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Esterification of Maleamic Acids without Double Bond Isomerization

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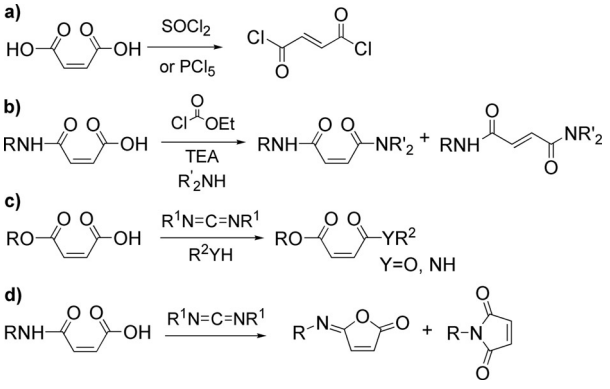
Activation of the carboxylic acid group of a maleamic acid by treatment with an arenesulfonyl chloride followed by addition of an alcohol affords a fumaramate or a maleamate, depending on the reaction conditions. The *E* isomer is obtained when the acid is treated with nearly equimolar amounts of 2,4,6-triisopropylbenzenesulfonyl chloride and an alcohol in pyridine. Replacement of pyridine by 2-picoline and use of a larger excess of activating agent (mesitylenesulfonyl chloride) and alcohol affords the *Z* isomer. In both cases, high diastereomeric excesses and yields are achieved.

Introduction

Maleic and fumaric acid esters are simple, versatile molecules that may undergo a variety of reactions, such as anionic or radical polymerization, hydrolysis under acid or basic conditions, Michael-type conjugate additions and Diels–Alder cycloadditions.

Over the years, maleic and fumaric acid derivatives have found application in many different areas. Their use in the field of polymers dates from long ago, but the synthesis of monomers and polymers with improved properties is still a subject of research.[1] They have also been used, for instance, in the preparation of prodrugs and drug delivery systems,[2] or to assess the properties of dual-acting drugs and to provide information on how spatial arrangement affects binding to a receptor.[3] The interconversion between *Z* and *E* isomers has been exploited in the preparation of mechanically interlocked molecules capable of responding to external signals (molecular shuttles),[4] or to induce water gelation by transforming microspheres into gel fibres.[5] Maleic and fumaric acid derivatives are common substrates for heat- and light-promoted [4+2] and [2+2] cycloadditions, which have been combined and exploited in the design of molecular switches,[6] and have also been used in [3+2] and 1,3-dipolar cycloadditions.[7] Quite recently, reactivity and structural studies of complexes involving maleates and maleamates as ligands have also been undertaken.[8]

Derivatization of fumaric acid is essentially straightforward, the main possible difficulty being the selective functionalization of one of the two carboxylic acid groups. However, the synthesis of maleic acid derivatives is usually accompanied by side reactions (Scheme 1). Treatment with acyl-chloride-forming reagents promotes *Z* to *E* isomerization (a),[9] whereas other reagents such as ethyl chloroformate yield maleic or fumaric acid derivatives, or mixtures of both, depending on the reaction conditions and, in particular, on temperature (b).[10] The carboxylic acid group of a maleic acid monoester can be activated with a carbodiimide to provide the unsymmetrical diester (c), but carbodiimide activation of maleamic acids (d) yields isomaleimides, maleimides or mixtures of both, depending on the substituents.[11] Treatment of maleamate salts with alkyl halides would seem a good alternative, but when we prepared the cesium salt of *N*-benzylmaleamic acid (**1**) and treated it with benzyl bromide the benzyl ester was not obtained (data not shown). This result deserves further investigation, but that is beyond the scope of this work.



Scheme 1. Reactions taking place upon activation of butenedioic acids or monosubstituted derivatives: a) double bond isomerization promoted by acyl-chloride-forming reagents; b) activation of the carboxylic acid group of a maleamate by treatment of a maleamic acid with ethyl chloroformate, TEA and an amine yield a mixture of maleamide and fumaramide derivatives; c) activation of maleic acid monoesters with carbodiimides does not promote isomerization; d) treatment of maleamic acids with carbodiimides yields mixtures of isomaleimides and maleimides.

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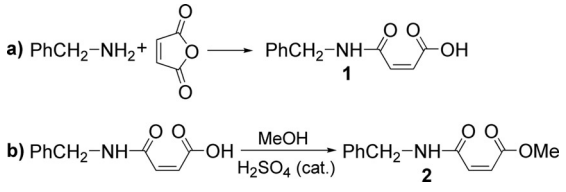
Few maleamate syntheses have been reported. The most commonly synthesized derivatives, methyl esters, have usually been prepared either by adid-catalysed esterification or by treatment with diazomethane.[11b,12] However, Fischer esterification, which can furnish esters other than methyl esters, does not allow phenyl esters to be obtained,[13] and use of strong acid catalysts is not compatible with substrates containing acid-labile groups. In this manuscript we wish to describe a study on the use of reagents that yield mixed carboxylic sulfonic anhydrides for the esterification of maleamic acids. We first looked for conditions that would allow the preparation of maleamates with high diastereomeric excesses, and final optimization provided high synthesis yields.

Results and Discussion

Experiments designed to establish suitable esterification conditions were carried out with *N*-benzylmaleamic acid, obtained from benzylamine and maleic anhydride as shown in Scheme 2, a). A sample of methyl maleamate was obtained through acid-catalysed esterification [Scheme 2, b)].

