A STEREOSELECTIVE SYNTHESIS OF 5-ARYL- AND 6-ARYLOXAZOLO[4,3-a]ISOQUINOLINES

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Abstract —— Reduction of N-(α,β-diaryl)ethyl and N-(β,β-diaryl)ethyl ethoxycarbonylmethyl carbamates, obtained from the corresponding 2,3-diaryl- and 3,3-diarylpropionic acids, with diisobutylaluminum hydride, followed by cyclization with formic acid at room temperature gave the corresponding 5-aryl- and 6-aryloxazolo[4,3-a]isoquinolines, respectively, with high stereoselectivity.

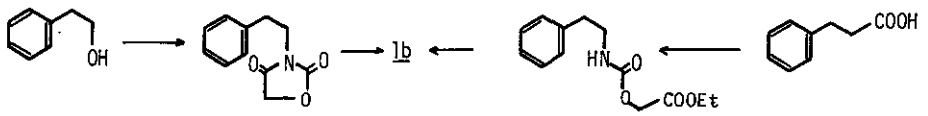
π Cyclization of several kinds of N-acyliminium ions have been used for a synthesis of a wide variety of heterocyclic systems[1]. From the pioneering work of Speckamp[1a-c], and the studies of others[1d-g], such cyclization have been found to achieve remarkable stereocontrol between proximate and remote chiral centers. N-Acyliminium ion cyclization onto aromatic ring have been used for a preparation of isoquinolines fused with heterocycles. Thiazolo[4,3-a]isoquinoline (2a)[1c], oxazolo[4,3-a]isoquinoline (2b)[2], imidazolidino[4,3-a]isoquinoline (2c)[3] and pyrazino[2,1-a]isoquinoline (2d)[4] were prepared by this method (Scheme 1). Recently, we reported a synthesis of isoquinoline and thienopyridine derivatives fused with oxazolidinone ring by cyclization of α-oxaacyliminium ion intermediates. The precursors (1b) for α-oxaacyliminium ions were readily obtained by two routes. One started with 2-phenethyl alcohols which condensed with oxazolidine-2,4-diones by an application of Mitsunobu reaction[5], followed by selective reduction[2a]. Another route involved a condensation of hydroxy esters with the isocyanates starting with 3-arylpropionic acids, followed by selective reduction[2b] (Scheme 2). In connection with our interest in aryl-1,2,3,4-tetrahydroisoquinolines, much attractive compounds owing to potentially biological activities[6], we investigated a stereoselective synthesis of 5-aryl- and 6-aryloxazolo[4,3-a]isoquinolines by an application of the latter route. The results of our studies are described in this paper.

Scheme 1

1 2

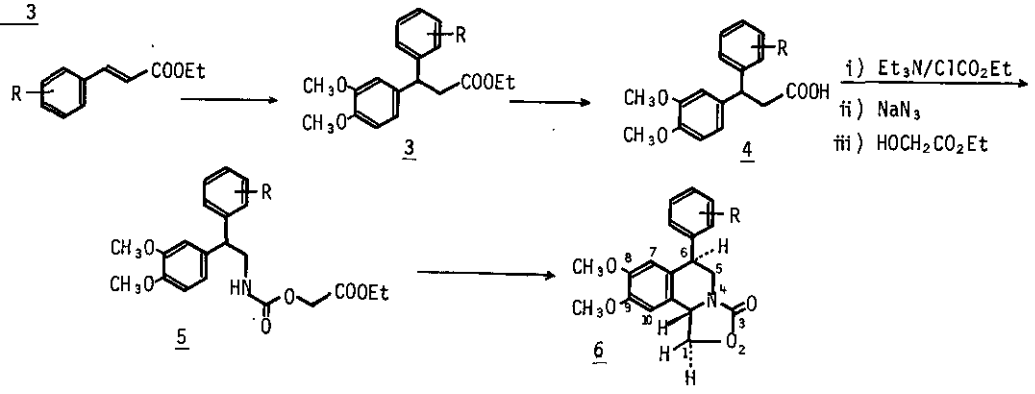
a: X-Y=CH_2-S; b: X-Y=CH_2-O; c: X-Y=CH_2-NH; d: X-Y=CH_2NH-CH_2

