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Development of a Mild Procedure for the Addition of Bisulfite to Electrophilic Olefins

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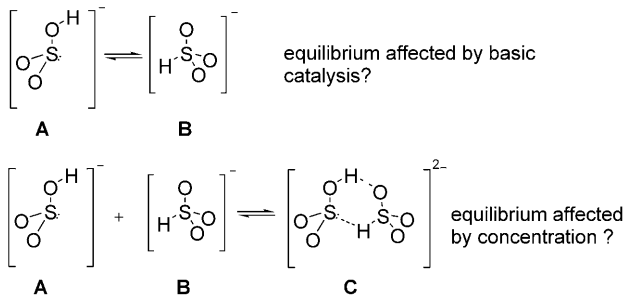
Abstract: The sulfonylation of activated alkenes is an important yet unexplored reaction due to the harshness of conditions required. We have identified a procedure which allowed the reaction of alkenes with equimolar amounts of bisulfite at room temperature.

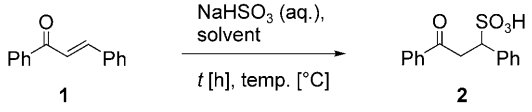
Keywords: alkenes; amine catalysis; sulfonic acids; thia-Mchael addition; triethylamine

Herein we report a mild, amine-promoted, room temperature procedure for the addition of aqueous sodium bisulfite to activated olefins to give organic sulfonic acids. Sulfonic acids are among the strongest acids in organic chemistry with a pK_a (DMSO) of 1.6.[1] For this reason, they have been often used as resolving agents for chiral racemic amines,[2] and families of sulfonic acids were prepared and used in "Dutch resolution" experiments.[3,4] Sulfonic acids and sulfonamides are isosteric with carboxylates which justifies their popularity in medicinal chemistry.[5] Taurine and some of its derivatives (e.g., homotaurine, guanidotaurine) have repeatedly being found to have activity on the central nervous system (CNS).[6]

The sulfonic acid functionality is also present in some naturally occurring compounds, for example, in 6-gingesulfonic acid, extracted from ginger (*Zingiberis Rhizoma*) which is used as an anti-ulcer drug.[7] Due to the biological activity of sulfonic acids, several multistep syntheses have been reported. For example, Corey prepared chiral sulfonic acids *via* a synthetic sequence in which acetophenone reduction was the key enantio-determining step.[8] Di Bella and co-workers successfully synthesized some enantiopure amino sulfonic acids starting from chiral amino acids.[9] Enders and co-workers have reported the α-alkylation of sulfonic acid esters with alkyl halides or with β-nitroalkenes using a chiral auxiliary strategy[10] and the nucleophilic addition of chiral nitrogen nucleophiles such as (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) to α,β-unsaturated sulfonic acid esters.[11] The same group reported an organocatalytic-mediated addition of a sulfur nucleophile to α,β-unsaturated sulfonic acid esters.[12] Despite all these efforts, the simple addition of bisulfite to olefins, discovered over a century ago,[13] still remains the most straight-forward access to aliphatic sulfonic acids. This reaction employs large excesses of reactants and requires high temperatures. The harsh conditions effectively limited the synthetic utility of this reaction with the reports of Kellogg[4] and Crowley[14] being the only variant described recently. Kellogg reported the addition of solid sodium bisulfite to chalcones in ethanol at reflux;[4] Crawley and co-workers have successfully optimized a microwave-assisted sulfonylation of cinnamic acid ester derivatives using aqueous sodium bisulfite.[14] Both these procedures required the use of high temperature and a large excess of bisulfite reactant. The need for forcing conditions could be understood when considering the behaviour of bisulfite in aqueous solutions (Scheme 1).



Scheme 1. Different equilibria existing in a bisulfite solution.



Scheme 2. The addition of bisulfite to chalcone.