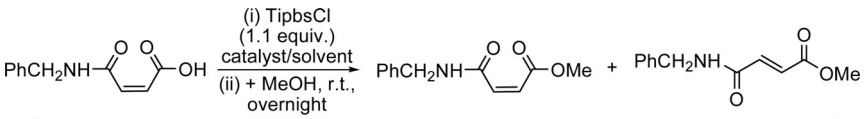


Scheme 2. Syntheses of a) *N*-benzylmaleamic acid, and b) the corresponding methyl ester under Fischer esterification conditions.

Arylsulfonyl-chloride-mediated esterification was devised as a one-pot procedure consisting of two sequential steps. In the first, the acid was activated by treatment with the arylsulfonyl chloride in the presence of pyridine both as solvent and nucleophilic catalyst. Methanol was then added and the reaction was allowed to proceed overnight. 2,4,6-Triisopropylbenzenesulfonyl chloride (TipbsCl) and mesitylenesulfonyl chloride (MessCl) were used in most of the experiments. 1-Mesitylenesulfonyl-3-nitro-1*H*-1,2,4-triazole was also tested, but its use is not recommended because the nitrotriazolide anion liberated upon formation of the mixed anhydride reacts with the double bond to afford a succinamate rather than a maleamate derivative.

The first experiment, involving nearly equimolar amounts of maleamic acid, arylsulfonyl chloride and alcohol (Table 1, Entry 1), afforded methyl *N*-benzylfumaramate (90% *de*) and a very small amount of methyl *N*-benzylmaleamate. It is worth pointing out here that NMR characterization may not be unequivocal with only one of the two isomers available, because the CH=CH coupling constants of the *Z* and *E* isomers are very similar[12b] (in our case, 13 and 15 Hz, respectively). The 2D ROESY spectra provided the key to the identification of the two compounds, because only maleamates exhibit the diagnostic cross peak (quick inspection of NOESY spectra may suggest that olefinic protons are coupled both in maleamates and in fumaramates). In addition to differences in chemical shifts (the NH and the olefinic protons of the *Z* isomer were downfield and upfield, respectively, from those of the *E* isomer), it was observed that the positions of the two doublets of the CH=CH system and the NH of the *E* isomer varied depending on the concentration of the sample, in contrast with the signals of the *Z* isomer, which did not. A plausible explanation for this behaviour is that the NH moiety in the *Z* isomer may form an intramolecular H bond with the CO component of the ester,[14] whereas in the case of the *E* isomer the association is intermolecular and thus concentration-sensitive (Figure 1).

Table 1. Results of the first esterification experiments: *Z*/*E* ratios.



Entry	Catalyst (equiv.)[a]/Solvent	Activation		Equiv. MeOH	Ester ratio (%)[b]	
		Time	Temp.		*Z*	*E*
1	pyridine	30 min	r.t.[c]	1.5	5	95
2	pyridine	30 min	r.t.	25	40	60
3	pyridine	30 min	r.t.	100	70	30
4	pyridine	30 min	0 °C	1.5	4	96
5	pyridine	30 min	0 °C	25	51	49
6	pyridine	30 min	0 °C	100	61	39
7	pyridine (10)/THF	30 min	r.t.	100	88	12
8	pyridine (20)/THF	30 min	r.t.	100	84	16
9	pyridine (30)/THF	30 min	r.t.	100	84	16
10	pyridine (20)/THF	10 min	r.t.	100	87	13
11	pyridine (30)/THF	5 min	r.t.	100	84	16
12	2-picoline (20)/THF	30 min	r.t.	100	>99	<1
13	2-picoline (30)/THF	30 min	r.t.	100	>99	<1
14	2-picoline	30 min	r.t.	1.5	97	3
15	2-picoline	30 min	r.t.	10	>99	<1
16	2-picoline	30 min	r.t.	50	>99	<1
17	2-picoline	30 min	r.t.	100	>99	<1

[a] When the catalyst is not used as solvent, the molar fold excess of catalyst with respect to the acid is indicated in brackets. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Room temp. (ca. 20 °C).

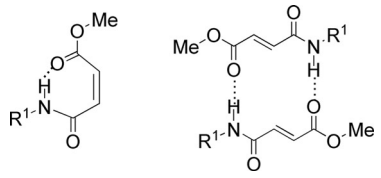


Figure 1. Plausible formation of H-bonds in intra- and intermolecular association of maleamates and fumaramates.

Olefin isomerization can be induced by light or radical initiators, or by totally different mechanisms such as in Pd/Bu_3SnH-mediated reactions.[15] The isomerization of double bonds, however, is most often accounted for by ionic intermediates. Conjugate addition of a nucleophile allows the CH–CH bond to rotate, and this is followed by a retro-Michael reaction.[16] Hydrogen halides and primary and secondary amines have been reported to promote *Z*-to-*E* isomerizations of maleic acid and maleates,[17] as has *N*-methylimidazole.[18]

In an experiment carried out with a larger excess of methanol, the two isomers were found in the reaction mixture in similar proportions (Table 1, Entry 2). This was the first evidence that the presence of an excess of alcohol could modify the outcome of the reaction. As can be seen in Entries 1–6, increasing amounts of methanol reversed the *Z*/*E* ratio when activation was effected either at room temp. or at 0 °C.

