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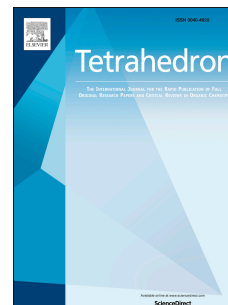
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An experimental investigation into the kinetics and mechanism of the aza-Michael additions of dimethyl itaconate

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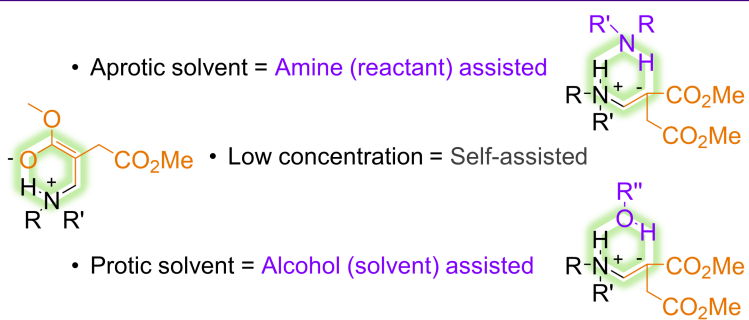
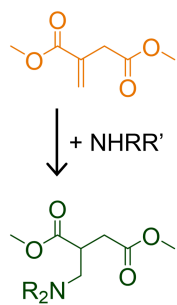
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Aza-Michael addition: New mechanistic insights



Journal Pre-proof

An experimental investigation into the kinetics and mechanism of the aza-Michael additions of dimethyl itaconate

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Abstract

The aza-Michael addition is a versatile reaction for the modification of α,β -unsaturated carbonyl compounds with amines. The reactivity of dimethyl itaconate as a bio-based Michael acceptor is explored in this work. Through its reactions with piperidine and dibutylamine, it was found that the order of reaction can be changed by the choice of catalyst, solvent, or the concentration of the amine reactant. The effectiveness of catalysts was proportional to their Lewis acidity. Competitive isomerisation of dimethyl itaconate into unreactive regioisomers can be suppressed using low-polarity solvents and lower temperatures. This investigation of the aza-Michael additions of dimethyl itaconate has clarified the possible reaction mechanisms and optimised the protocol, supporting further use of this reaction in small molecule synthesis and modification of polymers.

Keywords

Michael addition; Kinetics; Catalysis; Solvent effect

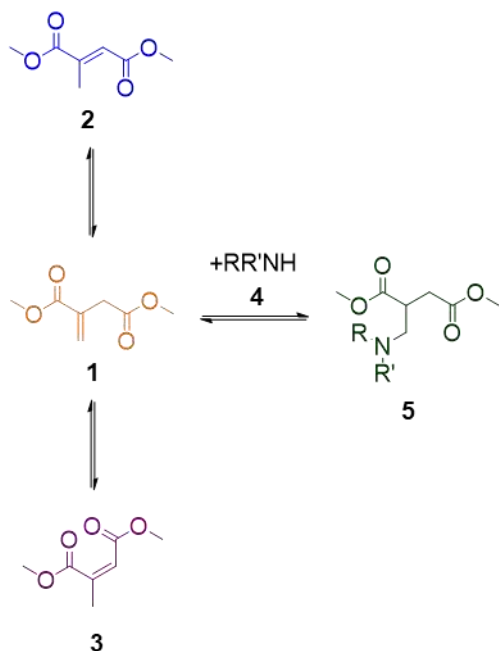
1. Introduction

Itaconic acid is an unsaturated dicarboxylic acid and a valuable bio-based chemical intermediate. Itaconic acid is produced from carbohydrates by microbial fungi fermentation.¹ The production of bio-based polymers from itaconic acid is of major interest,² as is the synthesis of small multifunctional molecules.³ The modification of itaconate polyesters by addition reactions has recently been explored as a means of modifying material properties.^{4,5,6,7,8} The conventional Michael addition undertaken by a nucleophilic carbanion (Michael donor) onto an α,β -unsaturated carbonyl compound (Michael acceptor) is well studied. As summarised by Mather,⁹ the Michael addition is base-catalysed with a rate limiting bimolecular 1,4-addition step.

Michael-type additions, such as those between an amine and a Michael acceptor (hereafter described as an aza-Michael addition) are commonplace in organic synthesis (Scheme 1). It is suggested from the calculated reaction intermediates (via a Density Functional Theory model) that the aza-Michael addition onto acrylates occurs via a third order reaction. A second amine molecule stabilises proton transfer in a 1,2-addition.^{10,11} Experimental evidence of a trimolecular, entropy-controlled reaction of nitroethylenes with amines has also been reported.¹² Thus the Michael addition and aza-Michael addition have fundamental differences. A base

40 catalyst is not required for aza-Michael additions, and instead Lewis acids are commonly used as catalysts.¹³
 41 Iodine is particularly interesting as an effective catalyst, owing to its ability to form halogen bonds.^{14,15,16,17}
 42 Furthermore, iodine can be supported on alumina or silica to aid recyclability.¹⁸

43



44

45 Scheme 1. The reaction of dimethyl itaconate (**1**) to form its isomers dimethyl mesaconate (**2**) and dimethyl citraconate
 46 (**3**) and reaction with an amine (**4**) to give a dimethyl 2-(dialkylamino)methyl butanedioate (**5**).

47

48 Alcohols are commonly used as solvents for aza-Michael additions, having previously been shown to provide
 49 rate enhancements.^{19,20,21} Solvents that do not interact as strongly with the reactants, e.g. hydrocarbons and
 50 hydrochlorocarbons, are preferred in asymmetric syntheses to preserve high stereoselectivity, sometimes at
 51 the expense of yields.^{22,23,24} It is not known if the assumed third order mechanism of aza-Michael addition
 52 applies to itaconates, or under what conditions the mechanism may change to accommodate catalysts or
 53 (hydrogen bonding) solvents.

54 In this work, the aza-Michael addition of dimethyl itaconate (**1**) has been studied to clarify its specific
 55 reaction pathways and inform future studies. Itaconic acid and its esters may be subject to isomerisation
 56 under certain conditions. **1** can form dimethyl mesaconate (**2**) and dimethyl citraconate (**3**), which have
 57 previously been shown to be unreactive towards amines (**4**).²⁵ Therefore, it was of interest to understand
 58 the equilibria between isomers **1-3**. Regarding the aza-Michael addition itself, the influence of **4** on the rate
 59 of reaction has been evaluated, as has the role of catalysts, solvents, and reaction temperature on the
 60 formation of the aza-Michael adduct (**5**). This fundamental mechanistic information has been used to
 61 develop an understanding of the mechanism and permit reaction optimisation on a challenging (i.e.,
 62 sterically hindered) substrate.

