A Simple Approach to β-Amino Acids by Acylation of Arenes with N-Acyl Aspartic Anhydrides

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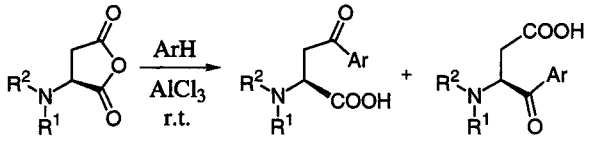
Abstract. Friedel-Crafts acylation of arenes (benzene, toluene, *o*-xylene) with N-protected (Bz, Ac, Ac-Bn, Ts, Tfac, N,N-Pht) aspartic anhydrides (**1a-1f**) resulted in mixtures of α- and β-amino acids. The β/α-selectivity could be optimized for alkylated arenes (toluene, xylene) and the N-Ac, N-Bn protected **1c**.

β-Amino acids constitute an important class of compounds in actual biochemical and medicinal research.[1] They are key building blocks for the synthesis of many biologically relevant and pharmaceutically active molecules (e.g. β-lactams, taxol).[2] Moreover, they are especially useful for the construction of peptidomimetics.[3]

Numerous methods for the preparation of enantiomerically pure β-amino acids have been developed.[4] The most convenient starting materials from the pool of chiral compounds are aspartic acid and asparagine, as they already possess the 3-aminopropanoic acid skeleton and a stereogenic center of defined absolute configuration at C-3. In order to differentiate between the α- and the β-carboxy group it is often necessary to perform multistep reactions. Herein we report a new and straightforward solution to this problem: by Friedel-Crafts acylation[5] of N-protected aspartic anhydrides not only the α-amino acid derivatives can be obtained but also the corresponding β-amino acids. This result came as a surprise because until now this reaction was solely applied to the synthesis of 3-acylated alanines.[6] An advantage of the Friedel-Crafts route is its experimental simplicity and the fact that all starting materials are easily available in both enantiomeric forms. The general reaction and selected results are summarized in Scheme 1 and Table 1.



R^1 =	R^2 =		R^1 =	R^2 =
1a Bz	H	**1d**	Ts	H
1b Ac	H	**1e**	Tfac	H
1c Ac	Bn	**1f**	Pht	Pht

Scheme 1

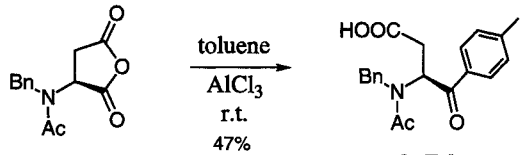
The N-benzoyl aspartic anhydride **1a**[7] gave a 55:45 mixture of α- and β-amino acid (**2a**-Ph and **3a**-Ph)[8] when reacted with three equivalents of aluminum chloride in benzene. Both toluene and *ortho*-xylene yielded higher amounts of the corresponding β-amino acid (61% and 70%, respectively, relative proportion, determined by ^{1}H NMR of the crude product mixture) with high regio(para)selectivity. In contrast to these results, mesitylene was transformed solely to the α-amino acid. A pronounced decrease in reactivity was observed with anisole and veratrole: both donor-substituted arenes were converted preferentially into the α-amino acid with moderate yields and high regio(*para*)-selectivity. Naphthalene showed the same reactivity as toluene, however, did only give 5% of the corresponding β-amino acid.

Thus, we concentrated on benzene, toluene, and *o*-xylene as the arene components. In nearly all cases, the acylation of *o*-xylene gave the highest relative amounts of β-amino acids. One exception of this rule was found for the N-acetyl, N-benzyl derivative **1c**[9]: in this case the highest β/α-selectivity (93:7) was obtained with toluene.[10] It was surprising to recognize that even with the aspartic anhydrides **1d-1f** which are the "traditional" substrates for α-acylation chemistry, relatively high amounts of the corresponding β-amino acid was formed with *o*-xylene (26% with the N-tosyl derivative **1d**[11], 44% with the N-trifluoroacetyl derivative **1e**[12], and 52% with the N,N-phthaloyl aspartic anhydride **1f**[13]).

Table 1. Reaction times, α/β-product ratios and total yields[a]

substrate	arene[b]	time (h) (rt)	α/β-ratio (%)	yield (%)
1a	benzene	5	55 / 45	51
1a	toluene	5	39 / 61	33
1a	o-xylene	15	30 / 70	65
1a	mesitylene	15	100 / 0	51
1a	anisole	72	50 / 50	31
1a	veratrole	96	100 / 0	18
1a	naphthalene	15	95 / 5	44
1b	benzene	5	95 / 5	76
1b	toluene	5	64 / 36	52
1b	o-xylene	15	58 / 42	67
1c	benzene	5	30 / 70	55
1c	toluene	5	7 / 93	47
1c	o-xylene	15	39 / 61	52
1d	benzene	5	84 / 16	76
1d	toluene	5	100 / 0	71
1d	o-xylene	15	74 / 26	83
1e	benzene	5	95 / 5	78
1e	toluene	5	80 / 20	62
1e	o-xylene	15	56 / 44	70
1f	benzene	5	100 / 0	64
1f	toluene	5	88 / 12	71
1f	o-xylene	15	48 / 52	83