Methyl *N*-benzylmaleamate was not altered by methanol, pyridine, pyridinium hydrochloride or aqueous workup. This suggested that isomerization was occurring prior to ester formation, in one of the precursor activated species (mixed carboxylic sulfonic anhydride or acyl pyridinium derivative), through a reaction between this species and a nucleophile. This assumption was consistent with the effect of using large amounts of MeOH, which should increase the rate of the reaction between the activated species and MeOH and thus reduce the risk of isomerization.

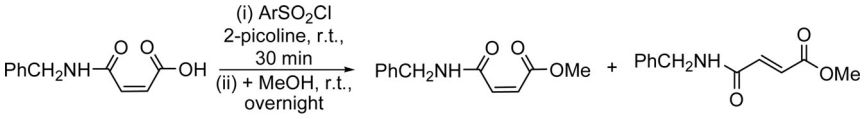
Experiments with smaller amounts of pyridine gave better but still unsatisfactory results (Table 1, Entries 7–9), and shortening the activation time had no significant influence on the ratio of diastereomers (cf. Entries 8 to 10 and 9 to 11). Replacement of pyridine by 2-picoline gave very high *Z*/*E* ratios (Entries 12–13). The 2-picoline methyl group reduced pyridine's nucleophilicity, and hence the extent of isomerization. Further experiments with 2-picoline as both catalyst and solvent (Entries 14–17) confirmed that the highest levels of isomerization are found with use of low molar ratios of alcohol. Surprisingly, NMR spectroscopic analysis showed that the higher the excess of methanol the more homogeneous the crude reaction product, which suggests the use of at least 5 equiv. of alcohol.

Our second concern was the reaction yield, which was below 25% in all the experiments that had given the maleamate in high diastereomeric excess. Because poor conversion of acid into ester was possibly due to steric hindrance around the sulfonyl group, less hindered reagents such as MessCl, 2-methylbenzenesulfonyl chloride (oMbsCl) and TsCl were tested (Table 2, Entries 18–20). Replacement of TipbsCl by MessCl gave a better esterification yield, with no change in the stereochemical outcome of the reaction. We have no explanation for the fact that MessCl performed better than oMbsCl and TsCl. Adjustments in the molar ratios of acid, MessCl and methanol (Table 2, Entries 21–26) allowed for high esterification yields, with isomerization being kept within satisfactory limits.

The two isomers have very similar R_f values and are difficult to separate, so the decision as to which are the best esterification conditions is not obvious. If the goal is the isolation of pure maleamate, the conditions of Entry 22 may be optimal. The esterification yield is not the highest, but the extent of isomerization is virtually nil. Should contamination with a small amount of the *E* isomer not be important, the conditions of Entry 24 (or 25 if the alcohol is not too valuable and can be easily separated) may be preferable.

The conditions that allowed essentially isomerization-free esterification (Table 2, Entry 22) were used for the synthesis of some other maleamates (Scheme 3, a). Different esters of *N*-benzylmaleamic acid were obtained after treatment with primary and secondary alcohols [methanol, 2-

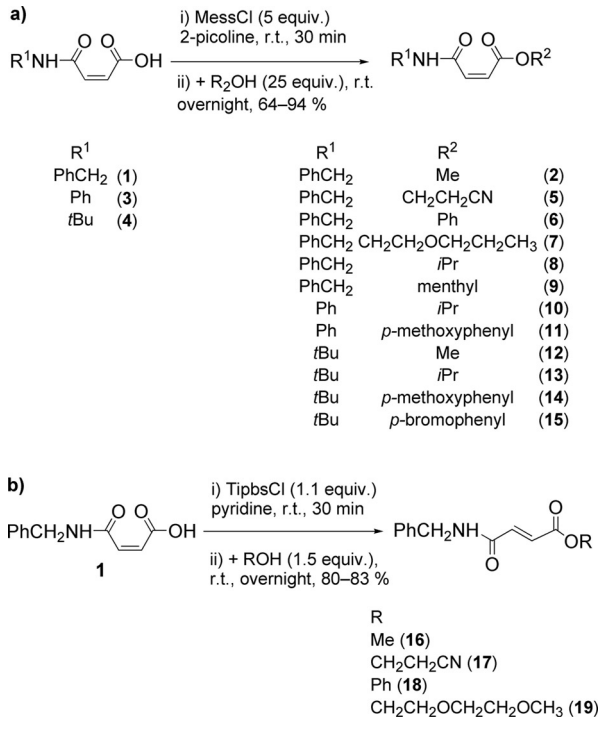
Table 2. Results of the second group of esterification experiments: maleamate yield.



Entry	$ArSO_2Cl$ (equiv.)	Equiv. MeOH	Ester ratio (%)[a]		Ester yield[a] (%)	Acid[a] (%)
			Z	*E*		
17[b]	TipbsCl (1.1)	100	>99	<1	24	76
18	TsCl (1.1)	100	>99	<1	35[3]	65
29	oMbsCl (1.1)	100	>99	<1	36	64
20	MessCl (1.1)	100	>99	<1	45	55
21	MessCl (5)	100	>99	<1	77	23
22	MessCl (5)	25	99	1	81	19
23	MessCl (10)	100	98	2	89	11
24	MessCl (10)	25	97	3	89	11
25	MessCl (20)	100	96	4	95	5
26	MessCl (20)	25	89	11	93	7

