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Cycloaddition Reactions of Azides and Electron-Deficient Alkenes in Deep Eutectic Solvents: Pyrazolines, Aziridines and Other Surprises

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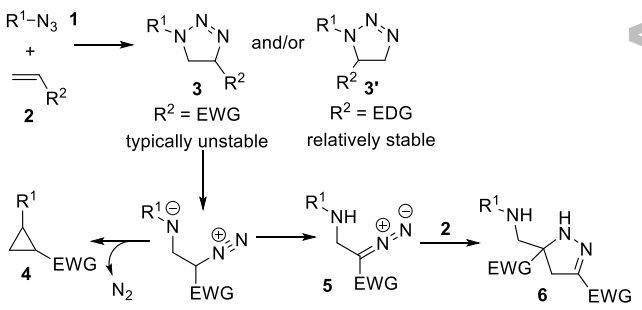
Abstract. The reaction of organic azides and electron-deficient alkenes was investigated in a deep eutectic solvent. A series of highly substituted 2-pyrazolines was successfully isolated and their formation rationalised by DFT calculations. The critical effect of substitution was also explored; even relatively small changes in the cycloaddition partners led to completely different reaction outcomes and triazolines, triazoles or enaminones can be formed as major products depending on the alkene employed.

Keywords: Alkenes; Azides; Cycloaddition; Heterocycles; Solvent Effects;

Introduction

Heterocycles are essential molecules both in chemistry and biology, and accordingly there is a relentless drive for efficient, selective and more sustainable methodologies for accessing these highly valuable products. 1,3-Dipolar cycloadditions represent a convergent and convenient route to five-membered heterocyclic molecules.[1] Compared to the ubiquitous azide–alkyne cycloaddition reaction to produce triazoles,[2] analogous azide–alkene cycloaddition to form triazolines has barely received any attention and no metal-catalysed version has been reported to date. Unactivated alkenes do not react or only sluggishly with organic azides and excruciatingly long reaction times (*i.e.* months) are often required.[3] Furthermore, triazolines are typically more reactive than either of the starting materials and while this can be regarded as an opportunity to access a range of heterocycles from simple starting materials,[4] only a handful of these examples are synthetically useful due to selectivity and decomposition issues.

It is well established that electron-deficient alkenes deliver 1,4-disubstituted triazolines regioselectively when reacted with azides.[5] However, these compounds are particularly unstable and to date only a handful of 1,4-disubstituted triazolines have been isolated.[6] In most cases, aziridines, imines or 2-pyrazolines are obtained instead (Scheme 1) Electron-withdrawing substituents in triazoline **3** relatively stabilise its open-ring isomer, often postulated as a zwitterion in the literature. This might in turn evolve into aziridine **4** upon N_2 extrusion, or alternatively undergo a second cycloaddition with the electron-poor alkene to generate, after tautomerisation, 2-pyrazoline **6**. The preferential pathway for 1,4-disubstituted triazolines is strongly dependent on the substitution on either cycloaddition partner. Long reaction times (up to 150 days!)[6d] are required for the formation of pyrazolines as these are typically carried out at room temperature to avoid undesired decomposition. Alternatively, this reaction can be promoted by the use of an external base, either NEt_3[6a,d] or DABCO,[7] although these reactions remain largely limited to acrylates.



Scheme 1. Evolution of disubstituted 1,2,3-triazolines.

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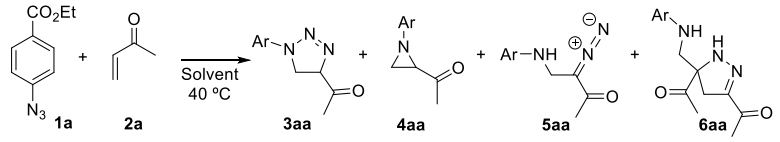
We were particularly interested in the preparation of pyrazolines, since they display a wide range of biological activities as well as very promising physical properties.[8] A reliable access to pyrazolines from easily accessible azides and alkenes would provide a convenient alternative to established routes to these heterocycles, namely the cyclisation under acidic conditions of hydrazones generated from α,β-unsaturated aldehydes or ketones and hydrazines,[9, 10] or the 1,3-dipolar cycloaddition of electron-rich nitrilimines and electron-deficient alkenes.[11, 12] We recently reported the cycloaddition of azides and relatively electron-rich alkenes in a deep eutectic solvent (DES) composed of choline chloride and urea.[13] This strategy allowed the isolation of Δ^2-triazolines on a gram scale, whilst minimising the use of volatile organic solvents. DESs are non-flammable mixtures with a much lower melting point than any of their individual components. These eutectic mixtures are held together through hydrogen bonds and are liquid at the reaction temperature. The reported applications of deep eutectic solvents keep on increasing powered by their competitive cost and enhanced environmental friendliness,[14] and include thermal,[15] Lewis acid-[16] and metal-catalysed[17] cycloaddition reactions.

In this article, we present the straightforward preparation of highly substituted 2-pyrazolines from azides and alkenes *via* transient 1,4-disubstituted triazolines in DES. The critical effect of substituents of alkenes is explored and specifically, we show how relatively small changes can lead to 1,5-disubstituted triazolines, enaminones or, triazoles as major reaction products.

