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Article

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Exploration of the Differences Between Amine and Thiolate Addition to Acetylenedicarboxylates

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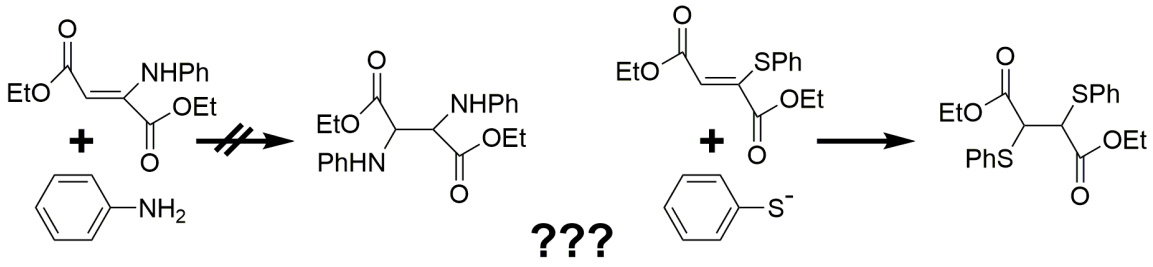


Abstract

Nucleophilic addition of thiolates to diethyl acetylenedicarboxylate in chloroform at room temperature affords solely the meso dithioaddition product, whereas the addition of amines in ethanol gives only the corresponding (Z)-enamine, as confirmed by X-ray crystal analysis. The monoaddition product of thiolate addition, prepared and isolated at lower temperatures, also exhibited (Z)-stereochemistry. The accompanying computational study on simplified model systems explains the reasons for the observed stereochemistry and why the acetylene dicarboxylate readily undergoes two addition reactions with thiolate nucleophiles, whereas the (Z)-enamine is much less reactive towards addition of thiolate or amine nucleophiles.

Introduction

The conjugate addition of primary amine and thiolate nucleophiles to diesters of acetylene dicarboxylic acid has been known for many years.[1,2] The reaction has occasionally been used in the synthesis of amino[3,4] and thio[1] heterocycles but has to our knowledge not been used as the first step in the synthesis of multifunctional acyclic compounds.

This reaction was potentially useful in the synthesis of some complex targets in which we were interested, however several questions needed to be addressed. The first was stereochemistry. The addition of one equivalent of nucleophile affords an alkene. Reactions described in the earlier literature usually reported mixtures of isomers and there was considerable discussion regarding the mechanism of addition and why mixtures were obtained.[5] The stereochemistry of the products was determined by IR,[6] dipole moment[7] and by ^{1}H NMR.[8,9] However, the only stereochemically significant signal in the NMR spectra was the single alkene singlet, so that if reaction conditions could be chosen such that a single stereoisomer were obtained, stereochemical determination by routine NMR alone would be more difficult. Therefore, we wished to confirm the stereochemistry of the monoaddition and diaddition products by X-ray crystal structure. It should be noted that the earlier literature is pre-Z,E nomenclature, and although Huisgen defined cis and trans for his trisubstituted alkenes,[7] it is not at all clear that the authors of some subsequent papers were aware of this definition. It was clear, however, that the nature of the product(s) was dependant on the reaction conditions, particularly the solvent,[10,11] and Sarrafini and co-workers[12] have more recently reported the stereospecific addition of thiols and secondary amines in water in the presence of potassium carbonate.

Unfortunately, their attempted reaction with primary amines "did not give satisfactory results". Solvent-free reaction of primary amines with DEAD (diethyl acetylenedicarboxylate) was found to often give the (Z)-isomer, but not in all cases.[13]

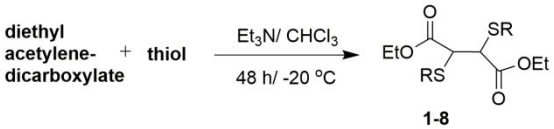
The second issue needing clarification was the reaction pathway. To our knowledge, there is only one example in the literature of addition of two equivalents of amine to the acetylene dicarboxylate.[14] The paper gives a general experimental method, and there are no stated changes to the general reaction procedure for this one purported example of diaddition. By contrast, the addition of two equivalents of thiolate in chloroform[15] leads to diaddition, although recent examples carried out in water use one equivalent and give monoaddition only.[12]

Results and Discussion

Experimental Results

Diethyl acetylenedicarboxylate (DEAD) was treated with thiols[15] and amines[14] under literature conditions. In each case a single stereoisomer was isolated, usually in good yield (**1**–**7, 9, 10**). The exception was diethyl 2,3-bis(4'-hydroxyphenylthio)succinate **8**, which was obtained in only 24% yield. We suggest that the low yield may be due partly to the presence of other nucleophilic sites in the reactant, but probably mostly to the insolubility of the product in both chloroform and water, the solvents used in our general method. This meant that the product, a white solid, was suspended in both the aqueous and organic layers during the initial extraction, and although it was subsequently extracted from the aqueous phase with ethyl acetate, product was certainly lost. Since enough of the product was obtained for our subsequent investigations, the reaction was

not repeated with a different workup procedure. The reaction conditions and yields for the synthesis of compounds **1-11** are summarised in Figure **1**.



1-8

Entry	R	% yield
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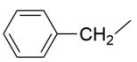
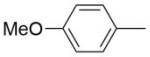
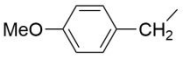
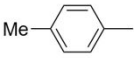
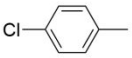
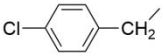
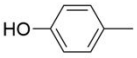
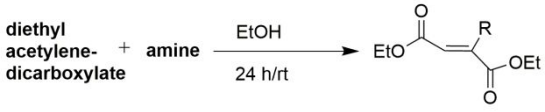
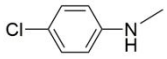
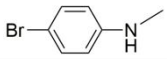
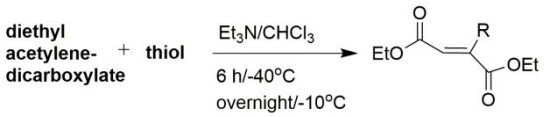
2		80
3		79
4		73
5		78
6		68
7		55
8		24



Entry	R	% yield
9		74
10		85



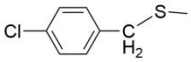
Entry	R	% yield
11		56

Figure **1**. Reaction conditions and yields for the synthesis of **1-11**.

