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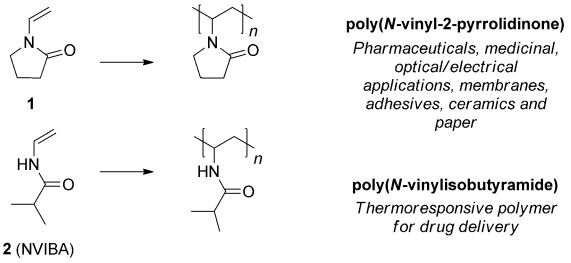
Unexpected Direct Synthesis of *N*-Vinyl Amides through Vinyl Azide–Enolate [3+2] Cycloaddition

Hans Choi, Harry J. Shirley, Paul A. Hume, Margaret A. Brimble, and Daniel P. Furkert**

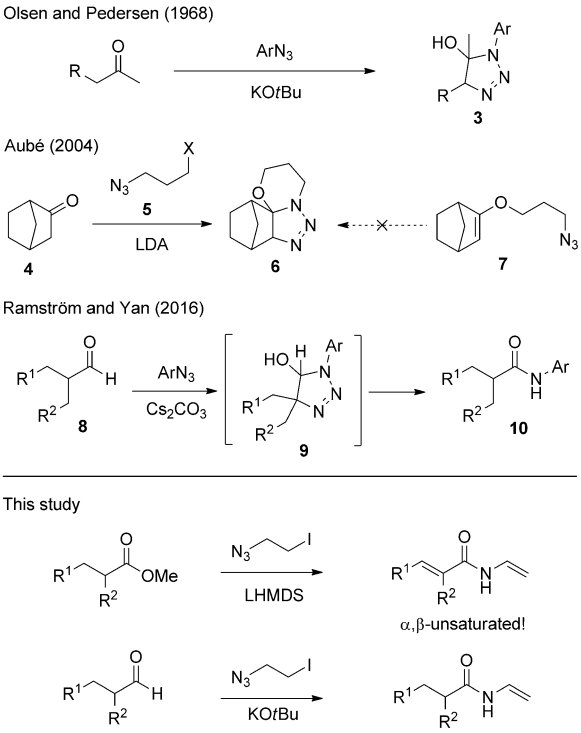
Abstract: *The unexpected synthesis of industrially important N-vinyl amides directly from aldehydes and α,β-unsaturated N-vinyl amides from esters is reported. This reaction probably proceeds through an initial [3+2] azide–enolate cycloaddition involving a vinyl azide generated in situ. A survey of the reaction scope and preliminary mechanistic findings supported by quantum computational analysis are reported, with implications for the future development of atom-efficient amide synthesis. Intriguingly, this study suggests that (cautious) reevaluation of azidoethene as a synthetic reagent may be warranted.*

N-Vinyl amides, a subset of the wider class of enamides,[1] display useful reactivity as synthetic intermediates.[2] They are also of increasing importance for the synthesis of poly(vinyl amides) with an array of applications, including drug formulation and tissue engineering.[3] *N*-Vinyl amide polymer variants have not yet been widely explored owing to the lack of convenient general methods to access the monomer feedstocks (Scheme 1).[4–6] Given the utility of these compounds, it is surprising that methods to access *N*-vinyl amides remain relatively scarce. We report herein a novel method involving the generation of a vinyl azide in situ for the direct synthesis of *N*-vinyl amides from α-substituted aldehydes and, remarkably, α,β-unsaturated *N*-vinyl amides from α-substituted esters. The application of substituted vinyl azides to the synthesis of amides and heterocycles has attracted considerable attention as an important and versatile emerging technology.[7]



Scheme 1. Industrially important *N*-vinyl amides **1** and **2**.[3a]

Azide–enolate cycloaddition reactions are known, but have not been well explored. In a series of early publications, Olsen originally described enolate-mediated reactions of aryl azides with ketones or aldehydes to afford hydroxytriazolines, such as **3** (Scheme 2).[8] Aubé and co-workers reported that the lithium enolate of ketone **4** underwent [3+2] cycloaddition with azide **5** to give triazole **6**, but a potential precursor, enol ether **7**, was unreactive.[9] In 2016, Ramström, Yan, and co-workers reported the enolate-mediated reaction of aldehydes with aryl azides to give *N*-aryl amides (e.g. **10**).[10] This reaction was proposed to proceed via a 1,2,3-triazoline intermediate **9** generated by [3+2] cycloaddition of the aryl azide with the enolate of aldehyde **8**.