[a] Determined by ^1H NMR analysis of the crude product. [b] Entry 17 is repeated for purposes of comparison, so subsequent experiments are numbered consecutively.

cyanoethanol, (2-methoxyethoxy)ethanol, 2-propanol, (–)-menthol] and phenol. In all cases ^{1}H NMR analysis of the crude products showed the proportion of diastereomers to be the same as that found for the methyl ester in the preliminary experiment (Table 2, Entry 2), or even lower. Treatment of *N*-phenyl- and *N*-*tert*-butylmaleamic acids (synthesized as shown in Scheme 2, a) with secondary alcohols [propan-2-ol, (–)-menthol] and other phenols also furnished the corresponding esters satisfactorily. Although this methodology allowed different esters to be synthesized in good to very good yields (from 64 to 95%), the need to use a considerable excess of alcohol or phenol may be a problem if this is a valuable compound. Moreover, it proved not to be suitable for the preparation of esters of tertiary alcohols. A signal with the *m*/*z* ratio expected for *tert*-butyl *N*-benzylmaleamate was detected in the ESI-MS spectrum of the reaction mixture, but analysis of the ^{1}H NMR spectrum showed that the ester had been formed in less than 15% yield. Hence, with the exception of the *tert*-butyl ester, maleamates were obtained in fairly good to high yields irrespective of the amic acid *N*-substituent.



Scheme 3. Preparation of a) different maleamates and b) fumaramates.

The conditions that afforded the *E* isomers (Table 1, Entry 1) were used to prepare some fumaramates (Scheme 3, b), which were obtained with high yields and diastereoselectivities.

Conclusions

In summary, fine-tuning of the esterification conditions allowed a maleamic acid to be transformed into either a maleamate or a fumaramate on treatment with a hydroxy-containing compound, in very good yields and in particular with high diastereomeric excesses. To the best of our knowledge, isomerization-free activation of maleamic acid carboxylic acid groups has not previously been reported. Under the reaction conditions studied here – activation of the maleamic acid carboxylic acid group with an arylsulfonyl chloride and treatment with an alcohol at room temperature – the relative proportions of reagents required to afford the best yields of maleamates are substantially different from those needed to give fumaramates. The excess of alcohol has a strong influence on the degrees of isomerization, but the key point for prevention of isomerization is substitution of 2-picoline for pyridine. The described methodology allows maleamic acids to be esterified with primary and secondary alcohols, as well as the synthesis of phenyl maleamates, which cannot be prepared by acid-catalysed Fischer esterification.

Experimental Section

Syntheses of Maleamic Acids

***N*-Benzylmaleamic Acid (1):** Maleic anhydride (2.63 g, 26.8 mmol) was dissolved in anhydrous THF (40 mL), and benzylamine (2.7 mL, 24.4 mmol) was subsequently added. The mixture was stirred for 2 h at room temp., and the solvent was eliminated in vacuo. The resulting crude product was dissolved in CH_2Cl_2 (25 mL) and extracted with aqueous citric acid (10%, 3 × 50 mL) and water (1 × 50 mL). The organic phase was dried with anhydrous $MgSO_4$. Solvent removal by rotary evaporation afforded pure *N*-benzylmaleamic acid. White crystals; quantitative yield; m.p. 137–138 °C; R_f 0.47 (CH_2Cl_2/MeOH/AcOH, 88:10:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.43 (m, 5 H, Ar), 7.19 (br. s, 1 H, NH), 6.51 (d, $^3J_{H,H}$ = 12.9 Hz, 1 H, NCOCH), 6.44 (d, $^3J_{H,H}$ = 12.9 Hz, 1 H, CHCOO), 4.73 (d, $^3J_{H,H}$ = 5.9 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 165.0, 136.9, 135.8, 130.7, 129.1, 128.3, 128.2, 44.6 ppm. HRMS (ESI+): calcd. for $C_{11}H_{12}NO_3$ [M + H]$^+$ 206.0811; found 206.0821; calcd. for $C_{11}H_{11}NNaO_3$ [M + Na]$^+$ 228.0631; found 228.0633; calcd. for $C_{22}H_{22}N_2NaO_6$ [2M + Na]$^+$ 433.1370; found 433.1366.

***N*-Phenylmaleamic Acid (3):** Maleic anhydride (593 mg, 6.04 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL), and aniline (0.5 mL, 5.49 mmol) was subsequently added. The mixture was stirred for 1 h at room temp. (precipitation of the acid was observed after a few minutes). The pure solid was obtained by filtration and washing with CH_2Cl_2. White powder; quantitative yield; m.p. 193–194 °C; R_f = 0.26 (CH_2Cl_2/MeOH/AcOH, 88:10:2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 13.12 (s, 1 H, COOH), 10.38 (s, 1 H, NH), 7.62 (m, 2 H, Ar), 7.33 (m, 2 H, Ar), 7.09 (m, 1 H, Ar), 6.48 (d, $^3J_{H,H}$ = 12.2 Hz, 1 H, NCOCH), 6.31 (d, $^3J_{H,H}$ = 12.2 Hz, 1 H, CHCOO) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.7, 163.1, 138.4, 131.6, 130.3, 128.7, 123.8, 119.4 ppm. HRMS (ESI+): calcd. for $C_{10}H_{10}NO_3$ [M + H]$^+$ 192.0655; found 192.0656.

