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The first synthesis of β-phenylchalcogeno-α,β-unsaturated esters via hydrochalcogenation of acetylenes using microwave and solvent-free conditions

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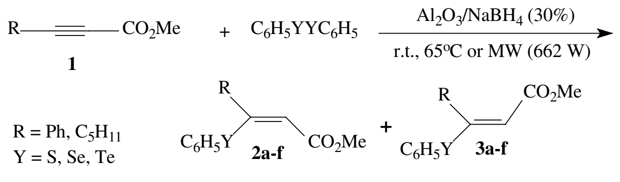
Abstract—A simple, clean, and efficient solvent-free protocol was developed for hydrochalcogenation of methyl propiolate derivatives with phenylchalcogenolate anion generated in situ from the respective diphenyl dichalcogenide (S, Se, Te) using alumina supported sodium borohydride. This efficient and improved method is general and furnishes the (*Z*)-β-phenylchalcogeno-α,β-unsaturated esters in yields and with selectivity comparable to those using organic solvent and inert atmosphere. The use of MW irradiation facilitates the procedure and accelerates the reaction.

Functionalized vinyl chalcogenides (S, Se, and Te) have been found to be a potential tool in organic synthesis, since they are very versatile intermediates for the selective construction of isolated or conjugated olefins.[1] Among the functionalized vinyl chalcogenides, those containing a Michael acceptor, like an ester group at the adjacent sp^2 carbon (a β-organylchalcogeno-α,β-unsaturated ester), are of greatest interest since they combine the chemical reactivity of the vinyl chalcogenides and the vinyl ester.[2]

The method of choice to prepare (*Z*)-1,2-disubstituted vinyl chalcogenides is the addition of organo chalcogenols, or the respective chalcogenolate anions, to acetylenes.[1,3] Despite the practicality of experimental procedure and high regio- and stereoselectivity, this method shows some disadvantages, such as, the use of stinking, volatile, and toxic thiophenol, unstable and air sensitive tellurolate and selenolate anions, use of long heating time and inert atmosphere. The in situ generation of organyl thiolate,[4] selenolate,[2c,4,5] and tellurolate anions[2c,e,5,6] has solved the unpleasant smell problem. Unfortunately, these improvements were not extended to alkynes bearing electron-withdrawing groups, like esters, and have not eliminated the use of organic solvents and inert atmosphere. Due to the increasing interest on functionalized vinyl chalcogenides, the development of new and efficient methods for the preparation of these compounds with defined regio- and stereochemistry is of general interest in organic synthesis.

Looking for cleaner approaches to classical syntheses, we have developed several protocols involving solid supported catalyst under solvent-free conditions[7] and MW irradiation.[8,9] As a continuation of our studies toward the development of new methods for the synthesis of vinyl sulfides, selenides, and tellurides, we report herein the synthesis of β-phenylchalcogeno esters **2** and **3** by



Scheme 1.

Keywords: Microwave irradiation; Solvent-free reaction; β-Phenylchalcogeno esters.

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hydrochalcogenation of acetylenes using $Al_2O_3/NaBH_4$ without any solvent[10,11] (Scheme 1, Table 1).

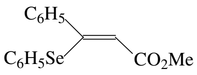
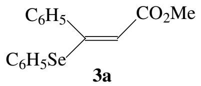
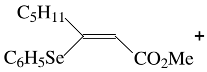
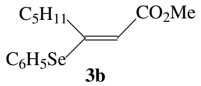
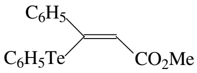
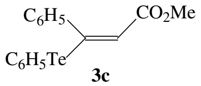
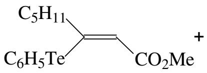
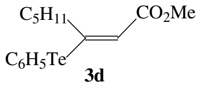
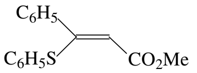
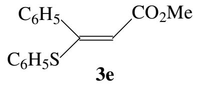
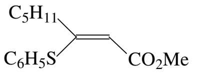
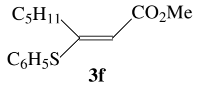
Our initial efforts were made toward the determination of the optimum conditions to perform the protocol. Thus, we chose methyl phenylpropiolate (1 equiv) and diphenyl diselenide (0.5 equiv) to establish the best conditions for the hydrochalcogenation reaction.

We examined the reaction time, amount of $Al_2O_3/NaBH_4$ (30%), temperature and use of microwave.[11] It was found that using 0.050 g of $Al_2O_3/NaBH_4$, at room temperature, the reaction proceeded slowly in 60% yield after 6 h. However, by using 0.080 g of sodium borohydride supported on alumina, the desired product was obtained in very good yield (83%). The appearance of two different signals in the olefinic region of the ^1H NMR (6.32 and 5.64 ppm) indicated the formation of two isomers, which were identified as being **2a** and **3a**. The reaction was stereoselective, giving predominantly the (*Z*)-stereoisomer **2a** in a *Z*:*E* ratio = 79:21 (Table 1, entry 1, Method A). The use of 0.127 g of the catalytic system has not significantly increased the yield.