The ^{1}H NMR spectra of the diaddition products from reactions using the thiolate nucleophile (**1-8**) were as expected. The methylene ester protons in the benzylic adducts **2**, **4** and **7** were seen to be non-equivalent and the methyne protons adjacent to the carbonyl groups and sulphur lay in the range of δ 3.51 to δ 4.00, dependant on the sulphide substituent. All products gave good high resolution mass spectra for $[M+H]^+$ or $[M+Na]^+$.

Monoaddition of the thiolate was achieved by conducting the reaction at -40°C with subsequent workup at 0°C (Figure **1**, conditions and yield for **11**). Reactions at higher temperatures gave mixtures of starting materials and diaddition product, with very little if any monoaddition product by ^{1}H NMR spectroscopy**.** The signal from the vinyl proton of

the chlorobenzythiofumarate **11** was found at δ 6.36, analogous to the thiofumarates prepared by Sarrifini.[12]

As described in the literature (with the single exception mentioned previously), reaction with the amine nucleophiles afforded only the monoaddition products (Figure **1**, conditions and yields for **9** and **10**). The ^{1}H NMR spectrum of the bromophenylaminofumarate **10** was in accord with the published literature,[13,16] and that of the chlorophenylaminofumarate **9** was analogous to the data published for the dimethyl ester analogue.[7] The three monoaddition products **9**, **10** and **11** also gave good high resolution mass spectra for $[M+H]^{+}$.

Stereochemistry

X-ray crystal structures were obtained for diethyl 2-(4'-chlorobenzythio)fumarate **11** and diethyl 2-(4'-chlorophenylamino)fumarate **9** as represen**t**atives of the monoaddition products. Both products had (Z)-stereochemistry, with the **ester** functional groups trans to each other. An x-ray crystal structure was also obtained for diethyl 2,3-bis(4'-methylphenylthio)succinate **5** as representative of the dithioaddition products. The compound was found to have meso (RS)-stereochemistry with the two sulphide groups anti to each other. Thermal ellipsoid plots of the crystal structures are provided in the supporting information.

Reaction Pathways

Amines and thiolates are both good nucleophiles so the difference in their reactivity with acetylene dicarboxylates under standard conditions was intriguing. The difference in the reactivity of amino and thiolate nucleophiles with the alkene intermediates was investigated experimentally by varying the reaction conditions as shown in Table **1**. It is to be noted that in reactions with amines, more forcing conditions gave more degradation and lower recovery of the monoaddition product. The fact that the thiolate did not react with the enamine or the amine with the thioalkene was unexpected.

Table **1**: Attempted Synthesis of Diamino and Mixed Diaddition Products

Alkene	**Nucleophile**	**Solvent**	**Temperature (°C)**	**Time (days)**	**Result**
10	4-bromo benzenethiolate	$CHCl_3$ with TEA	0	9	no reaction
10	4-bromoaniline	$CHCl_3$ with TEA	0	9	no reaction
10	4-bromoaniline	THF	reflux	2	starting material + degradation only
10	4-bromoaniline	toluene	reflux	2	starting material + degradation only
11	4-bromoaniline	$CHCl_3$ with TEA	0	9	no reaction

Computational Study and Discussion

Simplified model compounds were investigated. Phenyl thiolate was used as the sulphur nucleophile and aniline as the nitrogen containing nucleophile. Dimethyl acetylenedicarboxylate (DMAD) was used. Cis and trans nomenclature is used for clarity and refers to the relative position of the ester groups.

Unless otherwise indicated, energy values are Gibbs free energy values (G^o in $kcalmol^{-1}$) obtained after a final geometry optimisation at DFT level (ωB97X-D/6-31G*)[17] in a C-PCM implicit solvent model[18,19], followed by calculation of the IR spectra and thermodynamic quantities as implemented in the Spartan software (wavefun.com). These values are provided in the supporting information.

As expected, all transition states show a high intensity imaginary frequency which, when animated, resonates along the proposed reaction coordinate.

Table **2**: Imaginary Frequencies in Model Compounds

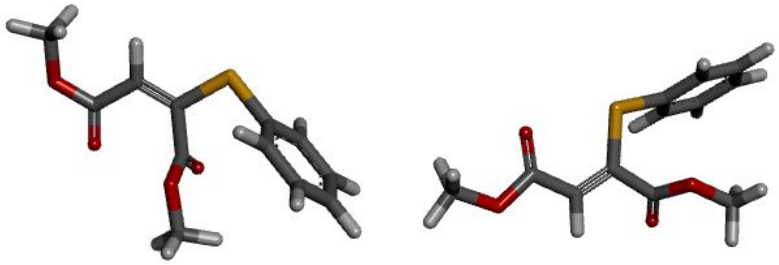
Compound	**-υ (cm^{-1})**	**Relative Intensity**
N transition state 1	284 i	1.00
N transition state 2	257 i	1.00
meso di-N product	15 i	$>0.50 \times 10^{-5}$
S transition state 1	218 i	0.48
S transition state 2	182 i 25 i	0.71 0.94×10^{-3}
S dianion	23 i 23 i	0.93×10^{-3} 0.18×10^{-2}
cis mixed diproduct	4 i	0.27×10^{-2}
mixed dianion	32 i 7 i	0.15×10^{-2} 0.59×10^{-3}
mixed transition state 2	193 i 37 i 27 i	1.00 0.83×10^{-3} 0.33×10^{-2}

Table **2** provides these transition state imaginary frequencies, as well as a number of additional, unexpected imaginary frequencies. We were not able to change the geometries of these structures to avoid those extra imaginary frequencies. However, they are in all cases small in terms of wavenumber (<40 cm^{-1}) and intensity. These problems occur in three sulphur containing compounds, and in one of the two largest nitrogen containing compounds and in two sulphur containing transition states more than one imaginary

frequency is observed. We propose that they are not physical but rather are the result of numerical inaccuracies as suggested in the user manual of the Spartan software. Kleingeld *et al.*[20] investigated numerical accuracy of different DFT methods including ωB97X-D/6-31G(d) for coordination complexes of fullerene and proposed that the very small imaginary frequencies obtained (<17 cm^{-1}) could be the result of small numerical errors.