Scheme 2. Azide–enolate [3+2] cycloaddition reactions implicated in amide and triazoline synthesis. LDA = lithium diisopropylamide, LHMDS = lithium hexamethyldisilazide.

Our own investigations began as part of synthetic studies towards N-heterocyclic systems. Alkylation of methyl ester **11** (Scheme 3) with alkyl iodides was investigated as a means to access α-quaternary esters **13** and **15**. Accordingly, the treatment of ester **11** with LHMDS and addition of the

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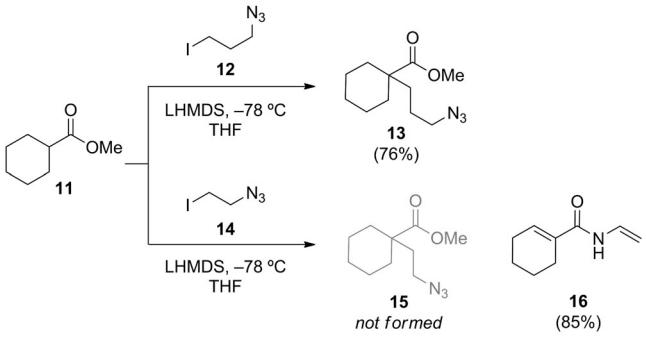


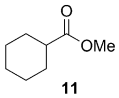
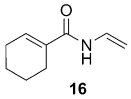
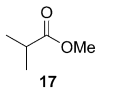
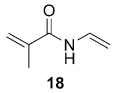
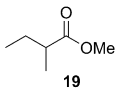
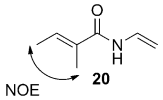
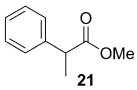
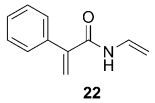
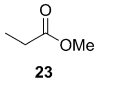
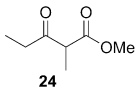
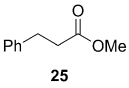
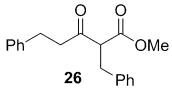
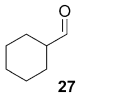
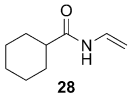
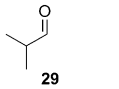
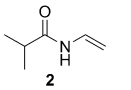
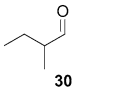
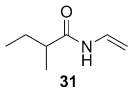
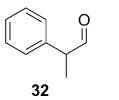
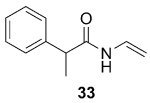
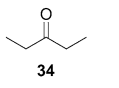
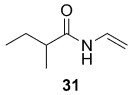
Scheme 3. Initial observation of unexpected *N*-vinylacrylamide formation.

three-carbon-atom iodo azide **12** delivered the expected product **13** in high yield. In contrast, in the analogous reaction of **11** with the two-carbon-atom iodo azide **14**,[11] the desired azido ester **15** was not observed. Instead, the unexpected *N*-vinyl amide **16** was isolated in 85% yield. Of particular note was the new α,β unsaturation present in amide **16**.

This discovery prompted a survey of the reactivity of further esters with iodo azide **14** (Table 1). Methyl isobutyrate (**17**) was converted into the novel *N*-vinylacrylamide **18** (entry 2), and methyl 2-methylbutanoate (**19**) into acrylamide **20** (entry 3), both in high yield. The *E*-alkene geometry of **20** was determined by NOE analysis. 2-Phenylpropionate **21** similarly afforded acrylamide **22** (entry 4). Submission of α-unsubstituted esters **23** and **25** to the reaction conditions only returned known Claisen condensation products **24** (entry 5) and **26** (entry 6), respectively. The analogous reactivity of aldehydes was also investigated; the treatment of **27** with LHMDS and addition of **14** returned only unreacted aldehyde. Changing the base to KO*t*Bu led to the isolation of *N*-vinyl amide **28** (entry 7). Intriguingly, **28** did not possess the acrylamide α,β unsaturation obtained from the analogous ester substrate (entry 1 vs. 7). Notably, isobutyraldehyde **29** was transformed into the valuable monomer *N*-vinylisobutyramide (NVIBA, **2**; entry 8). The initially moderate yields were significantly improved after brief optimization. Similarly, aldehydes **30** and **32** afforded the novel *N*-vinyl amides **31** and **33**, respectively (entries 9 and 10). Finally, a second method to access **31** was demonstrated from 3-pentenone **34** (entry 11).

