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Stereoselective synthesis of vinylic chalcogenides through vinylic substitution by lithium organylchalcogenolates

C. C. Silveira,[a,*] R. B. Guerra[a] and J. V. Comasseto[b]

[a]*Departamento de Química, Universidade Federal de Santa Maria, Caixa Postal 5001, 97105-900 Santa Maria, RS, Brazil*
[b]*Instituto de Química, Universidade de São Paulo, 05508-900 São Paulo, SP, Brazil*

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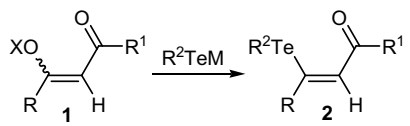
Abstract—Enol phosphates and enol tosilates of β-dicarbonyl compounds react with lithium organoselenolates to give β-organoseleno (*Z*)-α,β-unsaturated carbonyl compounds. Tetrasubstituted vinylic *vic*-bis(organylchalcogenides) of (*E*)-geometry have been prepared by this method.

1. Introduction

Organoselenium[1a] and organotellurium[1b,c] compounds find use in organic synthesis. In view of the peculiar reactivity of vinylic selenides and tellurides, these classes of organochalcogen compounds have attained a special attention. Recently their preparation and reactivity have been reviewed.[2] Among the reactions of synthetic interest involving vinylic chalcogenides are the metal catalyzed couplings of such species with other functionalities, leading to chalcogen free olefins of defined stereochemistry.[2] In view of the stereospecificity of these carbon–carbon bond formation reactions, the stereoselective synthesis of vinyl chalcogenides continues to be a challenge. Some years ago one of us described a general method for the synthesis of *Z*-vinylic tellurides through a stereoselective vinylic substitution by metal organotellurolates on activated enol derivatives of easily obtained β-dicarbonyl compounds (Scheme 1).[3] *Z*-vinylic tellurides **2** were formed in all cases, irrespective of the stereochemistry of the starting enol **1**.



Scheme 1. Preparation of *Z*-vinylic tellurides by vinylic substitution.

Prior to this publication, few studies on the vinylic substitution by metal organotellurolates have been reported.[4] On the contrary, the vinylic substitution by metal selenolates have been more explored.[5] Most of the methods of synthesis of vinyl chalcogenides refer to monochalcogen derivatives.[2] The synthesis of *vic*-vinylic bis-chalcogenides is little explored. Most of the methods available for their synthesis employ alkynes as the starting materials. These methods include the photochemical addition of diorganodisulfides, diselenides, and ditellurides to alkynes,[6] and the Pd catalyzed addition of dichalcogenides to alkynes.[7] For the free radical addition of dichalcogenides, the reaction seems to be effective only for terminal and activated alkynes. This reaction was also effective for terminal and internal alkynes when a binary system of $(PhS)_2$–$(PhSe)_2$ was employed. The products are formed exclusively or preferentially with the *E*-configuration.[6a] The thiotelluration and selenotelluration of acetylenes also occurs with terminal alkynes, although less efficiently.[8] The addition of internal alkynes with very high *Z*-selectivity was attained using Ti-species.[9] A new procedure was recently described for the polymer-supported Pd stereoselective S–S bond addition to terminal alkynes; however, the methodology was not useful for Ph_2Se_2 addition.[10] A sequence of hydroboration-iodination of 1,2-bis-alkylselenoacetylenes furnished *vic*-bis(selenides) of *Z*-preferential stereochemistry.[11] Methods were also developed for the synthesis of less substituted *vic*-bis(chalcogenides).[12]

In view of the above comments it is of interest to develop practical stereoselective methods of the synthesis of

* Corresponding author. Tel./fax: +55 55 2208754; e-mail: silveira@quimica.ufsm.br

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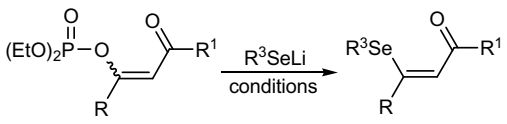
vic-vinylic bis-chalcogenides, aiming to their use in the construction of three- and tetrasubstituted olefins of defined stereochemistry. Keeping in mind the initial observations summarized in Scheme 1, the vinylic substitution reaction is a good choice to prepare vinylic mono- and bis-chalcogenides, specially due to its stereoselectivity and to the easy access to the starting materials.