Table 1. Solvent screening.[a]



Entry	Solvent	t (h)	Recov (%)[b]	Conv (%)[b]				Overall (%)
			1a	**3aa**	**4aa**	**5aa**	**6aa**	
1	ChCl/urea	8	28	--	--	<5	59	72
	(1:2)	24	14	--	--	6	69	84
2	i-PrOH	8	55	--	<5	10	34	45
		24	28	--	<5	14	52	68
3	EtOH	8	73	--	--	12	11	23
		24	44	--	--	21	28	49
4	THF	8	75	--	--	14	6	20
		24	49	--	--	20	24	44
5	Toluene	8	69	13	--	12	<5	31
		24	41	19	--	23	20	43
6	Water	8	37	--	6	18	41	63
		24	15	--	9	22	54	85
7	ChCl/water	8	33	--	--	--	66	66
	(1:2)	24	25	--	--	<5	67	69
8[c]	ChCl/DMU	8	18	--	--	--	68	68
	(1:2)	24	10	--	--	--	71	71
9	Gly/Urea	8	59	--	--	--	44	44
	(10:4)	24	50	--	--	--	46	46
10[d]	4% NH_3 in	8	91	--	--	--	--	9[c]
	EtOH	24	92	--	--	--	--	8[c]

[a] Reaction conditions: Azide **1a** (1.0 mmol), alkene **2a** (2.2 mmol) in 2 mL of solvent. [b] ^{1}H NMR recoveries/yields are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard. [c] Decomposition products were also observed. [d] Ethyl 4-amino benzoate was the only reaction product.

Results and Discussion

Preparation of 2-pyrazolines: Strong solvent effects were observed when a first screening was performed with ethyl 4-azidobenzoate **1a** and methyl vinyl ketone **2a** as the model substrates (Table 1).[18] In a first screening, the highest conversion to pyrazoline **6aa** was obtained in a choline chloride/urea DES after 24 h, presumably due to the presence of basic urea, although acceptable conversions were also obtained in protic solvents such as isopropanol or pure water in the absence of a base (Table 1, entries 1, 2 and 6). Triazoline **3aa** was only detected in toluene (Table 1, entry 5), while significant amounts (up to 23% by ^{1}H NMR) of diazo compound **5aa** were observed in all tested solvents except for DES. No or at most traces of aziridine **4aa** were produced in these reactions, except for the one carried out on water (Table 1, entry 6).

It has been reported in the literature that urea containing DESs might decompose when heated originating ammonia as by-product.[19] To confirm whether ammonia played a role in our reactions, we next tested several DESs known to produce different amounts of ammonia. DESs with no urea (ChCl/water, Table 1, entry 7) or reported to form similar amounts of ammonia than ChCl/urea (ChCl/DMU, Table 1, entry 8) led to comparable results. However, a mixture of glycerol and urea, expected to produce 10 times more ammonia, actually inhibited the formation of pyrazoline **6aa** (Table 1, entry 9). To confirm this trend a commercially available solution 4% of ammonia in ethanol was also screened and no cycloadduct, only an aniline by-product was then formed (Table 1, entry

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10). These results clearly show that the improved yields in pyrazoline in DES are not due to the incidental formation of ammonia under the reaction conditions.

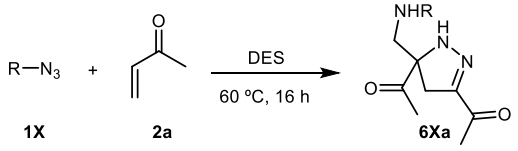
Since incomplete conversions were observed in all solvents after 24 h, higher reaction temperatures were also tested with ChCl/urea as DES. Identical results were obtained at 50 ºC, but slightly better conversion into pyrazoline **6aa** was obtained at 60 ºC after 16 h (78% by ^{1}H NMR). Longer reaction times or higher temperatures resulted in no further conversions and formation of decomposition products. Hence, the scope of the reaction was explored at 60 ºC in DES with a slight excess of the alkene partner.

Pyrazolines **6** were isolated in good yields from the reaction of various aryl and heteroaryl azides with methyl vinyl ketone (Table 2, entries 1–11). The exceptions were reactions with 1-azido-2-trifluoromethylbenzene **1g** and 3-azidopyridine **1k**, where even if some of the starting azide could be recovered, significant decomposition was also observed (Table 2, entries 7 and 11). Nevertheless, increased steric hindrance was well tolerated in general and pyrazolines from 2-chlorophenyl azide or mesityl azide were successfully prepared (Table 2, entries 8 and 9). Adamantyl azide also reacted under these conditions, although a lower yield in pyrazoline **6la** was obtained, partially due to incomplete conversion of the starting azide. All other screened alkyl azides, such as benzyl azide (Table 2, entry 13), led to the complete decomposition of the reaction mixture, even when the reactions were carried out at lower temperatures.