***N*-*tert*-Butylmaleamic Acid (4):** The synthesis procedure was the same as for compound **1** (see above). White powder; quantitative yield; m.p. 152–153 °C; R_f 0.45 (CH_2Cl_2/MeOH/AcOH, 88:10:2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.74 (s, 1 H, NH), 6.42 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H, NCOCH), 6.20 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H, CHCOO), 1.32 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 165.4, 165.0, 132.7, 132.7, 51.5, 27.9 ppm. HRMS

(ESI+): calcd. for $C_8H_{14}NO_3$ $[M + H]^+$ 172.0968; found 172.0970; calcd. for $C_8H_{13}NNaO_3$ $[M + Na]^+$ 194.0798; found 194.0796.

Acid-Catalysed Esterification

Methyl *N*-Benzylmaleamate (2): Concd. H_2SO_4 (500 μL) was added to a solution of *N*-benzylmaleamic acid (500 mg) in anhydrous MeOH. The mixture was stirred for 4 h at room temp. and the solvent was removed by rotary evaporation. The resulting crude product was dissolved in CH_2Cl_2 (25 mL), and washed with aq. $NaHCO_3$ (10%, 3 × 50 mL) and brine (1 × 50 mL). The organic phase was dried with $MgSO_4$. Elimination of the solvent under reduced pressure afforded pure methyl *N*-benzylmaleamate as a colourless oil in quantitative yield. R_f 0.40 (CH_2Cl_2/EtOAc, 75:25). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (br. s, 1 H, NH), 7.37–7.27 (m, 5 H, Ar), 6.38 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, NCOCH), 6.15 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, CHCOO), 4.54 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H, CH_2), 3.76 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 163.8, 138.5, 137.8, 128.7, 127.8, 127.5, 125.0, 52.4, 43.8 ppm. HRMS (ESI+): calcd. for $C_{12}H_{14}NO_3$ $[M + H]^+$ 220.0968; found 220.0972; calcd. for $C_{12}H_{13}NNaO_3$ $[M + Na]^+$ 242.0787; found 242.0791; calcd. for $C_{24}H_{26}N_2NaO_6$ $[2M + Na]^+$ 461.1683; found 461.1686.

Synthesis of Maleamates. General Procedure: The *N*-substituted maleamic acid (200 mg) and MessCl (5 equiv.) were dissolved in anhydrous 2-picoline. The mixture was stirred under Ar at room temp. for 30 min, after which the required alcohol (or phenol, 25 equiv.) was added. After 12–15 h stirring at room temp., the solvent was eliminated by rotary evaporation. The resulting crude product was dissolved in CH_2Cl_2 (25 mL), and washed with aq. citric acid (10%, 3 × 50 mL), aq. $NaHCO_3$ (10%, 2 × 50 mL) and brine (1 × 50 mL). The organic phase was dried with $MgSO_4$ and the solvent was removed under vacuum. Esters were purified by silica gel column chromatography. In the case of **2**, **5**, **6** and **7**, elution was carried out with CH_2Cl_2 and increasing amounts of EtOAc (up to 30%). Esters **8**–**10**, **12** and **13** were purified by elution with hexanes and increasing amounts of Et_2O (up to 30%). Finally, esters **11**, **14** and **15** were purified by elution with hexanes and increasing amounts of EtOAc (up to 30%).

Methyl *N*-Benzylmaleamate (2): Colourless oil; yield 71%; R_f 0.41 (CH_2Cl_2/EtOAc, 7:3). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.47 (br. s, 1 H, NH), 7.37–7.26 (m, 5 H, Ar), 6.38 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, NCOCH), 6.15 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, CHCOO), 4.54 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H, CH_2), 3.76 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 163.9, 137.7, 137.4, 128.5, 127.7, 127.3, 125.3, 52.2, 43.5 ppm. HRMS (ESI+): calcd. for $C_{12}H_{14}NO_3$ $[M + H]^+$ 220.0968; found 220.0967; calcd. for $C_{12}H_{13}NNaO_3$ $[M + Na]^+$ 242.0788; found 242.0790; calcd. for $C_{24}H_{26}N_2NaO_6$ $[2M + Na]^+$ 461.1683; found 461.1679.

2-Cyanoethyl *N*-Benzylmaleamate (5): Pale yellow oil; yield 68%; R_f 0.33 (CH_2Cl_2/EtOAc, 7:3). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (br. s, 1 H, NH), 7.36–7.26 (m, 5 H, Ar), 6.37 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, NCOCH), 6.15 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, CHCOO), 4.49 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H, Ar-CH_2), 4.33 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, OCH_2), 2.70 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, CH_2CN) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 163.7, 137.5, 128.7, 127.9, 127.6, 125.1, 116.5, 59.4, 43.8, 17.7 ppm. HRMS (ESI+): calcd. for $C_{14}H_{15}N_2O_3$ $[M + H]^+$ 259.1077; found 259.1073; calcd. for $C_{14}H_{14}N_2NaO_3$ $[M + Na]^+$ 281.0897; found 281.0892; calcd. for $C_{28}H_{28}N_4NaO_6$ $[2M + Na]^+$ 539.1901; found 539.1900.

