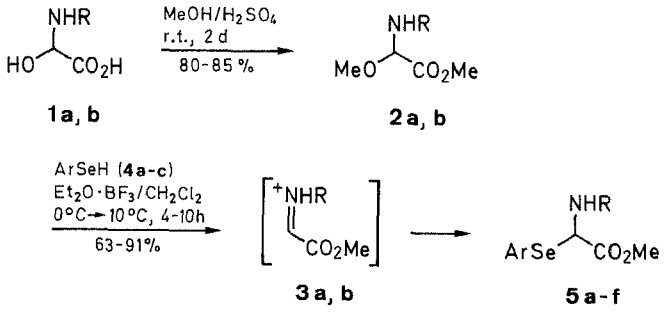
Synthesis of α-Arylselenoglycine Derivatives from Methyl α-Methoxyhippurate or Methyl α-Methoxy-*N*-Benzyloxycarbonylglycinate and Areneselenols

Bonchul Ku, Kyeongho Chang, Dong Young Oh*

Department of Chemistry, Korea Advanced Institute of Science and Technology, P.O. Box 150, Chong-yang Ni, Seoul 131-650, South Korea

α-Arylselenoglycine derivatives were synthesized from methyl α-methoxyhippurate or methyl α-methoxy-*N*-benzyloxycarbonylglycinate and areneselenols under boron trifluoride etherate catalysis in dichloromethane.

As a part of our synthetic approaches to α-heteroatom-substituted amino acids of synthetic interest,[1] we report here the synthesis of α-arylselenoglycine derivatives **5a–f**.



1–3	R	4	Ar
a	PhCO	a	Ph
b	$PhCH_2OCO$	b	$4\text{-}MeC_6H_4$
		c	$4\text{-}MeOC_6H_4$

5	R	Ar	5	R	Ar
a	PhCO	Ph	d	$PhCH_2OCO$	Ph
b	PhCO	$4\text{-}MeC_6H_4$	e	$PhCH_2OCO$	$4\text{-}MeC_6H_4$
c	PhCO	$4\text{-}MeOC_6H_4$	f	$PhCH_2OCO$	$4\text{-}MeOC_6H_4$

A suitable method for the preparation of the starting materials, methyl α-methoxyhippurate (**2a**)[2] and methyl α-methoxy-*N*-benzyloxycarbonylglycinate (**2b**),[2] consists in the treatment of α-hydroxyhippuric acid (**1a**) and α-hydroxy-*N*-benzyloxycarbonylglycine (**1b**) with methanolic sulfuric acid. The compounds **2a, b** were converted into α-arylselenoglycine derivatives **5a–f** by the reaction with areneselenols **4a–c**[3] under Lewis acid catalysis as described in Table 1 and in the experimental section.

Ether–boron trifluoride complex was the Lewis acid selected, because other acids (sulfuric acid, aluminum chloride, tin tetrachloride, titanium tetrachloride) also gave the products, but in lower yields. As shown in Table 1 the reaction was clean, and no side products could be detected on thin layer chromatography. The intermediate immonium ions **3a, b**[4] were assumed as the reactive species resulting from the primary reaction of the substrates and ether–boron trifluoride. Benzyloxycarbonyl derivative **1b** was more reactive than **1a**; this reactivity could be explained by the fact that electrophilic immonium ion **3b** was more reactive than **3a** under the reaction condition mentioned above.

In summary, α-arylselenoglycine derivatives,[5] a new type of synthetic amino acid derivative, were synthesized from readily available starting materials.