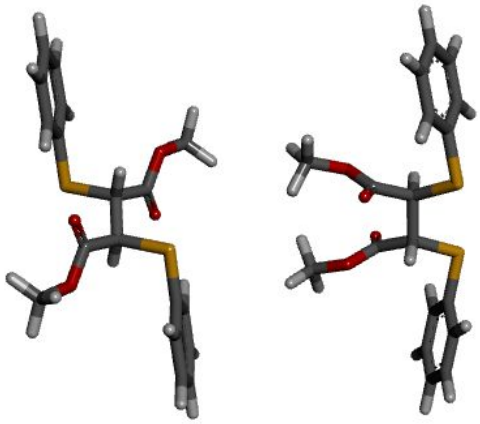
Stereochemistry

Our computational studies showed that the lowest energy conformers did not have both carbonyl groups coplanar with the S substituted alkene in either diastereomer. Structures A and B in Figure **2** show the two thioalkene diastereomers in the lowest energy conformations that were identified. The cis isomer was 6.7 $kcalmol^{-1}$ higher in energy. This modest difference together with a variety of low energy conformers with various combinations of π–bond overlap with no substantial energy differences, add evidence that the observed sole formation of the trans product (**11**) is due to a trans addition mechanism rather than thermodynamic considerations. The lowest energy conformation in the trans thioalkene came closest to having both carbonyl groups coplanar with the alkene whilst the cis thioalkene was severely twisted, with the two carbonyl groups perpendicular.



A B

Figure **2**: The lowest energy conformations of the model compounds of the cis (A) and trans (B) thiolate monoaddition products. Elements are colour-coded: C-grey, O-red, S-yellow and H-white.



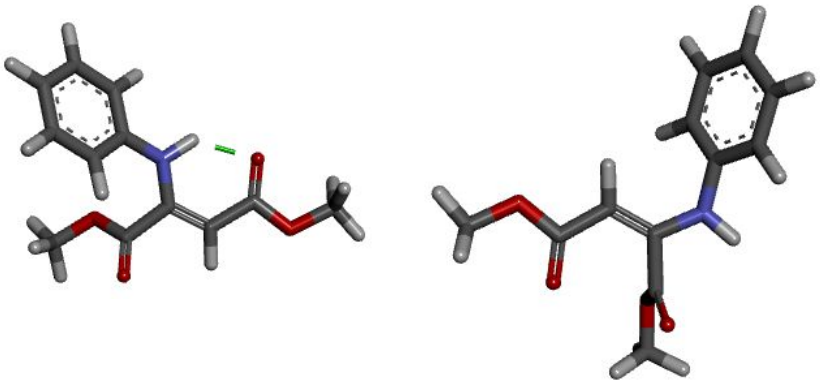
A B

Figure **3**: The lowest energy conformations of the model compounds of the meso (A) and (RR) (B) thiolate diaddition products. Elements are colour-coded: C-grey, O-red, S-yellow and H-white.

The second trans addition of the thiolate could lead to the racemic mixture [(RR) and (SS) diastereomers] or solely the meso (RS) product. Computations showed that the (RR)

diastereomer exhibited substantial electronic repulsion in all conformations, whereas the lowest energy conformation of the meso diastereomer showed the two sulphide groups anti to each other (Figure **3**). Despite this, the meso form is only 3.1 kcalmol^{-1} lower in energy. However, this difference in energy for our model compounds appears to be enough to account for the sole formation of the all trans meso product we observed for the more complex compound **5**.

Our calculations indicated the two enamines were of similar energy and again, none of the lowest energy conformations had the alkene coplanar with both carbonyl groups. The trans isomer exhibited different modes of hydrogen bonding in all its lowest energy conformations with resultant stabilising 5- and 6-membered rings (Figure **4** A). The lowest energy conformations of the cis isomer contained no hydrogen bonds and hence no resultant ring structures (Figure **4** B). Despite the hydrogen bonding, the trans isomer was only 3.1 kcalmol^{-1} lower in energy. Again, this adds evidence that the observed sole formation of the trans products (**9** and **10**) is due to a trans addition mechanism rather than thermodynamic considerations.

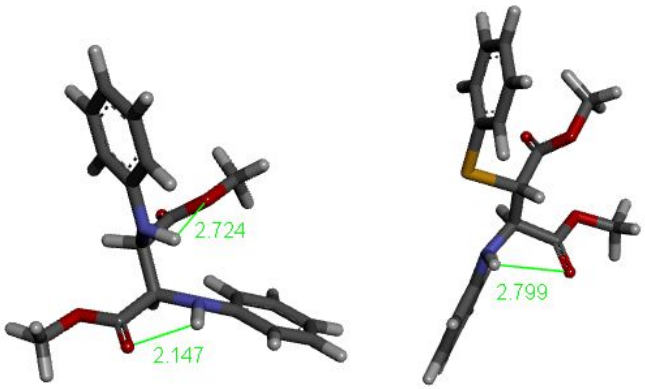


A B

Figure **4**: The lowest energy conformations of the model compounds of the trans (A) and cis (B) enamine products. Elements are colour-coded: C-grey, O-red, N-blue and H-white. The green dashed line in A indicates a hydrogen bond.

The aniline diaddition products were never formed in our hands, and it is interesting to note that the (RR) product was more stable than the meso product by 3.5 kcalmol^{-1}. This can probably be attributed to favourable electronic interactions (distorted hydrogen bonds), which have been indicated by green lines in Figure **5** A.

A putative mixed addition product resulting from attack of a thiolate on the enamine (which was also not observed), also showed a more stable cis configuration (by 1.7 kcalmol^{-1}), which can again be attributed to favourable electronic interactions (Figure **5** B).



A B

Figure **5**: The lowest energy conformation of the model compounds of the putative (RR) aniline diaddition product (A) and of the mixed addition product (B). Elements are colour-coded: C-grey, O-red, N-blue S-yellow and H-white. The green lines indicate favourable electronic interactions, with the distances provided in Å.

Reaction Pathways

Previous workers have stated that the thioalkene is formed by trans addition of the thiolate nucleophile, and the dithio product formed from a second trans addition.[5] The idea that the enamine resulting from monoaddition of amine to DEAD is formed *via* cis addition to afford initially the (E) product (ester groups cis), but this product subsequently rearranges to the (Z) product (ester groups trans) is unusual,[5] and we did not find any experimental evidence for the (E) product. As described in the previous section, the energies differences between cis and trans adducts were moderate to small, thus adding evidence for trans addition. We therefore modelled all additions as trans additions

and were able to construct all transition states with satisfactory geometries. The transition states for the two monoadditions are shown in Figure **6**. The aniline transition state is stabilized by a hydrogen bond.

