

Synthesis of Pyrroles from Isoxazoles by an O-to-C Skeletal Edit

Corresponding Author: Professor Mark Levin

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Version 0:

Reviewer comments:

Referee #1

(Remarks to the Author)

This manuscript by Bracken et al. presents a highly compelling contribution to the field of skeletal editing, describing an O-to-C atom replacement that converts isoxazoles into pyrroles. The authors identify an N-propargylic enaminone as the key intermediate bridging these two important heterocyclic classes. The primary concern regarding this manuscript is that the overall transformation is fundamentally a combination of three known reactivities: isoxazole alkylation, reduction, and pyrrole formation from the enaminone. Specifically, the crucial enaminone-to-pyrrole cyclization is inspired by the prior work of Cheng and coworkers (referenced as ref 24). While the individual elementary steps possess literature precedent, the successful integration of these processes into highly compatible one-pot conditions is what makes the work valuable and transformative. The functional group tolerance demonstrated in this methodology is excellent. As shown in Figure 3, the reaction accommodates a wide array of useful functionalities, which will make this a highly practical tool for synthetic chemists.

The mechanistic details provided in this study are a standout feature, delivering new insights that were not previously known. The investigations detailed in Figure 4 are exceptionally well done. The authors identified potential competition between the desired pathway and a Conia-Ene process, and successfully established a quantitative predictive model based on physical organic parameters of the substrate. This rigorous approach is impressive and marks an important step forward in heterocyclic chemistry.

In summary, while there is a legitimate concern regarding absolute novelty given the reliance on known reactivity patterns, I believe this work is an important step forward. It demonstrates the power of skeletal editing to synthesize difficult-to-access pyrroles that are highly relevant to medicinal chemistry campaigns.

Points:

- The authors note that the tendency of pyrroles to undergo oxidative decomposition. While purification under ambient conditions is understandably difficult, it would be informative for readers to understand the fundamental reactivity patterns of less-substituted (e.g., singly-substituted) isoxazoles. The authors can clarify whether the reaction sequence is actually compatible with these simpler substrates. Explicitly addressing whether this limitation is strictly a purification challenge or an inherent failure of the O-to-C skeletal editing methodology would strengthen the discussion of the reaction's scope.
- To improve clarity for the readers, it would be highly helpful to explicitly draw the structure of the α -methyl propargyl triflate reagent in Figure 4.

Referee #2

(Remarks to the Author)

This manuscript presents a synthetically valuable one-pot conversion of isoxazoles into pyrroles via direct O-to-C atom

replacement. While numerous strategies for editing the isoxazole skeleton into pyrroles have been reported, achieving this transformation without introducing extraneous functional groups at other positions remains a significant challenge. This work accomplishes a significant O-to-C atom replacement in the isoxazole-to-pyrrole conversion. The authors describe a regioretentive, three-step sequence involving N propargylation, reductive ring opening, and base mediated cyclization. The mechanistic study is thorough, encompassing the identification of a competing Conia ene pathway and development of a predictive steric reaction model. The reaction scope is broad, and several examples were illustrated to show synthetic advantages over traditional pyrrole syntheses. Overall, this work provides a new approach for pyrrole synthesis and in-depth mechanistic insights, and is recommended for publication. It would be beneficial to provide additional supporting data to further demonstrate its synthetic and practical value. The following revisions, however, should be considered to further strengthen the manuscript.

1 In arguing for the importance of atom-replacement synthesis from isoxazoles to pyrroles, the author claims that isoxazoles are easier to synthesize than pyrroles, noting that existing pyrrole methods “are highly specific to a narrow range of substitution patterns, and such reactions leave often-undesired functional groups on the pyrrole.” At the same time, the author emphasizes that “In stark contrast, isoxazoles are easily synthesized from readily-accessible building blocks.” However, this argument is not sufficiently convincing. The author’s assertion that pyrrole synthesis often leaves undesired functional groups is overly simplistic. In reality, existing synthetic methods for pyrroles are well-established and highly complementary. By selecting appropriate synthetic strategies, target pyrroles can be obtained without introducing unwanted functional groups. Furthermore, the author mentions that isoxazoles can be readily prepared via 1,3-dipolar cycloaddition of nitrile oxides with alkynes, yet this approach may similarly result in residual undesired functional groups—a limitation analogous to the criticism directed at pyrrole synthesis. Therefore, it is recommended that the author revise such statements.

2 It would be beneficial for readers to better understand this area if some recent achievements on atom replacement such as C-to-N and N-to-C replacement, were incorporated into the introduction section.

3 The late-stage modification of complex molecules including pharmaceuticals and natural products represents a key merit of skeletal editing. Although isoxazole motifs are not widely prevalent in natural products, we encourage the authors to include several representative examples of such applications to further highlight the synthetic utility of this methodology.