Table 1. α-Arylselenoglycine Derivatives **5a–f** Prepared

Product	Reaction Time (h)	Isolated Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c]
5a	8	63	80–81 (MeOH)	$C_{16}H_{15}NO_3Se$ (348)
5b	7	85	70–71 (EtOH)	$C_{17}H_{17}NO_4Se$ (378)
5c	10	90	75–76 (EtOH)	$C_{17}H_{17}NO_3Se$ (362)
5d	4	70	70–71 (EtOAc)	$C_{17}H_{17}NO_4Se$ (378)
5e	4	87	60–61 (EtOAc)	$C_{18}H_{19}NO_5Se$ (408)
5f	5	91	76–77 (EtOAc)	$C_{28}H_{19}NO_4Se$ (392)

[a] Yield based on **2a** and **2b**.
[b] Uncorrected, measured with an Electrothermal Melting Point Apparatus (Electro thermal Engineering LTD).
[c] Satisfactory microanalyses obtained: C ±0.07, H ±0.09, N ±0.16.

Table 2. Spectroscopic Data for **5a–f**

Product	^{1}H-NMR ($CDCl_3$/TMS)[a] δ, *J*(Hz)	IR (KBr)[b] ν(cm^{-1})	MS (70 eV)[c] *m/z* (%)
5a	7.5 (m, 10H); 6.9 (br d, 1H); 6.1 (d, 1H, *J* = 9); 3.7 (s, 3H)	3320, 2950, 1749, 1661, 1532, 1501, 1450, 1347, 1237, 1180	349, 105 (100)
5b	8.4 (m, 9H); 6.8 (d, 1H, *J* = 9); 6.0 (d, 1H, *J* = 9); 3.7 (s, 3H); 3.7 (s, 3H)	3310, 2970, 1752, 1661, 1533, 1501, 1450, 1352, 1260, 1187	379, 105 (100)
5c	7.5 (m, 9H); 7.0 (br d, 1H); 6.1 (d, 1H, *J* = 9); 3.7 (s, 3H); 2.3 (s, 3H)	3310, 2980, 1750, 1660, 1531, 1500, 1450, 1345, 1237, 1175	363, 105 (100)
5d	7.2 (m, 10H); 5.5 (br m, 1H + 1H); 5.0 (s, 2H); 3.8 (s, 3H)	3350, 3005, 1752, 1728, 1510, 1450, 1351, 1231, 1180, 1049	379, 91 (100)
5e	7.2 (m, 9H); 5.7 (br m, 1H + 1H); 5.2 (s, 2H); 3.7 (s, 3H); 3.7 (s, 3H)	3230, 3010, 1751, 1715, 1540, 1509, 1358, 1260, 1237, 1075	409, 91 (100)
5f	7.2 (m, 9H); 5.8 (br m, 1H + 1H); 5.2 (s, 2H); 3.7 (s, 3H); 2.4 (s, 3H)	3315, 3008, 1749, 1710, 1540, 1450, 1356, 1237, 1062	393, 91 (100)

[a] Obtained on a Varian T-60A and a Varian FT-80A.
[b] Recorded on a Perkin Elmer Model 283-B.
[c] Recorded on a Hewlett Packard 5985A GC/MS by electron impact (EI) method.

Dichloromethane was distilled from sodium before use. Ether–boron trifluoride was freshly distilled. Areneselenols were prepared by known methods and used immediately.[3]

N-Protected α-Arylselenoglycines 5a–f; General Procedure:
To a stirred solution of methyl α-methoxyhippurate (**2a**; 1 mmol) or methyl α-methoxy-*N*-benzyloxycarbonylglycinate (**2b**; 1 mmol) and areneselenols (**4**; 1.1 mmol) in CH_2Cl_2 (3 mL) under nitrogen atmosphere is added dropwise ether–boron trifluoride complex (1 mmol) at 0 °C. The reaction mixture is allowed to warm to 10 °C and is monitored by TLC. The solution is quenched by pouring into a cold sat. aq. $NaHCO_3$ solution (10 mL). Extraction with ether (3 × 20 mL), washing with water (20 mL), drying ($MgSO_4$), and removal of the solvent under reduced pressue give the crude products. Pure samples are obtained by column chromatography (EtOAc/*n*-hexane, 1:2) and recrystallization ($CHCl_3$/*n*-hexane, 1:5).

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