63

64 **2. Results and Discussion**65 **2.1 Isomerisation of dimethyl itaconate**

66 Dimethyl itaconate (**1**) has 2 common regioisomers: dimethyl mesaconate (**2**) and dimethyl citraconate (**3**).
 67 The regioisomerisation is not spontaneous and no isomers of **1** were present in the start material. However,
 68 amines catalyse the isomerisation of **1**, and so by performing an aza-Michael addition, isomers of **1** are likely
 69 to be formed.²⁵ Fortunately, the aza-Michael addition was observed only to occur on the itaconate isomer
 70 under the conditions used in this work. A methyl group sterically blocks addition reactions onto **2** or **3**. By
 71 contrast, fumarates do undergo Michael additions.²⁵

72 The isomerisation of **1** in the presence of non-nucleophilic amines and Lewis acids was observed by ¹H NMR
 73 spectroscopy after 24 hours at 30 °C without an auxiliary solvent (Table 1 and Figure S1). Lewis acids do not
 74 catalyse the isomerisation of **1** without the addition of an amine (Table 1 entries 1-3). The weak base
 75 pyridine also did not cause the isomerisation of **1** (Table 1 entry 4). A 2.5 mol% loading of triethylamine (TEA)
 76 resulted in 7% conversion from **1** to **2**, increasing to 25% conversion with 1 equivalent of triethylamine
 77 present (Table 1 entries 5-6). Cooperative catalysis by a Lewis acid in the presence of triethylamine (1
 78 equivalent) modestly increased the proportion of **2** (Table 1 entries 7-9). The stronger base 1,8-
 79 diazabicyclo[5.4.0]undec-7-ene (DBU) was more effective, and able to convert 67% of **1** into **2** within 24
 80 hours, and additionally 3% conversion to **3** was observed (Table 1 entry 10). Reactions with 1 equivalent of
 81 DBU caused the decomposition of **1** and were not pursued further. When DBU (2.5 mol%) was used in
 82 conjunction with a Lewis acid, the proportion of **2** present was reduced (Table 1 entries 11-13), the opposite
 83 of what occurred with triethylamine. This is likely to be caused by an acid-base interaction between DBU and
 84 the Lewis acid, reducing the basicity of DBU and preventing the desired coordination between the Lewis acid
 85 and **1**.

86

87 Table 1. Catalysed isomerisation of dimethyl itaconate (**1**) to dimethyl mesaconate (**2**). Visualised data is provided as
 88 ESI, Figure S1.

Entry	Lewis acid (2.5 mol%)	Base (mol%)	Molar ratio		
			1	2	3
1	Iodine	None	100%	0%	0%
2	Scandium triflate	None	100%	0%	0%
3	Zinc chloride	None	100%	0%	0%
4	None	Pyridine (2.5%)	100%	0%	0%
5	None	TEA (2.5%)	93%	7%	0%
6	None	TEA (100%)	75%	25%	0%
7	Iodine	TEA (100%)	67%	33%	0%
8	Scandium triflate	TEA (100%)	54%	45%	2%
9	Zinc chloride	TEA (100%)	70%	30%	0%
10	None	DBU (2.5%)	30%	67%	3%
11	Iodine	DBU (2.5%)	78%	22%	1%
12	Scandium triflate	DBU (2.5%)	72%	27%	1%
13	Zinc chloride	DBU (2.5%)	90%	10%	0%

89

90 In the absence of solvent, 77% conversion to **2** can be achieved in the presence of TEA (but only after 1
 91 month). The internal alkene of **2** is therefore more stable than the terminal alkene of **1** but the isomerisation
 92 has a high activation barrier that requires a catalyst to overcome. Anticipating that most transformations of
 93 itaconates will require a solvent, the influence of the solvent on the equilibria between **1**, **2**, and **3** was

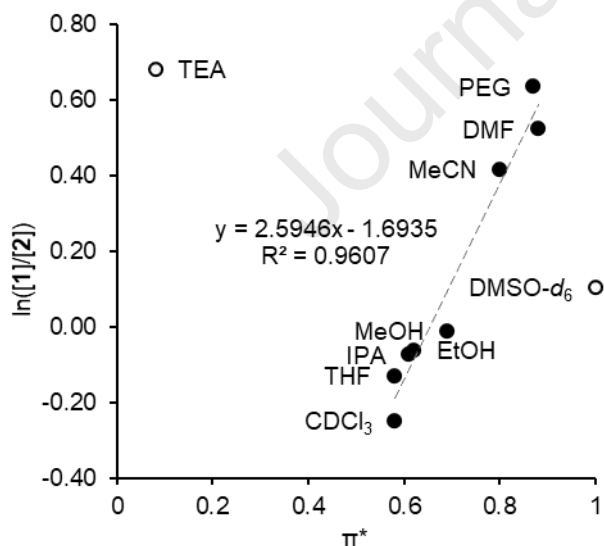
94 explored (Figure 1 and Figure S2). A linear solvation energy relationship (LSER) describes the effect of
 95 solvent polarity on chemical phenomena, typically rate constants (k) and equilibrium constants (K). Solvent
 96 polarity is usually described for this purpose using the Kamlet-Abboud-Taft solvatochromic parameters. A
 97 combination of hydrogen bond donating ability (α), hydrogen bond accepting ability (β) and dipolarity (π^*)
 98 can be used to quantify solvent effects.²⁶ Solutions of **1** in the presence of triethylamine (1 eq.) were stirred
 99 at 30 °C for 2 weeks. At this time, the equilibrium was reached or was approaching equilibrium based on
 100 analysis at earlier intervals. The proportion of **3** was small across this study of ten solvents, so as an
 101 approximation, a simple equilibrium between **1** and **2** was presumed to construct the LSER. In eight solvents,
 102 $\ln(K)$ was proportional to π^* : methanol (MeOH), ethanol (EtOH), isopropanol (IPA), tetrahydrofuran (THF),
 103 *N,N*-dimethyl formamide (DMF), acetonitrile (MeCN), polyethylene glycol-400 (PEG), and chloroform-*d*
 104 (CDCl_3) (Figure 1). The most effective solvent (PEG) resulted in 64% conversion, and conversely only 43%
 105 conversion to **2** was achieved in CDCl_3 . This solvent effect (i.e., proportionality with π^*) is also observed in
 106 keto-enol tautomerisation. It was previously found that keto tautomers are more stable in dipolar solvents,
 107 and the equilibrium begins to favour the enol tautomer in less polar solvents (with a low π^* value).²⁷ If the
 108 base catalysed isomerisation of **1** into **2** occurs via an enol or enolate, low polarity solvents will stabilise the
 109 enol tautomer of **1** and reduce the equilibrium constant.

