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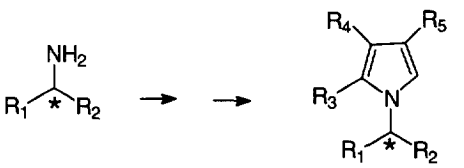
Conversion of homochiral amines, β-amino alcohols and α-amino acids to their chiral 2-methylpyrrole derivatives

Ayhan S. Demir,* Idris M. Akhmedov, Cihangir Tanyeli, Zuhal Gerçek and Raik A. Gadzhili †

Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

Abstract: 5-Chloro-3-penten-2-one reacts with the amino group of homochiral amines, amino alcohols, amino acid esters to form corresponding 2-pyrrole derivatives in good yield and without racemization. © 1997 Elsevier Science Ltd. All rights reserved.

Homochiral pyrrole derivatives of amines and amino acids are important starting materials for the synthesis of many different biologically active compounds. A stereoselective approach to the synthesis of indolizidine alkaloids, based on the reduction of bicyclic pyrroles, has been reported[1]. Paal–Knorr synthesis starting from primary amines and 1,4-dicarbonyl compounds and their masked equivalents such as tetrahydro-2,5-dimethoxyfuran is often used for the construction of pyrrole rings[2]. During the condensation reaction for the formation of pyrrole ring with amino acids, partial racemization often occurs. We have developed a convenient method for the construction of different substituted pyrrole rings from amines, amino alcohols and amino acids with chloroenones prepared from acid chlorides and allylchlorides in the presence of $AlCl_3$[3] (Scheme 1).



Scheme 1.

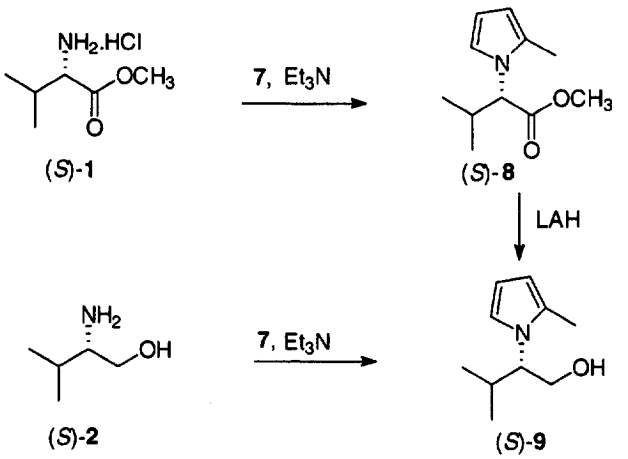
In this paper we describe the formation of 2-methylpyrrole derivatives of amines, amino alcohols and amino acids with 5-chloro-3-pentene-2-one **7**. The reaction of valine methyl ester hydrochloride **1** with 5-chloro-3-pentene-2-one **7** in triethylamine gave the 2-methylpyrrole derivative of valine methyl ester **8** in 75–81% yield. Under similar conditions valinol **2** with **7** gave the pyrrole derivative **9** in 68–72% yield. The compound (*S*)-**9** was also synthesized from the LAH reduction of (*S*)-**8** in 82% yield (Scheme 2).

The valinol derivatives, synthesized by these different routes showed the same specific rotation value. This result showed that the formation of pyrrole derivative from valine ester proceeds without racemization. The measurement of the enantiomeric excess using other methods described below gave also the same result, that is, that in the formation of pyrrole ring from valine ester hydrochloride, no racemization occurs. The same reaction was repeated with racemic and (*R*)-valine methyl ester salt with similar results.

As shown in Table 1 different amino acid esters, amino alcohols and amines are converted into their 2-methylpyrrole derivatives in good yield (Scheme 3).

* Corresponding author. Email: asdemir@rorqual.cc.metu.edu.tr

† Permanent address: Institute of Polymer Materials, Azerbaijan Academy of Science, Sumgait- 373204 Azerbaijan.



Scheme 2.