Phenyl *N*-Benzylmaleamate (6): Colourless oil; yield 70%; R_f 0.66 (CH_2Cl_2/EtOAc, 7:3). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (br. s, 1 H, NH), 7.42–7.11 (m, 10 H, Ar), 6.50 (d, $^3J_{H,H}$ = 12.9 Hz, 1 H, NCOCH), 6.36 (d, $^3J_{H,H}$ = 12.9 Hz, 1 H, CHCOO), 4.51 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 163.7, 150.0, 139.0, 129.6, 128.7, 128.6, 127.8, 127.5, 126.4, 125.0, 122.0, 43.8 ppm. HRMS (ESI+): calcd. for $C_{17}H_{16}NO_3$ $[M + H]^+$ 282.1125; found 282.1120; calcd. for $C_{17}H_{15}NNaO_3$ $[M + Na]^+$ 304.0944; found 304.0939; calcd. for $C_{34}H_{30}N_2NaO_6$ $[2M + Na]^+$ 585.1996; found 585.1992.

2-(2-Methoxyethoxy)ethyl *N*-Benzylmaleamate (7): Colourless oil; yield 70%; R_f 0.19 (CH_2Cl_2/EtOAc, 7:3). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (br. s, 1 H, NH), 7.36–7.26 (m, 5 H, Ar), 6.37 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, NCOCH), 6.15 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, CHCOO), 4.53 (d, $^3J_{H,H}$ = 5.6 Hz, 2 H, CH_2), 4.32 (t, $^3J_{H,H}$ = 4.8 Hz, 2 H, $COOCH_2CH_2O$), 3.72 (t, $^3J_{H,H}$ = 4.8 Hz, 2 H, $COOCH_2CH_2O$), 3.64–3.62 (m, 2 H, OCH_2CH_2O), 3.54–3.52 (m, 2 H, OCH_2CH_2O), 3.36 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 163.9, 138.6, 137.8, 128.6, 127.8, 127.4, 125.0, 71.8, 70.5, 68.7, 64.5, 59.0, 43.7 ppm. HRMS (ESI+): calcd. for $C_{16}H_{22}NO_5$ $[M + H]^+$ 308.1492; found 308.1488; calcd. for $C_{16}H_{21}NNaO_5$ $[M + Na]^+$ 330.1312; found 330.1307.

Isopropyl *N*-Benzylmaleamate (8): Yellow oil; yield 72%; R_f 0.58 (Et_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.73 (br. s, 1 H, NH), 7.36–7.24 (m, 5 H, Ar), 6.33 (d, $^3J_{H,H}$ = 13.0 Hz, 1 H, NCOCH), 6.10 (d, $^3J_{H,H}$ = 13.0 Hz, 1 H, CHCOO), 5.06 (sept, $^3J_{H,H}$ = 6.2 Hz, 1 H, CH), 4.53 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, CH_2), 1.27 (d, $^3J_{H,H}$ = 6.2 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 163.9, 137.9, 137.8, 128.5, 127.7, 127.3, 126.0, 69.3, 43.6, 21.6 ppm. HRMS (ESI+): calcd. for $C_{14}H_{18}NO_3$ $[M + H]^+$ 248.1281; found 248.1285; calcd. for $C_{14}H_{17}NNaO_3$ $[M + Na]^+$ 270.1101; found 270.1101; calcd. for $C_{28}H_{34}N_2NaO_6$ $[2M + Na]^+$ 517.2309; found 517.2309.

Menthyl *N*-Benzylmaleamate (9): Pale yellow solid; yield 64%; R_f 0.80 (Et_2O); m.p. 68–70 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.92 (br. s, 1 H, NH), 7.34–7.27 (m, 5 H, Ar), 6.36 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, NCOCH), 6.13 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, CHCOO), 4.74 (dt, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 10.8 Hz, 1 H, COOCH menthyl), 4.54 (d, $^3J_{H,H}$ = 5.6 Hz, 2 H, $ArCH_2$), 2.02–1.97 (m, 1 H, CH menthyl), 1.82 (dsept, $^3J_{H,H}$ = 2.5, $^3J_{H,H}$ = 6.9 Hz, 1 H, $CHCH_3$ menthyl), 1.70–1.67 (m, 3 H, CH menthyl), 1.54–1.45 (m, 1 H, CH menthyl), 1.44–1.36 (m, 2 H, CH menthyl), 1.08–1.04 (m, 1 H, CH menthyl), 0.91 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3 menthyl), 0.89 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3 menthyl), 0.74 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3 menthyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 164.0, 138.7, 137.9, 128.6, 127.7, 127.3, 125.7, 75.9, 46.8, 43.7, 40.6, 34.1, 31.4, 26.2, 23.4, 21.9, 20.7, 16.3 ppm. HRMS (ESI+): calcd. for $C_{21}H_{30}NO_3$ $[M + H]^+$ 344.2220; found 344.2232; calcd. for $C_{21}H_{29}NNaO_3$ $[M + Na]^+$ 366.2040; found 366.2042; calcd. for $C_{42}H_{59}N_2O_6$ $[2M + H]^+$ 687.4368; found 687.4365; calcd. for $C_{42}H_{58}N_2NaO_6$ $[2M + Na]^+$ 709.4187; found 709.4185.

