Tetrahedron Letters,Vol.25,No.32,pp 3387-3390,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

UNSYMMETRICAL SELENIDES FROM SELENOCYANATES AND METHYL GRIGNARD

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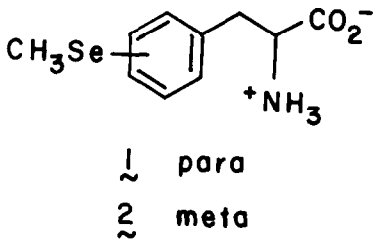
ABSTRACT: The addition of methyl Grignard to diethyl acetamido(cyanoselenobenzyl)malonates 3 and 4 at -78° followed by hydrolysis yields the 3-(4-and 3-methylselenophenyl)alanines 1 and 2.

In a program for the synthesis of new selenium-containing amino acids[1] for eventual testing as pancreatic imaging agents, we have included the methylseleno derivatives of phenylalanine, 1 and 2. To facilitate the incorporation of ^{75}Se, we sought to introduce the selenium into an appropriately protected amino acid. Starting with the diethyl aminobenzylmalonates 3[2] and 4[3], the selenium atom was inserted by diazotization of the aromatic amine followed by decomposition of the intermediate in the presence of aqueous selenocyanate salts[4a] generated from elemental selenium[4b].



1 para

2 meta

Guided by the analogous reaction of dimethyl cadmium with arylselenyl chlorides[5] and the formation of diaryl selenides from aryl selenocyanates and aryl Grignards[6], we chose to investigate the reaction of methyl Grignard with the functionalized aryl selenocyanates 5 and 6. Addition of 5 or 6 to a three-fold excess of methyl Grignard at -78° gave an instantaneous precipitate that was quenched after ten min to give the methylseleno intermediates 7 or 8. Rigorous purification of the starting materials and the use of a molar equivalent of acetic acid in ethanol at -78° as the quenching solution are required to eliminate variations in yield arising from ester hydrolysis. Although acyl halides[7] are known to react with Grignard reagents at -78°, no evidence was obtained for the direct reaction of methyl Grignard with either the ester or amide moieties. This simple synthetic method for unsymmetrical selenides should find further application in organoselenium chemistry.

On refluxing in 12 N HCl the protected amino acids 7 and 8 were hydrolyzed to the amino acid hydrochlorides, 1·HCl and 2·HCl. The free amino acids were obtained upon neutralizing with aqueous ammonia. An attempt to recrystallize 1·HCl from ethanol led to a product which contained 25% of the ethylseleno analog, apparently formed in an acid-catalyzed transalkylation reaction. The identification of the ethylselenyl group by nmr led to the observation that the

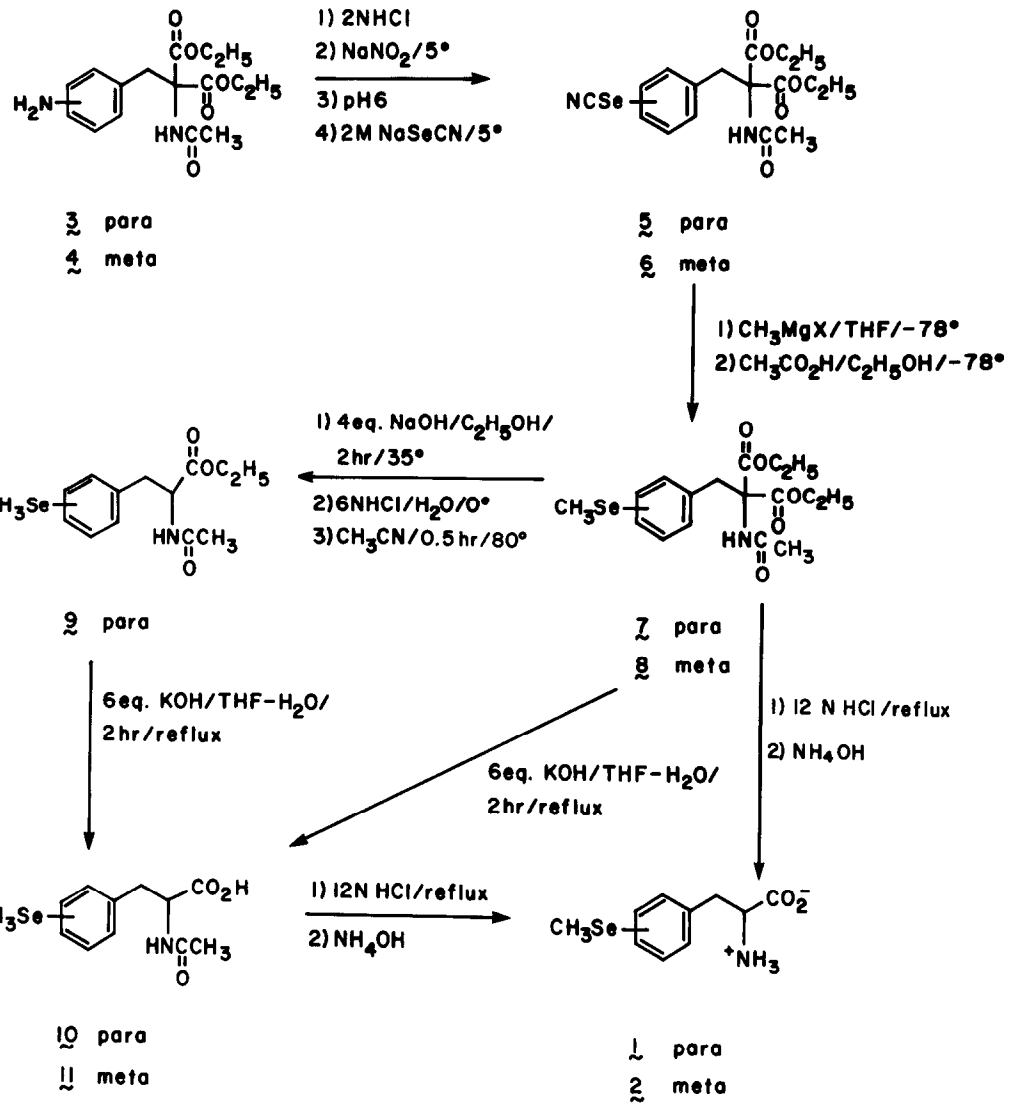
CHARACTERIZATION OF NEW COMPOUNDS[a]

