Stereospecific Synthesis of 2-Amino-3-arylbutanoic Acids from 2-Phenyl-4-(1-arylethylidene)-5-oxo-4,5-dihydro-1,3-oxazoles

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In continuation of our investigation on the reactivity of 5-oxo-4,5-dihydro-1,3-oxazoles[1,2], we now report on the catalytic hydrogenation of the (*E*/*Z*)-isomers of 2-benzoylamino-3-phenyl-2-butenoic acids **(1)** at room temperature and atmospheric pressure which leads to the diastereomeric *d,l*-pairs of 2-benzoylamino-3-phenylbutanoic acids **(2)** in quantitative yield, on their hydrolysis to give 2-amino-3-phenylbutanoic acids **(4)**, and on the physical characteristics of products **2** and **4**.

There are several general methods, employing reduction and hydrolysis, for the conversion of 5(4*H*)-oxazolones to the corresponding benzoylamino acids or amino acids. Reduction can be effected with sodium or sodium amalgam in water or ethanol[3], with hydriodic acid/red phosphorus in acetic acid

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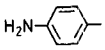
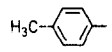
Table 1. 2-Benzoylamino-3-arylbutanoic Acids (2)

2	R^1	R^2	Isomers	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (nujol) ν_{N-H} (amide), $\nu_{C=O}$ (acid), $\nu_{C=O}$ (amide)	U.V. (ethanol) λ_{max} [nm] (logε)	^{1}H-N.M.R. (DMSO-d_6/ TMS_{int})[b] δ [ppm]
a	H_3C-		(1*R*,2*S*)+(1*S*,2*R*)	90	95°	$C_{17}H_{17}NO_3$ (283.3)	3300, 1735, 1630	201 (4.56); 226 (4.22)	0.99 (d, 3H, J=6.5 Hz); 3.0 (m, 1H); 4.5 (m, 1H); 6.7–7.6 (m, 10H)
b		H_3C-	(1*R*,2*R*)+(1*S*,2*S*)	92	182°	$C_{17}H_{17}NO_3$ (283.3)	3300, 1710, 1640	201 (4.51); 232 (4.06)	0.99 (d, 3H, J=6.5 Hz); 2.9 (m, 1H); 4.4 (m, 1H); 6.8–7.3 (m, 10H)
c	H_3C-		(1*R*,2*S*)+(1*S*,2*R*)	85	211°	$C_{17}H_{18}N_2O_3$ (298.3)	3270, 1640, 1630	202 (4.86); 222 (4.53)	1.19 (d, 3H, J=6.5 Hz); 2.9 (m, 1H); 4.5 (m, 1H); 6.3–8.5 (m, 9H)
d	H_3C-		(1*R*,2*S*)+(1*S*,2*R*)	82	132°	$C_{17}H_{18}N_2O_3$ (298.3)	3310, 1640, 1630	210 (4.47); 224 (4.29)	1.03 (d, 3H, J=7 Hz); 2.9 (m, 1H); 4.55 (m, 1H); 6.3–7.6 (m, 9H)
e		H_3C-	(1*R*,2*R*)+(1*S*,2*S*)	86	110°	$C_{17}H_{18}N_2O_3$ (298.3)	3320, 1640, 1625	209 (4.46); 224 (4.25)	1.02 (d, 3H, J=7 Hz); 3.0 (m, 1H); 4.5 (m, 1H); 6.3–7.5 (m, 9H)
f	H_3C-		(1*R*,2*S*)+(1*S*,2*R*)	85	99°	$C_{17}H_{16}ClNO_3$ (317.8)	3300, 1740, 1635	201 (4.37); 225 (4.13)	0.96 (d, 3H, J=6.5 Hz); 3.0 (m, 1H); 4.4 (m, 1H); 6.7–7.5 (m, 9H)
g	H_3C-		(1*R*,2*S*)+(1*S*,2*R*)	90	170°	$C_{18}H_{19}NO_3$ (297.3)	3340, 1715, 1640	202 (4.54); 220 (4.09)	0.98 (d, 3H, J=7 Hz); 1.87 (s, 3H); 2.9 (m, 1H); 4.5 (m, 1H); 6.5–7.5 (m, 9H)
h		H_3C-	(1*R*,2*R*)+(1*S*,2*S*)	90	175°	$C_{18}H_{19}NO_3$ (297.3)	3340, 1715, 1620	201 (4.58); 218 (4.34)	0.97 (d, 3H, J=7 Hz); 1.86 (s, 3H); 2.9 (m, 1H); 4.4 (m, 1H); 6.6–7.3 (m, 9H)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.34; H, ±0.21; N, ±0.28.

[b] We could not detect the other pair of diastereomers in the mother liquor. The structural assignments were made on the basis of the N.M.R. spectral data with Eu(tfc)$_3$ as shift reagent (unpublished results).

or acetic anhydride[4], or by catalytic hydrogenation in alcoholic ammonia over Raney nickel[5], or over platinum or palladium[6]. The widely employed method using hydriodic acid/red phosphorus lacks stereospecificity, the method using sodium or sodium amalgam is only of limited applicability, and catalytic reduction has been less favored owing to the resistence of the tetrasubstituted 5(4*H*)-oxazolones to hydrogenation.