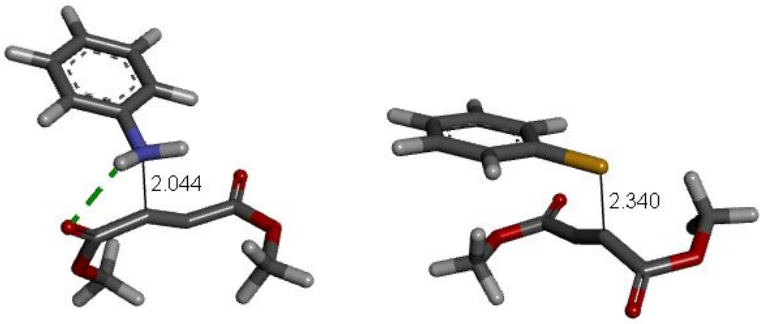


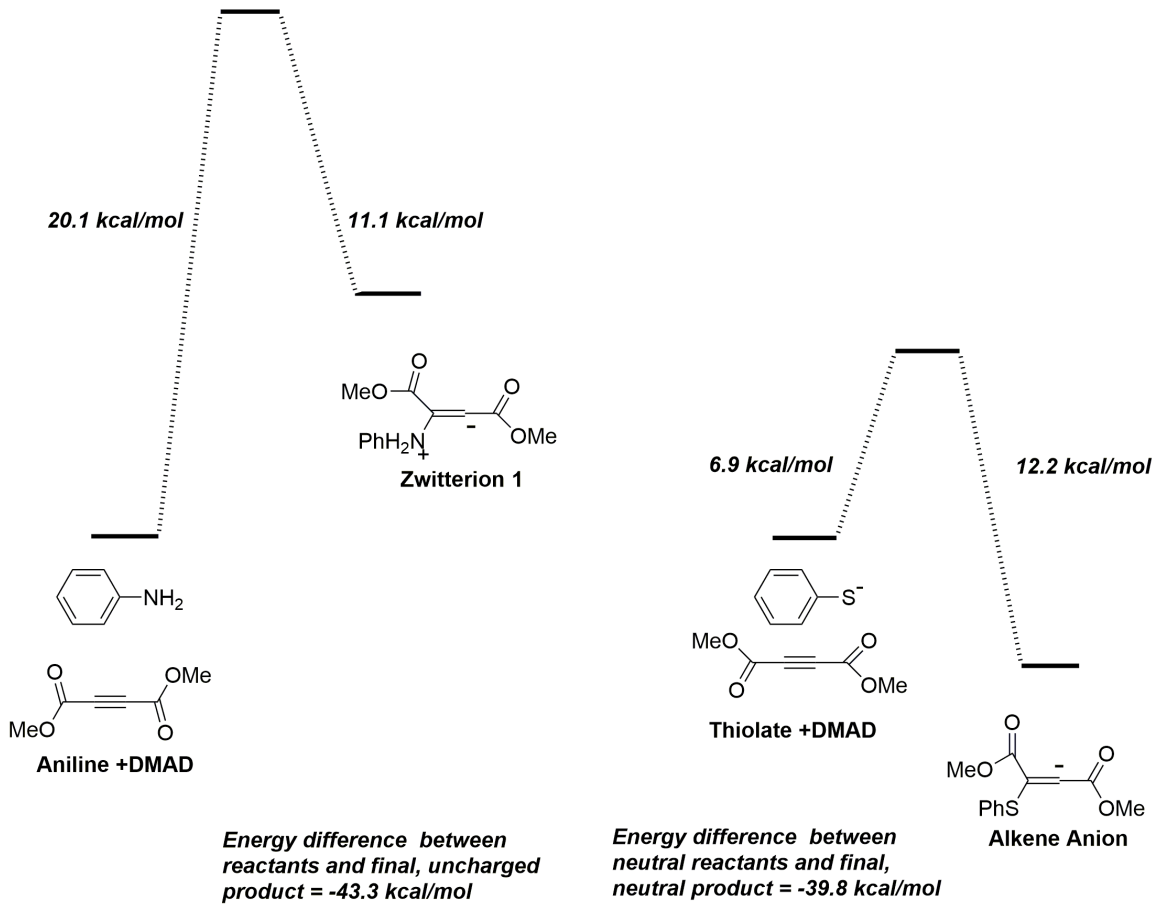
Figure **6**: Monoaddition transition states. Colours and symbols as in previous figures. Newly formed bonds indicated by thin, black lines.

The monoaddition of aniline to DMAD is summarized on the left in Scheme **1**. This is the same, stepwise reaction mechanism *via* a zwitterionic intermediate as proposed by Gurjar *et al.*[21] for the addition of dimethylamine, pyrrolidine, and benzylamine to DMAD. Our calculations show a zwitterionic product from a trans attack of aniline that was only 11 $kcalmol^{-1}$ lower in energy than the transition state, and a barrier of 20 $kcalmol^{-1}$ between the reactants and the transition state. The trans enamine product was 43 $kcalmol^{-1}$ lower in Gibbs free energy than the starting materials. We propose that the zwitterion will quickly rearrange to the final trans enamine, which is 52 $kcalmol^{-1}$ more stable than the zwitterion.

Gurjar *et al.* report activation energies of around 13 kcalmol^{-1} in toluene and exothermic ΔH^0 values of 29 to 44 kcalmol^{-1}. Table **3** provides our H^0 values for comparison. These were obtained in an implicit polar solvent model to mimic our reaction conditions (ethanol as a solvent). The activation energy for our model reaction is 7 kcalmol^{-1}, and the exothermic ΔH^0 is 58 kcalmol^{-1}. These values are in excellent agreement with the values obtained by Gurjar *et al*., considering the different solvent conditions and different amines modelled.

Table **3**. H^0 values for selected model compounds

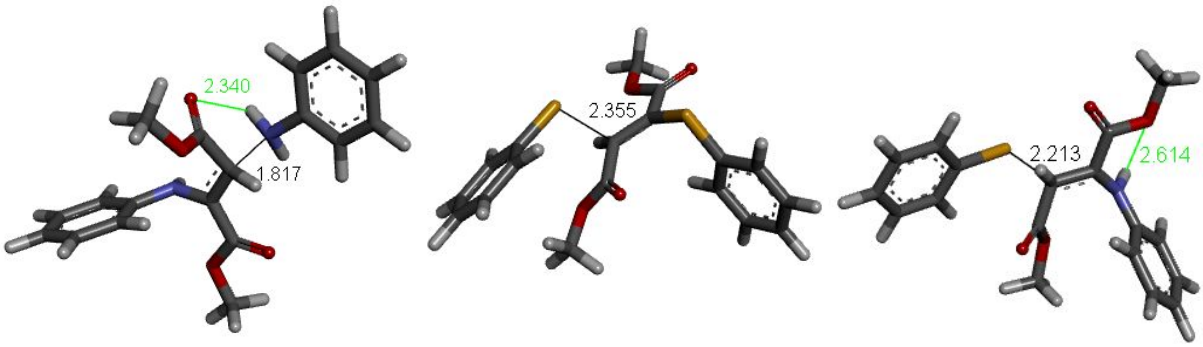
Compound	**-H^o (kcalmol^{-1})**
DMAD	334320
aniline	180340
N transition state 1	514653
zwitterion 1	514665
trans enamine	514718



Scheme **1**: The monoaddition reactions of aniline and the thiolate anion to DMAD. All energies are Gibbs free energy (G^o) values.