The work of Olsen/Pedersen, Aubé, and Malmström/Yan (see Scheme 1) suggested that this process probably proceeds through a formal azide–enolate [3+2] cycloaddition. In the aldehyde manifold (Table 1, entries 7–10), this transformation would be expected to initially give an intermediate triazoline **35** (Scheme 4, path A). The triazole could then undergo either cyclization to **36**[9] or a 1,2-hydride shift with extrusion of nitrogen to give amide **37**. On further consideration, however, neither **36** nor **37** appeared sufficiently activated to undergo elimination to form *N*-vinyl amide **38**.[12] Furthermore, the mechanism shown for path A would not account for the different reactivity observed between the three-carbon-atom iodo azide **12** and the two-carbon-atom iodo azide **14**. A control experiment conducted in the absence of an aldehyde (Scheme 4, path B) showed rapid conversion of **14** into

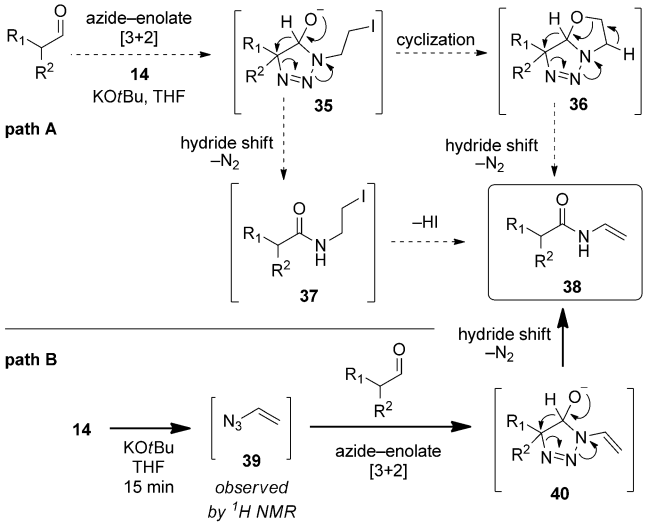
Table 1: Scope of the direct synthesis of *N*-vinyl amides.

Entry	Substrate	Product	Conditions[a]	Yield [%]
1	 11	 16	A	85
2	 17	 18	A	74
3	 19	 NOE 20	A	68
4	 21	 22	A	54
5	 23	 24	A	(14)
6	 25	 26	A	(24)
7	 27	 28	B	72
8	 29	 2	B	72
9	 30	 31	B	87
10	 32	 33	B	67
11	 34	 31	C	29

[a] Method A: **14**, LHMDS, THF, −78 °C→rt, 16 h; method B: KO*t*Bu (5 equiv), **14** (2.5 equiv), CH_2Cl_2, 0 °C→rt, 16 h; method C: **14**, LDA, Et_2O, −78 °C.

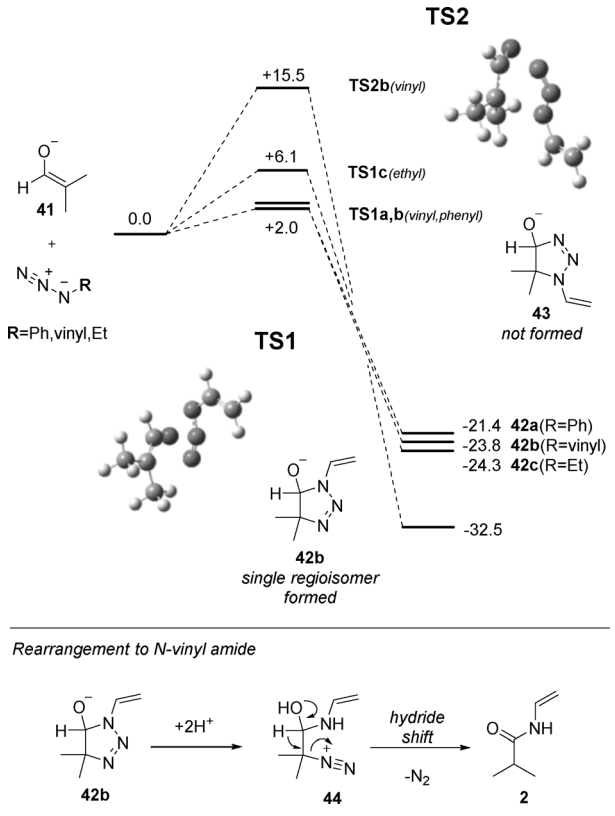
azidoethene (**39**) by NMR spectroscopy upon exposure to potassium *tert*-butoxide.[13] These conditions are similar to those originally developed by Hassner and co-workers in a series of seminal studies on the formation of substituted vinyl azides.[14] Azidoethene (**39**) could then undergo rapid cycloaddition with an enolate to give a triazole intermediate **40**, from which nitrogen extrusion and a 1,2-hydride shift would give *N*-vinyl amide **38** either through a concerted process or an asynchronous sequence involving an intermediate diazonium ion. Although azidoethene (**39**) was described as early as 1910,[15] it has been used for little further practical chemistry;[16] however, it has been the subject of a number of computational studies.[17]

