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"On-Water" Michael-Type Addition Reactions Promoted by PhSeZnCl

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In this communication we report that our reagent PhSeZnCl can be conveniently used to effect Michael addition like reactions of unsaturated ketones and electron-deficient alkynes, leading to synthetically useful β -seleno derivatives and vinyl selenides, respectively. The reactions are effected

at room temperature in THF as well as under "on water" conditions. When the addition occurs on a triple bond, good stereoselectivity is observed, and the reaction shows a rate acceleration in water suspension.

Introduction

The addition of selenolates represents a convenient procedure to introduce a selenium-containing functionality into electrophilic organic substrates. It is well known that once selenium is incorporated into a molecule, it can be easily manipulated and removed in many different ways by using mild reaction conditions to usually afford the target compounds in good yields even with the use of catalytic amounts of reagents.^[1] Conjugate addition is one of the most important and common bond-forming strategies in synthetic organic chemistry.^[2] Few examples reported that treatment of α,β -unsaturated carbonyl derivatives with nucleophilic selenium species affords β-seleno derivatives through Michael-like addition.^[3] This reaction has been applied to protected α , β -unsaturated lactones, ^[4] in natural product synthesis,^[5] and in asymmetric Michael additions in the presence of an alkaloid.^[6] Seleno-Michael reactions were effected by using in situ prepared selenolates starting from the corresponding diselenides in the presence of In-TMSCl^[7] or Zn/RuCl₃^[8] by using ceric(IV) ammonium nitrate^[9] in a radical process or β -cyclodextrins^[10] as catalysts and benzenselenol as the nucleophile. All these procedures suffer from low yields and the disadvantage of using airand moisture-sensitive reagents such as selenols. Continuing investigations into the synthetic applicability of zinc selenolates and bench-stable PhSeZnCl (1),^[11] we report herein the results of some Michael-type addition reactions on conjugated alkenes 2a-g and electron-deficient alkynes 3a-g to give the corresponding β -selenocarbonyl derivatives 4a-g and vinyl selenides 5/6a-g, respectively (Scheme 1).



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Scheme 1. PhSeZnCl in Michael-type reactions.

Results and Discussion

In order to identify the best experimental conditions, preliminary investigations were carried out starting from cyclohexen-2-one (2a). The reaction of 1 with electrophile 2a was effected in H_2O suspension as well as in THF solution, evaluating the effect of L-proline and DMF as additives.

All the conversions were performed at room temperature, and the yields reported in Table 1 refer to the amount of isolated products after purification by silica gel column chromatography.

When the reaction was carried out in an on-water suspension, the reaction was very slow and 4a was obtained in only 30% yield after 140 h (Table 1, Entry 1). Nevertheless, no addition products were observed when the reaction was carried out in THF (Table 1, Entry 4), and in both cases the yields increased slightly when DMF (2 equiv.) was added (Table 1, Entries 2 and 5).

L-Proline has been reported to be a powerful catalyst for a number of asymmetric Michael addition reactions;^[12] however, when it was added to the water suspension (Table 1, Entry 3) an increase in yield but no significant stereocontrol was observed in the formation of **4a**, which was isolated as a racemic mixture.

We observed that in THF the reaction mixture progressively became yellow, probably indicating the formation of

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Table 1. Preliminary investigations.



[a] Calculated for the isolated compound. [b] Racemic mixture. [c] The reaction was carried out in colorless transparent Pyrex glass under room light.

the unreactive diphenyl diselenide reasonably through a photoactivated radical mechanism. To support this hypothesis, a THF solution of PhSeZnCl (1 mmol in 1 mL of THF) was quantitatively converted into the corresponding diselenide by irradiation for 30 min with a visible-light lamp. On the basis of these results and to prevent reagent decomposition, the reaction mixture was protected from light. Under these conditions (Table 1, Entries 6–9) better results could be obtained in water as well in THF, and it is interesting to note that the presence of DMF did not have any appreciable effects. Unfortunately, under the same conditions, PhSeZnBr^[11b] did not lead to the formation of **4a** in water or in THF solution, and in both cases, starting enone **2a** was quantitatively recovered.

With the optimized conditions in hand we explored the scope of the reaction that appears to be strongly limited by the nature of the electron-withdrawing group conjugated to the double bond. Only conjugated ketones were sufficiently reactive to afford the corresponding β-phenylseleno derivatives. Conjugated esters (with the only exception being methyl acrylate, which gave the addition product in 10% yield in THF and 15% yield in water suspension), aldehydes, nitro derivatives, nitriles, and selenones were completely unreactive under both above-described reaction conditions. The results obtained starting from ketones 2a-g are summarized in Table 2. In all cases, the reactions in water suspension were slower than those in THF, affording generally low yields (Table 2, Entries 1, 2, 4, 7) or no reaction products (Table 2, Entries 3, 5) even after 140 h. Only terminal alkene 2f gave quantitative yield of addition product 4f at room temperature after 140 h. In THF, the same reactions afforded β -phenylseleno ketones 4a-g in moderate to good yields after 24 h. All the compounds were purified by flash chromatography on silica gel and fully characterized by GC-MS and NMR spectroscopy.