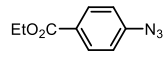
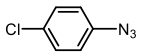
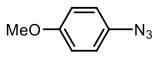
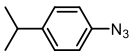
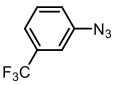
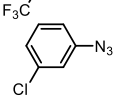
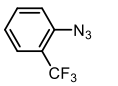
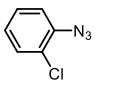
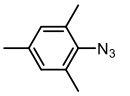
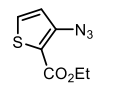
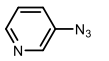
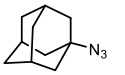
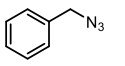
In these reactions no triazoline or aziridine products were evidenced and only traces of the corresponding diazo intermediates were observed by ^{1}H NMR. Interestingly, the reaction of 1-azido-3-chlorobenzene **1f** also delivered 1,4-disubstituted triazole **7fa** (5% by ^{1}H NMR), which was isolated in 4% yield and fully characterised. Formation of analogous triazoles was not observed in any other reaction.

A different electron-poor alkene, diethyl vinyl phosphonate, also produced the expected pyrazoline **6nb** in an excellent yield when reacted with 4-azidobenzonitrile at 70 ºC for 24 h (Scheme 2).

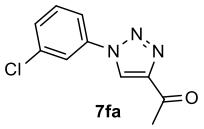
Table 2. Synthesis of pyrazolines with methyl vinyl ketone.[a]



1X **2a** **6Xa**

Entry	Azide		**1X** recovery (%)[b]		Yield (%)[c]
1		**1a**	9	**6aa**	73 (78)
2		**1b**	9	**6ba**	70 (70)
3		**1c**	<5	**6ca**	40 (57)
4		**1d**	5	**6da**	68 (74)
5		**1e**	<5	**6ea**	77 (79)
6[d]		**1f**	<5	**6fa**	70 (71)
7		**1g**	25	**6ga**	-- (37)
8		**1h**	7	**6ha**	73 (77)
9		**1i**	<5	**6ia**	72 (81)
10		**1j**	12	**6ja**	72 (78)
11		**1k**	11	**6ka**	20 (25)
12		**1l**	22	**6la**	40 (47)
13		**1m**	Decomposition		

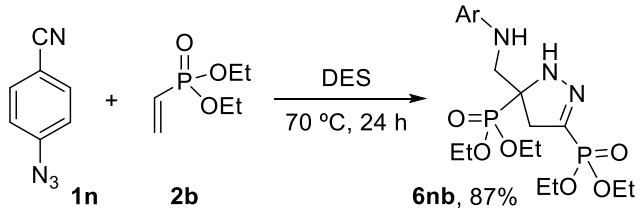
[a] Reaction conditions: Azide **1X** (1.0 mmol), alkene **2a** (2.2 mmol) in 2 mL DES, choline chloride/urea (1:2). [b] ^{1}H NMR recoveries were determined with respect to 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yields are the average of two independent experiments, ^{1}H NMR yields are provided in brackets and were determined with respect to 1,3,5-trimethoxybenzene as internal standard. [d] Triazole **7fa** was also isolated from this reaction.



7fa

The structure of **6nb** was confirmed by X-ray crystallography (Figure 1). The pyrazoline ring in **6nb** has a small envelope deformation with N1 lying

ca. 0.14 Å out of the {N2,C3,C4,C5} plane, which atoms are coplanar within ca. 0.01 Å.



Scheme 2. Cycloaddition of 4-azidobenzonitrile and diethyl vinyl phosphonate. DES = choline chloride/urea (1:2).

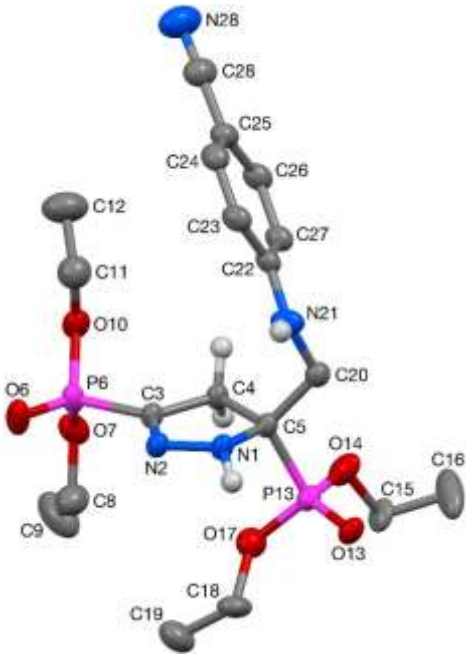
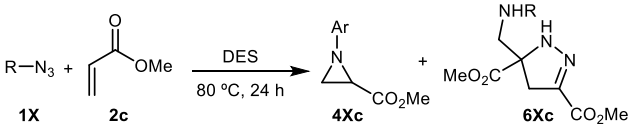


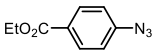
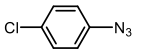
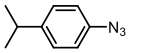
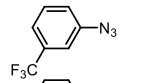
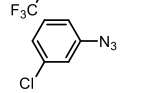
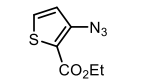
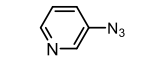
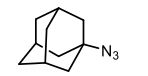
Figure 1. Structure of pyrazoline **6nb** (50% probability ellipsoids). Most hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): N(1)–N(2) 1.362(3), N(2)–C(3) 1.290(3), C(3)–C(4) 1.505(3), C(4)–C(5) 1.554(3), C(5)–N(1) 1.484(3); C(5)–N(1)–N(2) 112.03(16); N(1)–N(2)–C(3) 109.55(18); N(2)–C(3)–C(4) 114.05(19); C(3)–C(4)–C(5) 101.31(17); N(1)–C(5)–C(4) 102.04(16).