To investigate the feasibility of our mechanistic hypothesis, as there are no previous reports of the computational analysis of azide–enolate cycloaddition reactions, we calcu-



Scheme 4. Mechanistic possibilities for direct *N*-vinyl amide formation from aldehydes.

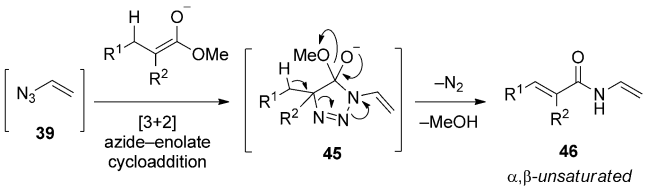
lated the reaction of aldehyde enolate **41** with azidoethene (**39**) by using DFT B3LYP/6-31G + (d,p) with a polarizable continuum model to account for solvent effects (Scheme 5; see the Supporting Information for details). Analogous cycloaddition reactions for phenyl and ethyl azide were also calculated to assess the effects of orbital delocalization on reactivity and facilitate comparison with the literature and our own observations.



Scheme 5. DFT calculations for the regioisomeric transition states **TS1** and **TS2** (B3LYP/6-31G + (d,p); values in kcal mol^{-1}) support the observed selectivity of cycloaddition and the energetic feasibility of subsequent rearrangement.

The theoretical calculations displayed excellent agreement with our experimental results and the regiochemistry observed in previous [3+2] azide–enolate cycloaddition reactions.[8–10] Transition states for three virtual azides leading to the experimentally observed regioisomer, exemplified by **TS1b** leading to **42b** (R = vinyl), were associated with lower activation energies of 2.0–6.1 kcal mol^{-1} (phenyl **TS1a** ≈ vinyl **TS1b** < ethyl **TS1c**). The activation energy of 6.1 kcal mol^{-1} estimated for ethyl azide suggests that cycloaddition of the enolate of **11** and azide **12** (see Scheme 3) could plausibly proceed at room temperature, but the alkylation pathway to give **13** is observed to predominate. Conversely, in the reaction of **11** and **14**, facile formation of azidoethene (**39**) would lower the required activation energy for cycloaddition, thus eventually leading to formation of the α,β-unsaturated *N*-vinyl amide **16** as the sole product. In contrast to **TS1**, it was determined that transition state **TS2b** for the formation of the unobserved regioisomer **43** required a significantly larger energetic barrier of 15.6 kcal mol^{-1} to be overcome. Interestingly, the cycloaddition reactions proceeding via **TS1** displayed pronounced asynchronicity, in contrast to **TS2**. Subsequent rearrangement of the intermediate triazoline **42b** was found to be dependent on protonation of both the alkoxide and the amide nitrogen atom; direct rearrangement of the alkoxide **42b**, with concomitant nitrogen extrusion, was calculated to require a prohibitively high activation energy of > 25 kcal mol^{-1}, but double protonation essentially abolished this energetic barrier. This prediction was borne out both by our studies, which involved a mildly acidic workup,[18] and the much earlier finding of Olsen that hindered triazolines obtained by aryl azide–enolate cycloaddition were stable to isolation and required exposure to a Lewis acid to undergo an analogous rearrangement.[8a] Our calculations additionally indicate that the rearrangement–nitrogen-extrusion process is likely to be an asynchronous process (see the reaction movie in the Supporting Information); initial protonation leads immediately to the formation of diazonium ion **44** through cleavage of the N–N bond, and **44** then undergoes slower reformation of the carbonyl functionality and a 1,2-hydride shift to afford vinyl amide **2**. The fundamental mechanistic processes proposed herein also appear to be in broad agreement with a recent computational study on related azide–enamine cycloaddition reactions to give ring-contracted amidines.[19] The current work does not appear to rule out the possible intermediacy of an aziridine species in these processes.