Bisulfite establishes two equilibria, the first one between its forms **A** and **B** and a second one involving interaction of **A** plus **B** to give **C**. Pertinent to this discussion, form **A** is the active nucleophile (Scheme 1).[15] It has been reported that at high concentration, e.g., commercial 38% w/v aqueous bisulfite, the two forms **A** and **B** interact by hydrogen bonding to form mainly the non-nucleophilic dimer **C**; conversely at low concentrations ($<10^{-2}$ M) dimer **C** decomposes to give isomeric forms **A** and **B** (Scheme 1). From this report, commercial concentrated solutions of bisulfite, which mostly contain dimeric **C**, could not add to alkenes at room temperature, but rather require heating in order to dissolve dimeric **C**. Considering that faster sulfonylation occurs when the concentration of **A** is maximised, we hyphothesised that addition of bisulfite to alkenes could be promoted by: (i) using diluted solutions to move equilibrium from dimeric **C** to monomeric **A** and **B**; (ii) using Brønsted bases, for example an amine, to shift the equilibrium from unreactive **B** to reactive **A**.

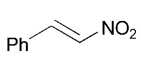
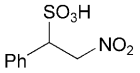
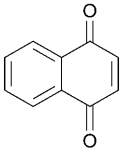
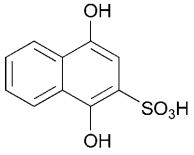
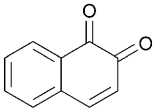
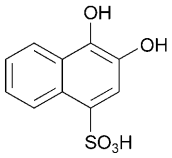
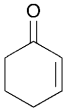
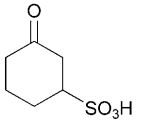
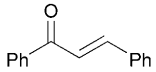
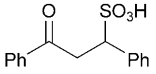
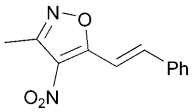
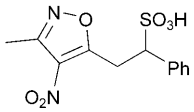
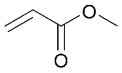
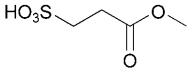
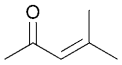
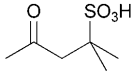
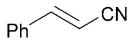
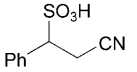
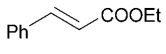
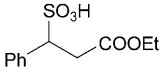
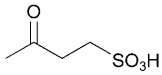
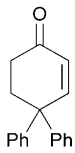
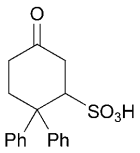
In analogy with the phosphonate–phosphite tautomerism,[16] it was thought that triethylamine may have an effect on the **A**–**B** equilibrium towards the most reactive species **A**, increasing therefore the reaction rate with electrophilic alkenes. With this in mind, we have tested the effect of bisulfite concentration and basic catalysis independently (Scheme 2 and Table 1). Initial studies run using commercial aqueous sodium bisulfite (5 M) showed that amines accelerated the reaction rate. Reaction of chalcone **1** (Scheme 2) with a large excess of bisulfite at room temperature gave limited conversion (Table 1, entry 1), however, when chalcone **1** was reacted with 10 equivalents of bisulfite and 10 equivalents of triethylamine, the reaction proceeded to full conversion within an hour (Table 1, entry 2). Use of lower amounts of triethylamine gave incomplete conversions or longer reaction times. This procedure allowed the reaction of a few alkenes at room temperature although in order to get high conversions and yields large excesses of both reagents were needed.[17] Secondary amines such as piperidine and pyrrolidine gave equally a full conversion at room temperature but required longer reaction times. Having established that amines had an effect on the reaction rate we then investigated the role of bisulfite concentration. Importantly, the use of a diluted solution of bisulfite (0.5 M) allowed us to obtain a 50% conversion of chalcone **1** in 18 h using only 1.2 equivalents of bisulfite and 0.2 equivalents of triethylamine (Table 1, entry 3). The reaction efficiency increased when THF was replaced by methanol. Hence, reaction of chalcone **1** with 1.2 equivalents of bisulfite and 0.2 equivalents of triethylamine (Table 1, entry 4) proceeded to full conversion in 18 h. Significantly, the same reaction excluding triethylamine (Table 1, entry 5) gave negligible conversion after 360 hours (15 days), demonstrating the rate acceleration imparted by triethylamine. The novel procedure identified was complemented by a straight-forward method of purification. The pure sulfonic acid was therefore obtained by passing the crude material through a plug of freshly activated acidic ion exchange resin. With the optimised reaction conditions in hand, the reactivity of other electrophilic olefins was explored (Table 2). The new conditions were highly effective and sulfonylation of strong electrophilic alkenes, for instance, β-nitrostyrene **3**, was complete in minutes in the presence of only 10 mol% of triethylamine (Table 2, entry 1). Noteworthy, the sulfonylation of substrates **5** and **7** arose from a nucleophilic process rather than an electrophilic substitution (Table 2, entries 2 and 3).[18] Less reactive electrophiles (Table 2, entries 4–7) reacted equally well proceeding to a full conversion in 18–24 h, using 20 mol% of triethylamine (entries 4–7). Less activated olefins showed a significantly lower reactivity (entry 8–12), not achieving a full conversion after four days (entries 8–12) under the conditions used.[19] 4-Methyl-3-penten-2-one **15** (entry 8) and methylvinylketone **21** (entry 11) reacted at room temperature with bisulfite (1.2 equiv.) in the presence of a slight excess of triethylamine (1.2 equiv.) giving the corresponding sulfonic acids **16** and **22** in high yields.[19] However, when the catalyst loading was limited to 0.2 equiv., the reaction rate was significantly slower and sulfonic acids **16** and **22** were obtained in poor yields (Table 2, entries 8 and 11).