4 It should be noted that the claim “an O-to-C replacement reaction of heteroaromatic systems has yet to be disclosed” overlooks existing literature. Several transformative approaches for the oxazole-to-pyrrole conversion have been documented, albeit sometimes introducing residual substituents. To ensure a comprehensive and clear perspective for readers, the manuscript would benefit from citing these key developments. Relevant references, for example: *J. Org. Chem.* 2026, 91, 767-779; *Tetrahedron* 2014, 70, 4631-4639; *J. Org. Chem.* 2017, 82, 256-268; *Org. Biomol. Chem.* 2021, 19, 1976–1984; *Org. Lett.* 2015, 17, 5224-5227.

5 The calculations were performed using the PCM model with DMF as the solvent, whereas the experimental cyclization was conducted in NMP. Notably, as shown in Table S5 (solvent screening), DMF afforded only a 13% yield, while NMP gave a significantly higher yield of 76%. This discrepancy raises questions about the suitability of using DMF in the computational model to represent the actual reaction environment. Although DMF and NMP are structurally similar, NMP may exhibit different Lewis basicity or solvation effects. It is recommended that the authors comment on the potential solvent effects or provide single-point calculations in NMP for key transition states to better align the computational and experimental findings.

6 The use of TEMPO to inhibit side reactions during the reduction step in synthesizing 2g and 2h raises questions about the nature of these side pathways and the generality of this requirement. Specifically, what by-products are formed without TEMPO, and must other diaryl substrates employ the same precaution? A mechanistic explanation (e.g., radical trapping or oxidation prevention) alongside control experiments omitting TEMPO would be valuable. Such additions would provide deeper insight into the reaction’s robustness and guide future substrate selection.

7 Isothiazole is another widely prevalent heterocyclic scaffold. Could the author’s methodology be extended to achieve S-to-C replacement for the synthesis of pyrroles from isothiazoles?

8 To ensure the professionalism and consistency of the manuscript, all NMR spectra should be processed and presented using a uniform template. It is recommended that the integral values be added to the ¹H NMR spectrum on page S198.

Version 1:

Reviewer comments:

Referee #2

(Remarks to the Author)

Most of my comments have been addressed during the previous round of review, and the manuscript has been substantially improved. I do not have more important concerns regarding the revised manuscript. The study presents an interesting and valuable synthetic strategy that will likely be of interest to the broad readership of the journal. It is a pity that the applicability of the method to structurally complex substrates remains limited.

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Point-by-Point Response

Reviewer 1

This manuscript by Bracken et al. presents a highly compelling contribution to the field of skeletal editing, describing an O-to-C atom replacement that converts isoxazoles into pyrroles. The authors identify an N-propargylic enaminone as the key intermediate bridging these two important heterocyclic classes.

We thank the reviewer for this positive assessment of our work.

The primary concern regarding this manuscript is that the overall transformation is fundamentally a combination of three known reactivities: isoxazole alkylation, reduction, and pyrrole formation from the enaminone. Specifically, the crucial enaminone-to-pyrrole cyclization is inspired by the prior work of Cheng and coworkers (referenced as ref 24).

While the individual elementary steps possess literature precedent, the successful integration of these processes into highly compatible one-pot conditions is what makes the work valuable and transformative. The functional group tolerance demonstrated in this methodology is excellent. As shown in Figure 3, the reaction accommodates a wide array of useful functionalities, which will make this a highly practical tool for synthetic chemists.