Isopropyl *N*-Phenylmaleamate (10): Yellow oil; yield 78%; R_f 0.21 (hexanes/Et_2O 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.97 (br. s, 1 H, NH), 7.66 (m, 2 H, Ar), 7.33 (m, 2 H, Ar), 7.11 (m, 1 H, Ar), 6.40 (d, $^3J_{H,H}$ = 13.3 Hz, 1 H, NCOCH), 6.16 (d, $^3J_{H,H}$ = 13.3 Hz, 1 H, CHCOO), 5.13 (sept, $^3J_{H,H}$ = 6.3 Hz, 1 H, CH), 1.31 (d, $^3J_{H,H}$ = 6.3 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 161.6, 140.0, 137.9, 128.9, 125.9, 124.4, 120.0, 69.9, 21.6 ppm. HRMS (ESI+): calcd. for $C_{13}H_{16}NO_3$ $[M + H]^+$ 234.1125; found 234.1122; calcd. for $C_{13}H_{15}NNaO_3$ $[M + Na]^+$ 256.0944; found 256.0940; calcd. for $C_{26}H_{30}N_2NaO_6$ $[2M + Na]^+$: 489.1994; found 489.1994.

4-Methoxyphenyl *N*-Phenylmaleamate (11): Yellow oil; yield 71%; R_f 0.21 (hexanes/EtOAc, 3:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.34 (br. s, 1 H, NH), 7.62 (m, 2 H, Ar), 7.31 (m, 2 H, Ar), 7.11

(m, 1 H, Ar), 7.09 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, $CH_{ar,\alpha}$), 6.92 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, $CH_{ar,\beta}$), 6.58 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, NCOCH), 6.43 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, CHCOO), 3.81 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 161.3, 157.8, 143.4, 141.0, 137.5, 134.2, 128.9, 124.8, 122.0, 120.2, 114.6, 55.6 ppm. HRMS (ESI+): calcd. for $C_{17}H_{16}NO_4$ $[M + H]^+$ 298.1074; found 298.1081.

Methyl *N*-*tert*-Butylmaleamate (12): White powder; yield 95%; m.p. 61–62 °C; R_f 0.16 (hexanes/Et_2O 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (br. s, 1 H, NH), 6.24 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, NCOCH), 6.02 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, CHCOO), 3.76 (s, 3 H, OCH_3), 1.38 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 163.2, 140.2, 123.6, 52.2, 51.4, 28.4 ppm. HRMS (ESI+): calcd. for $C_9H_{16}NO_3$ $[M + H]^+$ 186.1125; found 182.1122.

2-Propyl *N*-*tert*-Butylmaleamate (13): Yellow oil; yield 94%; R_f 0.29 (hexanes/Et_2O 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (br. s, 1 H, NH), 6.20 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, NCOCH), 5.99 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, CHCOO), 5.07 (sept, $^3J_{H,H}$ = 6.5 Hz, 1 H, CH), 1.39 (s, 9 H, CH_3), 1.28 (d, $^3J_{H,H}$ = 6.5 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 163.2, 140.1, 124.7, 69.1, 51.4, 28.4, 21.7 ppm. HRMS (ESI+): calcd. for $C_{11}H_{20}NO_3$ $[M + H]^+$ 214.1438; found 214.1434; calcd. for $C_{11}H_{19}NNaO_3$ $[M + Na]^+$ 236.1257; found 236.1254; calcd. for $C_{22}H_{38}N_2NaO_6$ $[2M + Na]^+$ 449.2622; found 449.2612.

4-Methoxyphenyl *N*-*tert*-Butylmaleamate (14): Yellow oil; yield 81%; R_f 0.35 (hexanes/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (br. s, 1 H, NH), 7.04 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, $CH_{ar,\alpha}$), 6.88 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, $CH_{ar,\beta}$), 6.37 (d, $^3J_{H,H}$ = 12.7 Hz, 1 H, NCOCH), 6.21 (d, $^3J_{H,H}$ = 12.7 Hz, 1 H, CHCOO), 3.77 (s, 3 H, OCH_3), 1.35 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 163.1, 157.4, 143.5, 140.4, 123.6, 122.1, 114.4, 55.4, 51.6, 28.4 ppm. HRMS (ESI+): calcd. for $C_{15}H_{20}NO_4$ $[M + H]^+$ 278.1387; found 278.1385; calcd. for $C_{15}H_{19}NO_4Na$ $[M + Na]^+$ 300.1206; found 300.1206; calcd. for $C_{30}H_{38}N_2NaO_8$ $[2M + Na]^+$ 577.2520; found 577.2518.

4-Bromophenyl *N*-*tert*-Butylmaleamate (15): Yellow oil; yield 87%; R_f 0.35 (hexanes/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, $CH_{ar,\beta}$), 7.05 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, $CH_{ar,\alpha}$), 6.97 (br. s, 1 H, NH), 6.41 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H, NCOCH), 6.22 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H, CHCOO), 1.37 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 163.0, 149.1, 140.3, 132.5, 123.5, 123.2, 119.3, 51.7, 28.5 ppm. HRMS (ESI+): calcd. for $C_{14}H_{17}BrNO_3$ $[M + H]^+$ 326.0386; found 326.0383; calcd. for $C_{14}H_{16}BrNNaO_3$ $[M + Na]^+$ 348.0206; found 348.0202; calcd. for $C_{28}H_{32}Br_2N_2NaO_6$ $[2M + Na]^+$ 673.0519; found 673.0519.