110

(a) Reaction scheme



(b) LSER



111

112 Figure 1. The relationship between the isomerisation of dimethyl itaconate (**1**) to dimethyl mesaconate (**2**) and solvent
 113 dipolarity. (a) Reaction scheme. (b) Linear solvation energy relationship (LSER).

114

115 There were two exceptions to the correlation in Figure 1. Excess TEA in the role of the solvent produced a
 116 high concentration of **2** (66% conversion) relative to its dipolarity. This cannot be directly attributed to the
 117 catalytic nature of TEA, but the excess base may create an environment conducive to an alternative
 118 mechanism. By contrast, deuterated dimethyl sulphoxide (DMSO- d_6) produced a lower equilibrium constant

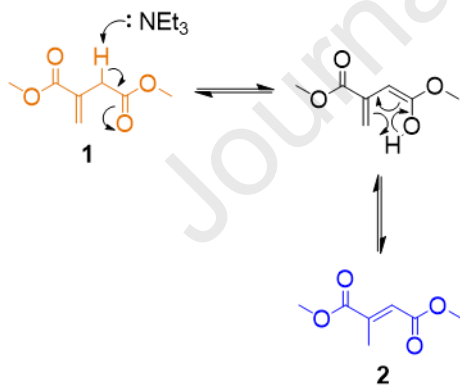
119 than predicted from its dipolarity. The solution turned a dark purple colour, which is indicative of side
 120 reactions.

121 Previous reports of fumarate-maleate isomerisation in the presence of amines show the reaction is third
 122 order, catalysed by nucleophilic primary and secondary amines but not tertiary amines.^{28,29,30} Isomerisation
 123 of itaconate esters must occur by a different mechanism in which tertiary amines can participate. The
 124 greater rate of isomerisation of **1** caused by DBU compared to triethylamine, and no reaction in the presence
 125 of pyridine, implies base catalysis. Additional kinetic experiments were conducted with triethylamine in
 126 either isopropanol (IPA) or tetrahydrofuran (THF) applying the Variable Time Normalisation Analysis of Burés
 127 (Figure S3).³¹ At 50 °C the observed reaction is consistent with a bimolecular mechanism, first order with
 128 respect to **1** and first order with respect to catalyst (triethylamine), in either solvent. By contrast, fumarate
 129 isomerisation is second order with respect to amine concentration, with one equivalent of amine acting as a
 130 nucleophile and the second equivalent of amine transferring a proton. The reaction has a greater rate
 131 constant in IPA than THF, although both were slow to progress. Conversely, further reactions in ethanol and
 132 DMSO-*d*₆ progressed rapidly, quickly reaching the presumed equilibrium and thus unsuitable for accurate
 133 kinetic studies under equivalent conditions to the reactions already performed in IPA and THF.

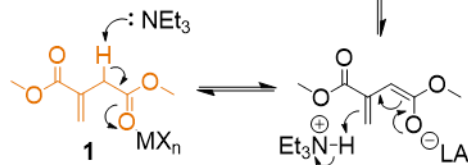
134 As represented in Scheme 2, the kinetic analysis suggests deprotonation of **1** by a base will result in an enol
 135 that undergoes rearrangement. A low energy cyclic transition state favours the formation of **2**. The
 136 formation of **3** was limited, when observed at all. The ability of a Lewis acid to modify the observed quantity
 137 of **2** after 24 hours (see Table 1) implies an interaction with a Lewis acid may also have a role, potentially
 138 stabilising an enolate intermediate.

139

(a) *Base catalysed*



(b) *Base and Lewis acid catalysed*



140

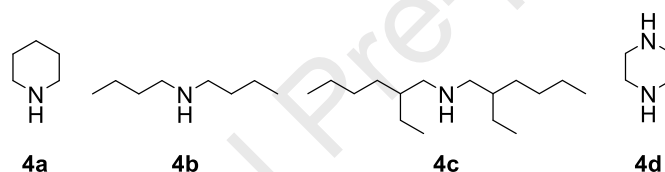
141 Scheme 2. Isomerisation of dimethyl itaconate (**1**) to dimethyl mesaconate (**2**) catalysed by (a) triethylamine and (b) co-
 142 catalysed by triethylamine and a Lewis acid represented as LA.

143

144 2.2 Michael donors

145 The reactions of dimethyl itaconate (**1**) with piperidine (**4a**), dibutylamine (**4b**), and *bis*(2-ethylhexyl)amine
 146 (**4c**) (Scheme 3) were performed neat at 30 °C and 50 °C to ascertain the relative reactivity of the three
 147 secondary amines in aza-Michael additions. Primary amines were excluded to avoid secondary
 148 reactions.^{32,33,34} Reactions were once again monitored by ¹H NMR spectroscopy. Increasing the temperature
 149 had a minor effect on conversions to the intended product **5** but did enhance isomerisation (Table 2 and
 150 Figure S4). Piperidine (**4a**) reacted rapidly with **1** at 30 °C, resulting in 85% conversion to dimethyl 2-(1-
 151 piperidinylmethyl)butanedioate (**5a**) in 90 minutes, and 4% conversion to **2** (Table 2 entry 1). An increase in
 152 temperature to 50 °C only slightly improves the conversion to **5a**, reaching 91% after 24 hours (Table 2 entry
 153 4). Dibutylamine (**4b**) is less reactive than **4a**, which can be attributed to steric hindrance (Table 2 entries 5-
 154 8). The conversion is only 3% after 90 minutes regardless of the temperature, improving marginally after 24
 155 hours. The addition of 10 equivalents of **4b** was more effective at promoting the aza-Michael addition at 30
 156 °C than an increase in temperature to 50 °C, but still only 23% conversion to dimethyl 2-
 157 (dibutylamino)methyl butanedioate (**5b**) was observed (Table 2 entry 9). Ultimately we concluded that 30 °C
 158 is an appropriate reaction temperature, for the formation of isomerisation products **2** and **3** is suppressed
 159 and conversion to the intended product is similar to that achieved in reactions at the higher temperature of
 160 50 °C.

161



162

163 Scheme 3. Amine reactants used in this study.

164

165 Table 2. The reactivity of amines (**4**) with dimethyl itaconate (**1**) in solvent-free equimolar reactions (unless otherwise
 166 stated). The complete set of visualised data is provided as ESI, Figure S4.

Entry	Duration /hours	Temp. /°C	Amine	Molar ratio			
				1	2	3	5
1	1.5	30	4a	11%	4%	0%	85%
2	24	30	4a	1%	4%	0%	95%
3	1.5	50	4a	7%	8%	0%	86%
4	24	50	4a	1%	8%	0%	91%
5	1.5	30	4b	86%	10%	0%	3%
6	24	30	4b	45%	45%	2%	8%
7	1.5	50	4b	74%	24%	0%	3%
8	24	50	4b	27%	61%	2%	11%
9	24	30	4b ^a	35%	40%	1%	23%
10	24	30	4d ^b	1%	4%	0%	94%

167

a. Ten equivalents of **4b**.