Considering that useful procedures to prepare vinylic selenides involve nucleophilic or electrophilic organoselenium addition to terminal or internal alkynes^[13] and that these

Table 2.	Michael-type	addition	reaction	of	conjugated	alkenes.
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[a] In H₂O, 23 °C for 140 h. [b] In THF, 23 °C for 24 h.

intermediates play an important role in the synthesis of organoselenium compounds, we decided to investigate electron-deficient alkynes **3a–g** as Michael acceptors in the reaction with PhSeZnCl for the stereoselective preparation of functionalized alkenes.^[14]

It is known that nucleophilic addition of phenylselenol to alkynes affords, preferentially, the (Z)-vinylic selenides even if some of these strategies^[13] are usually complicated by long conversion times at room temperature. The reaction can be accelerated by increasing the temperature, but in this case a mixture of (Z)- and (E)-vinylic selenides is obtained in a quite equimolar ratio.^[15] The results collected in Table 3 clearly indicate that, in contrast to previous examples, nucleophilic addition of PhSeH promoted by PhSeZnCl through a Michael-type reaction of activated alkynes in water suspension is faster than that in THF and affords almost quantitative yield of corresponding vinyl selenides **5a**–g and **6a**–g in 2 h at 23 °C.

In these cases, the reaction was highly stereoselective (Table 3, Entries 1–3 and 7) or stereospecific (Table 3, Entries 4–6), leading to (Z)-vinylic selenides 5 as the major

SHORT COMMUNICATION

Entry	Substrate	Products 5 (<i>major</i>)/ 6 (<i>minor</i>)	Yield ^[a] [%] 5/6	Yield ^[b] [%] 5/6
1	Ŷ	PhSe O	99 (66:34)	90 (83:17)
		5a (Z)/ 6a (E)		
2		PhSe O	95 (79:21)	90 (87:13)
	3b	5b (Z)/ 6b (E)		
3	О С ₅ Н ₁₁	PhSe O C ₅ H ₁₁	99 (75:25)	93 (85:15)
	3c	5c (Z)/6c (E)		
4	OMe	PhSe O OMe	99 (100:0)	99 (85:15)
	3d	5d (Z)/6d (E)		
5	OMe	PhSe O Ph	99 (100:0)	35 ^[c] (100:0)
	3e	5e (Z)/ 6e (E)		
6	MeO	PhSe O MeO O O MeO	100 (100:0)	90 (100:0)
	3f	5f (<i>Z</i>)/ 6f (<i>E</i>)		
7		PhSe O C ₅ H ₁₁ H	83 (80:20)	93 (80:20)
	3g	5g (Z)/ 6g (E)		

Table 3. Michael-type addition reaction of electron-deficient alkynes.

[a] In H₂O, 23 $^\circ C$ for 2 h. [b] In THF, 23 $^\circ C$ for 24 h. [c] Refluxing THF for 24 h.

isomer. The reaction products were purified by flash chromatography and fully characterized by GC–MS and NMR spectroscopy. The *Z/E* ratios were calculated by NMR spectroscopic analysis of the crude mixture, and the geometry of the double bond was assigned on the basis of the vicinal olefinic coupling constants for **5b–6b**, **5c–6c**, and **5d–6d** and on the basis of nOe correlations (Scheme 2) obtained by a standard NOESY experiment for compounds **5a** and **5e–g**.

From a synthetic point of view it is interesting to underline that the range of electron-deficient alkynes that can be successfully employed in this reaction is more general than that observed for alkenes conjugated to an electron-withdrawing group. Ketones **3a–c** as well as esters **3e–f** and aldehydes **3g** were used as conjugating groups for the triple carbon–carbon bond. The stereoselectivity for substrates **3a–c** is slightly better in THF, whereas no appreciable difference was observed in all other examples. Surprisingly, the reaction for compound **3e** in THF is very slow but can be accelerated by temperature, whereas the corresponding carboxylic acid was completely unreactive under both conditions.



Scheme 2. nOe correlations used to assign the E/Z geometry of trisubstituted olefins.

Conclusions

In this communication we reported the PhSeZnCl-promoted Michael-type addition reactions of conjugated alkenes and alkynes under neutral and mild conditions by using water as a green solvent. The corresponding β -selenocarbonyl compounds and vinylic selenides were obtained in good yields, and the latter are obtained with good stereoselectivity in favor of the (Z) isomer. The different rate acceleration observed for the reaction effected under "on-water" conditions seems to be strongly correlated to the nature of the substrates and leads us to speculate that water should play a role in activating the substrate and does not influence the reactivity of our nucleophilic reagent. The synthetic strategy described in this communication offers significant advantages with regard to operation and yields and thus presents an efficient and eco-friendly alternative to existing methods. Finally, the reported procedure demonstrates the synthetic utility of PhSeZnCl as a nucleophilic organoselenium reagent, stressing its versatile applicability under "onwater" conditions.