Scheme 2



At the first stage, a facile synthesis of 3-aryl-3-(3,4-dimethoxyphenyl)propionic acids was examined. Condensation of ethyl cinnamate with veratrole in the presence of boron trifluoride etherate in 1,1,1-trichloroethane under reflux gave ethyl 3-(3,4-dimethoxyphenyl)-3-phenylpropionate (3a), hydrolysis of which with ethanolic sodium hydroxide afforded the acid (4a)[7] in 75 % yield based on ethyl cinhamate. In a similar fashion, 3-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-propionic acid (4b)[8], 3-(3,4-dimethoxyphenyl)-3-(2-methoxyphenyl)propionic acid (4c), 3-(3,4-dimethoxyphenyl)-3-(4-methylphenyl)propionic acid (4d), and 3,3-bis-(3,4-dimethoxyphenyl)propionic acid (4e) were obtained from the corresponding ethyl β-arylacrylate via esters (3b-3e), respectively. These acids (4a-4e) were converted to the corresponding ethoxycarbonylmethyl carbamates (5a-5e)[4, $Et_3N/ClCOOEt$, NaN_3, then $HOCH_2COOEt$], respectively, in nearly quantitative yield. Reduction of 5 with diisobutylaluminum hydride (DIBAH) in toluene at -78°C, followed by cyclization with formic acid at room temperature gave the corresponding 6-aryloxazolo[4,3-a]isoquinolines (6a-6e), respectively. In the ^1H NMR ($CDCl_3$) spectrum of 6a, the characteristic signals were observed at δ 3.18 (d,d, J=13 and 15 Hz, ax. 5-H), 4.85 (t[9], J=7.5 Hz, 1-H) and 5.13 (d,d, J=7 and 7.5 Hz, 10b-H). The vicinal coupling parameter for $J_{5,6}$ indicates that the relative configuration of 6-H and 10b-H is trans from the consideration of the Dreiding molecular model and the Karplus relation[10]. The signals due to eq. 5-H, the one in the deshielding zone of the amide carbonyl, was concealed beneath 6-H and one of $1\text{-}H_2$.

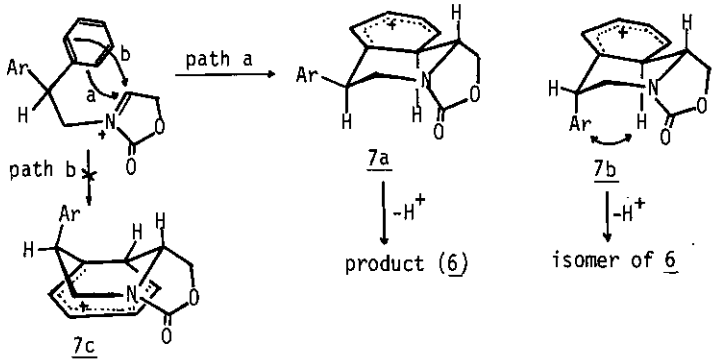
Scheme 3



a: R=H; b: R=4-OCH_3; c: R=2-OCH_3; d: R=4-CH_3; e: R=3,4-$(OCH_3)_2$

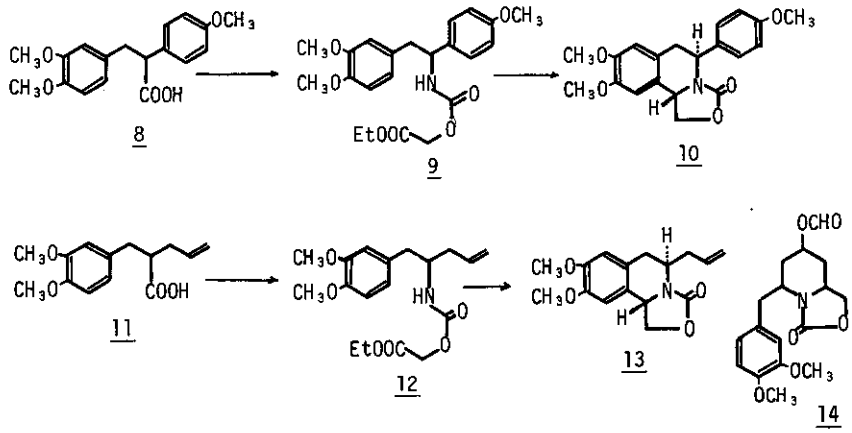
The stereoselectivity in the formation of 6-aryloxazolo[4,3-a]isoquinolines can be accounted for the minimum 1,3-interaction between 10a-H and phenyl group in the transition state (7a), rather

than 7b, formed by the proximal attack of aromatic ring to the iminium carbon. The boat-like transition state (7c), formed by the distal attack, should be excluded because of high strain.