The monoaddition of the phenyl thiolate nucleophile to DMAD is also summarized in Scheme **1**. Our calculations show the alkene anion product 12 kcalmol^{-1} lower in energy than the transition state with a barrier of only 7 kcalmol^{-1} and the final uncharged trans alkene product 40 kcalmol^{-1} lower than the starting materials. The reaction conditions (catalytic amounts of triethylamine in dry, ethanol-free chloroform) allow for the presence of the much more nucleophilic thiolate, which we have used in the calculations, despite its higher energy (by 295 kcalmol^{-1}). The alkene anion is 329 kcalmol^{-1} higher in energy than the uncharged, trans alkene and we suggest that it will quickly pick up a

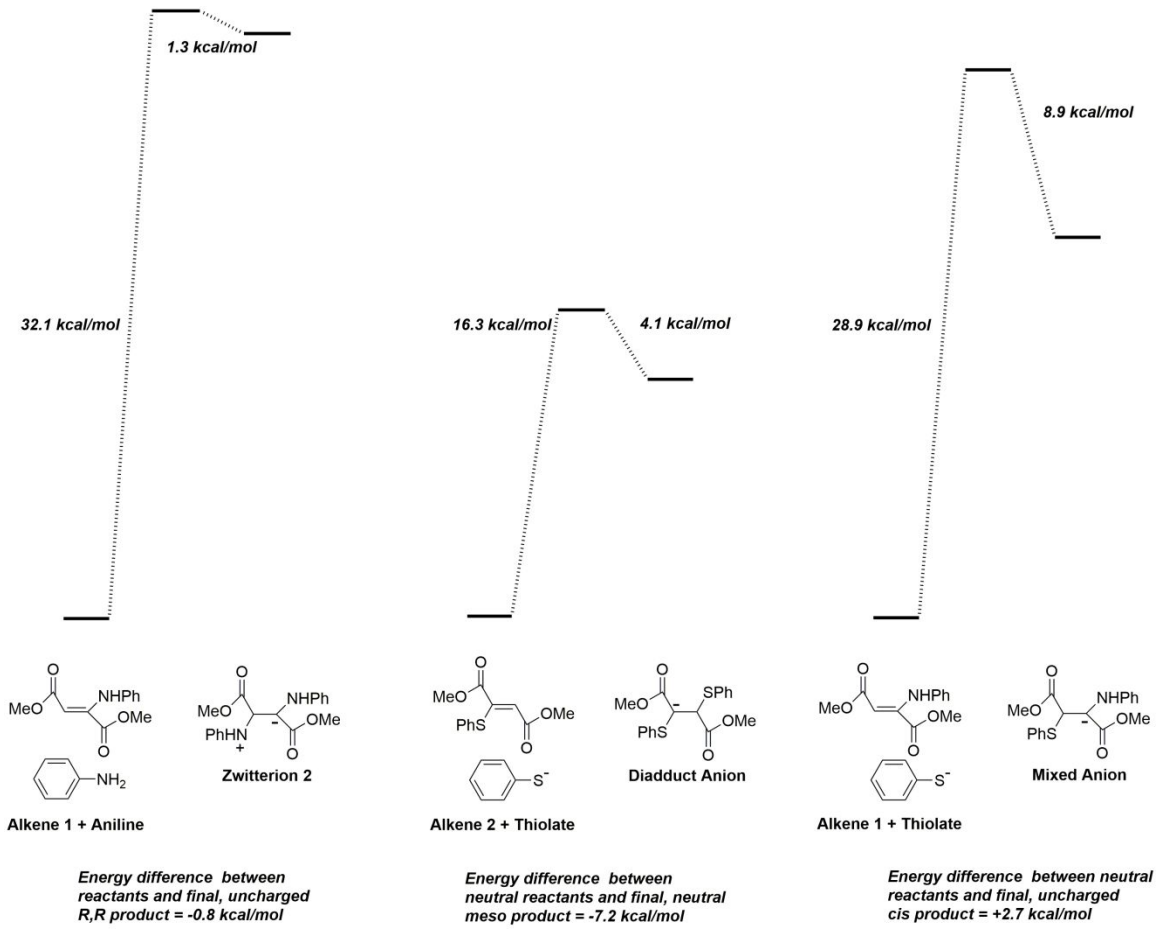
proton. The proposed diaddition reactions are summarized in Scheme **2** and the proposed transition states are shown in Figure **7**.



A B C

Figure **7**: Proposed diaddition transition states. Colours and symbols as in previous figures.

Modelling of the attack of aniline to the enamine showed a barrier of 32 kcalmol^{-1}. We propose that this barrier is higher than the one for the rearrangement of the intermediate zwitterion to the uncharged product and that this high barrier explains why the addition of an amine nucleophile to an enamine never proceeded in our hands. In addition, the calculated reaction would be only just exothermic with ΔG^0 of 0.8 kcalmol^{-1} overall and the energy of the product anion (zwitterion 2) is only 1.3 kcalmol^{-1} lower than the transition state.



Scheme **2**: Diaddition reactions. All energies are Gibbs free energy (G^o) values.

The reaction depicted on the right of Scheme **2** was also attempted. Our calculations predicted a high barrier of 29 kcalmol^{-1} and an overall endothermic reaction, explaining why this reaction did also not proceed in our hands.