Next, methyl acrylate was used as cycloaddition partner (Table 3). Unsurprisingly, a small loss of regioselectivity was observed with a less polarised alkene and traces of the corresponding 1,5-disubstituted triazolines were detected in some cases by ^{1}H NMR[6a,b]. In these reactions both pyrazolines and aziridines were formed, except with 3-azidopyridine and adamantyl azide, which exclusively produced the corresponding pyrazolines **6kc** and **6lc** (Table 3, entries 7 and 8). Full azide conversions were obtained in these reactions but decomposition was sometimes problematic, and for example, only 49% of 3-chlorophenyl azide **1b** was converted into cyclic products (Table 3, entry 5).

Table 3. Cycloaddition of azides and methyl acrylate.[a]



1X 2c 4Xc 6Xc

Entry	Azide		4Xc Yield (%)[b]	6Xc Yield (%)[b]
1		**1a**	(11)	69 (77)
2		**1b**	16 (21)	47 (49)
3		**1d**	(9)	28 (33)
4		**1e**	14 (17)	23 (25)
5		**1f**	(11)	36 (38)
6[c]		**1j**	26 (30)	41 (46)
7		**1k**	--	21(26)
8[c]		**1l**	--	66 (66)

[a] Reaction conditions: Azide **1X** (1.0 mmol), alkene **2c** (2.2 mmol) in 2 mL DES, choline chloride/urea (1:2). [b] Isolated yields are the average of two independent experiments, ^{1}H NMR yields are provided in brackets and were determined with respect to 1,3,5-trimethoxybenzene as internal standard. [c] Reaction carried out for 16 h.

Computational studies: In our previous report on the cycloaddition of azides and electron-rich alkenes, 1,5-disubstituted triazolines were the typical major reaction products, while regioisomeric 1,4-triazolines were never observed, and instead, were shown to evolve to either aziridine or imine derivatives.[5] Indeed, the presence of an EWG in the starting olefin not only switches the regioselectivity of the reaction, but also leads to a different reaction pathway with pyrazolines **6** as major products. A triazoline opening/cycloaddition sequence is often postulated to rationalise these reactions (see Scheme 1),[6a,d,7] but to date no computational mechanistic studies are available for this transformation.

A plausible reaction profile to rationalise the formation of pyrazolines **6** from azides and alkenes was elucidated through DFT calculations.[20] First, the initial cycloaddition of 4-chlorophenyl azide **1b** and methyl vinyl ketone **2a** was computed and a clear preference for the formation of the 1,4-disubstituted triazoline **3ba** was found, as expected for an electron-deficient alkene (Scheme 3, $\mathbf{TS1}_{1,4}$ *vs* $\mathbf{TS1}_{1,5}$). For completion, the evolution of the 1,5-disubstituted regioisomer **3ba'** was explored, and it resulted in the formation of imine by-products through a nitrogen extrusion/migration sequence. Considering the higher

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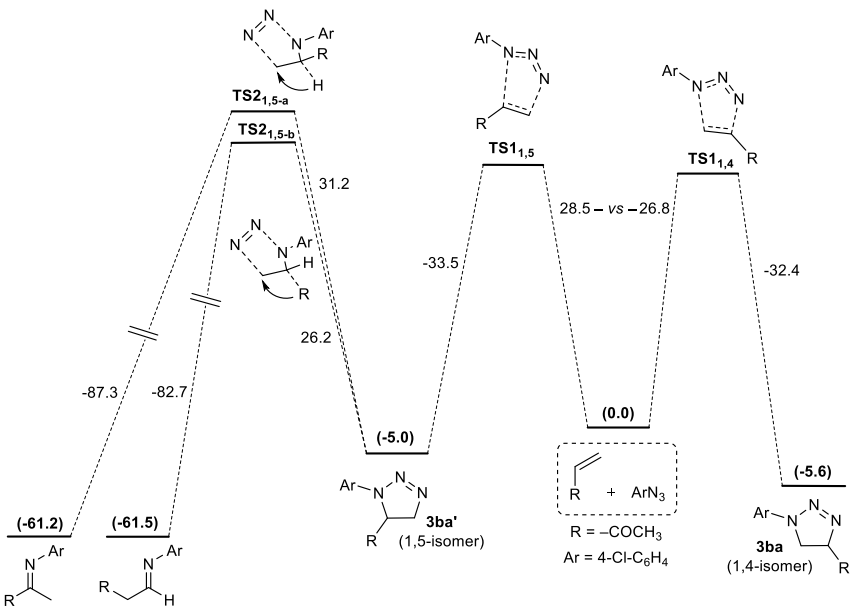
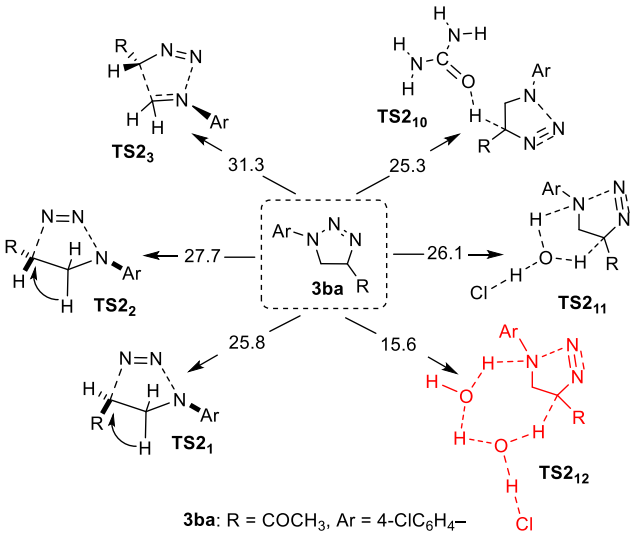