The method was applied to a synthesis of 5-aryloxazolo[4,3-a]isoquinoline. Cyclization of the reduction product obtained from the carbamate (9) derived from the acid (8)[11], afforded the 5-(4-methoxyphenyl)oxazolo[4,3-a]isoquinoline (10) in low yield (15 %). The relative configuration can be determined as trans since arylation proceeds more easily from the opposite side of the phenyl group. Furthermore, it is interesting to examine whether these iminium cyclization occurs at the olefinic carbon or aromatic ring. The carbamate (12) derived from the acid (11) was reduced and the reduction product was treated with formic acid to give the 5-allyloxazolo[4,3-a]isoquinoline (13) in 75 % yield without formation of the oxazolo[3,4-a]pyridine (14) (Scheme 4).

Scheme 4



EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 instrument. Mass spectra were taken at an ionizing voltage of 70 eV on a Hitachi RMU-7L instrument. IR spectra were recorded on a JASCO IRA-1 spectrometer. THF was distilled from $LiAlH_4$ before use.

General Procedure for a synthesis of 3,3-Diarylpropionic Acid (4) A mixture of ethyl β-arylacrylate (0.1 mol), veratrole (16.6 g, 0.12 mol), BF_3 Et_2O (16.4 g, 0.12 mol) and Cl_3CCH_3 (20 ml)

was heated under reflux for 14 h. The mixture was made basic with 28 % NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. Unreacted veratrole was removed by distillation at 180°C in vacuo (2 torr). A solution of the resulting residue in 10 % EtOH-NaOH (200 ml) was refluxed for 2 h. The solvent was evaporated and the remaining residue was made acidic with 10 % HCl and extracted with $CHCl_3$. The extract was washed with H_2O and dried (Na_2SO_4) and evaporated. The remaining residue was recrystallized from methanol-ether. Yields and physical data are summarized in the Table 1.

Table 1. Yields and Physical Data for 3-Aryl-3-(3,4-dimethoxyphenyl)propionic Acid (4)[a]

Compound	Yield (%)[b]	mp (°C)	IR ($CHCl_3$) cm^{-1}(C=O)	^1H NMR ($CDCl_3$)[c] δ 2-H	3-H
4a	73	89-91	1712	3.08 (d, J=8 Hz)	4.63 (t, J=8 Hz)
4b	78	76-78	1713	2.94 (d, J=8 Hz)	4.47 (t, J=8 Hz)
4c	75	129-131	1710	3.03 (d, J=7 Hz)	4.89 (t, J=7 Hz)
4d	72	124-126	1713	3.07 (d, J=8 Hz)	4.50 (t, J=8 Hz)
4e	80	161-163	1710	3.04 (d, J=8 Hz)	4.46 (t, J=8 Hz)

[a] All products gave satisfactory microanalyses (<± 0.3 % for C and H). [b] Based on ethyl β-arylacrylate. [c] Only signals due to 2-H and 3-H are shown.

2-Allyl-3-(3,4-dimethoxyphenyl)propionic Acid (11) To a stirred solution of LDA [prepared from diisopropylamine (5.56 g, 55 mmol) and n-BuLi (3.52 g, 34.5 ml of 1.6 M hexane solution, 55 mmol)] in THF (60 ml) was added a solution of ethyl 3,4-dimethoxyphenylpropionate (11.9 g, 50 mmol) at -78°C. After 40 min, allyl bromide (6.65 g, 55 mmol) was added to this solution at the same temperature. After the stirring had been continued for 1 h, the mixture was decomposed with H_2O (200 ml) and extracted with benzene. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. A solution of the resulting residue in 10 % EtOH-NaOH (200 ml) was refluxed for 2 h. The solvent was evaporated and the remaining residue was made acidic with 10 % HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The remaining solid was recrystallized from benzene-hexane to yield 11 (10.3 g, 82 %), mp 65-67°C, MS m/e 250 (M^+), ^1H NMR ($CDCl_3$) δ 1.90-2.27 (1H, m), 2.60-3.03 (4H, m), 3.88 (6H, s), 5.04-5.29 (2H, m), 5.63 -6.10 (1H, m), 6.73-6.93 (3H, m), IR ($CHCl_3$) cm^{-1}: 1700 (C=O), 1640 (C=C). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.26; H, 7.01.