168

b. 0.5 equivalents of **4d**.

169

170 The reactions of **4c** were unsuccessful, with a slow rate of isomerisation to **2** but no aza-Michael addition
 171 observed (Figure S4). The reaction of **1** with 0.5 equivalents of piperazine (**4d**) progressed rapidly at 30 °C

172 despite poor mixing of the solid reactants (Table 2 entry 10). A white crystalline solid was isolated (*N,N'*-
 173 *bis*(dimethyl 2-methylene butanedioate) piperazine, **5d**) which was characterised and consistent with the
 174 double aza-Michael addition of diamine **4d**.

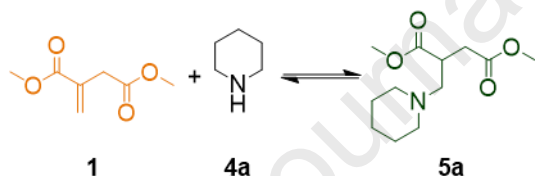
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176 2.3 Solvent effects

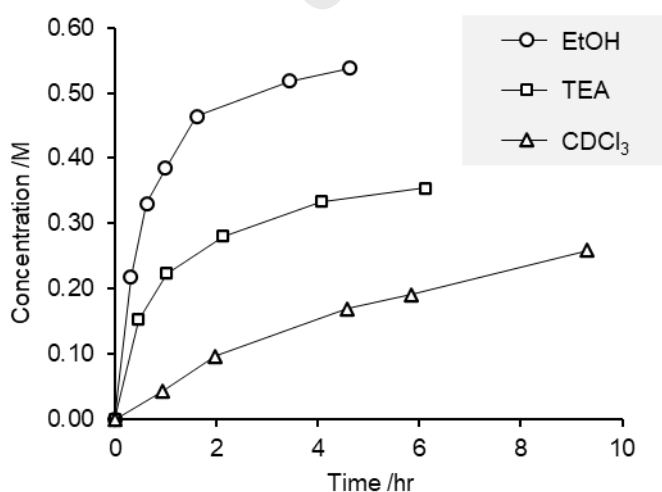
177 Given that the aza-Michael addition between **1** with **4a** is fast, this reaction was chosen for the study of
 178 solvent effects. The time scale of the uncatalysed reaction becomes suitable for kinetic analysis at low
 179 concentrations of the reactants. The formation of **5a** was conducted in the same ten solvents used to study
 180 the isomerisation of **1** (Section 2.1). Benzyl benzoate was added as an internal standard to calculate the
 181 concentration of the reaction components by ¹H NMR spectroscopy. Formation of **5a** was most rapid in the
 182 primary alcohols and dipolar aprotic solvents DMF and DMSO-*d*₆, although conversions were ultimately
 183 higher in methanol and ethanol (Figure S5). The remaining solvents performed similarly with the exception
 184 of CDCl₃, in which the reaction is considerably slower (Figure 2). It was expected that TEA would accelerate
 185 the reaction,¹² but no benefit over non-basic solvents was found. Although TEA catalyses the isomerisation
 186 of **1** to **2**, the aza-Michael addition is presumably not base catalysed (unlike the conventional Michael
 187 addition), and the possibility of an amine assisted mechanism must operate by other means. The competing
 188 isomerisation to **2** was significant in DMSO-*d*₆ but negligible in methanol, ethanol, and CDCl₃ in particular.
 189 Isomerisation in DMSO-*d*₆ and CDCl₃ followed the trend with π* established in Figure 1. Although
 190 isomerisation can be significant in alcohols (~50% of **2** was observed in previous experiments) the rapid aza-
 191 Michael addition consumes the majority of **1** so that it cannot be converted into **2** or **3**.

192

(a) Reaction scheme



(b) Product concentration



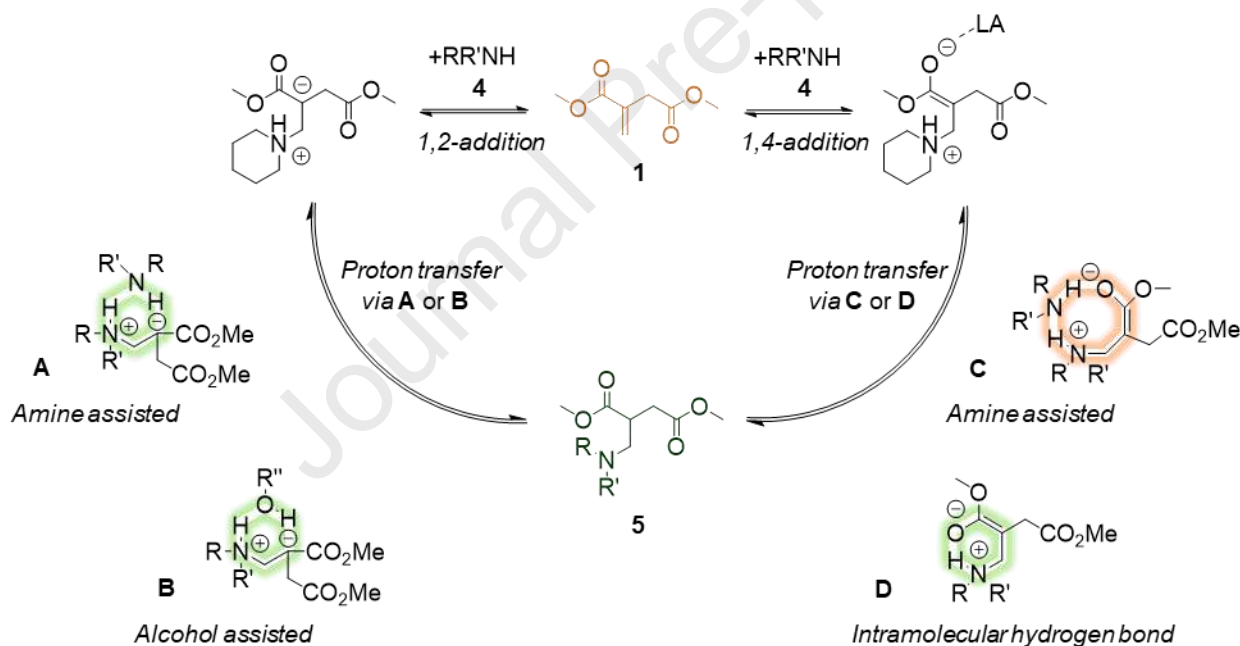
193

194 Figure 2. Production of aza-Michael adduct **5a** in selected solvents from an initial concentration of dimethyl itaconate
 195 (**1**) of 0.6 M. (a) Reaction scheme. (b) Rate of **5a** formation. Additional data is presented in Figure S5.