Scheme 3. Initial cycloaddition step and evolution of 1,5-disubstituted triazoline **3ba'**. $\Delta\Delta G^{\ddagger}_{333}$ values are provided in kcal/mol.

free energy barriers located for these processes, neither triazoline **3ba'** nor its decomposition products are expected to be formed in considerable amounts, as confirmed experimentally.

We then studied the possible evolution paths for triazoline **3ba**. Structures of all calculated transition states (**TS2$_1$** to **TS2$_{12}$**) are available *via* the data repository,[19] while the most energetically viable structures are depicted in Scheme 4. Firstly, N_2 loss may occur through two diastereomeric transition states (**TS2$_1$** and **TS2$_2$**) according to an asynchronous concerted retro-cycloaddition mechanism.



Scheme 4. Selected located transition states for the formation of diazo compound **4ba**. $\Delta\Delta G^{\ddagger}_{333}$ values are provided in kcal/mol.

We previously reported[13] that such transition states could lead to the formation of either an aziridine or an imine derivative. An alternative retro-cycloaddition to a diazo compound and an imine (**TS2$_3$**, Scheme 4) is a non-productive but non-competitive pathway ($\Delta\Delta G^{\ddagger}_{333}$ = 31.3 kcal/mol). For the present study, no transition state could be located for the direct cleavage of the N1–N2 bond in **3ba**, so we then attempted the initiation of the process by a proton shift from C4 to N1. While a direct hydrogen migration appeared to be energetically unviable (**TS2$_4$**, $\Delta\Delta G^{\ddagger}_{333}$ = 52.2 kcal/mol, see repository data for details[19]), an IRC calculation on this transition state nonetheless confirmed the desired cleavage of the N1–N2 bond, yielding in a single concerted (albeit non-synchronous) step to the diazo compound **5ba**.

It is well known that participation of solvent molecules in such proton migrations can lower the activation barriers.[21] Transition states including one to three water molecules as proton transfer agents, as well as one or two choline chloride molecules were located (**TS2$_5$**–**TS2$_9$**)[19] but the resulting activation free energies ranged between 40.1 and 52.2 kcal/mol, values significantly higher than the previous 25.8 kcal/mol required for **TS2$_1$**, as well as for the deprotonation of triazoline **3ba** with urea (**TS2$_{10}$**, $\Delta\Delta G^{\ddagger}_{333}$ = 25.3 kcal/mol). Overall, the most viable pathway located from **3ba** is **TS2$_{12}$**, which involves two molecules of water as well as a proton and a chlorine anion to form diazo compound **5ba**. The free energy barrier (computed for $[H^+]$ = 0.036 M = 1 atm at 333 K) is sufficiently low ($\Delta\Delta G^{\ddagger}_{333}$ = 15.6 kcal/mol) that even a much smaller proton concentration of *e.g.* 10^{-7} M would still lead to a facile barrier ($\Delta\Delta G^{\ddagger}_{333}$ = 24.1 kcal/mol) for the proton transfer. Furthermore, **TS2$_{12}$** would lead to diazo compound **5ba** in a single step with no other intermediates involved. From there, a second cycloaddition process with methyl vinyl ketone would yield the observed pyrazoline **6ba** after a final facile proton shift (Scheme 5).

Overall, our calculations indicate favourable free energy barriers for the reactions corresponding to our experimental results. A first thermal cycloaddition step leads to 1,4-disubstituted triazoline **3ba** as a single regioisomer, which is kinetically unstable and readily evolves to the corresponding diazo compound **5ba** in the highly polar, protic reaction media employed in these transformations. A straightforward second cycloaddition/tautomerisation sequence then delivers pyrazoline **6ba**, the only experimentally observed product under the reported conditions for the model substrates.

