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Stereoselective synthesis of α-phenylchalcogeno-α,β-unsaturated esters†

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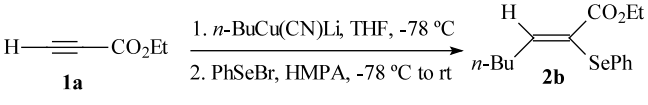
Abstract—Ethyl α-phenylchalcogeno α,β-unsaturated esters were prepared in a stereoselective manner by the reaction of ethyl propiolates with organocuprates, followed by the reaction with the appropriate electrophilic organosulfur, organoselenium or organotellurium source. © 2002 Elsevier Science Ltd. All rights reserved.

Considerable effort has been devoted to the development of new synthetic methods to access vinylic chalcogenides, specially the functionalized ones. These methods have been the subject of several review articles published in recent years.[1] Recently we described convenient methods for the synthesis of α-phenylseleno-α,β-unsaturated esters,[2] a potentially very useful class of vinylic selenides,[3,4] scarcely described in the literature.[4,5] Most of these methods furnishes the desired compounds as a mixture of *E*/*Z* isomers. Due to our interest in new methodologies for the synthesis of vinylic chalcogenides,[6] we intend to develop a stereoselective method to access α-phenylseleno-α,β-unsaturated esters. Our attention was focused to use the known regio- and stereospecific conjugated addition of organocuprates to α,β-acetylenic esters to generate *cis* 1,4 adduct,[7] which could be trapped by a convenient organoselenium source. By this method, along with the organoselenium derivatives, the corresponding organosulfur[8] and organotellurium[9] could be accessible equally, by the employment of the adequate electrophilic organochalcogen source.

We started our experiments by reacting ethyl propiolate **1a** with lithium butylcyano cuprate in THF, at –78°C, following a procedure that we had described some years ago.[10] After 1 h at this temperature, HMPA and a THF solution of benzeneselenenyl bromide were added (Scheme 1). The reaction mixture was then slowly warmed to room temperature, followed by a normal work-up and column chromatography purification.[11] ^{1}H NMR analysis of the crude and the purified material indicated that the reaction occurred with total retention of configuration, the *Z*-isomer being detected as the only product in 73% yield (entry 2, Table 1).

The method was then extended to other ethyl propiolate derivatives, such as pentyl **1b** and phenyl propiolate **1c**, reacting with sulfur, selenium and tellurium electrophiles. From our study, a very easy and general entry to the tetrasubstituted vinylic derivatives, not accessible by most of the other methods described, can now be disponible.[2,4,5]

On the reaction of *n*-BuCu(CN)Li with ethyl pentylpropiolate **1b** and phenylpropiolate **1c**, the same behavior as for ethyl propiolate was observed, and the reaction followed the same pattern, furnishing the desired products **2e–j** in moderate to good yields (entries 5–10, Table 1). Otherwise, on the addition of MeCu(CN)Li to pentylpropiolate, it was necessary to increase the temperature from –78 to –25°C for 1 h to observe the addition of the cuprate to the triple bond. A strict control of reaction temperature was necessary to avoid the formation of isomers. After cooling back to –78°C, followed by the addition of the electrophile, the reaction was slowly warmed to rt, and the desired products were isolated in moderate yields (entries 11–13). Again,



Scheme 1.

Keywords: selenium and compounds; sulfur compounds; tellurium and componds; esters; copper and compounds; vinylic chalcogenides.

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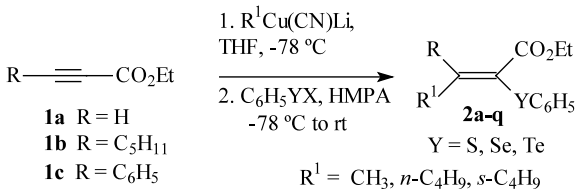
Table 1. α-Phenylchalcogeno-α,β-unsaturated esters prepared



1a R = H
1b R = C_5H_{11}
1c R = C_6H_5

Entry	R	R^1	Product	Y	Yield (%)[a]
1	H	n-C_4H_9	**2a**	S	44
2	H	n-C_4H_9	**2b**	Se	73
3	H	n-C_4H_9	**2c**	Te	52
4	H	s-C_4H_9	**2d**	Se	60
5	C_6H_5	n-C_4H_9	**2e**	S	59
6	C_6H_5	n-C_4H_9	**2f**	Se	81
7	C_6H_5	n-C_4H_9	**2g**	Te	58
8	C_5H_{11}	n-C_4H_9	**2h**	S	41
9	C_5H_{11}	n-C_4H_9	**2i**	Se	43
10	C_5H_{11}	n-C_4H_9	**2j**	Te	40
11	C_5H_{11}	CH_3	**2k**	S	41
12	C_5H_{11}	CH_3	**2l**	Se	51
13	C_5H_{11}	CH_3	**2m**	Te	42 (49)[b]
14	C_6H_5	CH_3	**2n**	S	40
15	C_6H_5	CH_3	**2o**	Se	55 (66)[b]
16	C_6H_5	CH_3	**2p**	Te	70
17	C_6H_5	s-C_4H_9	**2q**	Te	45

[a] Isolated yields after column chromatography. All new compounds were fully characterized.
[b] Isolated yield using cuprate:propiolate:electrophile = 1.5:1.5:1.0.

the formation of only one isomer, as analyzed by GC, ^{1}H and ^{13}C NMR, was observed.