196

197 The performance of the reaction in secondary alcohol IPA and diol PEG was noticeably different to methanol
 198 and ethanol. These alcohols can be differentiated by their hydrogen bond donating ability (α), with methanol
 199 and ethanol superior in this respect compared to IPA and PEG. Previous work has shown a relationship
 200 between the rate of aza-Michael additions and the pK_a of alcohol solvents.^{Error! Bookmark not defined.} The present
 201 experiments indicate a correlation between the rate of **5a** formation and hydrogen bond donating ability (α)
 202 in alcohol solvents. This supports the hypothesis that proton transfer is rate determining and assisted by
 203 protic solvents.^{Error! Bookmark not defined.} However, in this case the reaction may no longer proceed via a third
 204 order reaction (Scheme 4, species **A**) if a solvent molecule performs the proton transfer in place of an amine
 205 (Scheme 4, species **B**). Furthermore, the relationship between α and reaction rate does not explain the
 206 differences observed between aprotic solvents. To investigate further, the order of reaction was ascertained
 207 in ethanol, IPA, DMSO- d_6 , THF, and $CDCl_3$, again using Variable Time Normalisation Analysis (Figure S6).³¹ The
 208 order of reaction with respect to **1** was always found to be 1 (Table 3). In the aprotic solvents DMSO- d_6 and
 209 THF, the reaction was second order with respect to **4a** and therefore third order overall. As suspected, in
 210 ethanol the reaction was found to be bimolecular (first order with respect to **4a**). This finding suggests a 1,2-
 211 addition is preferred because the stabilisation offered to the 1,4-addition mechanism by a non-reactive
 212 equivalent of amine or alcohol can be expected to be weaker due to the 8-membered ring that is formed
 213 (Scheme 4, species **C**) instead of the more stable 6-membered ring.

214



215

216 Scheme 4. The reaction of dimethyl itaconate (**1**) with an amine (**4**) to give a dimethyl 2-(dialkylamino)methyl
 217 butanedioate (**5**) annotated with intermediates. Cycles are highlighted in green (6-membered ring) or orange (8-
 218 membered ring). There is the possibility of a Lewis acid (LA) interacting with the reaction components.

219

220

221

222

223

224 Table 3. Reaction rate parameters for the reaction between dimethyl itaconate (**1**) and piperidine (**4a**). Visualised data
 225 is provided as ESI, Figure S6-7. Error ranges correspond to 1 standard deviation.

Solvent	Reaction order		Activation parameters		$10^4 \cdot k_{\text{obs}}$ at 30 °C
	1	4a	$\Delta H^\ddagger / \text{kJ} \cdot \text{mol}^{-1}$	$\Delta S^\ddagger / \text{J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$	
EtOH	1	1	30.9±1.0	-203±3	7.25±0.18 dm ³ ·mol ⁻¹ ·s ⁻¹
IPA	1	1.6	26.0±0.6	-226±2	3.48±0.08 dm ^{4.8} ·mol ^{-1.6} ·s ⁻¹
THF	1	2	13.5±0.2	-268±1	2.90±0.06 dm ⁶ ·mol ⁻² ·s ⁻¹
DMSO- <i>d</i> ₆	1	2	n.d. ^a	n.d. ^a	23.9±0.89 dm ⁶ ·mol ⁻² ·s ⁻¹
CDCl ₃ ^b	1	2	n.d. ^a	n.d. ^a	0.88±0.03 dm ⁶ ·mol ⁻² ·s ⁻¹
CDCl ₃ ^c	1	1	n.d. ^a	n.d. ^a	0.30±0.01 dm ³ ·mol ⁻¹ ·s ⁻¹

- 226 a. Not determined.
 227 b. At concentrations of **4a** of 0.5 M and greater.
 228 c. At concentrations of **4a** less than 0.5 M.

229

230 The reaction in IPA did not fit the profile of an overall second or third order rate equation. A non-integer
 231 reaction order of 1.6 with respect to **4a** produced the best data fit (Table 3 and Figure S6). In this example,
 232 the competing bimolecular and trimolecular mechanisms must have a similar rate constant. This will occur if
 233 IPA (bimolecular mechanism, via species **B** of Scheme 4) and **4a** (trimolecular mechanism, via species **A** of
 234 Scheme 4) offer comparable proton transfer stabilisation. The reaction temperature was then varied and
 235 reactions repeated in ethanol, IPA, and THF to obtain the enthalpy and entropy of activation from the Eyring
 236 equation. Both terms decrease as the order of reaction with respect to **4a** increases from 1 to 2 (Figure S7).
 237 In THF, the trimolecular reaction has an enthalpy of activation (ΔH^\ddagger) of 13.5 kJ·mol⁻¹ and an entropy of
 238 activation (ΔS^\ddagger) of -268 J·mol⁻¹·K⁻¹ (Table 3). In ethanol, the enthalpy of activation increases to 30.9 kJ·mol⁻¹
 239 (despite the greater rate constant magnitude), higher than expected for a proton transfer. This may be
 240 explained by the lower basicity of ethanol compared to **4a** which is replaced in the activated complex
 241 (species **B** rather than species **A**, Scheme 4). The reason it is favourable to replace **4a** with the (relatively)
 242 poor proton transfer agent ethanol (or IPA) within the activated complex is the relative increase in the
 243 entropy term to -203 J·mol⁻¹·K⁻¹ (in ethanol, see Table 3). As expected, the bimolecular reaction undergoes a
 244 lesser reduction in entropy (ΔS^\ddagger) compared to the trimolecular reaction. The activation parameters in IPA are
 245 intermediate of ethanol and THF. The non-integer reaction order of 1.6 in IPA did not change at higher
 246 temperatures (Figure S6).