Table 1. Optimization of the reactions conditions for the direct sulfonylation of chalcone **1**.[a]

Entry	Equiv of $NaHSO_3$	Equiv of Et_3N	t [h]	Conv.[b] [%]
1[c]	10 (5 M)	–	6	<10%
2[c]	10 (5 M)	10	1	>98%
3[c]	1.2 (0.5 M)	0.2	18	<50%
4[d]	1.2 (0.5 M)	0.2	18	>98%
5[d]	1.2 (0.5 M)	–	360	<10%
6[d]	1.2 (0.5 M)	0.2	18	>98%

[a] Reactions carried out in a test tube on a 0.1-mmol scale.
[b] Conversion evaluated by ^{1}H NMR analysis run on the crude reaction mixture.
[c] THF used as solvent.
[d] MeOH used as solvent.

Table 2. Screening of the olefins for the catalytic sulfonylation reaction.[a,b]

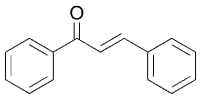
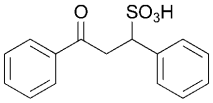
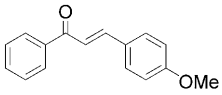
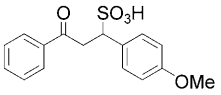
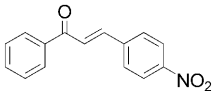
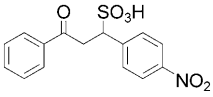
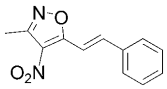
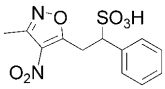
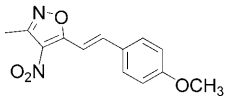
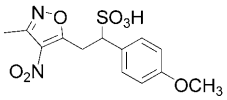
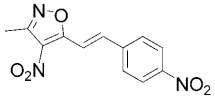
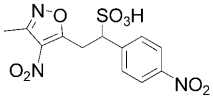
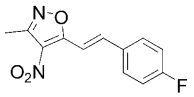
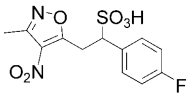
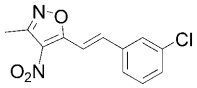
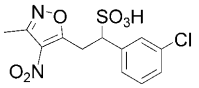
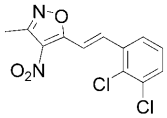
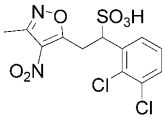
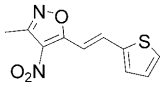
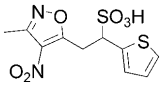
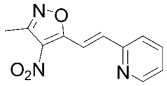
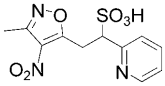
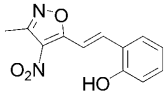
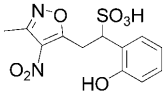
Entry		Reagent		Product	*t*	Yield [%][c]
1[d]	**3**		**4**		10 min	89
2[d]	**5**		**6**		10 min	87
3[d]	**7**		**8**		10 min	86
4	**9**		**10**		21 h	96
5	**1**		**2**		21 h	85
6	**11**		**12**		24 h	96
7	**13**		**14**		40 h	84
8	**15**		**16**		4d	18
9	**17**		**18**		4d	15
10	**19**		**20**		4d	16
11	**21**		**22**		4d	18
12	**23**		**24**		4d	15