The enantiomeric excess of the products was established by the NMR shift experiments using shift reagent [Eu(hfc)$_3$] comparing with racemic compounds. In additional experiments the esters are converted to the corresponding alcohols. The *l*-menthoxymethyl ether[4] checked by ^{1}H-NMR (acetal protons at 5.50–5.70 ppm) and (*S*)-O-acetyllactyl ester derivatives of chiral and racemic alcohols[5] checked by ^{1}H-NMR (methyl protons of lactyl moiety as doublet at 1.50–1.65 ppm) and by GC (capillary column HP-5 crosslinked 5%PhMe silicone). The results showed that the condensation reactions proceed without racemization.

As a result, chiral amines, β-amino alcohols, and α-amino acid esters can be converted into 2-methylpyrrole derivatives with 5-chloro-3-pentene-2-one in good yield without racemization. For this simple and efficient synthesis easily available compounds are used and the reactions work under mild conditions.

Experimental

The commercially available amino acids were converted to their methyl ester hydrochlorides by a standard procedure. For the determination of enantiomeric excess via *l*-menthoxymethyl ether derivatives and (*S*)-O-acetyllactyl ester derivatives alcohols are reacted with chloromethyl-*l*-menthyl ether and (*S*)-O-acetyllactyl chloride according to the literature procedure[4,5]. The enantiomeric excess was determined with these derivatives using NMR spectra and GC. The reduction reactions were carried out with $LiAlH_4$ in ether.

General procedure for amino alcohols

10 mmol of amine or amino alcohol, 10 mmol of 5-chloro-3-pentene-2-one and 10 mmol of triethylamine was refluxed in 20 ml of ether for 4 h (checked by TLC). The mixture was cooled to RT and 10 ml of water was added, then water layer was separated and extracted with ether (2×10 ml). The combined organic layers were washed with brine and dried ($MgSO_4$). After evaporation of solvent the crude product was purified by column chromatography.

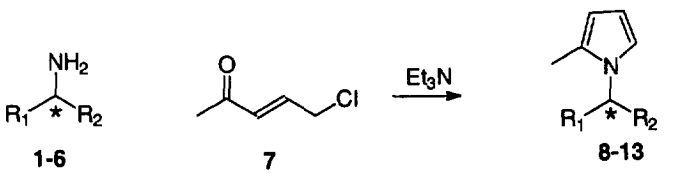
General procedure for amino acids

To the solution of amino acid hydrochloride (10 mmol) was added 10 mmol of 5-chloro-3-pentene-2-one, 20 mmol of triethylamine, 5 ml of water and 15 ml of benzene. The mixture was refluxed for 3 h (checked by TLC). The mixture was cooled to RT and organic layer was separated, aqueous layer was extracted with CH_2Cl_2 (2×15 ml). The combined organic layers were washed with water and brine and dried ($MgSO_4$). The crude product was purified by column chromatography.

Table 1. Preparation of 2-methylpyrrole derivatives **8–13** by the condensation of α-amino acid ester hydrochlorides, β-amino alcohols and amines with 5-chloro-3-pentene-2-one

Starting R_1	Material R_2	Yield (%)	$[\alpha]_D^{25}$= (c, solvent)[a]	Product
$(CH_3)_2CH$-	-$COOCH_3$			
(*S*)-**1**		75	-50.11 (4, CH_3OH)	(*S*)-**8**[b]
(R)-**1**		77	+51.43 (4, CH_3OH)	(*R*)-**8**[b]
Rac. **1**		81		*Rac.* **8**[b]
$(CH_3)_2CH$-	-CH_2OH			
(*S*)-**2**		68	- 13.2 (3, CH_3OH)	(*S*)-**9**[c,d]
(*R*)-**2**		72	+ 14.1 (3, CH_3OH)	(*R*)-**9**[c,d]
Rac. **2**		81		*Rac.* **9**[e]
CH_3-	-$COOCH_3$			
(*S*)-**3**		80	- 48.1 (2, CH_3OH)	(*S*)-**10**[b]
(*R*)-**3**		77	+ 48.8 (2, CH_3OH)	(*R*)-**10**[b]
-CH_2COOCH_3	-$COOCH_3$			
(*S*)-**4**		78	- 83.3 (1, CH_3OH)	(*S*)-**11**[b]
CH3	-CH(OH)Ph			
(1*R*,2*S*)-**5**		78	+ 52.6 (4,	(1*R*,2*S*)-**12**
(1*S*,2*R*)-**5**		76	C_2H_5OH) [c]	
			- 51.8 (4, C_2H_5OH) [c]	(1*S*,2*R*)-**12**
Ph	-CH_3			
(*R*)-**6**		90	- 16.7 (1, CH_3OH	(*R*)-**13**[b]