Compound	m.p. °C	Yield %	Cryst. Solv.	NMR
1	211-214	94 (from 10) 70 (from 7)	H_2O	2.40(s,3H),3.45(m,2H),4.65(m,1H), 7.20 and 7.43(two d,J=8,4H),7.00-7.40(br,4H)[b]
2	198-200	70 (from 8)	H_2O	2.40(s,3H),3.45(m,2H),4.63(m,1H), 7.05-7.45(m,8H)[b]
5	120-121	57	C_6H_6/c-C_6H_{12}	1.30(t,J=7,6H),2.05(s,3H),3.65(s,2H), 4.25(q,J=7,4H),6.50(br,1H),6.98 and 7.53(two d,J=8,4H)
6	112-114	25	C_6H_6/c-C_6H_{12}	1.33(t,J=7,6H),2.08(s,3H),3.68(s,2H), 4.23(q,J=7,4H),6.60(br,1H),6.95-7.55 (m,4H)
7	115-116	43	CCl_4/c-C_6H_{12}	1.31(t,J=7,6H),1.98(s,3H),2.28(s,3H), 3.55(s,2H),4.20(q,J=7,4H),6.47(br,1H), 6.81 and 7.23(two d,J=8,4H)
8	81-83	43	i-Pr_2O	1.30(t,J=7,6H),2.05(s,3H),2.32(s,3H), 3.62(s,2H),4.25(q,J=7,4H),6.57(br,1H), 6.70-7.30(m,4H)
9	79-81	49	CH_3COCH_3-Et_2O	1.21(t,J=7,3H),1.96(s,3H),2.30(s,3H), 3.03(d,J=6,2H),4.10(q,J=7,2H),4.78 (q,J=6,1H),6.10(br,1H),6.93 and 7.26 (two d,J=8,4H)
10	181-185	68	CH_3CN	1.85(s,3H),2.35(s,3H),2.96(m,2H),4.48 (m,1H),7.13 and 7.30(two d,J=8,4H), 8.00(br,1H)[c]
11	130-131	61	CH_3CN	2.31(s,3H),2.36(s,3H),3.25(m,2H),5.08 (m,1H),7.04-7.43(m,4H),7.86(br,1H)[b]

(a) Melting points were determined in a Meltemp apparatus and are uncorrected. ^{1}H-nmr spectra were determined in a Varian T-60 spectrometer in $CDCl_3$ unless otherwise noted. Elemental analyses were obtained commercially (Schwarzkopf Microanalytical Laboratory) and were within ± 0.4% of theoretical value for C, H, and N.

(b) CF_3CO_2H

(c) d_6-DMSO


1) 2NHCl
2) NaNO2/5°
3) pH6
4) 2M NaSeCN/5°
3 para
4 meta
5 para
6 meta
1) CH3MgX/THF/-78°
2) CH3CO2H/C2H5OH/-78°
1) 4eq. NaOH/C2H5OH/
2hr/35°
2) 6NHCl/H2O/0°
3) CH3CN/0.5hr/80°
9 para
7 para
8 meta
1) 12 N HCl/reflux
2) NH4OH
6eq. KOH/THF-H2O/
2hr/reflux
6eq. KOH/THF-H2O/
2hr/reflux
1) 12N HCl/reflux
2) NH4OH
10 para
11 meta
1 para
2 meta

transalkylated material was also formed during the original hydrolysis and was present in 2 to 6% in recrystallized 1.

To complete the synthesis without the risk of exchange of alkyl groups on selenium, the conversion of 7 to 1 was carried out in a stepwise fashion with alkaline hydrolysis of the esters preceding an acid-catalyzed removal of the amide group. The resultant products 1 and 2 were isolated in good yields free from transalkylated products.

Acknowledgements. This work was supported in part by Public Health Service Grant Number CA 19898. We thank Laura M. Kurtzer for the early hydrolysis experiments, and Norman A. Abood for developing the quenching method.

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(Received in USA 15 February 1984)