[a] Reactions carried out in a test tube without any precautions to exclude moisture and air, by means of 0.1 mmol of alkene, 0.12 mmol of aqueous sodium bisulfite (0.5 M) and 0.04 mmol of Et_3N in 2 mL of MeOH at 22 °C.
[b] A full characterisation of the pure sulfonic acids obtained is included in the Supporting Information.
[c] Isolated yield after passing the crude through freshly activated acidic ion exchange resin.
[d] Reaction performed with 10 mol% of Et_3N.

The scope of the catalytic sulfonylation reaction was therefore demonstrated by reacting several chalcones **1** and styryl nitroisoxazole **2**.[4,20]

Compounds **1**, **25** and **27** showed an excellent reactivity furnishing the corresponding products **2**, **26** and **28** in good yields (83–87%, Table 3, entries 1–3) and in 18–36 h regardless of the presence of either a strong electron-donating or electron-withdrawing group on the aromatic ring (Table 3, entries 2 and 3). Styryl nitroisoxazole **11** and derivatives showed slower reactivity compared to chalcones,[21] nevertheless giving the corresponding sulfonic acid in excellent yields (Table 3, entries 4–12). The reaction conditions were tolerable to a great variety of functional groups.

Table 3. Catalytic sulfonylation reactions of chalcones **1** and styryl nitroisoxazole **2**.[a]

Entry		Reagent		Product	*t* [h]	Yield [%][b]
1	**1**		**2**		21	85
2	**25**		**26**		36	87
3	**27**		**28**		36	83
4	**11**		**12**		42 (36)[c]	97 (99)[c]
5	**29**		**30**		90	97
6	**31**		**32**		75	99
7	**33**		**34**		36	98
8	**35**		**36**		36	99
9	**37**		**38**		42	93
10	**39**		**40**		48	99
11	**41**		**42**		36	91
12	**43**		**44**		75	88

[a] Unless otherwise noted, the reactions were carried out in a test tube without any precautions to exclude moisture and air, by means of 0.2 mmol of alkene, 0.3 mmol of aqueous sodium bisulfite (0.5 M) and 0.04 mmol of Et_3N in 2 mL of MeOH at 17 °C.

[b] Isolated yield after passing the crude material through freshly activated acidic ion exchange resin.

[c] Value in brackets refers to the reaction carried out on a 7-mmol scale.

Alkenes **11** bearing either an electron-donating or an electron-withdrawing group reacted equally well furnishing high yields of the desired sulfonic acid (97–99%, Table 3, entries 5 and 6); alkenes **11** carrying an halogen-substituted aromatic ring or an heteroaromatic group, for example **35** and **39** gave the corresponding sulfonic acids in excellent yields (93–99%, Table 3, entries 7–10). Remarkably, also acidic or basic functional groups were well tolerated and the corresponding products were obtained in 91% and 88% yields (Table 3, entries 11 and 12). The robust protocol introduced was further supported in a preparative-scale reaction, where **11** was obtained in 99% yields on a 7-mmol scale-reaction producing 2 grams of pure sulfonic acid after 36 h (Table 3, entry 4, values in brackets).