General Procedure for a Preparation of the Carbamates (5, 9 and 12) To a stirred mixture of 4 (or 8 and 11, 15 mmol), Et_3N (3.03 g, 30 mmol) and acetone (40 ml) was added ClCOOEt (1.8 g, 16.5 mmol) under ice-cooling. After 0.5 h, a solution of NaN_3 (1.3 g, 20 mmol) in H_2O (1.5 ml) was added to this cooled mixture. After the stirring had been continued for 1 h at room temperature,

the mixture was diluted with H_2O and extracted with toluene. The extract was dried over Na_2SO_4 and evaporated to 30 ml. A mixture of this solution and ethyl glycolate (2.1 g, 20 mmol) was refluxed for 14 h. The solvent was evaporated and the remaining residue was chromatographed on silica gel (30 g). Elution with benzene-hexane (1:1) afforded the corresponding carbamates. Yields and physical data are summarized in the Table 2.

Table 2. Yields and Physical Data for the Carbamates (5, 9 and 12)[a]

Compound	Yield (%)	Molecular Formula	m/e (M^+)	IR ($CHCl_3$) cm^{-1} NH	IR ($CHCl_3$) cm^{-1} C=O	^1H NMR ($CDCl_3$)[b] δ
5a	95	$C_{21}H_{25}NO_6$	387	3438	1735	1.27(3H,t,J=7 Hz), 3.84(6H,s), 4.23(2H,q,J=7 Hz), 4.57(2H,s), 6.77-7.02(3H,m), 7.36(5H,s)
5b	93	$C_{22}H_{27}NO_7$	417	3440	1730	1.27(3H,t,J=7 Hz), 3.78(3H,s), 3.84(6H,s), 4.27 (2H,q,J=7 Hz), 4.57(2H,s), 6.87(3H,broad s), 6.92 (2H,d,J=9 Hz), 7.25(2H,d,J=9 Hz)
5c	93	$C_{22}H_{27}NO_7$	417	3438	1730	1.27(3H,t,J=7 Hz), 3.81(3H,s), 3.84(6H,s), 4.28 (2H,q,J=7 Hz), 4.57(2H,s), 6.81-7.38(7H,m)
5d	95	$C_{22}H_{27}NO_6$	401	3440	1730	1.27(3H,t,J=7 Hz), 2.31(3H,s), 3.84(6H,s), 4.23 (2H,q,J=7 Hz), 4.57(2H,s), 6.73-7.00(3H,m), 7.20(4H,broad s)
5e	93	$C_{23}H_{29}NO_8$	447	3438	1730	1.28(3H,t,J=7 Hz), 3.83(6H,s), 3.87(6H,s), 4.23 (2H,q,J=7 Hz), 4.51(2H,s), 6.77-7.10(6H,m)
9	83	$C_{21}H_{25}NO_7$	417	3420	1725	1.24(3H,t,J=7 Hz), 3.04(2H,d,J=6 Hz), 3.74(3H,s), 3.82(3H,s), 3.86(3H,s), 4.23(2H,q,J=7 Hz), 4.57 (2H,s), 4.81-5.04(1H,m), 6.48-7.24(7H,m)
12	90	$C_{18}H_{29}NO_6$	351	3420	1730	1.28(3H,t,J=7.5 Hz), 2.08-2.43(2H,m), 2.80(2H,d, J=6 Hz), 3.88(3H,s), 3.90(3H,s), 4.25(2H,q,J=7.5 Hz), 4.59(2H,s), 4.91-5.28(2H,m), 5.66-6.13(1H, m), 6.84(3H,broad s)

[a] All compounds were obtained as an oil except 9: 9, mp 114-116°C (methanol-ether). [b] Signals due to NCH (for all compounds) and Ar_2CH (for 5) are concealed beneath other signals.