2. Results and discussion

The starting enolphosphates were prepared by reaction of β-dicarbonyl compounds with sodium hydride, followed by diethylchlorophosphate.[13] With the enolphosphates in hands we started the study by reacting enolphosphate **3a** with lithium *n*-butylselenolate at 0 °C. After 20 min all the starting materials have been consumed. However, a 2:1 mixture of *Z*/*E* isomers in low yield was detected. At lower temperatures a better control of the stereochemistry was possible. At −78 °C the pure *Z* isomer was isolated in 69% yield after purification by column chromatography on silica gel eluting with hexane/ethyl acetate (95:5).[14] In this way, contrary to the vinylic substitution using lithium organotellurolates,[3b] the reaction of lithium organoselenolates requires a strict control of the reaction temperature to avoid the formation of stereoisomers.

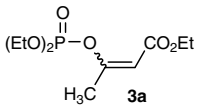
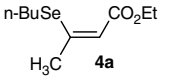
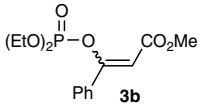
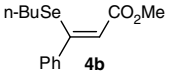
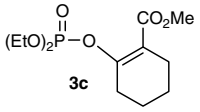
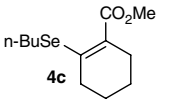
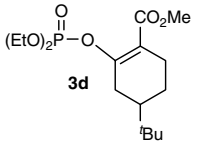
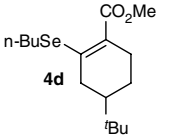
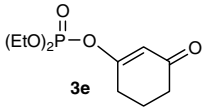
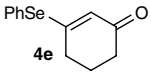
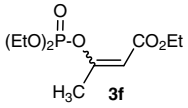
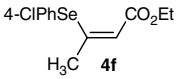
After determining the best experimental condition for the vinylic substitution reaction, a detailed study was performed by reacting several cyclic and acyclic enol phosphates with alkyl and aryl selenolates (Scheme 2). Good yields were usually obtained in most cases (Table 1). Detailed ^{1}H and ^{13}C analysis of products **4a**–**f** indicated the exclusive formation of only one stereoisomer, irrespective of the stereochemistry of the starting material. Products **4** presented the *Z*-stereochemistry, as confirmed by an NOESY experiment showing a cis-relationship between the vinylic H and the R group on **4a** and **4f**.

Aiming to expand the scope of the above discussed reaction we explored the synthesis of 1,2-bis-organochalcogen compounds by vinylic substitution on β-*O*-phosphate/tosyl α-arylchalcogeno α,β-unsaturated carbonyl compounds by chalcogenolate anions. The expected product would be a tetrasubstituted alkene bearing vinylic sulfide and vinylic selenide functions that could be further used to perform other carbon–carbon bond forming reactions.[15] The starting materials for these reactions were prepared from 1,3-dicarbonyl compounds by the introduction of organosulfur or organoselenium groups at the 2-position to give intermediate **5**, followed by in situ treatment with a second equivalent of base (NaH) and diethyl chlorophosphate or tosyl



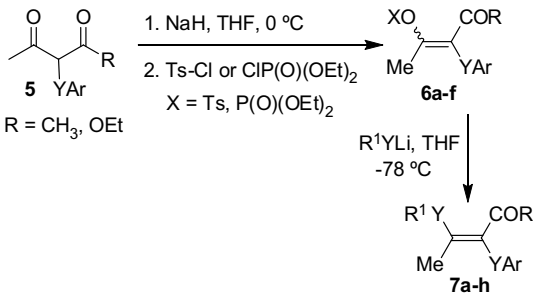
Scheme 2.