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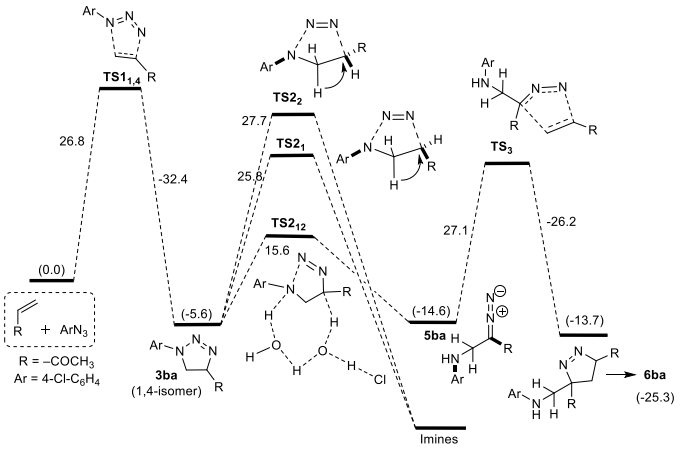
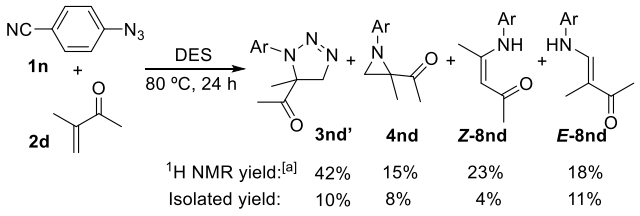


Scheme 5. Complete reaction profile with $\Delta\Delta G^{\ddagger}_{333}$ for the formation of pyrazoline **6ba**.

Further reactivity with electron-poor alkenes: With a mechanistic profile charted computationally, we next explored experimentally the effect of introducing additional substituents on the alkene moiety. This had dramatic effects on the outcome of the reaction, and no pyrazolines were obtained from substituted enones. Furthermore, either higher reaction temperatures or longer reaction times were required for these substrates. The reaction of 4-azidobenzonitrile with a *gem*-disubstituted 3-methyl-3-buten-2-one allowed isolation of four different products: a triazoline, an aziridine, and two enaminones (Scheme 6). The significant formation of the first two products shows that the presence of the *gem*-methyl substituent has a significant impact both on the regioselectivity of the azide-alkene cycloaddition and on the preferred evolution path for the transient 1,4,4-trisubstituted triazoline.



Scheme 6. Cycloaddition of 4-azidobenzonitrile with 3-methyl-3-buten-2-one. DES = choline chloride/urea (1:2). [a] ^{1}H NMR yields/recovery are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard.

The spectroscopic data for all of these products was in accordance with that reported for similar compounds, and notably the ^{1}H NMR spectra of isomeric enaminones **8nd** displayed chemical shifts of the N–H protons at 12.69 and 6.51 ppm, respectively, as expected due to the influence of intramolecular hydrogen bonding in ***Z*-8nd**.[22] The structures of **3nd'** and ***E*-8nd** were further confirmed by X-ray crystallography (Figure 2), and that of ***Z*-8nd** was in accordance with the literature.[23] The structure of **3nd'** was found to contain two crystallographically independent molecules (**3nd'-A** and **3nd'-B**) in the asymmetric unit. An envelope deformation of the triazoline ring was observed in both cases and the bond lengths and angles on the heterocyclic ring for this 1,5,5-trisubstituted triazoline were essentially identical to those reported for 1,5-disubstituted triazolines except for a longer N(1)–C(5) bond and smaller N(1)–C(5)–C(4) angle, which might be attributed to the additional substituent in the 5-position.[24]

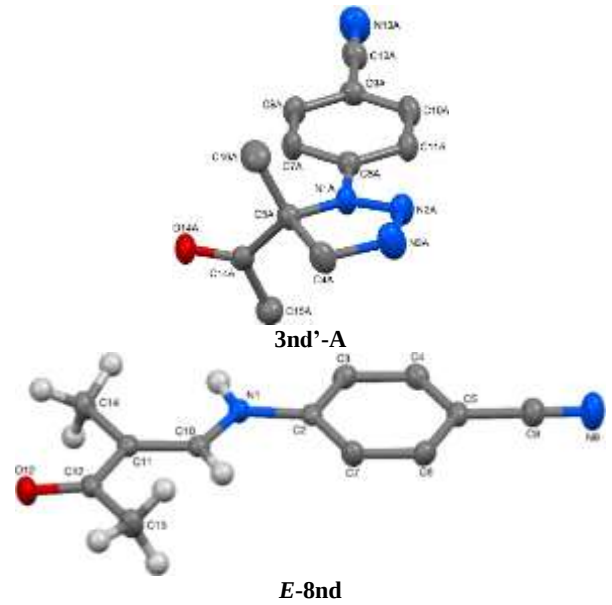
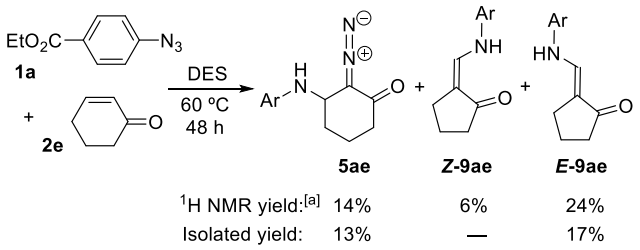


Figure 2. Structure of one (**3nd'-A**) of the two independent molecules present in the crystal of triazoline **3nd'**, and enaminone ***E*-8nd** (50% probability ellipsoids). Most hydrogens are omitted for clarity.

