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Direct synthesis of *N*-substituted, functionalized aspartic acids using alkali maleates and amines

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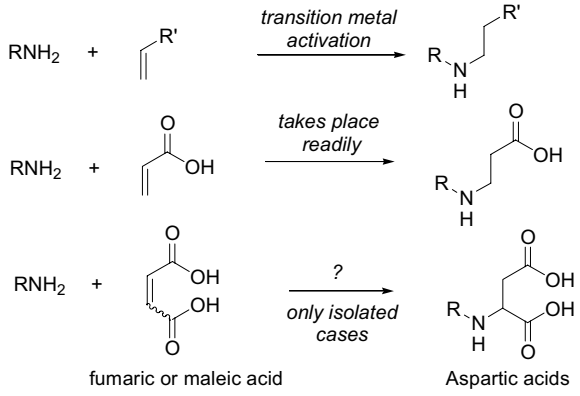
Abstract—A practical and general one-pot synthesis of mono-*N*-substituted, functionalized aspartic acids has been developed. The *N*-substituted aspartic acids are formed directly from alkali maleates and primary amines in hot DMSO. Products from several different primary amines can be prepared chemoselectively in moderate to good yields.

1. Introduction

The synthesis of amino acids is of great importance. Non-proteinogenic α-amino acids are important in biological, medicinal and synthetic chemical applications.[1–7] Furthermore, β-amino acids[8] and their derivatives are common in a large number of natural products, antibiotics[9] and chiral auxiliaries.[10]

The direct addition of amines to unactivated alkenes is very difficult to accomplish, and such addition reactions always have to proceed via activation of the amine or the alkene.[11–13] Although the direct amination of α,β-unsaturated carboxylic acids can readily be effected,[14] amination of unsaturated *di*-carboxylic acids, such as maleic and fumaric acid, is most successfully performed by the aspartase enzyme class.[15] No man-made catalyst for this transformation has been discovered, and no general one-step method for the synthesis of *N*-substituted functionalized aspartic acids has been reported (see Scheme 1).

Known multi-step, indirect methods for this transformation proceed via activating protecting groups. These include derivatization of the acid as its mono-[16] or di-ester[17] or monoamide.[18–20] While the Michael addition to these protected compounds proceeds smoothly, two additional synthetic steps are required to install and remove the activating/protecting groups. Previously



Scheme 1. Typical methods for amination of alkenes.

reported one-step synthetic approaches proceed either via activation of the double bond by use of stoichiometric amounts of lanthanides[21,22] or via maleate salts in aqueous media. In nearly all cases, these methods are limited to functionalized amines capable of chelation to the lanthanide ion (i.e., hydroxyl- or carboxyl-containing amines[23–25]). The only reported example of an uncatalyzed addition reaction is the production of *N*-methyl aspartic acid in ethanol.[26] Scattered examples of the addition of amines to monohydrogen maleate in aqueous solution have been reported, including the addition of benzylamine[18,27,28] and long, straight-chain alkyl amines.[29] However, no general method for the Michael addition of a wide array of primary amines is available.

In this communication, we present a novel and facile one-step method for the preparation of a number of

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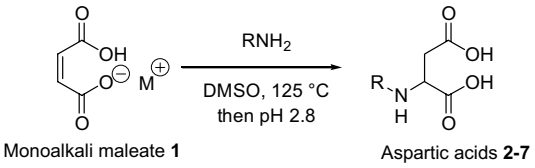

Scheme 2. General reaction scheme.

alkyl as well as functionalized *N*-substituted aspartic acids from inexpensive maleic anhydride and amines via the simple monolithium salt of maleic acid (Scheme 2).

Our initial experiments in aqueous media gave mixed results, with only benzylamine giving fair reaction rates.[30] We discovered, however that the Michael addition of primary amines to monolithium maleate takes place smoothly in hot DMSO (125 °C). Other organic solvents gave poorer yields of the desired product and gave more by-products such as fumarate and aminolyzed solvent.[31]

Both monolithium and monosodium salts readily afforded the products in good yields (Table 1). However, increasing the size of the alkali metal cation also increased the rates of side reactions such as isomerization and polymerization. Reactions with potassium salts always gave increased amounts of decomposition and side reactions.

Simple primary alkylamines readily underwent the reaction, as did benzylamine, albeit much more slowly. Remarkably, 2-aminoethanol also gave a clean reaction with no *O*-alkylation observed (entry 6). However, poor conversions were observed with aromatic amines as well as more hindered amino alcohols (see footnote a, Table 1).