Table 1. β-Organoselenium-α,β-unsaturated compounds prepared according to Scheme 2

Entry	Enol (**3**)	Product (**4**)	Yield (%)
1	 **3a**	 **4a**	90
2	 **3b**	 **4b**	86
3	 **3c**	 **4c**	82
4	 **3d**	 **4d**	79
5	 **3e**	 **4e**	68
6	 **3f**	 **4f**	69

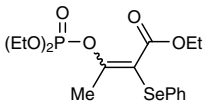
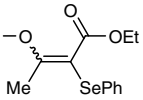
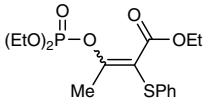
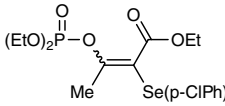
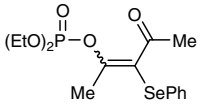
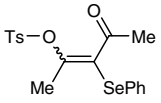
chloride to give the vinylic species **6a**–**f**, according to Scheme 3 and Table 2. By this route α-arylchalcogeno α,β-unsaturated carbonyl compounds functionalized at the β-position by a good leaving group can be prepared. Organosulfur and organoselenium species could be conveniently placed at the α-position of the β-dicarbonyl compounds. Otherwise, organotellurium compounds were too unstable to be isolated and purified. As can be observed in Table 2, the compounds were obtained as *E*/*Z* mixtures in a variable ratio. We did not pursue further efforts to determine which isomer of **6** was formed preferentially, since it is expected that one isomer of **7** will be preferentially formed, irrespective of the stereochemistry of **6**.

The same reaction conditions employed for the synthesis of **4** were employed for the synthesis of **7** (Scheme 3).



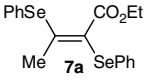
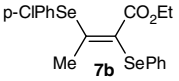
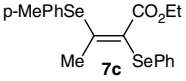
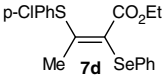
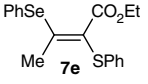
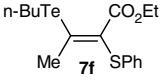
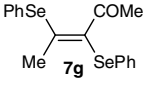
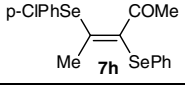
Scheme 3.

Table 2. Synthesis of enol compounds **6a**–**f** according to Scheme 3

Entry	6	Enol 6	Yield (%)	Isomer ratio
1	**6a**		88	50:50
2	**6b**		73	91:9
3	**6c**		57	55:45
4	**6d**		82	52:48
5	**6e**		81	50:50
6	**6f**		76	86:14

Starting from a 50:50 *E*/*Z* mixture of **6a** and PhSeLi as the nucleophile, **7a** was obtained as a 9:1 *E*/*Z* mixture in 76% yield (Table 3, entry 1). We tried different conditions, such as performing the reaction at higher temperatures and the use of sodium and magnesium organylselenolates, but in all cases lower yields (32–54%) and nearly 1:1 *E*/*Z* mixtures of isomers were observed. Having determined the best experimental condition, we explored the scope of the reaction with different nucleophiles of sulfur, selenium, and tellurium species.[16] As can be seen in Table 3, reasonable to good yields of the desired products were obtained. For most examples studied, a good stereoselectivity was observed in favor of *E*-isomer **7**, irrespective of the stereochemistry of the starting material **6**.

Table 3.

Entry	Enol (6)	Product (7)	Yield (%)	*E*/*Z* ratio
1	**6a**		76	90:10
2	**6a**		73	100:0
3	**6a**		70	100:0
4	**6a**		63	95:5
5	**6c**		40	100:0
6	**6c**		56	100:0
7	**6e**		73	90:10
8	**6e**		71	100:0

The stereochemistry of compounds **7** was confirmed by ^{1}H and ^{13}C NMR analysis. The *E*-configuration at the double bond has been proved unequivocally for compounds **7d** and **7g** by X-ray structural analysis of the major isomer.

In conclusion, we showed that the vinylic substitution by lithium organylchalcogenolates is a useful method for the stereoselective synthesis of functionalized vinylic selenides, vinylic sulfides, and vinylic tellurides using easily available 1,3-dicarbonyl compounds as starting materials. Tri- and tetrasubstituted alkenes containing organosulfur and organoselenium groups can be prepared.