Mechanistically, aziridine **4nd**, and enaminones **8nd** are generated by different evolution of the open-ring isomer of unstable triazoline **3nd** after nitrogen extrusion. Our previously reported calculations showed that aziridines **4** were solely formed from 1,4-disubstituted triazolines after the electrocyclic ring closure of a singlet biradical intermediate. Enaminones **8nd** would be formed from **3nd'** or **3nd** through similar intermediate after a 1,2-hydride (or acyl) shift and tautomerisation.[13**Fehler! Textmarke nicht definiert.**]

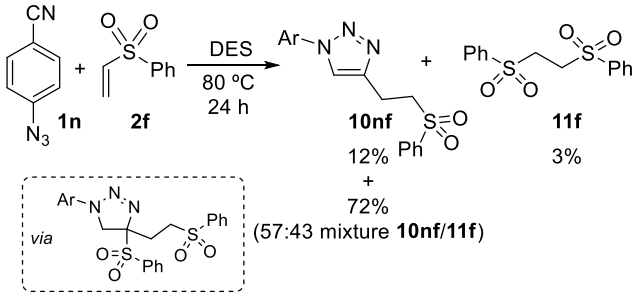
On the other hand, the reaction of 2-cyclohexen-1-one led to a similar outcome with the formation of two enaminones but no heterocycles were evidenced in the crude mixture, only diazo intermediate **5ae** (Scheme 7). This reaction was quite sluggish and 22% of the starting azide was recovered even after heating for 48 h. The formation of related ring-contracted enaminones from azides and 2-cyclohexen-1-one has been reported in the presence of a Lewis acid.[25] However, under such conditions

the *Z* isomer was the major product in most reported examples.



Scheme 7. Reaction of ethyl 4-azidobenzoate with 2-cyclohexen-1-one. DES = choline chloride/urea (1:2). [a] ^{1}H NMR yields are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard.

A last alkene was tested, phenyl vinyl sulfone, which led to an unexpected reaction outcome. In this case, no pyrazoline or any of the previously obtained products were observed and instead, 1,4-disubstituted triazole **10nf** and 1,2-bis(phenylsulfonyl)ethane **11f** were formed (Scheme 8). Disappointingly, only small amounts of pure products could be obtained since **10nf** and **11f** could hardly be separated either by column chromatography, or recrystallisation and most of triazole **10nf** (72%) was isolated as a 57:43 mixture with compound **11f**. Fortunately, both structures could still be fully confirmed by X-ray crystallography. That of triazole **10nf** is depicted in Figure 3, while data collected for **11f** was in accordance with the literature.[26]



Scheme 8. Reaction of 4-azidobenzonitrile with phenyl vinyl sulfone. DES = choline chloride/urea (1:2).

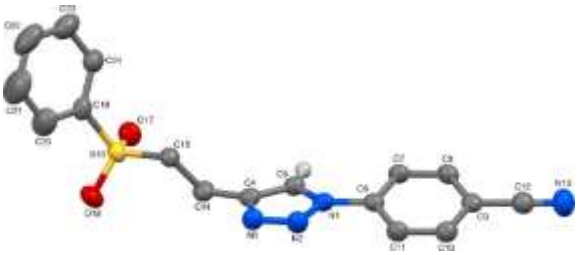


Figure 3. Structure of triazole **10nf** (50% probability ellipsoids). Most hydrogens are omitted for clarity.

Triazole **10nf** most probably originates from the expected 1,4-disubstituted triazoline followed by deprotonation at C4 and conjugate addition of a second molecule of vinyl phenyl sulfone. This step would be particularly supported by the stabilising effect of the sulfonyl group onto the corresponding carbanion.[27] An alkylation step at C4 would also prevent any isomerisation to linear diazo compounds since there would no longer be a proton available at that position. An elimination step from a transient 1,4,4-trisubstituted triazoline (Scheme 5)[28] would generate triazole **10nf** and phenylsulfonate, which would then form compound **11f** upon reaction with the starting vinyl sulfone.[29]

Conclusion

A range of trisubstituted 2-pyrazolines has been prepared from the corresponding azides and electron-deficient alkenes in DES and fully characterised. The reaction media not only reduces the amount of volatile organic solvent required, but also circumvents the need for an external base to promote the formation of the desired pyrazolines. Furthermore, the reaction times can be dramatically reduced in DES since higher temperatures than in the previously reported solvents (typically MeOH or toluene) are now possible. This is most probably due to a stabilising effect of the solvent on the transient triazolines, which minimises undesired decomposition and promotes the formation of cycloadducts.[13] Most remarkably, previous reports in organic solvents used basic conditions to promote the formation of pyrazolines, but in contrast, our DFT calculations points to formal acidic media (a combination of H^+ and Cl^-) as key for this reaction in DES.