a: Enantiomeric excess values of optically active compounds are ≥ 98 %. b: Enantiomeric excess values are determined by the NMR shift experiment using [Eu(hfc)$_3$]. c: Enantiomeric excess values are determined via their (*S*)-O-acetyllactyl ester derivatives by ^{1}H-NMR, and GC. d: Enantiomeric excess values are determined via their *l*-menthoxymethyl ether derivatives by ^{1}H-NMR. e: Enantiomeric excess values are determined after conversion to **9**.



Scheme 3.

(2S)-Methyl-2-(2-methylpyrrol-1-yl)-3-methylbutyrate (S)-*8*

Obtained according to the general procedure by using (*S*)-**1**. Colorless oil purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:4). ^{1}H NMR($CDCl_3$): δ 0.78 (d, J=6.5 Hz, 3H, CH_3), 1.07 (d, J=6.7 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.48 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 4.20 (d, J=10.4 Hz, 1H, NCH), 5.88 (s, 1H, CH), 6.12 (m, 1H, CH), 6.85 (d, J=2.3 Hz, 1H, CH). ^{13}C NMR($CDCl_3$): δ 12.72 (CH_3), 19.31 (CH_3), 20.05 (CH_3), 32.35 (CH_3), 52.80 (CH), 65.44 (CH), 107.56, 108.84, 118.91, 130.05, 172.37. Anal. calc. for $C_{11}H_{17}NO_2$ (195.25): C, 67.65; H, 8.77; N, 7.17. Found: C, 67.86; H, 8.61; N, 6.98.

*(2S)-2-(2-Methylpyrrol-1-yl)-3-methyl-1-butanol (S)-**9***

Obtained according to the general procedure by using (*S*)-**2**. Colorless oil purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:4). ^{1}H NMR($CDCl_3$): δ 0.70 (d, J=6.4 Hz, 3H, CH_3), 1.0 (d, J=6.4 Hz, 3H, CH_3), 1.90 (s, 1H, CH), 2.0 (m, 1H, CH), 2.15 (s, 3H, CH_3), 3.65 (m, 1H, CH), 3.7 (t, 2H, CH_2), 5.8 (m, 1H, CH), 6.10 (m, 1H, CH), 6.55 (m, 1H, CH). ^{13}C NMR($CDCl_3$): δ 13.00 (CH_3), 19.52 (CH_3), 20.28 (CH_3), 31.78 (CH), 64.77 (CH), 65.02 (CH_2), 107.03 (CH), 108.80 (CH), 116.99 (CH), 131.13. Anal. calc. for $C_{10}H_{17}NO$ (167.24): C, 71.80; H, 10.24; N, 8.37. Found: C, 71.96; H, 10.41; N, 8.51.

*(2S)-Methyl-2-(2-methylpyrrol-1-yl)-propionate (S)-**10***

Obtained according to the general procedure by using (*S*)-**3**. Colorless oil purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:4). ^{1}H-NMR($CDCl_3$): δ 1.70 (d, J=7.2 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.80 (q, J=7.0 Hz, 1H, CH), 5.95 (s, 1H, CH), 6.10 (m, 1H, CH), 6.75 (m, 1H, CH). ^{13}C NMR($CDCl_3$): δ 12.48 (CH_3), 18.57 (CH_3), 53.19 (CH_3), 54.26 (CH), 108.29 (CH), 108.58 (CH), 118.0 (CH), 129.77 (C), 173.30 (C=O). Anal. calc. for $C_9H_{13}NO_2$ (167.19): C, 64.64; H, 7.83; N, 8.37. Found: C, 64.77; H, 7.71; N, 8.18.