Synthesis of Fumaramates. General Procedure: *N*-Benzylmaleamic acid (200 mg) and TipbsCl (1.5 equiv.) were dissolved in anhydrous pyridine. The mixture was stirred under Ar at room temp. for 30 min, after which the required alcohol (or phenol, 1.1 equiv.) was added. After 12–15 h stirring at room temp., the solvent was eliminated by rotary evaporation. The resulting crude product was dissolved in CH_2Cl_2 (25 mL) and washed with aq. citric acid (10%, 3 × 50 mL) and brine (1 × 50 mL). The organic phase was dried with $MgSO_4$ and the solvent was removed under vacuum. The esters (**16**–**19**) were purified by silica gel column chromatography by elution with CH_2Cl_2 and increasing amounts of EtOAc (up to 30%).

Methyl *N*-Benzylfumaramate (16): White solid; yield 85%; R_f 0.65 (CH_2Cl_2/EtOAc, 7:3); m.p. 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H, Ar), 6.92 (d, $^3J_{H,H}$ = 15.3 Hz, 1 H, NCOCH), 6.87 (d, $^3J_{H,H}$ = 15.3 Hz, 1 H, CHCOO), 6.06 (br. s, 1 H, NH), 4.55 (d, $^3J_{H,H}$ = 5.9 Hz, 2 H, CH_2), 3.79 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 163.3, 137.3, 136.1, 130.5, 128.9, 127.9, 127.9, 52.2, 44.1 ppm. HRMS (ESI+): calcd. for $C_{12}H_{14}NO_3$ $[M + H]^+$ 220.0968; found 220.0965; calcd. for $C_{12}H_{13}NNaO_3$ $[M + Na]^+$ 242.0788; found 242.0784; calcd. for $C_{24}H_{26}N_2NaO_6$ $[2M + Na]^+$ 461.1683; found 461.1693.

Cyanoethyl *N*-Benzylfumaramate (17): White solid; yield 80%; R_f 0.86 (CH_2Cl_2/EtOAc, 7:3); m.p. 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H, Ar), 6.97 (d, $^3J_{H,H}$ = 15.3 Hz, 1 H, NCOCH), 6.87 (d, $^3J_{H,H}$ = 15.3 Hz, 1 H, CHCOO), 6.24 (br. s, 1 H, NH), 4.54 (d, $^3J_{H,H}$ = 5.6 Hz, 2 H, CH_2), 4.37 (t, $^3J_{H,H}$ = 6.2 Hz, 2 H, OCH_2), 2.74 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, CH_2CN) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.714, 162.920, 137.335, 137.204, 129.394, 128.871, 127.962, 127.893, 116.473, 59.236, 44.114, 17.970 ppm. HRMS (ESI+): calcd. for $C_{14}H_{15}N_2O_3$ $[M + H]^+$ 259.1077; found 259.1077; calcd. for $C_{14}H_{14}N_2NaO_3$ $[M + Na]^+$ 281.0896; found 281.0901; calcd. for $C_{28}H_{28}N_4NaO_6$ $[2M + Na]^+$ 539.1901; found 539.1903.

Phenyl *N*-Benzylfumaramate (18): White solid; yield 83%; R_f 0.86 (CH_2Cl_2/EtOAc, 7:3); m.p. 143–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.03 (m, 12 H, Ar), 6.28 (br. s, 1 H, NH), 4.54 (d, $^3J_{H,H}$ = 5.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 163.1, 150.3, 137.7, 137.3, 130.0, 129.5, 128.8, 127.9, 127.8, 126.2, 121.3, 44.1 ppm. HRMS (ESI+): calcd. for $C_{17}H_{16}NO_3$ $[M + H]^+$ 282.1124; found 282.1127; calcd. for $C_{17}H_{15}NNaO_3$ $[M + Na]^+$ 304.0944; found 304.0951; calcd. for $C_{34}H_{31}N_2O_6$ $[2M + H]^+$ 563.2176; found 563.2185; calcd. for $C_{34}H_{30}N_2NaO_6$ $[2M + Na]^+$ 585.1996; found 585.2011.

(2-Methoxyethoxy)ethyl *N*-Benzylfumaramate (19): White solid; yield 83%; R_f 0.30 (CH_2Cl_2/EtOAc, 7:3); m.p. 42–43 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.23 (m, 5 H, Ar), 6.98 (d, $^3J_{H,H}$ = 15.3 Hz, 1 H, NCOCH), 6.95 (br. s, 1 H, NH), 6.82 (d, $^3J_{H,H}$ = 15.3 Hz, 1 H, CHCOO), 4.49 (d, $^3J_{H,H}$ = 5.8 Hz, 2 H, CH_2), 4.24 (t, $^3J_{H,H}$ = 4.8 Hz, 2 H, $COOCH_2CH_2O$), 3.68 (t, $^3J_{H,H}$ = 4.8 Hz, 2 H, $COOCH_2CH_2O$), 3.64–3.61 (m, 2 H, OCH_2CH_2O), 3.54–3.52 (m, 2 H, OCH_2CH_2O), 3.35 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 163.5, 137.4, 136.8, 129.9, 128.6, 127.8, 127.6, 71.8, 70.4, 68.9, 64.2, 58.9, 43.8 ppm. HRMS (ESI+): calcd. for $C_{16}H_{22}NO_5$ $[M + H]^+$ 308.1492; found 308.1495; calcd. for $C_{16}H_{21}NO_5Na$ $[M + Na]^+$ 330.1311; found 330.1324; calcd. for $C_{32}H_{43}N_2O_{10}$ $[2M + H]^+$ 615.2912; found 615.2920; calcd. for $C_{32}H_{42}N_2NaO_{10}$ $[2M + Na]^+$ 637.2731; found 637.2735.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra.

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