A similar low reactivity was observed on the addition of the MeCu(CN)Li to ethyl phenylpropiolate, being necessary to warm the reaction mixture from –78 to –25°C or higher temperature, before cooling back to –78°C to add the electrophile. As a consequence of this lower reactivity, the formation of the isomers could not be avoided. All three products **2n–p** (entries 14–16, Table 1) were isolated as E/Z-mixture of isomers, with ratios from 1:1 (entries 14 and 16) to 2:1 (entry 15). In the same way, it was experimentally observed that yields were improved when 1.5 equiv. of propiolate were used instead of equimolar amounts of propiolate and electrophile (entries 13 and 15, Table 1).

We also carried out a few experiments with the cuprate derived from *sec*-butyllithium, to verify the generality of our method. The reaction was performed following the same conditions as described to n-BuCu(CN)Li. On the reaction of s-BuCu(CN)Li with ethyl propiolate **1a** and capture of the vinylic cuprate with PhSeBr, the desired product **2d** was isolated in 60% yield (entry 4). By the reaction with ethyl phenylpropiolate **1c** followed by addition of PhTeI, a moderate 45% yield of **2q** was obtained (entry 17). In both reactions, only one isomer was detected.

The isomeric purity of the compounds prepared was confirmed by the analysis of the ^{1}H and ^{13}C NMR spectra and by the comparison with authentic samples prepared by other methods, recently described by us.[2] In the case of reactions with ethyl propiolate, only the Z-isomer could be detected. In the case of reaction with ethyl pentylpropiolate and ethyl phenylpropiolate, only one isomer could be detected by GC and ^{1}H and ^{13}C NMR analysis.

As we discussed above, by our method the corresponding vinylic sulfides could be easily accessible by reaction of the intermediate vinylic cuprate with S-phenylbenzenethio sulfonate. The functionalized vinylic sulfides were isolated in good to fair yields (entries 1, 5, 8, 11, and 14, Table 1). Worth of mention it is that the use of other eletrophilic sources of PhS group, such as PhSCl and PhSSPh, was less effective, furnishing the desired products in very low yields. By the use of benzenetellurenyl iodide as the electrophile, the corresponding vinylic tellurides could be prepared in quite good yields (40–70%; entries 3, 7, 10, 13, 16 and 17; Table 1). To our knowledge, these α-phenyltellurium α,β-unsaturated esters are very scarcely described; the only method being the aryltellurenamides addition to dimethylacetylene dicarboxylate.[9] Methods for the preparation and synthetic applications of β-phenyltellurium α,β-unsaturated esters have been already described.[12]

In conclusion, the reaction of propiolate esters with organocopper(I) reagents, followed by addition of electrophilic phenylchalcogeno reagents, affords efficiently a variety of α-phenylchalcogeno α,β-unsaturated esters with high regio- and stereoselectivity. The products are tri- or tetrasubstituted alkenes in which two synthetically versatile groups are linked to the same sp^2-hybridized carbon atom.

Acknowledgements

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11. General experimental procedure: To a round bottom flask under argon was added CuCN (0.268 g; 3.0 mmol) and dry THF (10 mL). The suspension was cooled to −78°C and *n*-BuLi (1.84 mL; 3.00 mmol; 1.63 M solution) was added. After 30 min at this temperature, the propiolate (2.0 mmol) was added and the reaction mixture stirred for 1 h. HMPA (2 mL) and benzenechalcogenyl halide (2 mmol) were added and the reaction mixture was left to reach room temperature in 4 h. The reaction was poured into water and an aqueous ammonium chloride solution and extracted with ethyl acetate (3×50 mL). The organic phase was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by silica gel column chromatography. Selected spectral data: Ethyl (*Z*)-2-phenylthio-2-heptenoate (entry 1): IR (film): 1714.2 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$) 0.90 (t, 3H, $J=7.0$ Hz); 1.07 (t, 3H, $J=7.0$ Hz); 1.25–1.60 (m, 4H); 2.52 (q, 2H, $J=7.1$ Hz); 4.09 (q, 2H, $J=7.0$ Hz); 7.0–7.5 (m, 6H). ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 13.73; 13.79; 22.35; 30.41 (2C); 61.32; 125.83; 126.56; 128.01; 128.75; 135.97; 153.13; 165.30; *m/z* 264 (M^+); 218 (48); 189 (42); 147 (51); 81 (65); 29 (100%). Ethyl (*Z*)-2-phenylseleno-2-heptenoate (entry 2): IR (film): 1714.8 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$) 0.89 (t, 3H, $J=7.0$ Hz); 0.91 (t, 3H, $J=7.0$ Hz); 1.0–1.6 (m, 4H); 2.48 (q, 2H, $J=7.2$ Hz); 4.09 (q, 2H, $J=7.0$ Hz); 7.0–7.5 (m, 6H). ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 13.70; 13.80; 22.29; 30.36; 32.35; 61.35; 124.65; 126.53; 128.92; 130.06; 131.08; 152.95; 165.72. Ethyl (*E*)-3-phenyl-2-phenyltelluro-2-heptenoate (entry 7): IR (film): 1715.4 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$) 0.68 (t, 3H, $J=7.1$ Hz); 0.75–1.00 (m, 3H); 1.10–1.40 (m, 4H); 2.73 (m, 2H); 3.52 (q, 2H, $J=7.1$ Hz); 7.00–7.50 (m, 8H); 7.75–7.90 (m, 2H). ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 13.25; 13.67; 22.24; 29.92; 41.91; 60.26; 109.85; 113.27; 127.35 (2C); 127.81; 128.05; 128.95; 138.94; 140.71; 153.51; 168.63; *m/z* 438 (M+2); 436 (10); 205 (10); 184 (10); 128 (9); 115 (24); 77 (33); 28 (100%).
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