In conclusion, we have established a procedure which allowed the preparation of complex sulfonic

acids by the direct sulfonylation of activated olefins.[22] The procedure herein reported is significant for the following reasons: (i) it runs at room temperature; (ii) makes use of only slight excesses of bisulfite; (iii) it is catalysed by simple amines, for example, triethylamine; (iv) it is complemented by an easy purification method; (v) the method allows for the multi-gram preparation of sulfonic acids.

Further studies on the enantioselective version of this process are currently in process.

Experimental Section

General Procedure

In a test tube equipped with a magnetic stirring bar were added in sequence olefins **1**, **11**, **25**, **27**, **29**, **31**, **33**, **35**, **37**, **39**, **41** or **42** (0.20 mmol), MeOH (2.0 mL), triethylamine (5.5 μL, 0.04 mmol), and 0.5 M aqueous sodium bisulfite (0.6 mL, 0.3 mmol). The reaction mixture was vigorously stirred at 17 °C for the stated time. The crude mixture was filtered off over a celite pad and then dried under reduced pressure. The crude product was then passed through a plug of freshly activated acidic ion exchange resin and washed with deionized water (3×3 mL).[23] Finally, pure sulfonic acid was obtained by drying the aqueous solution under reduced pressure and in high vacuum.

3-Oxo-1,3-diphenylpropane-1-sulfonic acid (2): Off white solid; yield: 49.3 mg (85%); mp 175–177 °C; ^{1}H NMR (400 MHz, MeOD): δ = 7.96–7.92 (m, 2H), 7.60–7.53 (m, 1H), 7.51–7.42 (m, 4H), 7.30–7.19 (m, 3H), 4.69 (dd, J = 9.5, 4.3 Hz, 1H), 3.97 (dd, J = 17.4, 4.3 Hz, 1H), 3.88 (dd, J = 17.5, 9.5 Hz, 1H); ^{13}C NMR (100 MHz, MeOD): δ = 198.8, 138.1, 138.0, 134.4, 130.5, 129.7, 129.1, 129.0, 128.5, 63.2, 41.6; HR-MS: m/z = 291.0700, $C_{15}H_{15}O_4S$ $[M+H]^+$ requires 291.0691.

1-(4-Methoxyphenyl)-3-oxo-3-phenylpropane-1-sulfonic acid (26): Yellow solid; yield: 55.7 mg (87%); mp 186–188 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.97–7.89 (m, 2H), 7.60–7.52 (m, 1H), 7.50–7.41 (m, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.64 (dd, J = 9.6, 4.2 Hz, 1H), 3.93 (dd, J = 17.3, 4.2 Hz, 1H), 3.83 (dd, J = 17.3, 9.6 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 198.0, 160.7, 138.2, 134.5, 131.6, 129.9, 129.8, 129.2, 114.6, 62.7, 55.7, 41.8; HR-MS: m/z = 319.0646, $C_{16}H_{15}O_5S$ $[M-H]^-$ requires 319.0640.

1-(4-Nitrophenyl)-3-oxo-3-phenylpropane-1-sulfonic acid (28): Pale yellow solid ; yield: 55.6 mg (83%); mp 173–175 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 8.09 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 7.66–7.58 (m, 3H), 7.51 (t, J = 7.7, 7.7 Hz, 2H), 4.34 (dd, J = 9.9, 3.9 Hz, 1H), 3.9 (dd, J = 17.9, 4.0 Hz, 1H), 3.75 (dd, J = 17.8, 9.9 Hz, 1H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ = 197.5, 147.3, 146.0, 136.4, 133.2, 130.4, 128.7, 127.9, 122.5, 61.0, 40.8; HR-MS: m/z = 334.0374, $C_{15}H_{12}NO_6S$ $[M-H]^-$ requires 334.0385.