*(2S)-Dimethyl-2-(2-methylpyrrol-1-yl)-succinate (S)-**11***

Obtained according to the general procedure by using dimethyl L-aspartate hydrochloride (*S*-**4**). Colorless oil purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:4). ^{1}H NMR($CDCl_3$): δ 2.20 (s, 3H, CH_3), 2.92 (dd, J=15.68 Hz and J=6.96 Hz, 1H, CH), 3.30 (dd, J=15.68 Hz and J=7.90 Hz, 1H, CH), 3.70 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 5.18 (t, J=7.35 Hz, 1H, CH), 5.90 (broad s, 1H, CH), 6.11 (t, J=3.23 Hz, 1H, CH), 6.61 (s, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 12.37 (CH_3), 37.72 (CH_2), 52.79 (CH_3), 53.55 (CH_3), 54.99 (CH), 108.32 (CH), 109.57 (CH), 118.51 (CH), 130.22 (C), 171.63 (C=O), 171.82 (C=O). Anal. calc. for $C_{11}H_{15}NO_4$ (225.23): C, 58.65; H, 6.71; N, 6.21. Found: C, 58.46; H, 6.77; N, 6.43.

*(1R,2S)-2-(2-Methylpyrrol-1-yl)-1-phenylpropanol (1R,2S)-**12***

Obtained according to the general procedure by using (1*R*,2*S*)-norephedrine (1*R*,2*S*-**5**). Colorless solid purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:3), m.p. 55–56°C. ^{1}H NMR ($CDCl_3$): δ 1.37 (d, J=6.86 Hz, 3H, CH_3), 2.06 (s, 3H, CH_3)), 2.19 (s, 1H, OH), 4.28 (m, 1H, CH), 4.82 (d, J=5.23 Hz, 1H, CH), 5.83 (s, 1H, CH), 6.12 (t, J=2.77 Hz, 1H, CH), 6.80 (s, 1H, CH), 7.20–740 (m, 5H, Ar-H). ^{13}C NMR($CDCl_3$): δ 12.52 (CH_3), 15.61 (CH_3), 57.59 (CH), 77.60 (C–O), 107.48 (CH), 108.16 (CH), 117.93 (CH), 126.95 (CH), 128.95 (CH), 129.45 (CH), 129.60 (CH), 142.49 (C). Anal. calc. for $C_{14}H_{17}NO$ (215.28): C, 78.10; H, 7.96; N, 6.50. Found: C, 78.32; H, 7.77; N, 6.34.

*(1R)-1-(2-Methylpyrrol-1-yl)-1-phenylethane (S)-**13***

Obtained according to the general procedure by using (*R*)-phenylethylamine (*R*-**6**). Colorless solid purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:3), m.p. 51.5–52°C. ^{1}H NMR($CDCl_3$): δ 1.84 (d, J=7.1 Hz, 3H, CH_3), 2.13 (s, 3H, CH_3), 5.3 (q, J=7.1 Hz, 1H, CH), 5.96 (broad s, 1H, CH), 6.17 (broad s, 1H, CH), 6.83 (broad s, 1H, CH), 7.0–7.05 (m, 2H, Ar-H), 7.20–7.35 (m, 3H, Ar-H). ^{13}C NMR: 12.70 (CH_3), 22.99 (CH_3), 55.67 (CH), 107.83 (CH), 108.15 (CH), 118.12 (CH), 126.86 (CH), 127.07 (CH), 128.29 (CH), 133.34 (CH), 149.51 (C). Anal. calc. for $C_{13}H_{15}N$ (185.25): C, 84.27; H, 8.16; N, 7.56. Found: C, 84.38; H, 8.33; N, 7.56.

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