Aiming to reduce the reaction time, the mixture of ester, diphenyl diselenide, and $Al_2O_3/NaBH_4$ (0.080 g) was irradiated with MW (662 W, Method B). Complete conversion was observed after 3 min and the product was obtained in comparable yield and higher selectivity (Table 1, entry 2). When the same protocol was performed at reduced MW power (353 W), it was observed, after 20 min, incomplete conversion and the product could be isolated in 57% yield.

When the reaction was performed in the presence of alumina alone, without $NaBH_4$ no reaction took place in all the conditions tested and the starting materials were recovered. By using only $NaBH_4$, the desired products **2a** and **3a** were obtained only in 50% yield, together with several other byproducts (detected by GC).

Table 1. Synthesis of β-phenylchalcogeno-α,β-unsaturated esters under solvent-free conditions

Entry	R	Y	Products	Method[a]	Time (min)	Yield (%) 2+3[b]	Ratio[c] *Z*:*E*	δ_H (vinyl)	
								Z	*E*
1	C_6H_5	Se	 **2a** +  **3a**	A	360	83	79:21	6.32	5.64
2	C_6H_5	Se	**2a** + **3a**	B	3	82	85:15		
3	C_6H_5	Se	**2a** + **3a**	C	3	50	—		
4	C_6H_5	Se	**2a** + **3a**	C	30	69	73:27		
5	C_5H_{11}	Se	 **2b** +  **3b**	A	240	69	87:13	6.17	5.48
6	C_5H_{11}	Se	**2b** + **3b**	B	6	62	84:16		
7	C_6H_5	Te	 **2c** +  **3c**	A	300	73	98:2	6.72	5.90
8	C_6H_5	Te	**2c** + **3c**	B	3	73	92:8		
9	C_5H_{11}	Te	 **2d** +  **3d**	A	600	50	90:10	6.61	5.89
10	C_5H_{11}	Te	**2d** + **3d**	B	10	52	83:17		
11	C_6H_5	S	 **2e** +  **3e**	A	360	74	88:12	6.09	5.39
12	C_6H_5	S	**2e** + **3e**	B	10	61	76:24		
13	C_5H_{11}	S	 **2f** +  **3f**	C	240	50	83:17	5.85	5.14
14	C_5H_{11}	S	**2f** + **3f**	B	11	55	83:17		

[a] Method A: the experiments were performed at room temperature. Method B: the experiments were performed at 662 W. Method C: the reaction mixture was heated at 65 °C using an oil bath.[11]

[b] Yields of pure products isolated by column chromatography (AcOEt/hexanes) and identified by mass spectrometry, ^1H, ^{13}C NMR.[2]

[c] Determined by GC of the crude reaction mixture and confirmed after isolation of the individual isomers.

In order to check the possibility of intervention of specific (non-purely thermal) microwave effects, the reaction with $Al_2O_3/NaBH_4$ (30%) was also examined using a pre-heated oil bath for the same time (3 min) and final temperature (65 °C), as measured at the end of exposure during the MW-assisted synthesis. However, the products were obtained only in poor yield (Table 1, entry 3, Method C). It was observed that 30 min were required to completely consume the starting materials, but the yield and selectivity of *Z*-**2a** decreased (Table 1, entry 4). Although the energy transfer and distribution in a domestic microwave oven is not controlled as in professional chemistry oven, we found that the microwave-assisted reactions are more efficient, more convenient and cleaner.

Once the best conditions were established, the protocols were extended to other methyl propiolate derivatives and diphenyl chalcogenides. In all the studied cases, the β-organylchalcogeno-α,β-unsaturated esters **2** and **3** were obtained from reasonable to good yields by using the optimized conditions described above for the preparation of **2a** (Table 1, entries 1 and 2). However, for the synthesis of β-organyltelluro- and thio-α,β-unsaturated esters (entries 7–14) a larger amount of the $Al_2O_3/NaBH_4$ system was necessary.

It was found that using 0.080 g of $Al_2O_3/NaBH_4$, the reaction of methyl phenylpropiolate with diphenyl ditelluride at room temperature (Method A), occurred slowly (7 h), in 62% yield. However, the yield could be increased (73%) and the time reduced (5 h) by using 0.127 g of the supported hydride (Table 1, entry 7). The product was obtained almost exclusively with the *Z*-configuration (*Z*:*E* ratio = 98:2), as detected by GC and ^1H NMR. Otherwise, the use of argon atmosphere has displayed no significant increase in yield and selectivity of the product. When the same reaction was performed under MW irradiation (Method B), complete conversion after irradiation for 3 min was observed (Table 1, entry 8).