Experimental Section

General Procedure for the Reactions Effected in THF: To a solution of 1 (1.0 mmol) in THF (3 mL), under anhydrous conditions was added conjugated alkene **2a–g** or alkyne **3a–g** (1.0 mmol) dissolved in THF (2 mL). The resulting mixture was stirred at room temperature in a dark brown vial for 24 h, and the progress of the reaction was monitored by TLC and GC–MS. The reaction mixture was then poured into water and extracted with diethyl ether (3×). The organic phase was dried with Na₂SO₄ and filtered, and the solvent was removed under vacuum. All the reaction products were purified by flash chromatography. The yields reported in Tables 1–3 refer to isolated products and the *Z/E* ratios were measured on the crude by NMR spectroscopy. All isolated compounds were fully characterized by GC–MS and ¹H NMR and ¹³C NMR spectroscopy.

General Procedure for the Reactions Effected under "On-Water" Conditions: Compound 1 (1.0 mmol) and conjugated alkene 2a–g or alkyne 3a–g (1.0 mmol) were poured into water (6 mL), and the



mixture was vigorously stirred at room temperature for 140 h (2a– g) or 2 h (3a–g). The water was extracted with diethyl ether (3×). The combined organic layers were dried with Na₂SO₄ and filtered, and the solvent was removed under vacuum. All the reaction products were purified by flash chromatography. The yields reported in Tables 1–3 refer to isolated products and the Z/E ratios were measured on the crude by NMR spectroscopy. All isolated compounds were fully characterized by GC–MS and ¹H NMR and ¹³C NMR spectroscopy.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for the new compounds.

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 a) A. Krief, L. Havesi, Organoselenium Chemistry, Springer, Berlin, 1988, vol. 1; b) A. Krief in Comprehensive Organometallic Chemistry (Ed.: B. M. Trost), Pergamon, Oxford, 1991, p. 85; c) T. Wirth (Ed.), Topics in Current Chemistry Vol. 208: Organoselenium Chemistry – Modern Developments in Organic Synthesis, Springer, Berlin, 2000; d) T. G. Back (Ed.), Organoselenium Chemistry – A Practical Approach, Oxford, New York, 2000; e) T. Wirth, Angew. Chem. 2000, 112, 3890; Angew. Chem. *Int. Ed.* **2000**, *39*, 3740; f) D. M. Freudendahl, S. Santoro, S. A. Shahzad, C. Santi, T. Wirth, *Angew. Chem.* **2009**, *121*, 8559; *Angew. Chem. Int. Ed.* **2009**, *48*, 8409; g) C. Santi, S. Santoro, B. Battistelli, *Curr. Org. Chem.* **2010**, *14*, 2442.

- [2] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**.
- [3] M. Miyashita, A. Yoshikoshi, Synthesis 1980, 664.
- [4] P. A. Grieco, M. Miyashita, Tetrahedron Lett. 1974, 15, 1869.
- [5] K. Mori, Tetrahedron 1976, 32, 1101.
- [6] H. Pluim, H. Wynberg, Tetrahedron Lett. 1979, 20, 1251.
- [7] B. C. Ranu, A. Das, Adv. Synth. Catal. 2005, 347, 712.
- [8] B. Movassagh, A. Tatar, Synlett 2007, 1954.
- [9] C.-M. Chu, S. Gao, M. N. V. Sastry, C.-W. Kuo, C. Lu, J.-T. Liu, C.-F. Yao, *Tetrahedron* 2007, 63, 1863.
- [10] B. Srinivas, V. P. Kumar, R. Sridhar, V. P. Reddy, Y. V. D. Nageswar, K. R. Rao, *Helv. Chim. Acta* **2009**, *92*, 1080.
- [11] a) C. Santi, S. Santoro, L. Testaferri, M. Tiecco, Synlett 2008, 1471; b) C. Santi, S. Santoro, B. Battistelli, L. Testaferri, M. Tiecco, Eur. J. Org. Chem. 2008, 5387; c) S. Santoro, B. Battistelli, L. Testaferri, M. Tiecco, C. Santi, Eur. J. Org. Chem. 2009, 4921.
- [12] B. List, Tetrahedron 2002, 58, 5573.
- [13] a) J. V. Comasseto, J. Organomet. Chem. 1983, 253, 131; b)
 O. S. D. Barros, E. S. Lang, C. A. F. de Oliveira, C. Peppe, G. Zeni, *Tetrahedron Lett.* 2002, 43, 7921; c) M. J. Dabdoub, V. B. Dabdoub, M. A. Pereira, *Tetrahedron Lett.* 2001, 42, 1595; d)
 M. J. Dabdoub, A. C. M. Baroni, E. J. Lenardão, T. R. Gianeti, G. R. Hurtado, *Tetrahedron* 2001, 57, 4271.
- [14] M. J. Dabdoub, T. M. Cassol, A. C. F. Batista, *Tetrahedron Lett.* 1996, 37, 9005; J. V. Comasseto, L. W. Ling, N. Petragnani, H. A. Stefani, *Synthesis* 1997, 373.
- [15] J. V. Comasseto, J. T. B. Ferreira, J. Organomet. Chem. 1981, 216, 287

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