The impact of the substitution on the alkene of choice can only be described as dramatic and while pyrazolines were formed preferentially (or even as the only products) from mono-substituted alkenes, the formation of other heterocycles, namely aziridines, triazolines or triazoles can become competitive or even the preferred reaction path. In order to fully exploit the potential of these transformations a better understanding of the factors controlling the reaction selectivity is needed. Efforts in this regard are currently ongoing in our laboratory and will be reported in due course.

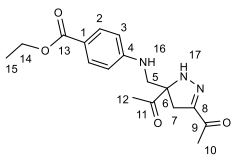
Experimental Section

General Considerations: All chemicals were obtained from commercial sources and used without further purification. The Deep Eutectic Solvent (DES) used in this work were prepared following a reported procedure.[30] Melting points were determined on an Electrothermal Gallenhamp apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer 100 series FT-IR spectrometer, equipped with a beam-condensing accessory (samples were sandwiched between diamond compressor cells). NMR spectra were measured on Bruker AVANCE 400 spectrometers (^{1}H: 400 MHz, ^{13}C: 101

MHz, ^{19}F: 377 MHz, ^{31}P: 162 MHz) at 20 °C. The chemical shifts (δ) are given in ppm relatively to a tetramethylsilane (0.00 ppm), $CDCl_3$ (77.2 ppm), DMSO-d6 (39.5 ppm), 1-fluorobenzene (–113.15 ppm) or phosphoric acid (0.00 ppm). The multiplicity is given as br, s, d, t, q, sept, and m for broad, singlet, doublet, triplet, quartet, septet, and multiplet. Assignments of some ^{1}H and ^{13}C NMR signals rely on COSY, HSQC, HMBC and/or DEPT-135 experiments. Single crystal X-ray diffraction data was collected using Xcalibur PX Ultra A and Agilent Xcalibur 3 E diffractometers, and the structures were refined using the SHELXTL[31] and SHELX-2013[32] program systems. Mass spectra (MS) were recorded on a Micromass Autospec Premier, Micromass LCT Premier or a VG Platform II spectrometer using EI, CI or ESI techniques at the Mass Spectrometry Service of Imperial College London. CCDC 1883194–1883197 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. FAIR data for NMR spectra, computational and crystallographic data, see DOI: 10.14469/hpc/4842.

General procedure for the formation of pyrazolines: Azide (1.0 equiv.) and alkene (2.2 equiv.) were stirred in deep eutectic solvent (choline chloride/urea = 1:2; 0.5 M) between 60–80 °C for 16 h, unless stated otherwise. The reaction mixture was cooled down to room temperature, diluted with water and EtOAc (2 mL each per mmol of azide) and the organic layer was separated. The aqueous layer was extracted twice with EtOAc (2 mL per mmol of azide), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (eluent: petroleum ether/EtOAc 10→50% gradient unless stated otherwise; reaction crude was dry-loaded onto stationary phase). Occasionally, the product recovered after column chromatography required trituration with pentane/Et_2O/MeOH (49:49:2) at −18 °C unless stated otherwise.

6aa: Following the general procedure at 60 °C from ethyl 4-azidobenzoate (1.50 g, 7.8 mmol) and methyl vinyl ketone (1.40 mL, 17.3 mmol), **6aa** was isolated as a yellow solid (1.89 g, 73%) after column chromatography (eluent: MeOH/EtOAc 0→20% gradient) and trituration with Et_2O. Mp 121.3–123.7 °C; R_f = 0.37 (petroleum ether/EtOAc = 50:50); IR: ν_{max} 3357 (m, N–H), 2982, 1706 (m, C=O), 1670 (s, C=O), 1596 (s), 1565 (m), 1539 (s, C=N), 1501, 1477, 1412 (m), 1363 (m), 1341 (m), 1287 (s), 1263 (s), 1209 (m), 1178 (s), 1124 (m), 1062 (m), 1022 (m), 951 (m), 882, 849 (m), 769 (m), 702, 679, 657, 639 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 9.0 Hz, 2H, H^2), 7.00 (br s, 1H, H^{17}), 6.59 (d, J = 9.0 Hz, 2H, H^3), 4.40–4.29 (br m, 1H, H^{16}), 4.32 (q, J = 7.0 Hz, 2H, H^{14}), 3.55 (dd, J = 13.5; 5.0 Hz, 1H, H^5), 3.47 (dd, J = 13.5; 8.0 Hz, 1H, H^5), 3.12 (d, J = 18.0 Hz, 1H, H^7), 3.00 (d, J = 18.0 Hz, 1H, H^7), 2.45 (s, 3H, H^{10}), 2.30 (s, 3H, H^{12}), 1.36 (t, J = 7.0 Hz, 3H, H^{15}); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 207.3 (C^{11}), 194.0 (C^9), 166.5 (C^{13}), 151.3 (C^4), 150.0 (C^8), 131.6 (C^2), 120.3 (C^1), 112.1 (C^3), 77.7 (C^6), 60.4 (C^{14}), 46.9 (C^5), 37.0 (C^7), 25.6 (C^{10}), 25.3 (C^{12}), 14.4 (C^{15}); HRMS (ES+) calculated for $C_{17}H_{22}N_3O_4$: 332.1610, found: 332.1613 ([M + H]$^+$).



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FULL PAPER

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