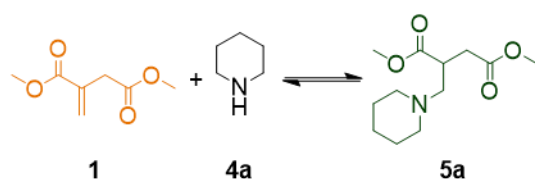
247 Both bimolecular and trimolecular reaction mechanisms are required to explain the reaction kinetics in
 248 CDCl₃. Unlike IPA, in which both mechanisms are simultaneously in operation, a preference for one
 249 mechanism prevails in CDCl₃ depending on the concentration of the reactants. At higher concentrations of
 250 **4a**, a trimolecular reaction, second order with respect to **4a**, accounts for the observed reaction kinetics
 251 (Figure S6). Unexpectedly, even though CDCl₃ will not stabilise proton transfer as an alcohol solvent might,
 252 the kinetic study was consistent with a bimolecular reaction at low initial reactant concentrations. The rate
 253 constant is about a third of the magnitude of the trimolecular reaction in CDCl₃. The bimolecular mechanism
 254 is observed when low reactant concentrations result in a greater rate of reaction than the trimolecular
 255 mechanism (i.e., the derivative of **5a** concentration as a function of time, d[**5a**]/dt, Figure S8). This
 256 observation is consistent with a change of mechanism rather than a change of rate determining step. If the
 257 latter were true, the order of reaction with the slower rate of reaction would be observed. Instead, we can
 258 deduce the entropy-controlled trimolecular reaction becomes unfavourable at low reactant concentrations.
 259 The reaction may now proceed via a bimolecular 1,4-addition so that an intramolecular hydrogen bond is
 260 formed to assist proton transfer (Scheme 4, species **D**). Previously published computational studies suggest
 261 that the 1,2-addition mechanism is often the most energetically favourable, but a 1,4-addition is competitive

262 depending on the nature of the reactants.^{10,35} The concentration of the reactants was not previously
 263 identified as a cause of a change in mechanism.

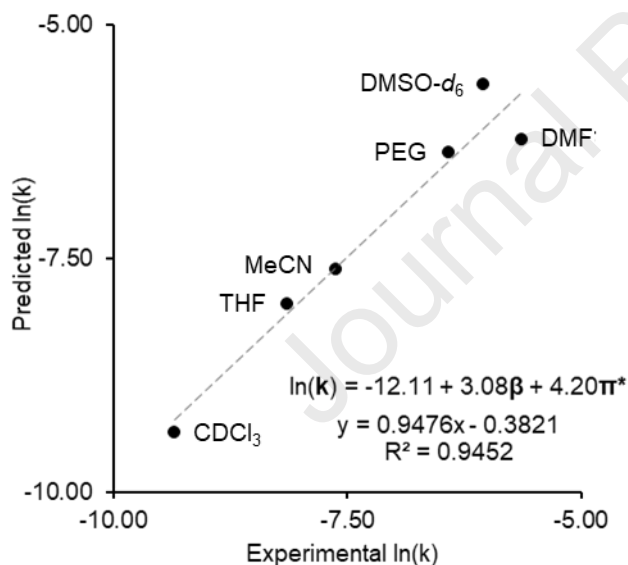
264 A LSER is needed for each mechanism to accurately describe the solvent effect in the reaction between **1**
 265 and **4a**. Six solvents promote the trimolecular reaction proceeding via species **A** in Scheme 4 (including CDCl₃
 266 but excluding IPA, see Figure S9). The Kamlet-Abboud-Taft parameters were correlated to rate constants in
 267 the form $\ln(k)$ (Figure 3). Both β and π^* were statistically significant in describing the trimolecular reaction,
 268 both being beneficial to the rate of reaction (see inset equation in Figure 3). This quantifies the observation
 269 that dipolar aprotic solvents accelerate the reaction. Polar solvents (with high π^* values) may stabilise the
 270 pericyclic activated complex, analogous to a Diels-Alder reaction.³⁶ Hydrogen bond accepting solvents (with
 271 high β values) may additionally stabilise the amine hydrogen atoms during proton transfer.

272

(a) Reaction scheme



(b) LSER



273

274 Figure 3. Predicted rate constants for trimolecular reactions between dimethyl itaconate (**1**) and piperidine (**4a**). (a)
 275 Reaction scheme. (b) Linear solvation energy relationship (LSER). The complete set of visualised data is provided as ESI,
 276 Figure S9.

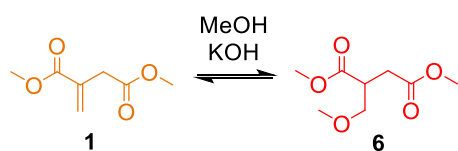
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278 Only four solvents produced bimolecular reactions (methanol, ethanol, low concentration reactants in CDCl₃,
 279 and TEA) and so a LSER was unreliable. However, α was statistically significant, reflecting the rate
 280 acceleration provided by alcohol solvents (Figure S9). The strength of the intermolecular interaction
 281 between an alcohol solvent's -OH hydrogen atom and the carbanion formed upon 1,2-addition onto **1**
 282 (Scheme 4, species **B**) would appear to be important in dictating the rate of reaction. For this reason,
 283 hexafluoroisopropanol was applied as the solvent. With an α value of 1.96,²⁶ about double that of typical
 284 alcohols, a high rate of reaction was anticipated. In practice, the intended reaction did not occur. The

285 exothermic addition of **4a** to the solvent suggested the nucleophilicity of the amine reactant is nullified by
 286 the acidity of the solvent. This is not true of every aza-Michael addition, for fluoroalcohols are effective
 287 solvents for the reaction of less basic anilines.^{Error! Bookmark not defined.,37,38} The significant health hazards
 288 possessed by fluoroalcohols should also be considered before being used as solvents.

289 The valuable rate-enhancing effect of alcohol solvents can only be exploited if the competitive oxa-Michael
 290 addition with the solvent or transesterification of **1** does not occur. The reaction in methanol did not
 291 produce any significant isomerisation of **1** or other observable by-products. The oxa-Michael addition of
 292 methanol onto **1** to give dimethyl 2-(methoxy)methyl butanedioate (**6**) can be achieved by the use of 50
 293 mol% potassium hydroxide as base and this method was used to provide a reference spectrum (Figure S10)
 294 and material for further study (Scheme 5). Replacing KOH with TEA produced a low conversion to **6** (~5%)
 295 after 24 hours at 50 °C. This suggests that in the presence of amines, alcohols can form the oxa-Michael
 296 addition product with **1**, but in the case of the synthesis of **5a**, the intended aza-Michael reaction is
 297 sufficiently faster than the competing oxa-Michael addition to preserve essentially 100% reaction selectivity.
 298 In a complementary experiment, **4a** was found to be unreactive in the presence of **6**, indicating the latter is
 299 not an unstable (and hence unobservable) intermediate during the formation of **5a** should methanol be used
 300 as the solvent. Additionally, transesterification of the methyl esters **1** and **5a** was not observed in ethanol or
 301 IPA under the standard reaction conditions used in this work (30 °C, <10 hours).