General Procedure for a Synthesis of Oxazolo[4,3-a]isoquinolines (6, 10 and 13) To a stirred solution of 5 (or 9 and 12, 5 mmol) in toluene (20 ml) was added diisobutylaluminum hydride (1.42 g, 10 mmol, 6.7 ml of 25 % toluene solution) at -78°C. After the stirring had been continued for 40 min at the same temperature, the mixture was decomposed with 5 % H_2SO_4 (40 ml) and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated. The resulting residue was mixed with formic acid (10 ml) under stirring at room temperature for 14 h. The mixture was made basic with 28 % NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. For 6, the resulting solid was recrystallized from methanol-ether. For 10 and 13, the products were chromatographed on silica gel (20 g). Elution with benzene-hexane (1:1) afforded 10 (or 13). Yields and physical data for the products are summarized in the Table 3.

Table 3. Yields and Physical Data for Oxazolo[4,3-a]isoquinolines (6, 10 and 13)[a]

Compound	Yield (%)	Molecular Formula	mp (°C)	m/e (M^+)	IR ($CHCl_3$) cm^{-1}(C=O)	H NMR ($CDCl_3$) δ
6a	72	$C_{19}H_{19}NO_4$	147-149	325	1750	3.18(1H,d,d,J=13, 15 Hz), 3.61(3H,s), 3.90(3H, s), 4.07-4.37(3H,m), 4.85(1H,t,J=7.5 Hz), 5.13 (1H,d,d,J=7, 7.5 Hz), 7.20-7.53(5H,m)
6b	70	$C_{20}H_{21}NO_5$	197-198	355	1755	3.13(1H,d,d,J=13.5, 16 Hz), 3.64(3H,s), 3.85 (3H,s), 3.91(3H,s), 4.06-4.38(3H,m), 4.85(1H,t, J=7.5 Hz), 5.17(1H,d,d,J=7, 7.5 Hz), 6.38(1H,s), 6.54(1H,s), 6.96(2H,d,J=7 Hz), 7.19(2H,d,J=7 Hz)
6c	65	$C_{20}H_{21}NO_5$	105-106	355	1753	3.29(1H,d,d,J=11, 14 Hz), 3.66(3H,s), 3.82(3H, s), 3.90(3H,s), 4.03-4.33(2H,m), 4.38-4.57(1H, m), 4.90(1H,t,J=7.5 Hz), 5.17(1H,d,d,J=7, 7.5 Hz), 6.40(1H,s), 6.57(1H,s), 6.90-7.50(4H,m)
6d	70	$C_{20}H_{21}NO_4$	216-217	327	1755	2.39(3H,s), 3.18(1H,d,d,J=13, 15 Hz), 3.65(3H, s), 3.92(3H,s), 4.07-4.40(3H,m), 4.87(1H,t,J=9 Hz), 5.17(1H,d,d,J=7, 6.42(1H,s), 6.59 (1H,s), 7.13-7.33(4H,m)
6e	70	$C_{21}H_{23}NO_6$	182-183	385	1753	3.18(1H,d,d,J=13, 15 Hz), 3.66(3H,s), 3.87(3H, s), 3.93(6H,s), 4.07-4.36(3H,m), 4.87(1H,t,J= 8 Hz), 5.17(1H,d,d,J=7.5, 8 Hz), 6.43(1H,s), 6.57(1H,s), 6.74-7.00(3H,m)
10	15	$C_{20}H_{21}NO_5$[b]	oil	355	1743	3.15(1H,d,J=18 Hz), 3.44(1H,d,d,J=6, 18 Hz), 3.78(3H,s), 3.85(3H,s), 3.93(3H,s), 4.25-4.86(3 H,m), 5.38(1H,d,J=6 Hz), 6.45(1H,s), 6.83(1H,s), 6.87(2H,d,J=8
13	63	$C_{16}H_{19}NO_4$	134-136	289	1743	2.27-2.50(2H,m), 2.58(1H,d,J=15 Hz), 3.13(1H, d,d,J=5, 15 Hz), 3.88(6H,s), 4.23-4.33(2H,m), 4.70-5.20(4H,m), 5.67-6.12(1H,m), 6.52(1H,s), 6.67(1H,s)

[a] All compounds gave satisfactory microanalyses except 10 (<± 0.3 % for C, H and N). [b] High MS m/e 355.1408. Calcd for $C_{20}H_{21}NO_5$: 355.1417.

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