The addition of further phenyl thiolate nucleophile to the alkene 2 is summarized in the middle of Scheme **2**. This is the only diaddition reaction we observed, and it proceeded rapidly in our hands. This reaction has a modest barrier of only 16 kcalmol^{-1}, although the energy difference between the transition state and the initial product formed in this reaction sequence, i.e. the diadduct anion, was only 4 kcalmol^{-1}. Again, we propose that

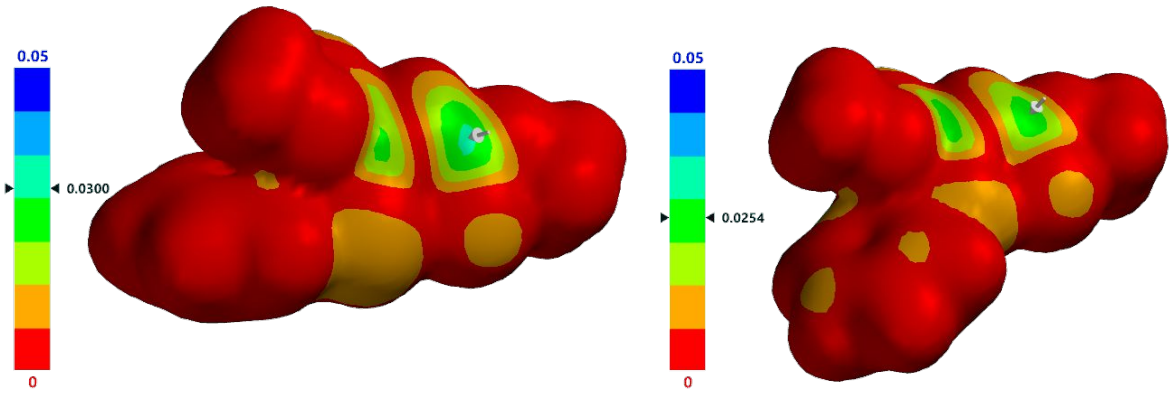
the anion will easily be able to pick up a proton to form the final product. The overall reaction was predicted to be exothermic (by 7 $kcalmol^{-1}$).

The frontier orbitals (HOMO and LUMO) of the trans alkenes were also examined. As shown in Table **4**, the HOMO and the LUMO of the enamine were higher in energy, which is consistent with the lower reactivity of this compound towards nucleophiles.

Table **4**: Frontier orbital details for the model alkenes.

Compound	**E LUMO (eV)**	**E HOMO (eV)**	**Bandgap (eV)**
enamine	0.19	-7.75	7.94
thioalkene	0.01	-8.35	8.36

The LUMO maps, where the absolute LUMO values are mapped onto the electron density surface, also show small differences between the two alkenes (Figure **8**). The LUMO value on the carbon to be attacked by a nucleophile (right hand carbon) is higher for the thioalkene (Figure **8** A; 0.0300 versus 0.0254).



A B

Figure **8**: LUMO maps of the thioalkene (A) and the enamine (B). Absolute LUMO values are mapped onto electron density surfaces and colour coded from red (low) through orange, yellow and green to aqua and blue (high).

Conclusions

The molecular modelling calculations are able to explain the observed trans and meso stereochemistry of the products. The trans and meso forms of the observed products are always lower in energy than cis or racemic products. However, the differences are not large and for the monoadditions this strongly suggests a trans addition mechanism.

The calculations provide plausible explanations for the facile diaddition of thiolate nucleophiles to acetylenedicarboxylates and for the failure of amines and thiolates to add to the enamine monoaddition products: the enamine is less reactive (lower LUMO coefficient; less stable LUMO) than the thioalkene and the barriers for the addition of the

second nucleophile to the enamine are much higher than for a second addition to the thioalkene.

Experimental

General Procedures

All solvents used were of AR grade and, where appropriate, were dried by the following techniques: THF, benzene and toluene were heated under reflux over sodium metal for 1 hour and were then distilled. Ethanol-free chloroform was obtained by washing commercially available chloroform with water and drying over barium oxide or passing the solvent though a neutral alumina column, then distillation. All amines and thiols were purified by recrystallization or distillation before use, except 4 hydroxybenzenethiol, which was supplied by the manufacturer as 90%. We were unable to determine the nature of the impurities from the manufacturer's website or ^{1}H NMR spectroscopy. TEA was dried over barium oxide and used without further purification. Melting points were measured in capillary tubes and are uncorrected. High resolution mass spectra were obtained using a Qtof spectrometer in ESI mode. Prior to analysis instrument was externally calibrated with a solution of 1 mg/mL cesium iodide (CsI) over the m/z acquisition range. 100-1000.

General Procedure for the Synthesis of Diethyl 2,3-Bis(phenylthio)succinate and Analogous Compounds 1-8[15]

Diethyl acetylenedicarboxylate (0.5 g, 2.94 mmol) was added over 30 min to a cooled stirred solution of the selected thiol (5.88 mmol) in dry, ethanol-free chloroform (10 mL) containing 2 drops of triethylamine at -10 ^{o}C. After addition, the solution was stirred at -20 ^{o}C for 48 h. The solvent was removed under reduced pressure at 0 ^{o}C. The residue was

washed with ether at 0 °C to yield the desired product. A sample was then recrystallised from ethanol for spectral analysis.

Diethyl 2,3-Bisphenylthiosuccinate 1

The product was washed with ether to yield white prisms (0.90 g, 78%), mp 76-77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, 6H, J = 7.1); δ3.92 (s, 2H); δ4.16 (q, 4H); δ7.40 (m, 10H). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 14.0; δ 52.0; δ 61.5; δ 128.9; δ 129.0; δ 131.9; δ 134.2; δ 169.2. HRMS (ESI) calcd for $[M+H]^+$ $C_{20}H_{23}O_4S_2$ 391.1038, found 391.1057.

Diethyl 2,3-Bis(phenylmethanethio)succinate 2

The product was washed with ether to yield white prisms (0.98 g, 80%), mp 113 °C (range < 1 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 6H, J = 7.0); δ 3.60 (s, 2H); υ_A 3.87, υ_B 3.84 (q_{AB}, 4H, J = 12.8); δ 4.15 (m, 4H); δ 7.28 (m, 10H). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 14.0; δ 36.6; δ 47.3; δ 61.5; δ 127.4 ;δ 128.5 ; δ 129.2 ; δ 136.8 ; δ 169.8. HRMS (ESI) calcd for $[M+H]^+$ $C_{22}H_{27}O_4S_2$419.1351, found 419.1354.

Diethyl 2,3-Bis(4'-methoxyphenylthio)succinate 3

The product was washed with ether to yield white prisms (1.04 g, 79%), mp 109°C (range < 1 °C)**.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 6H, J = 7.0); δ 3.72 (s, 2H,); δ 3.79 (s, 6H); δ 4.19 q, 4H); υ_A 6.82, υ_B 7.37 (q_{AB}, 8H, J = 9.0). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 14.0; δ 51.8; δ 55.3; δ 61.4; δ 114.5; δ 121.5; δ 137.23; δ 160.7; δ 169.2. HRMS (ESI) calcd for $[M+Na]^+$ $C_{22}H_{26}O_6NaS_2$ 473.1069, found 473.1084.