302



303

304 Scheme 5. The oxa-Michael addition between dimethyl itaconate (**1**) and methanol.

305

306 2.4 Catalysis

307 It was possible to conduct the reaction between **1** and a less reactive amine, dibutylamine (**4b**), in the
 308 absence of a solvent or catalyst, but the conversion to dimethyl 2-(dibutylamino)methyl butanedioate (**5b**)
 309 was slow (Table 2 and Figure S4). Following previous work employing iodine as a catalyst,¹⁸ the conversion to
 310 **5b** was much improved with the addition of 2.5 mol% iodine, reaching 75% in 24 hours. It was pertinent to
 311 determine the order of reaction and understand the role of the catalyst before a wider catalyst screening. In
 312 ethanol, IPA, and THF the reaction is first order with respect to each of **1**, **4b**, and the catalyst iodine (Table 4
 313 and Figure S11). With the addition of the catalyst, the reaction is no longer trimolecular in THF, and if a
 314 proton transfer agent is no longer required in THF, the same could be true of the reaction in alcohol
 315 solvents. The reaction is faster in IPA than it is in THF, as was the case in the reactions of **4a**, but now the
 316 rate of reaction in ethanol is suppressed, with a rate constant between that of IPA and THF. This is further
 317 evidence of a change in mechanism, the catalyst providing a lower energy reaction pathway than a proton
 318 transferring amine or solvent molecule. The rate constants are proportional to the hydrogen bond accepting
 319 ability (β) of the solvent (Figure S11), which implies the solvent stabilises the proton transfer through
 320 solvation but not necessarily as a direct participant.

321

322

323

324 Table 4. Reaction rate parameters for the reaction between dimethyl itaconate (**1**) and dibutylamine (**4b**) catalysed by
 325 iodine. Visualised data is provided as ESI, Figure S11.

Solvent	Reaction order			$10^4 \cdot k_{\text{obs}}$ at 30 °C
	1	4b	Iodine	
EtOH	1	1	1	$2.97 \pm 0.06 \text{ dm}^3 \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$
IPA	1	1	1	$5.22 \pm 0.20 \text{ dm}^3 \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$
THF	1	1	1	$2.40 \pm 0.07 \text{ dm}^3 \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$

326

327 The Lewis acid catalysed aza-Michael addition between **1** and **4b** is likely to be a 1,4-addition of the type
 328 preferred in CDCl_3 at low concentrations (Scheme 4, species **D**). A change in the rate determining step (i.e.,
 329 to the initial addition reaction) is again ruled out on the basis that the presence of a Lewis acid catalyst
 330 would only accelerate this step. What is unclear is whether it is the catalyst or the extra steric hindrance of
 331 **4b** compared to **4a** that prevents a second amine molecule from participating in the activated complex.
 332 Computational studies indicate a 1,4-addition is energetically preferable to a bimolecular 1,2-addition in the
 333 case of sterically hindered amines.¹⁰ However, this is not the only way in which a 1,4-addition might be
 334 favoured. Lewis acid catalysts will interact preferentially with the carbonyl oxygen of an enolate
 335 intermediate, drawing electron density away from the alkene moiety of **1** as in a 1,4-addition (Scheme 4,
 336 species **D**).^{39,40,41}

337 Additional catalysts (2.5 mol% loading) were studied without an auxiliary solvent and stirring at 30 °C to
 338 attempt to maximise the rate of product formation. Conversions to **5b** were calculated after 90 minutes, 24
 339 hours, and 4 days using ^1H NMR spectroscopy (Table 5 and Figure S12). Non-nucleophilic amines had a
 340 modest effect on the reaction (Table 5 entries 2 and 3). Metal triflates were all effective, generally providing
 341 a greater rate of reaction compared to iodine (Table 5 entry 4) initially and a slight improvement to the final
 342 conversion after 4 days (Table 5 entries 5-10). The differences in the Lewis acidity of the metal triflates do
 343 not correlate with the perceived rate of reaction,^{42,43} although the reaction was relatively rapid regardless of
 344 the metal triflate present. Scandium triflate ultimately provided the highest conversion of 88%. The
 345 concentration of **3** was negligible across this study.

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358 Table 5. Conversion of dimethyl itaconate (**1**) after four days reacting with dibutylamine (**4b**) in the presence of 2.5
 359 mol% catalyst.

Entry	Catalyst	Molar ratio		
		1	2	5b
1	No catalyst	23%	61%	17%
2	TEA	20%	60%	20%
3	DBU	25%	38%	37%
4	Iodine	5%	18%	77%
5	Copper triflate	8%	10%	83%
6	Magnesium triflate	2%	15%	83%
7	Indium triflate	5%	10%	85%
8	Bismuth triflate	2%	10%	87%
9	Scandium triflate	5%	8%	88%
10	Zinc triflate	6%	9%	84%
11	Zinc tosylate	11%	38%	51%
12	Zinc acetate	15%	50%	35%
13	Zinc sulphate	20%	51%	30%
14	Zinc chloride	1%	17%	82%
15	Zinc bromide	3%	17%	80%
16	Zinc iodide	2%	13%	85%

360

361 An extended investigation of zinc complexes was undertaken to optimise the reaction with a catalyst based
 362 on an inexpensive, low supply risk metal.⁴⁴ The zinc halides performed similarly to the triflate salts (Table 5
 363 entries 14-16). The conversion to **5b** that was achieved generally followed the order established by the pK_a
 364 of the acid form of the zinc salt, the notable exception being the poor performance of zinc sulphate (Table 5
 365 entry 13). This may be due to the use of the heptahydrate $ZnSO_4 \cdot 7H_2O$, thus introducing water into the
 366 reaction.

367 Further studies were performed with scandium triflate (as the best performing catalyst), zinc chloride (a
 368 simpler and more sustainable metal complex) and the molecular catalyst iodine. It was found that the
 369 scandium triflate or (to a lesser extent) iodine loading can be reduced significantly with minimal loss of
 370 product conversion (Figure S13). Changing the scandium triflate catalyst loading from 2.5 mol% to 0.25 mol%
 371 reduced conversion to **5b** from 88% to 81% (in the 4 day reaction). The reaction is more dependent on zinc
 372 chloride concentration, falling to 50% when using 0.25 mol% of catalyst.

373 It may be that the limited solubility or poor mixing of some catalysts in the neat reactants makes higher
 374 catalyst loadings irrelevant. To overcome any such limitations, solvents were introduced to the reaction
 375 between **1** and **4b**, both uncatalysed and catalysed by scandium triflate. Interestingly, methanol and DMSO-
 376 d_6 improved conversions to **5b** in the absence of a catalyst compared to the neat reaction (Figure S14).
 377 Reactions were performed as equimolar 2.4 M solutions, with methanol producing a satisfactory conversion
 378 to **5b** of 79%, albeit after 1 week. The addition of a solvent can increase the observed rate of reaction,
 379 despite considerably reducing the concentration of the reactants, due to the alleviation of mass transfer
 380 limitations. The solvent effect is also important, as the reaction in IPA was virtually identical to that without
 381 an auxiliary solvent. The relative performance of the solvents is analogous to the uncatalysed reaction
 382 between **1** and **4a**, but now the formation of **3** was measurable (up to 3%) and transesterification was
 383 observed in IPA. Minor signals in the 1H NMR spectrum of the reaction mixture in IPA after 1 week
 384 correspond to the isopropyl esters of **1** and **2** (Figure S15). An isopropyl ester equivalent of aza-Michael
 385 product **5b** was not identified, but the slow rate of reaction and low concentration of transesterified

386 substrates meant this by-product was not expected to be observed in significant quantities.
387 Transesterification by IPA was not observed in the catalysed reactions of **4b** (which were performed on a
388 shorter time scale).

