ¹H NMR (CDCl₃, 300 MHz) δ 0.91 (t, J = 7.5 Hz, 3H), 1.39 (sx, J = 7.5 Hz, 2H), 1.63 (qt, J = 7.5 Hz, 2H), 2.68–2.82 (m, 5H), 3.00–3.19 (m, 1H), 4.92 (d, J = 6.5 Hz, 1H), 7.34–7.36 (m, 4H). ¹³C NMR (CDCl₃, 125 MHz) δ 13.5, 20.3, 21.3, 22.8, 25.3, 25.4, 32.3, 42.1, 42.6, 72.5, 72.8, 119.0, 119.3, 127.4, 127.8, 128.9, 129.0, 134.6, 134.7, 137.9, 138.5. ¹²⁵Se NMR (CDCl₃, 500 MHz) δ 161.8, 163.4. IR (film) ν, cm⁻¹ 3442, 2958, 2929, 2872, 2246, 1907, 1787, 1701, 1597, 1491, 1091, 1013, 839. HRMS calc. for [C₁₄H₁₈ClNOSeNa]⁺: 354.0139. Found: 354.0123.
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12. One-pot preparation of a Baylis–Hillman adduct through an electroselenylation followed by oxidation/elimination. 2-((4-chlorophenyl)-(hydroxy)methyl)acrylonitrile (**19**). The procedure described above⁵ was repeated in a 3 mmol scale. After the addition of the *p*-chlorobenzaldehyde and the acrylonitrile, the mixture was heated to room temperature as described above⁵ and then Ti(O^{*i*}Pr)₄ (0.07 mL, 0.3 mmol), and DHP (1.5 mL, 4.5 mmol) were added. After 10 min., ^tBuOOH (0.5 mL of a 5.5 M aq solution, 3.0 mmol) was added dropwise to the reaction mixture, which was stirred for 10 min. After this period, 5.0 g of flash silica gel was added to the reaction flask and the solvent was removed under reduced pressure. The solid was filtered through a flash silica cake using CH₂Cl₂ (2 × 30 mL). The filtrate was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. Column chromatography of the crude oil in flash silica gel eluting with hexane/ethyl acetate (2:1) afforded **19** as a colorless oil. Yield 0.35 g (61%). ¹H NMR (500 MHz, CDCl₃): δ 5.30 (s, 1H), 6.05 (s, 1H), 6.12 (s, 1H), 7.33–7.40 (m, 4H). ¹³C NMR (125 MHz, CDCl₃): δ 73.4, 116.8, 125.9, 127.9, 129.0, 130.3, 134.7, 137.7. IR (film) ν, cm⁻¹ 3467, 3119, 3034, 2872, 2233, 1905, 1489, 1399, 1069, 818.