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Selenium-Directed Conjugate Addition of Amines to Dimethyl 2-Phenylseleno Fumarate : Regio and Diastereoselective Synthesis of 2-Phenylseleno-3-Amino Succinates

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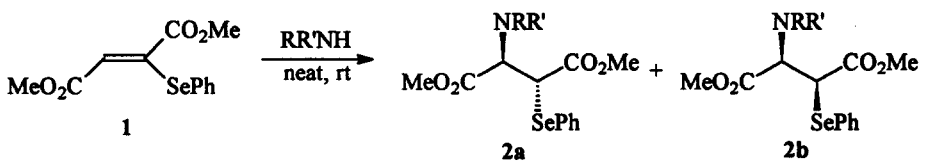
Abstract: Dimethyl 2-phenylseleno fumarate **1** acts as a strong Michael acceptor of amines, providing the corresponding 2-phenylseleno-3-amino succinates **2a** and **2b** in very high yields with complete regio- and good diastereoselectivity. © 1997 Elsevier Science Ltd.

Stereocontrolled bond-forming reactions by conjugate additions in the readily available, simple four-carbon dicarboxylic acids, such as fumaric and maleic acids, are currently among the more challenging areas of practical importance in organic synthesis.[1] In particular, the regio- and stereodirected amination in the above acyclic molecules has recently attracted considerable attention, since the functionalized succinates with dissimilar substituents serve as versatile building blocks in organic chemistry.[2]

More recently, the regioselectivity of the addition of nitrogen nucleophiles to unsymmetrical fumaric esters was studied: the authors reported that the addition of azoles, carried out at 100°C, gave the corresponding regioisomers 2-azol-1-ylsuccinates; on the other hand, the addition of primary alkylamines proved to be depending on the nature of the amines: only primary amines were reactive enough to be used successfully, giving the corresponding (alkylamino) succinic esters; *tert*-butylamine and secondary amines were practically unreactive.[3a]

Continuing our studies on the reactivity and the stereochemical issues related to dimethyl 2-phenylseleno fumarate **1**, easily available in large amount from dimethyl maleate,[4] we report herein examples of remarkably complete regio- and good diastereoselectivity in the direct amination of **1**.

We have found that amines can be spontaneously added to the olefinic double bond of **1**, at room temperature, without using any solvent (Scheme 1).



1 **2a** **2b**

Scheme 1

All the reactions proceeded with complete regioselectivity, giving the corresponding 2-phenylseleno-3-amino succinates in very high yields (Table 1). Selenium has proven to be particularly effective as directing and activating atom in the conjugate addition of amines to **1** and this transformation can be considered an original

and interesting outcome, since the use of selenium as a directing element to control regio- and stereoselectivities in organic reactions is limited.[5]

Table 1. Direct Amination of Dimethyl 2-Phenylseleno-Fumarate **1** at Room Temperature[a]

Entry	R	R'	*anti/syn* (a/b)[b]	yield (%)
1	*n*-Pr	H	72 : 28	95
2	*t*-Bu	H	75 : 25	96
3	Bz	H	81 : 19	98
4	Et	Et	52 : 48	95
5		$-(CH_2)_5-$	63 : 37	90

a. The amination reactions were carried out by adding the amine (1.1 mmol) directly to **1** (1 mmol, 300 mg) at room temperature; the reactions were stirred until **1** was no more detectable by TLC (30-60 min).The resulting pale yellow oil was directly purified by flash chromatography on silica gel (hexane/ethyl acetate 9:1) to give the pure adducts **2a** and **2b**.[6]

b. *Anti/syn* designations refer to the relative orientations of substituents in an extended zig-zag chain. Ratio determined by GC; in case of entry 2 the ratio was determined by ^{1}H-NMR of the crude sample.

Primary aliphatic amines were very reactive in the addition process. The enhanced efficiency of **1** as Michael acceptor was furtherly witnessed by its capability to add sterically hindered primary amines, such as *tert*-butylamine (entry 2), and linear and cyclic secondary amines (entries 4, 5), never successfully described uptodate.[3a, b] The stereochemistry of two diastereoisomers **2a** and **2b** was determined using analysis of ^{1}H-^{13}C long-range coupling constants as determined by HMBC experiments.

We have shown that the phenylseleno group incorporated into the fumarate ester may be now used for regio- and stereocontrolled addition of the amines to the olefinic double bond of **1**, developing an efficient methodology for the production of *anti* and *syn* 2-phenylseleno-3-amino succinates **2**. These functionalized products are versatile synthons for further manipulations.[7]

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6. Representative ^{1}H and ^{13}C-NMR spectra: a) R= *t*-Bu, R'= H (entry 2): **2a**: ^{1}H-NMR δ ($CDCl_3$): 0.97 (s, 9H), 1.8 (s, 1H), 3.58 (d, 1H, J= 10.1 Hz), 3.60 (s, 3H), 3.68 (s, 3H), 3.77 (d, 1H, J= 10.1 Hz), 7.2-7.4 (m, 3H), 7.5-7.6 (m, 2H). ^{13}C-NMR δ ($CDCl_3$): 29.77, 48.05, 51.43, 52.41, 57.96, 128.73, 128.87, 129.49, 135.44, 171.61, 175.64. **2b:** ^{1}H-NMR δ ($CDCl_3$): 1.02 (s, 9H), 2.1 (s, 1H), 3.49 (s, 3H), 3.60 (s, 3H), 3.97 (d, 1H, J= 7.1 Hz), 3.89 (d, 1H, J= 7.1 Hz), 7.2-7.4 (m, 3H), 7.5-7.6 (m, 2H).^{13}C-NMR δ ($CDCl_3$): 29.74, 51.57, 52.65, 52.81, 57.50, 128.80, 129.49, 129.67, 136.07, 171.76, 174.91. b) R= Et, R'= Et (entry 4): **2a**: ^{1}H-NMR δ ($CDCl_3$): 0.90 (dd, 6H, J_1= 7.1 Hz, J_2= 7.1 Hz), 2.28 (dq, 2H, J_1= 7.1 Hz, J_2= 7.1 Hz, 2.67 (dq, 2H, J_1= 7.1 Hz, J_2= 7.1) Hz, 3.59 (s, 3H), 3.65 (s, 3H), 3.75 (d, 1H, J= 12.0 Hz), 3.90 (d, 1H, J= 12.0 Hz), 7.2-7.3 (m, 2H), (7.5-7.6 (m, 2H). ^{13}C-NMR δ ($CDCl_3$): 13.87, 44.48, 44.76, 51.47, 52.13, 64.91, 128.47, 129.12, 129.50, 136.07, 170.50, 172.04. **2b:** ^{1}H-NMR δ ($CDCl_3$): 1.10 (dd, 6H, J_1= 7.1 Hz, J_2= 7.1 Hz) 2.54 (dq, 2H, J_1= 7.1 Hz, J_2= 7.1 Hz), 2.70 (dq, 2H, J_1= 7.1 Hz, J_2= 7.1 Hz), 3.16 (s, 3H), 3.64 (s, 3H), 3.99 (d, 1H, J= 11.3 Hz), 4.44 (d, 1H, J= 11.3 Hz), 7.2-7.4 (m, 3H), 7.5-7.6 (m, 2H). ^{13}C-NMR δ ($CDCl_3$): 13.86, 44.70, 45.07, 51.47, 63.55, 128.12, 128.56, 137.14, 171.37, 171.73.
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