2-(3-Methyl-4-nitroisoxazol-5-yl)-1-phenylethanesulfonic acid (12): Off white solid; yield: 60.6 mg (97%); mp 176–178 °C; ^{1}H NMR (400 MHz, MeOD): δ = 7.47–7.39 (m, 2H), 7.31–7.20 (m, 3H), 4.55 (dd, J = 10.0, 6.0 Hz, 1H), 4.12 (dd, J = 15.4, 6.0 Hz, 1H), 4.05 (dd, J = 15.4, 10.0 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 173.4, 156.7, 136.6, 131.7, 130.3, 129.2, 129.1, 64.0, 31.1, 11.5; HR-MS: m/z = 311.0329, $C_{12}H_{11}N_2O_6S$ $[M-H]^-$ requires 311.0338.

1-(4-Methoxyphenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethanesulfonic acid (30): Pale brown solid; yield. 66 mg (97%); mp 191–193 °C; ^{1}H NMR (400 MHz, MeOD): δ = 7.34 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.50 (dd, J = 10.1, 6.0 Hz, 1H), 4.09 (dd, J = 15.3, 6.0 Hz, 1H), 4.02 (dd, J = 15.3, 10.2 Hz, 1H), 3.74 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 173.5, 161.0, 156.8, 131.7, 131.4, 128.3, 114.6, 63.3, 55.6, 31.1, 11.5; HR-MS: m/z = 341.0430, $C_{13}H_{13}N_2O_7S$ $[M-H]^-$ requires 341.0443.

2-(3-Methyl-4-nitroisoxazol-5-yl)-1-(4-nitrophenyl)ethanesulfonic acid (32): Pale brown solid; yield: 71 mg (99%); mp 193–195 °C; ^{1}H NMR (400 MHz, MeOD): δ = 8.17 (d, J = 8.9 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 4.70 (dd, J = 10.1, 5.7 Hz, 1H), 4.21 (dd, J = 15.7, 5.7 Hz, 1H), 4.05 (dd, J = 15.6, 10.1 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 172.9, 156.9, 149.0, 144.6, 131.6, 124.2, 63.3, 31.0, 11.5; HR-MS: m/z = 356.0202, $C_{12}H_{10}N_3O_8S$ $[M-H]^-$ requires 356.0189.

1-(4-Fluorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethanesulfonic acid (34): Off white solid; yield: 64.7 mg (98%); mp 165–168 °C; ^{1}H NMR (400 MHz, MeOD): δ = 7.50–7.40 (m, 2H), 7.05–6.94 (m, 2H), 4.55 (dd, J = 10.24, 5.76 Hz, 1H), 4.12 (dd, J = 15.41, 5.76 Hz, 1H), 4.01 (dd, J = 15.4, 10.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 173.3, 163.9 (d, J = 245 Hz), 156.8, 132.8 (d, J = 3 Hz), 132.2 (d, J = 8 Hz), 131.7, 115.9 (d, J = 22 Hz), 63.1, 31.1, 11.5; HR-MS: m/z = 329.0233, $C_{12}H_{10}FN_2O_6S$ $[M-H]^-$ requires 329.0244.

1-(3-Chlorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethanesulfonic acid (36): Off white solid; yield: 68.6 mg (99%); mp 118–120 °C; ^{1}H NMR (400 MHz, MeOD): δ = 7.57–7.43 (m, 1H), 7.41–7.30 (m, 1H), 7.29–7.19 (m, 2H), 4.54 (dd, J = 10.1, 5.8 Hz, 1H), 4.13 (dd, J = 15.5, 5.8 Hz, 1H), 4.00 (dd, J = 15.4, 10.1 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 173.1, 156.8, 139.1, 135.0, 131.7, 130.7, 130.3, 129.1, 128.8, 63.4, 31.0, 11.5; HR-MS: m/z = 344.9940, $C_{12}H_{10}ClN_2O_6S$ $[M-H]^-$ requires 344.9948.