The reaction works only with the maleate salt, but not with uncharged maleic acid. Under the same reaction conditions maleic acid also isomerizes to unreactive fumaric acid. The reaction proceeds best in highly polar solvents, but water, or even amines with several hydroxyl groups, inhibit the reaction and reduce the product yield. Use of a large excess of maleate also reduces the rate of reaction. Gradual addition of maleate to a solution of the amine increased the yield considerably. Despite these limitations, the method described here works well for the chemoselective preparation of a potentially large number of previously inaccessible *N*-alkyl/aryl aspartic acids in one synthetic step, followed by simple purification.

In all reactions, only trace amounts of amides were formed. Thus, the carbonyl groups of monolithium maleate are sufficiently protected towards nucleophiles to only allow for a Michael-like addition to the double bond of the maleate. The conjugate addition reaction proceeds most effectively with monoalkali maleates. Isomerization to fumarate takes place rapidly especially with disodium maleate.[32] However, with *n*-hexylamine, the rate of the Michael addition was sufficiently rapid to allow even dilithium maleate to give a good yield of the product.

Regarding the mechanism of the reaction, we can only suggest that the reactive species is a charged and perhaps structurally distorted maleic acid alkali salt. Complexes of maleate with other metal ions are known to possess a distorted maleate structure.[33] Such a distortion might activate the maleate towards addition and/or isomerization. The reaction appears to be sensitive to steric effects, with straight-chain alkyl amines generally affording the highest yields.

Typically, the only observed side reaction that takes place in the reactions reported is the isomerization of maleate to fumarate. Although the conditions are relatively harsh, they are justified in view of the difficulty of the reaction. Importantly, non-polar, lipophilic amines of low water solubility, such as *n*-octylamine, also afford the aspartic acid product under our non-aqueous conditions. Non-dry or recycled solvents can readily be used. The reaction gives access to racemic material at a very low cost and the procedure is a useful alternative in cases where direct synthesis of the amino acid is required.

In summary, we have developed an efficient, general protocol for the addition of both unfunctionalized and functionalized primary amines to monoalkali maleates. The reaction affords various *N*-substituted aspartic acids, including some previously unreported hydrophobic compounds, in moderate to high yields and uses a very simple purification method and inexpensive starting materials. No metal catalysts are required.

Table 1. Synthesis of *N*-substituted aspartic acids[a] produced via Scheme 2

Entry	Product	R	Yield (%); Method A (M = Li)[b]	Yield (%); Method B (M = Li)[c]	Yield (%); Method A (M = Na)
1	**2**	*n*-Hexyl	59[d]	85	85
2	**3**	*n*-Octyl	—	54	65
3	**4**	Cyclohexyl	30	36	39
4	**5**	Cyclohexanemethyl	—	62	—
5	**6**	Benzyl	19	62	—
6	**7**	2-Hydroxyethyl	35	76	—

[a] The following amines were also tested with Method A: 3-methylbutylamine (28% conversion); L-*tert*-leucinol (24% conversion); *p*-anisidine (11% conversion); L-phenylalaninol (23% conversion).
[b] Method A: all reactants were added together in the beginning.
[c] Method B: the monoalkali maleate was added in three portions over the course of the reaction.
[d] The dilithium salt and the monopotassium maleates afforded **2** in 77% and 53% yields, respectively.

2. General procedure for the preparation of *N*-alkyl/aryl aspartic acids

Method A: To a mixture of maleic anhydride (1.00 g; 10.20 mmol; 200 mol %) in DMSO (15 mL) was added the alkali metal hydroxide (e.g., $LiOH \times H_2O$: 0.490 g; 11.67 mmol; 228 mol %), and the mixture was heated to 50 °C with stirring for 20 min to allow the alkali maleate to form. The temperature was then raised to 125 °C. The reaction flask was left open for 10 min to allow water to evaporate. The amine (5.10 mmol, 100 mol %) was then added dropwise to the now wine-red mixture. The mixture was stirred and heated at 125 °C for up to 72 h and was then worked up as described below.

Method B is otherwise identical to Method A with the exception that equimolar amounts of monolithium maleate (prepared as in Method A from 10.20 mmol of maleic anhydride and 11.67 mmol $LiOH \times H_2O$) and amine (10.20 mmol) were initially used. Two further portions of monolithium maleate were added as a suspension in DMSO (prepared as in Method A from maleic anhydride (5.10 mmol), $LiOH \times H_2O$ 5.84 mmol and DMSO (6 mL)) after 24 h and 48 h. The mixture was allowed to react for a further 48–72 h after the last maleate addition, and was then worked up as described below.