Diethyl 2,3-Bis(4'-methoxyphenylmethanethio)succinate 4

The product was washed with ether to yield white prisms (1.03 g, 73%), mp 122-123°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 6H, J = 7.1); δ 3.59 (s, 2H); δ 3.78 (s, 6H); υ_A 3.80, υ_B 3.84 (q_{AB}, 4H, J = 12.6); δ 4.17 (m, 4H,); υ_A 6.82, υ_B 7.19 (q_{AB}, 8H, J = 8.8). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 13.8; δ 35.8; δ 47.1; δ 55.0; δ 61.2; δ 113.6; δ 128.5; δ 130.1; δ 158.6; δ 169.7. HRMS (ESI) calcd for $[M+H]^+$ $C_{24}H_{31}O_6S_2$ 479.1562, found 479.1571. HRMS (ESI) calcd for $[M+Na]^+$ $C_{24}H_{30}O_6NaS_2$ 501.1382, found 501.1402.

Diethyl 2,3-Bis(4'-methylphenylthio)succinate 5

The product was washed with ether to yield white prisms (0.96 g, 78%), mp 110-111°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, 6H, J = 7.1); δ 2.32 (s, 6H); δ 3.81 (s, 2H); δ 4.17(m, 4H); υ_A 7.10, υ_B 7.33 (q_{AB}, 8H, J = 7.8). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 14.0; δ 21.3; δ 51.9; δ 61.4; δ 127.9; δ 129.8; δ 134.8; δ 139.3; δ 169.2. HRMS (ESI) calcd for $[M+H]^+$ $C_{22}H_{27}O_4S_2$ 419.1351, found 419.1344.

Diethyl 2,3-Bis(4'-chlorophenylthio)succinate 6

The product was washed with ether to yield white prisms (0.92 g, 68%), mp 120-121°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 6H, J = 7.1); δ 3.82 (s, 2H); δ4.18 (m, 4H); υ_A 7.23, υ_B 7.44 (q_{AB}, 8H, J = 8.6). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 14.1; δ 51.9; δ 61.8; δ 129.3; δ 130.1; δ 135.5; δ 135.7; δ 169.0. HRMS (ESI) calcd for $[M+Na]^+$ $C_{20}H_{20}O_4NaS_2Cl_2$ 481.0073, found 481.0078.

Diethyl 2,3-Bis(4'-chlorophenylmethanethio)succinate 7

The product was washed with ether to yield white prisms (0.79 g, 55%), mp 98-100°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 6H, J = 7.2); δ 3.51 (s, 2H,); υ_A 3.78, υ_B 3.81 (m, 4H, J = 13.17); δ 4.14 (m, 4H); υ_A 7.20, υ_B 7.26 (q_{AB}, 8H, J = 8.3). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 14.0; δ 36.0; δ 47.1; δ 61.6; δ 128.7; δ 130.5; δ 133.2; δ 135.5; δ 169.7. HRMS (ESI) calcd for $[M+H]^+$ $C_{22}H_{24}O_4S_2Cl_2$ 487.0571, found 487.0557.

Synthesis of Diethyl 2,3-Bis(4'-hydroxyphenylthio)succinate 8

This reaction was carried out using the general procedure given above, using 4'-hydroxybenzenethiol (90%, 6.60 mmol). The product mixture, containing a heavy precipitate, was diluted with water, the precipitate remaining largely suspended in the aqueous phase. The chloroform phase was removed, and the aqueous phase extracted with ethyl acetate (3x100mL). The ethyl acetate solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was washed with ether to yield white needles, (0.3 g, 24%). mp 213-215°C. ^{1}H NMR (300 MHz, d^{6}DMSO): δ 1.68 (t, 6H, J = 7.2); δ 4.0 (s, 2H); δ 4.62 (q, 4H, J = 6.9); υ_A 7.26, υ_B 7.70 (q_{AB}, 8H, J = 6.9), δ10.4 (s, 2H) ppm. ^{13}C NMR {1H} (75 MHz, $CDCl_3$):δ 14.0; δ 52.0; δ 61.5; δ 128.9; δ 129.0; δ 132.2; δ 131.9; δ 134.2; δ 169.2ppm. HRMS (ESI) calcd for $[M+Na]^+$ $C_{20}H_{22}O_6NaS_2$ 445.0756, found 445.0739.

Synthesis of Diethyl 2-(4'-Chlorobenzythio)fumarate 11

A solution of diethyl acetylenedicarboxylate (2.14 g, 12.56 mmol) in chloroform (5 ml) was cooled to -40°. (4-Chlorophenyl)methanethiol (2 g, 12.56 mmol) and TEA (5 drops) were dissolved in chloroform (5 mL) and then added drop wise to the DEAD solution.

The reaction was left for a further 6h at -40º and then left overnight at -10º. The solution was washed 3 times with sulfuric acid (0.01 M, 10 mL). The aqueous layers were combined and extracted with chloroform twice (10 mL). The organic layers were then combined and dried over anhydrous $MgSO_4$. The mixture was evaporated at room temperature under pressure (2.31 g, 56%). ^{1}H NMR spectroscopy showed the product to be a 7:3 mixture of Z:E diastereomers. The Z isomer was obtained after column chromatography on alumina (95:5, hexane: benzene) (1.55g, 39%). A sample for spectral analysis was further purified by recrystallization from ethanol. (mp 62 ºC, range < 1 ºC). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.1); δ 1.28 (t, 3H, *J* = 7.1); δ 4.08 (s, 2H); δ 4.19 (q, 2H); δ 4.20 (q, 2H); δ 6.36 (s, 1H); δ 7.24- δ 7.26 (m, 4H). ^{13}C NMR {1H} (75 MHz, $CDCl_3$):δ 14.0; δ14.2; δ 36.1; δ 60.8; δ 62.4; δ 120.7; δ 128.7; δ 130.5; δ 133.3; δ 135.0; δ 147.6; δ 164.0; δ 165.1. HRMS (ESI) calcd for $[M+H]^+$ $C_{15}H_{18}O_4SCl$ 329.0614, found 329.0626.