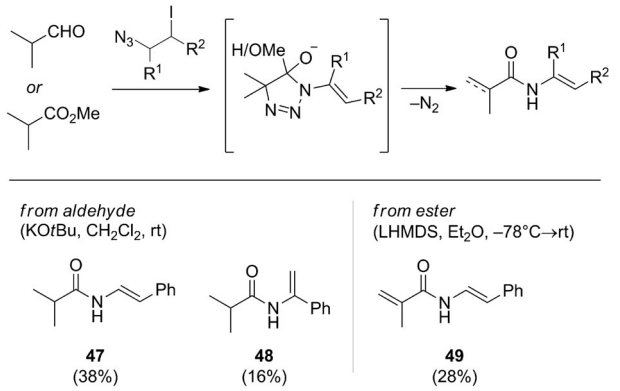
Mechanistically, the original unexpected observation of the formation of α,β-unsaturated *N*-vinyl amides from esters is also consistent with an enolate–azide cycloaddition mechanism (Scheme 6). The initially formed triazole intermediate **45**, however, lacks a hydride to undergo the 1,2-shift. Instead, regeneration of the carbonyl group eliminates methoxide, followed by β-deprotonation under the basic reaction conditions and extrusion of nitrogen. This direct formation of α,β-unsaturated *N*-vinyl amides of general structure **46** from α-substituted esters is a very unusual example of oxidative



Scheme 6. Proposed mechanism for the direct formation of α,β-unsaturated *N*-vinyl amides from esters.

amide formation from an otherwise unactivated carbonyl component.

Finally, as an extension of this work, the vinyl azide–enolate cycloaddition approach was further explored to successfully access substituted *N*-vinyl amide systems **47**–**49** (Scheme 7), thus suggesting potential for future wider development.



Scheme 7. Extension to substituted *N*-vinyl amides (yields have not been optimized).

In conclusion, we have reported the remarkable and unexpected direct synthesis of α,β-unsaturated *N*-vinyl amides from esters and *N*-vinyl amides from aldehydes. The reaction most likely proceeds through the in situ formation of an *N*-vinyl azide, which undergoes facile azide–enolate [3+2] cycloaddition, followed by rearrangement and nitrogen extrusion. The proposed mechanism and observed regiochemistry are in accordance with quantum calculations performed to estimate transition-state activation energies for alkyl, aryl, and vinyl azides. Both experimental data and calculations indicate that protonation of the initial triazoline cycloaddition product is required before rearrangement to a diazonium ion and nitrogen extrusion can occur to form the final *N*-vinyl amides. These investigations contribute useful data to aid the ongoing development of atom-efficient methods for amide formation and offer new possibilities in synthesis for drug discovery and the applications of industrially important *N*-vinyl amide polymeric materials. Finally, this study suggests that, given recent progress in batch and flow reaction technology,[20] (cautious) reevaluation of azidoethene as a useful synthetic reagent may be warranted.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amides · [3+2] cycloaddition · rearrangement · transition states · vinyl azides

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Communications

Synthetic Methods

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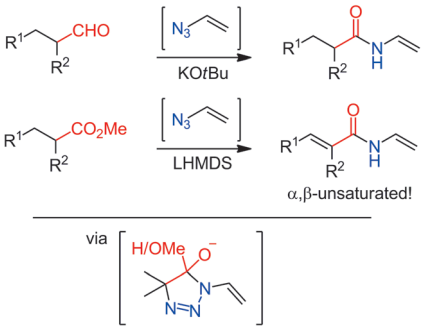
Unexpected Direct Synthesis of *N*-Vinyl Amides through Vinyl Azide–Enolate [3+2] Cycloaddition



Worth another look: Industrially important *N*-vinyl amides were synthesized directly from aldehydes/esters and 1-azido-2-iodoethane. Quantum-chemical calculations support the proposed mechanism involving [3+2] cycloaddition of the enolate derived from the aldehyde or ester with a vinyl azide generated in situ (see scheme). The results suggest that azidoethene itself may be worth (cautious) reevaluation as an atom-efficient synthetic reagent.