3. Purification of *N*-alkyl/aryl aspartic acids

The reaction mixture was allowed to cool to rt. Acetone (Method A: 40–80 mL; Method B: 80–160 mL; higher amounts were used with more polar products) was added to the reaction mixture. The solution was cooled to +4 °C for 1–2 h and the precipitated crude product was filtered off and washed with further acetone (10–15 mL) and Et_2O (10 mL) to afford a crude mixture consisting of the product and alkali fumarate. With lipophilic compounds such as **3** and **6**, higher yields could be obtained as follows: 10 M NaOH (1.0 mL, 10 mmol, 100 mol %) was added to the reaction mixture at 50 °C and the mixture was heated to 120 °C for 10 min to allow all the water to evaporate. The reaction mixture was then worked up exactly as above.

Analytically pure *N*-substituted aspartic acids were isolated as follows. The salt mixture was dissolved in H_2O (2–5 mL); if necessary the solution was heated to 60 °C. The pH of the solution was adjusted to 2.77 by the addition of 4 M HCl. The solution was cooled to +4 °C for 1–2 h. The precipitated fumaric acid was filtered off and the solution was concentrated to a volume of 2 mL. Ethanol (8 mL) was added dropwise to the mother liquor and the resulting solution was cooled to +4 °C to allow crystals of the pure product to form. The crystals of the neutral product were isolated by filtration and dried in vacuo. The recrystallization procedure was repeated three more times, adding further ethanol (8–20 mL each time) to obtain additional crops of the pure product.

Very lipophilic compounds such as **3** and **6** were preferentially recrystallized from 5:1 water/ethanol and additional crops were obtained by concentration of the mother liquor.

3.1. *N*-Hexyl aspartic acid (2)

Yield: 59% (Method A), 85% (Method B or Method A/Na); colourless crystals; mp 167.9–168.8 °C (from water/ethanol), lit.[16] mp 168 °C; IR (KBr) 3424, 2960, 2932, 2860, 1711, 1643, 1592, 1405, 767, 738 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.96 (dd, 1H, $J = 5$, 7 Hz), 3.11 (t, 2H, $J = 6$ Hz), 3.04 (dd, 1H, $J = 5$, 18 Hz), 2.98 (dd, 1H, $J = 7$, 18 Hz), 1.71 (qn, 2H, $J = 8$ Hz), 1.30–1.40 (m, 6H), 0.87 (t, 3H, $J = 7$ Hz); ^{13}C NMR (400 MHz, D_2O) δ 13.1, 21.6, 25.2, 25.3, 30.3, 33.8, 47.1, 57.7, 172.1, 174.0 (neutral compound); ^{13}C NMR (400 MHz, D_2O) δ 13.9, 22.4, 25.9, 26.3, 31.0, 36.4, 47.3, 60.1, 174.3, 178.1 (monolithium salt).

3.2. *N*-Octyl aspartic acid (3)

Yield: 54% (Method B); 65% (Method A/Na); white crystals; mp 159.7–160.8 °C (from water/ethanol); IR (KBr) 3430, 2925, 2860, 1643, 720 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.96 (dd, 1H, $J = 5$, 6 Hz), 3.12 (m, 2H), 3.03 (dd, 1H, $J = 5$, 18 Hz), 2.97 (dd, 1H, $J = 6$, 18 Hz); 1.73 (qn, 2H, $J = 7$ Hz), 1.41–1.28 (m, 10H), 0.87 (t, 3H, $J = 7$ Hz); ^{13}C NMR (400 MHz, D_2O) δ 174.3, 172.2, 57.8, 47.1, 34.0, 30.9, 28.1, 28.0, 25.6, 25.4, 21.9, 13.3 (neutral compound); ^{13}C NMR (400 MHz, D_2O) δ 178.1, 174.1, 60.0, 47.3, 36.2, 31.7, 28.8 (2C), 26.3 (2C), 22.6, 14.1 (monolithium salt); HRMS (ESI−) calcd for $C_{12}H_{22}NO_4$ (M−H): 244.1549, found: 244.1537.