1-(2,3-Dichlorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)-ethanesulfonic acid (38): Pale yellow solid; yield: 71 mg (93%); ^{1}H NMR (400 MHz, MeOD): δ = 7.77 (dd, J = 7.9, 1.5 Hz, 1H), 7.4 (dd, J = 8.0, 1.5 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 5.36 (dd, J = 10.4, 5.5 Hz, 1H), 4.17 (dd, J = 15.4, 5.5 Hz, 1H), 3.97 (dd, J = 15.4, 10.4 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 172.8, 156.9, 137.3, 134.4, 133.9, 131.7, 131.1, 128.9, 128.5, 59.4, 31.4, 11.5; HR-MS: m/z = 378.9551, $C_{12}H_9Cl_2N_2O_6S$ $[M-H]^-$ requires 378.9558.

2-(3-Methyl-4-nitroisoxazol-5-yl)-1-(thiophen-2-yl)ethanesulfonic acid (40): Pale brown solid; yield after 48 h: 63 mg (99%); mp 128–130 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.33–7.24 (m, 1H), 7.10–7.03 (m, 1H), 6.92 (dd, J = 5.1, 3.6 Hz, 1H), 4.84 (dd, J = 10.2, 5.6 Hz, 1H), 4.13 (dd, J = 15.3, 5.6 Hz, 1H), 3.98 (dd, J = 15.3, 10.3 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 173.0, 156.8, 138.5, 131.8, 128.7, 127.4, 126.7, 59.4, 32.6, 11.5; HR-MS: m/z = 316.9912, $C_{10}H_9N_2O_6S_2$ $[M-H]^-$ requires 316.9902.

2-(3-Methyl-4-nitroisoxazol-5-yl)-1-(pyridin-2-yl)ethanesulfonic acid (42): White solid; yield: 57 mg (91%); mp 250 °C (dec.); ^{1}H NMR (400 MHz, D_2O): δ = 8.72 (d, J = 4.9 Hz, 1H), 8.45 (t, J = 8.0 Hz, 1H), 8.10 (d, J = 8.1 Hz,

1H), 5.08 (dd, $J=8.3$, 6.8 Hz, 1H), 4.35 (dd, $J=16.1$, 6.7 Hz, 1H), 4.13 (dd, $J=16.1$, 8.6 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, D_2O): $\delta=173.6$, 159.8, 152.7, 148.1, 146.8, 133.7, 129.7,129.3, 63.4, 31.0, 13.6; HR-MS: $m/z=312.0296$, $C_{11}H_{10}N_3O_6S$ $[M-H]^-$ requires 312.0290.

1-(2-Hydroxyphenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethanesulfonic acid (44): Pale brown solid; yield: 58 mg (88%); mp 150–152 °C; ^{1}H NMR (400 MHz, CD_3OD): $\delta=7.52$ (d, $J=7.8$ Hz, 1H), 7.0 (t, $J=7.3$ Hz, 1H), 6.78 (t, $J=7.5$ Hz, 1H), 6.70 (d, $J=8.1$ Hz, 1H), 5.19 (dd, $J=10.7$, 5.4 Hz, 1H), 4.12 (dd, $J=14.8$, 5.4 Hz, 1H), 3.94 (dd, $J=14.8$, 10.7 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): $\delta=173.5$, 156.9, 156.6, 131.7, 130.1, 130.0, 122.9, 120.5, 116.6, 56.4, 31.0, 11.5; HR-MS: $m/z=327.0285$, $C_{12}H_{11}N_2O_7S$ $[M-H]^-$ requires 327.0287.

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[21] In other studies, styryl nitroisoxazoles **2** showed faster reactivity compared to chalcones; in this context the slower reactivity observed is attributed to the poor solubility of these starting materials in the hydroalcoholic medium.
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[23] A 5-mL syringe packed with acidic ion exchange resin (3 mL, *ca.* 2.2 g) was washed with 6M HCl (4×3 mL) and then with deionized water (4×3 mL). After that the resin pad was ready to be used.