389 The introduction of a solvent also had a small but beneficial effect on the conversion to **5b** when in the
390 presence of scandium triflate (Figure S16). This enhancement only occurred with small quantities of solvent.
391 More than a few equivalents of solvent slowed the reaction significantly (due to dilution). The choice
392 between methanol, IPA and DMSO-*d*₆ was not significant, all were capable of >80% conversion to **5b** after 24
393 hours (slightly higher than the 76% conversion without solvent). Although this is likely to be a matter of
394 improved mixing and mass transfer, it is surprising that only 0.44 equivalents of methanol resulted in the
395 optimum conversion (88%). This mass of methanol is similar to the mass of catalyst used.

396 At this point, the reaction of **4c** with **1** was revisited. Previously no aza-Michael addition was observed to
397 occur (without a solvent or catalyst). Now with an understanding of solvent, catalyst and temperature
398 effects, the reaction was repeated in the presence of 2.5 mol% scandium triflate and 0.44 equivalents of
399 methanol at 50 °C. The reaction was slow but after 4 days 64% conversion to dimethyl 2-(di(2-
400 ethylhexyl)amino)methyl butanedioate (**5c**) was observed (Figure S19). Thus, conditions were found to
401 transform a previously assumed unreactive amine into the intended aza-Michael adduct.

402

403 3. Conclusions

404 It was found that the aza-Michael additions of dimethyl itaconate are very susceptible to changes in
405 conditions and can access different mechanisms. By controlling the observed reaction pathway, conversion
406 and selectivity can be maximised. The hypothesis of an amine assisted proton transfer step was previously
407 accepted, but superior rates of reaction are achieved by an alternative bimolecular reaction, be it via an
408 alcohol or other catalyst. This work has clarified the acceleration of reaction rates by alcohol solvents and
409 revealed other phenomena such as the effect of concentration on the preferred reaction mechanism. These
410 findings can be used to optimise the synthesis of other aza-Michael additions including the synthesis of
411 pharmaceuticals and post-polymerisation modification of polymers.

412

413 4. Experimental

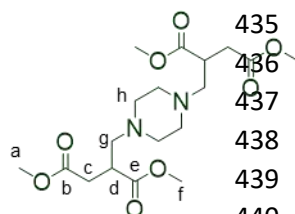
414 All reactions were performed under air in sealed vials. Solutions of dimethyl itaconate (**1**) were preheated
415 (typically to 30 °C) prior to addition of amine (**4**) and catalyst. Reactions were typically conducted on a 2 mL
416 scale and monitored by ¹H NMR spectroscopy using 300 MHz and 400 MHz spectrometers. Aliquots of the
417 reaction mixture were studied as solutions in CDCl₃ or DMSO-*d*₆. The concentration of compounds was
418 calculated from the known concentration of internal standard benzyl benzoate (CH₂ signal) and compared to
419 the integrals of characteristic signals belonging to the reaction components **1-5**. Representative spectra are
420 provided as Figure S17-S20.

421 Kinetic analysis was performed using Variable Time Normalisation Analysis. The literature method was
422 followed,³¹ from which orders of reaction and rate constants were derived. This technique requires the
423 visual interpretation of several overlaid datasets, which must be adjusted to consider the potential orders of
424 reaction. To avoid producing a large number of similar charts, the data is provided in an interactive format as
425 a supplementary spreadsheet (ESI) which can be manipulated freely.

426 Solvent effects were determined using linear solvation energy relationships (LSER). Correlations were found
 427 using the regression function of Microsoft Excel. Variables were excluded if p-values were above 0.1. In all
 428 cases, molar volume was not determined as significant.

429 Dimethyl 2-(1-piperidinylmethyl)butanedioate (**5a**), dimethyl 2-(dibutylamino)methyl butanedioate (**5b**), and
 430 dimethyl 2-(di(2-ethylhexyl)amino)methyl butanedioate (**5c**) were not isolated, but representative ¹H NMR
 431 spectra of the crude products are provided in Figures S17-S19 for reference. *N,N'*-bis(Dimethyl 2-methylene
 432 butanedioate) piperazine (**5d**) was isolated (method below). ¹H NMR and ¹³C NMR spectra are provided in
 433 Figure S20.

434



5d

435 *N,N'*-bis(Dimethyl 2-methylene butanedioate) piperazine (**5d**). To 0.949 g (6.0
 436 mmol) of dimethyl itaconate (**1**) was added 0.258 g (3.0 mmol) of piperazine (**4d**)
 437 and stirred for 24 hours at 30 °C. The resultant solid was washed with cold
 438 acetone, filtered and dried to give a white crystalline solid (*ca.* 1 g, 94%
 439 conversion). ¹H NMR 300 MHz (CDCl₃). 3.69 (6H, s, H_a), 3.67 (6H, s, H_f), 3.07 (2H,
 440 m, H_d), 2.71-2.55 (6H, m, H_c and H_g), 2.43-2.36 (10H, m, H_c and H_h). ¹³C NMR 75
 441 MHz (CDCl₃). 174.5 (C_e), 172.5 (C_b), 59.3 (C_c), 53.1 (C_h), 51.9 (C_a), 51.7 (C_f), 39.7
 442 (C_d), 34.3 (C_g). HRMS (ESI). Calculated 403.2075, observed 403.2077 (MH⁺).

443

444 Dimethyl 2-(methoxymethyl)butanedioate (**6**). To 0.237 g (1.5 mmol) of dimethyl itaconate (**1**) was added
 445 methanol (*ca.* 1 g, 20 equivalents) and 0.042 g of ground potassium hydroxide (0.75 mmol),⁴⁵ and stirred for
 446 24 hours at 30 °C. The reaction mixture was then concentrated, to which was added water (5 mL) and
 447 extracted with dichloromethane (3 x 5 mL). The combined organic phase was dried with magnesium
 448 sulphate, filtered and concentrated. The crude product also contains **1** and its isomers. This was used directly
 449 in subsequent reactions. Characterisation was consistent with an earlier synthesis.⁴⁶ An annotated ¹H NMR
 450 spectrum is provided as Figure S10.

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- The mechanism of the aza-Michael addition is solvent-dependent.
- Lewis acid catalysts also change the mechanism.
- Optimised conditions allow the reaction of very sterically hindered amines.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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