The present investigation of the synthesis of new amino acids from 2-phenyl-4-(1-arylethylidene)-5-oxo-4,5-dihydro-1,3-oxazoles was undertaken to devise a method which combines high yields and stereospecificity. The yields of 2-benzoylamino-3-phenylbutanoic acids (**2**), obtained by catalytic hydrogenation over palladium were substantially better that those obtained by existing methods (Table 1). The sequence of reactions leading to the amino acids involves the synthesis of pure isomers of 5(4*H*)-oxazolones by suitable isomerization procedures[1], alkaline hydrolysis to 2-benzoyl-3-aryl-2-butenoic

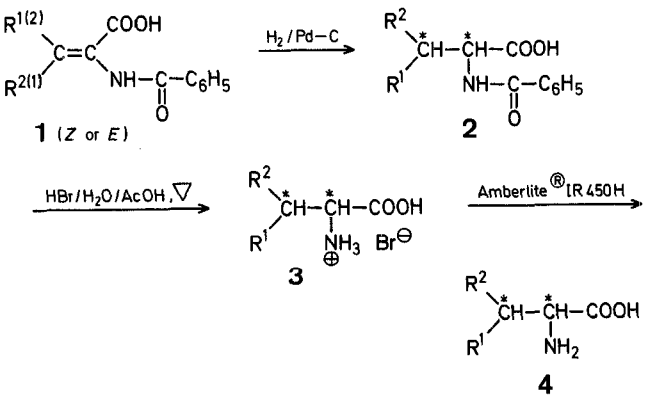


Table 2. 2-Amino-2-arylbutanoic Acids (**4**)

4[a]	Isomers	Yield [%]	m.p. [°C]	Molecular formula[b]	^{1}H-N.M.R. (D_2O/TMS_{ext}) δ [ppm]
a	(1*R*,2*S*)+(1*S*,2*R*)	54	196–199°	$C_{10}H_{13}NO_2$ (179.2)	1.40 (d, 3H, J=7 Hz); 3.4 (m, 1H); 3.99 (d, 1H, J=6.5 Hz); 7.29 (s, 5H)
b	(1*R*,2*R*)+(1*S*,2*S*)	61	189–192°	$C_{10}H_{13}NO_2$ (179.2)	1.46 (d, 3H, J=7 Hz); 3.5 (m, 1H); 3.99 (d, 1H, J=6.5 Hz); 7.35 (s, 5H)
c	(1*R*,2*S*)+(1*S*,2*R*)	48	240–242°	$C_{10}H_{14}N_2O_2$ (194.2)	1.40 (d, 3H, J=7 Hz); 3.4 (m, 1H); 4.02 (d, 1H, J=6.5 Hz); 7.35 (s, 4H)
d	(1*R*,2*S*)+(1*S*,2*R*)	50	232–234°	$C_{10}H_{14}N_2O_2$ (194.2)	1.43 (d, 3H, J=7 Hz); 3.4 (m, 1H); 4.08 (d, 1H, J=6.5 Hz); 7.39 (s, 4H)
e	(1*R*,2*R*)+(1*S*,2*S*)	42	243–245°	$C_{10}H_{14}N_2O_2$ (194.2)	1.41 (d, 3H, J=7 Hz); 3.44 (m, 1H); 4.05 (d, 1H, J=6.5 Hz); 7.39 (s, 4H)
f	(1*R*,2*S*)+(1*S*,2*R*)	45	206–209°	$C_{10}H_{12}ClNO_2$ (213.8)	1.40 (d, 3H, J=7 Hz); 3.35 (m, 1H); 3.97 (d, 1H, J=6.5 Hz); 7.26 (s, 4H)
g	(1*R*,2*S*)+(1*S*,2*R*)	46	197–200°	$C_{11}H_{15}NO_2$ (193.2)	1.31 (d, 3H, J=7 Hz); 2.2 (s, 3H); 3.24 (m, 1H); 3.93 (d, 1H, J=6.5 Hz); 7.08 (s, 4H)
h	(1*R*,2*R*)+(1*S*,2*S*)	43	192–194°	$C_{11}H_{15}NO_2$ (193.2)	1.36 (d, 3H, J=7 Hz); 2.3 (s, 3H); 3.3 (m, 1H); 3.92 (d, 1H, J=6.5 Hz); 7.15 (s, 4H)

[a] For R^1 and R^2, see Table 1. All compounds **4** gave a positive ninhydrin test.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.40; H, ±0.19; N, ±0.25.

acids[2], followed by catalytic hydrogenation over palladium, and finally, hydrolysis to the amino acids.

2-Benzoylamino-3-arylbutanoic Acids (2); General Procedure:
A solution of the (*Z*/*E*)-2-benzoylamino-3-aryl-2-butenoic acid (**1**; 0.01 mol) in methanol (50 ml) is hydrogenated over 10% palladium on carbon catalyst (0.1 g) at room temperature and atmospheric pressure. Within 2–8 h, the theoretical amount of hydrogen is taken up and absorption ceases. The catalyst is removed by filtration and washed with methanol (20 ml). The solvent is distilled off to leave an oil which quickly solidifies. Recrystallization from ethanol/water gives colorless crystals of an analytically pure sample.

2-Amino-3-arylbutanoic Acids (4); General Procedure:
A mixture of the 2-benzoylamino-3-arylbutanoic acid (**2**; 0.01 mol), 48% hydrobromic acid (25 ml), and glacial acetic acid (50 ml) is heated under reflux for 6 h and the volatile material then distilled off under reduced pressure. The residue is dissolved in water (20 ml) and the solution extracted with ether (2 × 10 ml). [Evaporation of the organic extract gives crystals of benzoic acid]. The aqueous phase is decolorized with charcoal and concentrated to give the colorless crystalline amino acid hydrobromide. The hydrobromide is dissolved in water (50 ml), the solution passed through a column of a suitable resin (Amberlite® IR 450 H) at a rate of 5 ml/min, and the column washed with distilled water (20 ml). The whole eluate (including the last eluate obtained from the washing) is evaporated to give the pure 2-amino-3-arylbutanoic acid (**4**).

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