Acknowledgments

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14. *General procedure for the synthesis of* **4a–f**: To a stirred solution of PhSeLi (1.5 mmol, prepared in situ)[17] under argon at −78 °C was added the appropriate enol **3** (1 mmol) in THF (2 mL). The solution was stirred for 1 h at the same temperature until completion of the reaction. After this time the mixture was diluted with ethyl acetate (50 mL) and washed with brine. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure to give an oil, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 95:5) to give **4**. *Selected spectral and analytical data*: Compound **4a**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (m, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 2.79 (t, $J = 7.5$ Hz, 2H), 2.30 (d, $J = 1.12$ Hz, 3H), 1.67 (qui, $J = 7.2$ Hz, 2H), 1.45 (sex, $J = 7.2$ Hz, 2H), 1.27 (t, $J = 7.2$ Hz, 3H), 0.93 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.62, 157.32, 114.99, 59.55, 31.66, 24.92, 23.09, 22.86, 14.14, 13.35. IR ν_{max}/cm^{-1} 1695 (CO), 1584 (C=C); LRMS *m*/*z* (relative intensity) 250 (M^++1), 193, 113. Anal. Calcd for $C_{10}H_{18}O_2Se$: C, 48.20; H, 7.28. Found: C, 48.40, H, 7.46. Compound **4d**: mp 45–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 2.70 (t, $J = 7.6$ Hz, 2H), 2.5–2.3 (m, 2H), 2.0–1.8 (m, 2H), 1.64 (qui, $J = 7.2$ Hz, 2H), 1.44 (sext, $J = 7.2$ Hz, 2H), 1.3–1.2 (m, 3H), 0.93 (t, $J = 7.2$, 3H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 149.5, 123.2, 51.3, 43.4, 33.2, 32.1, 31.6, 29.0, 27.2, 27.0, 24.8, 23.1, 23.1, 13.5; IR ν_{max}/cm^{-1} 1682 (CO), 1571 (C=C); LRMS *m*/*z* (relative intensity) 332 (M^++1), 275, 57. Anal. Calcd for $C_{16}H_{28}O_2Se$: C, 58.00; H, 8.52. Found: C, 58.24; H, 8.55.
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16. *General procedure for the synthesis of vinylic vic-bis(arylselenides)* **7**: To a stirred solution of the organylchalcogenolate (1.5 mmol, prepared in situ) under argon at −78 °C was added appropriate enol **6** (1 mmol) in THF (2 mL). The solution was stirred for 1 h at the same temperature until completion of the reaction. After this time the mixture was diluted with ethyl acetate (50 mL) and washed with brine. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure to give an oil, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 95:5) to give **7**. *Selected spectral and analytical data*: Compound **7b**: 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, $J = 8.4$ Hz, 2H), 7.37–7.20 (m, 7H), 4.13 (q, $J = 7.2$ Hz, 2H), 2.27 (s, 3H), 1.09 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 157.4, 137.8, 135.5, 131.9, 130.7, 129.3, 129.0, 128.2, 126.6, 115.8, 61.6, 27.6, 13.8; IR ν_{max}/cm^{-1} 1667 (CO), 1571 (C=C); LRMS *m*/*z* (relative intensity) 460 (M^++1), 115, 77. Anal. Calcd for $C_{18}H_{17}ClO_2Se_2$: C, 47.13; H, 3.74. Found: C, 46.84; H, 3.84. Compound **7h**: mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, $J = 8.2$ Hz, 2H), 7.32–7.16 (m, 7H), 2.49 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.9, 164.9, 137.7, 135.5, 132.2, 129.4, 129.3, 129.0, 128.6, 126.3, 121.2, 29.9, 28.4; LRMS *m*/*z* (relative intensity) 430 (M^++1), 348, 273, 237, 193, 115, 77. Anal. Calcd for $C_{17}H_{15}ClOSe_2$: C, 47.63; H, 3.53. Found: C, 47.73; H, 3.32.
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