3.3. *N*-Cyclohexyl aspartic acid (4)

Yield: 30% (Method A), 36% (Method B), 39% (Method A/Na); white crystalline powder; mp 216.3–217.4 °C (from water/ethanol), lit.[16] mp 216 °C; IR (KBr) 3424, 2927, 2856, 1637, 1598, 1411, 726 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.92 (dd, 1H, $J = 4$, 9 Hz), 3.14 (m, 1H), 2.79 (dd, 1H, $J = 4$, 17 Hz), 2.63 (dd, 1H, $J = 9$, 17 Hz), 2.07 (m, 2H), 1.80 (m, 2H), 1.64 (m, 1H), 1.18–1.51 (m, 5H) (neutral compound); ^{13}C NMR (400 MHz, D_2O) δ 177.3, 173.6, 57.1, 56.9, 36.0, 29.6, 28.8, 24.4, 23.74, 23.67; ^{13}C NMR (400 MHz, D_2O) δ 23.7, 23.8, 24.4, 28.5, 29.5, 36.0, 56.8, 57.0, 173.7, 177.4 (monolithium salt).

3.4. *N*-(Cyclohexanemethyl) aspartic acid (5)

Yield: 62% (Method B); white crystalline powder; mp 209.8–210.8 °C (from water/ethanol); lit.[34] mp 194–195 °C; IR (KBr) 3424, 2924, 2856, 1648, 1595, 1411, 738 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.76 (dd, 1H, $J = 4$, 9 Hz), 2.97 (dd, 1H, $J = 6$, 12 Hz), 2.87 (dd, 1H, $J = 7$, 12 Hz), 2.79 (dd, 1H, $J = 4$, 18 Hz), 2.65 (dd, 1H, $J = 9$, 18 Hz), 1.75 (m, 5H), 1.65 (m, 1H,), 1.13–1.32 (m, 3H), 1.03 (m, 2H); ^{13}C NMR (400 MHz, D_2O) δ 24.9, 24.9, 25.5, 29.6, 29.7, 34.6, 35.1, 52.4, 59.7, 173.1, 177.5 (neutral compound); ^{13}C NMR (400 MHz, D_2O) δ 25.9, 26.0, 26.5, 30.9, 31.0, 36.5, 39.2, 53.9, 61.4, 175.3, 179.5 (monolithium salt); HRMS

(ESI+) calcd for $C_{11}H_{20}NO_4$ (M+H): 230.1392, found: 230.1398.

3.5. *N*-Benzyl aspartic acid (6)

Yield: 19% (Method A); Yield: 62% (Method B); white crystals; mp 193.7–194.6 °C (from water/ethanol); lit.[18] mp 195 °C; IR (KBr) 3430, 3070, 2992, 2932, 2860, 1721, 1633, 1578, 1409 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.18 (m, 5H), 4.05 (d, 1H, $J = 13$ Hz), 3.99 (d, 1H, $J = 13$ Hz), 3.65 (dd, 1H, $J = 5$, 7 Hz), 2.69 (dd, 1H, $J = 5$, 18 Hz), 2.64 (dd, 1H, $J = 7$, 18 Hz); ^{13}C NMR (400 MHz, D_2O) δ 174.0, 171.9, 134.2, 130.4, 129.9, 129.7, 129.3 (2C), 57.1, 50.5, 34.1 (neutral compound); ^{13}C NMR (400 MHz, D_2O) δ 177.3, 173.1, 135.3, 131.0, 129.7, 129.6, 129.3, 120.9, 58.7, 49.9, 35.6 (monolithium salt).

3.6. *N*-(2-Hydroxyethyl) aspartic acid (7)

Yield: 35% (Method A), 76% (Method B); off-white crystals; mp > 280 °C dec (from water/ethanol; phase transition occurs at 230–235 °C); lit.[35] mp 231–233 °C; IR (KBr) 3420, 3244, 2997, 2930, 2878, 1642, 1413, 719 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.88 (m, 2H), 3.86 (m, 1H), 3.29 (m, 1H), 3.19 (m, 1H), 2.84 (dd, 1H, $J = 4$, 18 Hz), 2.71 (dd, 1H, $J = 9$, 18 Hz); ^{13}C NMR (400 MHz, D_2O) δ 35.3, 48.2, 56.8, 59.4, 173.0, 177.3 (neutral compound); ^{13}C NMR (400 MHz, D_2O) δ 36.2, 48.5, 57.5, 59.9, 174.2, 178.0 (monolithium salt).

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra of all products are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.159.

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31. The solvents screened included DMF, tetrabutylurea, tetramethylurea, tri-*n*-butylphosphate, *N*-methylpyrrolidone and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU).
32. Isomerization of a 0.1 M solution of maleic acid into fumaric acid was attempted at 125 °C in DMSO for 72 h. Less than 1% isomerization could be detected during this period. A control experiment with added NaBr (200 mol %) gave identical results. A mixture of maleic acid (3 mmol), *n*-hexylamine (1 mmol) and NaBr (6 mmol) in DMSO did not give any reaction even at +125 °C except for the slow formation of *n*-hexylmaleamide.

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