A search in literature[2b] showed that the hydrotelluration of phenylpropiolate esters with methyl phenyltellurolate anion in presence of EtOH/THF under inert atmosphere yielded exclusively the methyl (*Z*)-3-phenyl-3-(phenyltelluro)propenoate **2c**. On the other hand, by using our solvent-less protocols (Methods A and B), we have obtained two isomers (**2c** and **3c**), with a large predominance of the *Z* isomer **2c**. Attempts to explain this apparent losts of control in selectivity, we repeated the described procedure using the solvent (THF/ethanol) and argon atmosphere. Surprisingly and in contrast to the reported data,[2b] **2c** was obtained in 75% yield as mixture of isomers (*Z*:*E* ratio = 96:4). The *Z* and *E* esters were easily separable by column chromatography (AcOEt/hexanes as eluent), with the more polar isomer showing the *E*-configuration (**3c**), according to analysis of GC and their ^1H and ^{13}C NMR spectra.[11]

In order to exploit the generality of our method, we have also carried out few experiments employing phenyl thiolate anion, generated in situ from diphenyl disulfide. It was found that the hydrosulfurylation of methyl phenylpropiolate using 0.080 or 0.127 g of $Al_2O_3/NaBH_4$ furnished **2e**, respectively, in 40% and 44% yield, after stirring for 6 h at room temperature. However, the yield could be increased to 74% by using 0.253 g of $Al_2O_3/NaBH_4$ (Table 1, entry 11, Method A). However, for the hydrosulfurylation of the methyl pentylpropiolate, it was observed that the reaction occurs only under heating or microwave and the respective β-phenylthio esters **2f** and **3f** were obtained only in modest yields (Table 1, entries 13 and 14). In all the studied cases, the *Z* and *E* isomers can be easily separated by column chromatography (hexane/AcOEt as eluent).

In conclusion, several β-phenylchalcogeno esters could be prepared from moderate to good yields by hydrochalcogenation of acetylenes under solid supported ($Al_2O_3/NaBH_4$) and solvent-free conditions at room temperature, gently heating or under MW irradiation. This improved, simple, fast, and clean protocol eliminates the use of inert atmosphere and minimizes the organic solvent and energy demands. Besides these advantages, the reaction time could be reduced from several hours to few minutes (when MW was employed), under milder conditions and with non-aqueous work-up.

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10. The solid supported catalysts were prepared by the following procedure: to a pestle mortar was added alumina (0.7 g of Al_2O_3 90, 0.063–0.200 mm, Merck) and $NaBH_4$ (0.3 g) and the mixture was stirred for 1 min and immediately used in the reaction.[12]
11. *General procedure for the synthesis of β-phenylchalcogeno esters* **2a**–**f** *and* **3a**–**f**. *Method A*: a mixture of methyl phenylpropiolate (0.160 g; 1 mmol) and diphenyl ditelluride (0.207 g; 0.5 mmol) was added to aluminum oxide impregnated with $NaBH_4$[10] (0.127 g). The mixture was stirred at room temperature. The reaction progress was followed by TLC, and after 300 min (see Table 1) the reaction vessel was cooled, and the product was filtered off the aluminum oxide by washing with ethyl acetate (10 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel (SiO_2) eluting with hexane/ethyl acetate (98:2), yielding the esters **2c** and **3c** as a mixture of *Z* and *E* isomers (0.269 g, 73%, *Z*:*E* ratio = 98:2). The spectral data are in perfect agreement with those reported in the literature.[2] (*Z*)-**2c** (first eluted fraction): MS *m*/*z* (rel int.) 368 (M^+, 58.0), 205 (45.0), 161 (100.0), 77 (31.0). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38–7.43 (m, 2H); 6.88–7.14 (m, 8H); 6.72 (s, 1H); 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 156.1, 140.9, 140.4 (2C), 133.6, 128.4, 128.0 (2C), 127.8, 127.5, 127.2, 120.9, 118.8, 113.9, 52.0. (*E*)-**3c** (second eluted fraction): MS *m*/*z* (rel int.) 368 (M^+, 40.0), 205 (100.0), 161 (87.0), 77 (85.0). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83–7.88 (m, 2H); 7.25–7.43 (m, 8H); 5.90 (s, 1H); 3.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 140.5, 140.4, 130.0, 129.5, 128.4, 128.1, 127.9, 127.2, 126.8, 122.6, 114.9, 51.0. *Method B*: the aforementioned whole mixture was previously stirred for 1 min and then irradiated with microwave (used a domestic Brastemp model VIP-38 Sensor Crisp operating at 2.45 GHz) at 662 W[13] for 3.0–11.0 min (Table 1) and the product extracted and purified according to described on Method A. *Method C*: the procedure described on Method A was followed and the reaction mixture was stirred under heating at 65 °C (oil bath) for 3–240 min (Table 1).
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