General Method for the Synthesis of Diethyl 2-(Phenylamino)fumarate

Analogues 9 and 10[14]

A solution of the selected amine (2.94 mmol) in ethanol was added to a solution of diethyl acetylenedicarboxylate (0.5 g, 2.94 mmol) in ethanol. The reaction mixture was stirred for 24 h at room temperature. H_2SO_4 (1-2 drops, 0.1 M) was added and the solution stirred for 1 h. The solution was neutralised with NaOH (10 mL, 0.2 M). The aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic phases washed with brine, dried ($MgSO_4$) and the solvent removed under reduced

pressure to yield the desired compound. A sample was then recrystallised from ethanol for spectral analysis.

Diethyl 2-(4'-Chlorophenylamino)fumarate 9

The product precipitated from solution when the reaction mixture was neutralised, yielding yellow crystals of high purity and yield (0.65 g, 74%) mp 55 ^{o}C (range < 1 ^{o}C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, 3H, J = 7.3), δ 1.30 (t, 3H, J = 7.3), δ 4.17 (q, 4H), δ 4.19 (q, 4H), δ 5.43 (s, 1H), υ_A 6.83, υ_B 7.22 (q_{AB}, 4H, J = 8.8), δ 11.11 (s, 1H, NH). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 13.7; δ 14.3; δ 60.1; δ 62.2; δ 94.9; δ110.0; δ 122.2; δ 129.1; δ 139.0; δ 147.8; δ 164.0; δ 169.5. HRMS (ESI) calcd for $[M+H]^+$ $C_{14}H_{17}NO_4Cl$ 298.0846, found 298.0849.

Diethyl 2-(4'-Bromophenylamino)fumarate 10

The product precipitated from solution when the reaction mixture was neutralised, yielding yellow crystals of high purity and yield (0.85 g, 85%) mp 47-48^{o} C, lit. [16] 49.5-51.5^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, 3H, J = 7.2); δ 1.30 (t, 3H, J = 7.2); δ 4.17 (q, 2H); δ 4.19 (q, 2H); δ 5.43 (s, 1H); υ_A 6.77, υ_B 7.37 (q_{AB}, 4H, J = 8.8); δ 9.60 (s, 1H, NH). ^{13}C NMR {1H} (75 MHz, $CDCl_3$): δ 13.7; δ 14.3; δ 60.1; δ 62.2; δ 95.0; δ 117.0; δ 122.5; δ 132.0; δ 139.6; δ 147.7; δ 164.0; δ 169.5. HRMS (ESI) calcd for $[M+H]^+$ $C_{14}H_{17}NO_4Br$ 342.0341, found 342.0355.

Attempted Synthesis of Diamino and Mixed Diaddition Products

Experiments aimed at synthesising the diamino or aminothioaddition product from the alkene intermediate are summarised in Table 1. After the stated times, the solutions were

evaporated, and the products examined by ^{1}H NMR spectroscopy. The spectra showed unreacted substrates with small amounts of polymeric degradation products.

X-ray crystallography

Crystals of compounds **5**, **9** and **11** were prepared by recrystallisation from ethanol. Suitable single crystals were selected under the polarizing microscope (Leica M165Z), mounted on a MicroMount (MiTeGen, USA) consisting of a thin polymer tip with a wicking aperture. The X-ray diffraction measurements were carried out on a Bruker kappa-II CCD diffractometer at 150 K by using graphite monochromated Mo-Kα radiation (λ = 0.710723 Å). The single crystal, mounted on the goniometer using cryo loops for intensity measurements, was coated with paraffin oil and then quickly transferred to the cold stream using an Oxford Cryo stream attachment. Symmetry related absorption corrections using the Bruker program SADABS were applied and the data were corrected for Lorentz and polarisation effects using Bruker APEX2 software. The structure was solved by Direct methods and the full-matrix least-square refinement was carried out using SHELX[22]. The non-hydrogen atoms were refined anisotropically.

The three crystal structures were deposited at the Cambridge Crystallographic Data Centre and were assigned to the following deposition numbers: CCDC 1552250-1552252.

Computations

The Spartan software was used for all calculations (wavefunction.com), the Discovery Studio visualizer and ChemDraw were used to prepare figures and schemes.

Default parameters were used for geometry optimisations, except for the number of cycles which had to be increased in some cases to 5000 to achieve convergence, particularly for sulphur-containing transition states. The default convergence criteria include a maximum gradient component of $3x10^{-4}$ Hartrees/Bohr and a maximum change in bond length of $1.2x10^{-3}$ Å. If there was no Hessian matrix from previous calculations, the default was MMFF molecular mechanics for geometry optimization and PM3 semiempirical for transition state optimisation. Final geometry optimisations were performed at DFT level (ωb97X-D/6-31G*)[17] in a C-PCM implicit solvent model[18,19], followed by single point energy calculation of a Hessian matrix and of the IR spectra and thermodynamic quantities as implemented in the Spartan software at the same level as the final geometry optimisation (including implicit solvent). In some cases, this last Hessian matrix was used to improve the final geometry optimisation and calculation of IR spectra and thermodynamic quantities. Two variants of the implicit solvent model were used to mimic the reaction conditions: a "polar" (dimethylformamide, dielectric constant of 37.22) solvent for aniline and a "nonpolar" (tetrahydrofuran, dielectric constant of 7.43) solvent for thiophenolate reactions.

Racemic products were drawn as the (RR) diastereomer. All modelling was done using the analogous dimethyl esters and aniline and the thiophenolate anion as the nucleophiles.

For examining the likely conformer distribution, a Monte-Carlo search was carried out on a selection of low energy conformers, with an initial temperature of 5000K, using a default pruning method based on the energy and RMS torsion definition of nearness to keep a diverse set. The lowest energy conformers in each group were examined and the energies minimised at lower levels, then subsequently rerun and minimised at the final DFT level of theory. Because lowest energy conformations achieved using this methodology counter intuitively showed contiguous π-systems out of plane, the structures were redrawn with the π-systems planar and re-optimised, however the optimised structures were all twisted and without extended π-overlap.

For finding the transition states, the reactants were manipulated such that the nucleophile was poised for attack at the double or triple bond. The transition state geometries were then sketched using "Guess Transition State" and refined by drawing appropriate "curved arrows", followed by transition state geometry optimisation in stages.

Supporting Information. This material is available free of charge *via* the Internet at http://pubs.acs.org.

List of contents:

1. Supporting information: ^{1}H, ^{13}C and HRMS Spectra of Compounds **1**-**11**; Energies and other details of model compounds used in computations; Coordinate Files (output after minimisation; mol2 format); Tables with information on crystal data, data collection and refinements for crystallography of compounds **5**, **11** and **9**; Thermal Ellipsoid Plots for compounds **5**, **11** and **9**.
2. CIF format files: crystallography output files for compounds **5**, **11** and **9**.

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