[a] after purification of the regioisomeric mixture
[b] arene as solvent (exception: naphthalene in CH_2Cl_2)



1c **3c-Tol**
93 % selectivity

Scheme 2

In all cases three equivalents of aluminum chloride were necessary to complete the reaction. With only two equivalents no reaction could be detected, thus precomplexation of two molecules of $AlCl_3$ occur prior to the activation of the anhydride functionality. Similar results were obtained with ethyl aluminum dichloride as the Lewis acid. With $FeCl_3$, $ZnCl_2$ and BF_3.Et_2O the yields were less than 10% for all anhydride/arene combinations. The fact that the electron-rich arenes anisole and veratrole needed much longer reaction times can also be explained by Lewis acid complexation (i.e. deactivation) of these substrates.

In summary, Friedel-Crafts acylation of arenes by N-acylated aspartic anhydrides is a versatile reaction for the synthesis of β-acylated β-amino acids and the corresponding β-branched β-amino acids.[14]

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(8) General procedure: 1-10 mmol of **1** were suspended in 10-100 ml of the arene and treated with 3-30 mmol of aluminum chloride at 0°C. After stirring for 5-72 h at r.t. the mixture was hydrolyzed with water, extracted with CH_2Cl_2, acidified with 10 M HCl, reextracted with CH_2Cl_2, and dried over $MgSO_4$. Most amino acids could be isolated in pure form by subsequent crystallization.
Selected spectral data for the α-and β-amino acid derivatives: ^{1}H-NMR (300 MHz) of **2a-Ph** ($CDCl_3$): δ = 3.63 (dd, 1H, *J* = 4.1 Hz, 18.4 Hz, CH_2), 3.70 (dd, 1H, *J* = 4.1 Hz, 18.4 Hz, CH_2), 5.10 (m, 1H, CH), 7.23-7.67 (m, 5H, Ar-H), 7.30-7.81 (m, 5H, Ar-H), 7.45 (d, *J* = 8.2 Hz, NH), 10.31 (br, 1H, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 40.3 (2C, CH_2), 48.7 (1C, CH), 127.1 (2C, Ar-CH), 128.5 (2C, Ar-CH), 128.7 (2C, Ar-CH), 128.1 (2C, Ar-CH), 131.9 (1C, Ar-CH), 133.1 (1C, Ar-C), 133.7 (1C, Ar-CH), 134.1 (1C, Ar-C), 167.6 (1C, CONH), 175.0 (1C, COOH), 198.1 (1C, CO). ^{1}H-NMR of **3a-Ph** ($CDCl_3$): δ = 2.84 (dd, 1H, *J* = 4.9 Hz, 16.8 Hz, CH_2), 2.98 (dd, 1H, *J* = 4.9 Hz, 16.8 Hz, CH_2), 5.90 (m, 1H, CH), 7.23-7.65 (m, 5H, Ar-H), 7.30-7.89 (m, 5H, Ar-H), 7.71 (d, J = 8.2 Hz, NH), 10.31 (br, 1H, COOH). ^{13}C-NMR ($CDCl_3$): δ = 36.4 (2C, CH_2), 51.2 (1C, CH), 127.1 (2C, Ar-CH), 128.5 (2C, Ar-CH), 128.6 (2C, Ar-CH), 128.7 (2C, Ar-CH), 131.9 (1C, Ar-CH), 133.1 (1C, Ar-C), 133.7 (1C, Ar-CH), 135.6 Ar-C), 167.3 (1C, CONH), 175.1 (1C, COOH), 197.0 (1C, CO).

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(10) Spectral data for the α-and β-amino acid derivative of N-acetyl-N-benzoyl aspartic acid anhydride **2c-Tol** and **3c-Tol**: ^{1}H-NMR ($CDCl_3$) of **2c-Tol**: δ = 2.12 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.32 (dd, 1H, *J* = 6.2 Hz, 18.2 Hz), 4.23 (dd, 1H, *J* = 5.8 Hz, 18.2 Hz), 4.68 (dd, 2H, *J* = 17.5 Hz, 21.8 Hz, CH_2), 4.69 (dd, 1H, CH), 6.91-7.55 (m, 5H, Ar-H), 7.80-7.95 (m, 4H, Ar-H). ^{1}H-NMR ($CDCl_3$) of **3c-Tol**: δ = 2.01 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.53 (dd, 1H, *J* = 5.2 Hz, 16.5 Hz, CH_2), 3.01 (dd, 1H, *J* = 9.0 Hz, 16.5 Hz, CH_2), 4.37 (dd, 2H, *J* = 17.5 Hz, 21.8 Hz, CH_2), 6.38 (dd, 1H, *J* = 5.3 Hz, 9.0 Hz, CH), 6.90-7.55 (m, 5H, Ar-H), 7.80-7.95 (m, 4H, Ar-H).

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(14) The keto group of the β-acylated β-amino acids as well as the acylated α-amino acids can be chemoselectively reduced by catalytic hydrogenation (5% Pd-C, 1 atm H_2, r.t.).