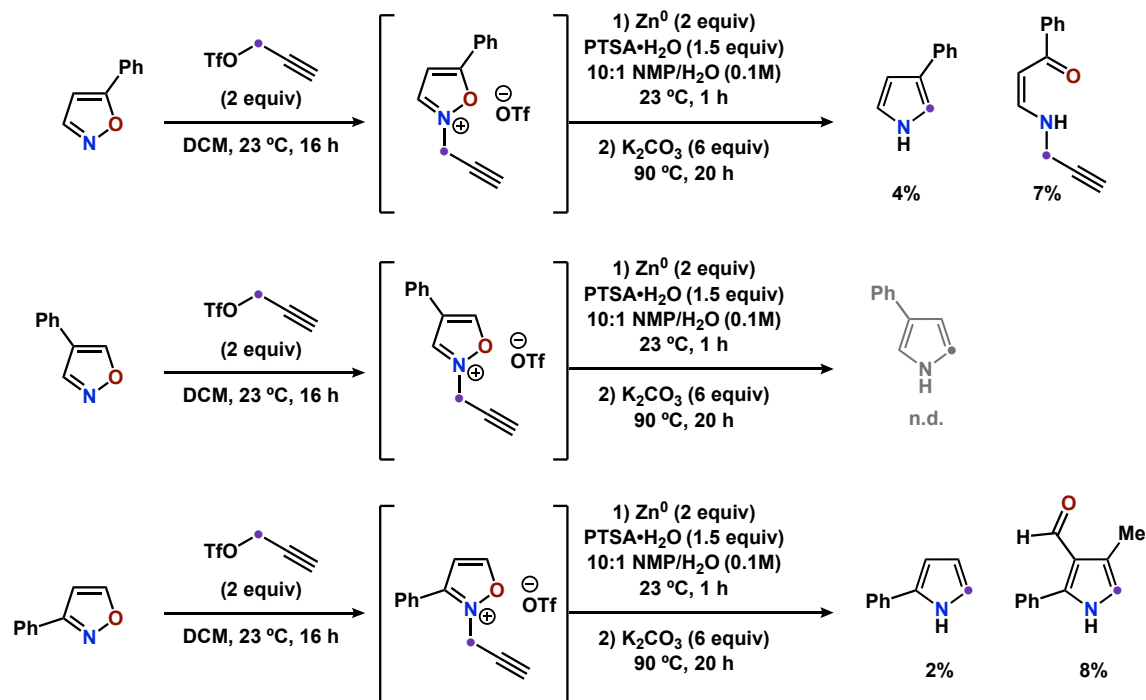
The mechanistic details provided in this study are a standout feature, delivering new insights that were not previously known. The investigations detailed in Figure 4 are exceptionally well done. The authors identified potential competition between the desired pathway and a Conia-Ene process, and successfully established a quantitative predictive model based on physical organic parameters of the substrate. This rigorous approach is impressive and marks an important step forward in heterocyclic chemistry.

In summary, while there is a legitimate concern regarding absolute novelty given the reliance on known reactivity patterns, I believe this work is an important step forward. It demonstrates the power of skeletal editing to synthesize difficult-to-access pyrroles that are highly relevant to medicinal chemistry campaigns.

We thank the reviewer for this balanced assessment of the strengths and weaknesses of our work. In response to the one weakness noted, we would only add (largely in line with the reviewer's assessment) that while it is true that the pyrrole-forming cyclization was documented in a single prior report, its usefulness for O-to-C replacement was not apparent until our work. Moreover, we have significantly expanded the scope and available substitution patterns for the cyclization, which is in part due to the newfound regiospecific accessibility of the *N*-propargyl enaminone intermediates from isoxazoles. As the reviewer notes, we revised the originally proposed mechanism for this cyclization (supported by both experimental and computational work) and harmonized the understanding of several competing side reactions. As such, this work brings new knowledge to the underlying reactivity pattern, and when this is combined with the other strengths noted by the reviewer, we are confident that this work is appropriate for *Nature*.

1) The authors note that the tendency of pyrroles to undergo oxidative decomposition. While purification under ambient conditions is understandably difficult, it would be informative for readers to understand the fundamental reactivity patterns of less-substituted (e.g., singly-substituted) isoxazoles. The authors can clarify whether the reaction sequence is actually compatible with these simpler substrates. Explicitly addressing whether this limitation is strictly a purification challenge or an inherent failure of the O-to-C skeletal editing methodology would strengthen the discussion of the reaction's scope.

We thank the reviewer for raising this point, as our focus on highly substituted pyrroles had left this otherwise simple class as a gap in the evaluated scope. To test monosubstituted substrates, we chose to examine the three isomers of phenyl isoxazole as representative examples, as the resulting phenyl pyrroles are expected to be more resistant to oxidative decomposition than alkyl pyrroles.



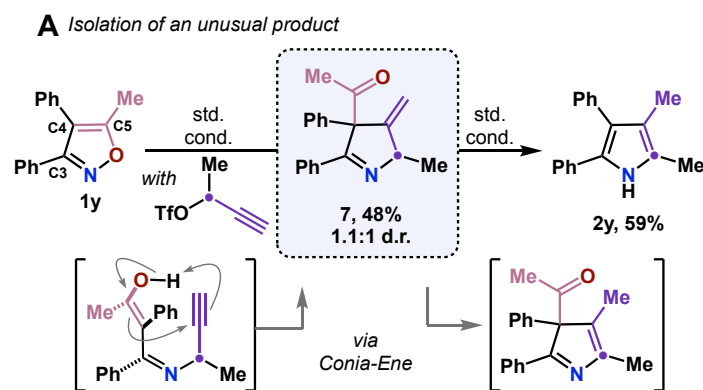
0.2 mmol scale; all qNMR yields using TMB as an internal standard

Based on these results, the 3- and 5- substituted substrates are somewhat compatible with the title method, as they did yield the desired pyrroles, albeit in very low yields. The observed products also agree with our predictive steric model and thus proposed mechanism—C5-aryl did not result in competitive Conia-Ene products, while C3-substitution resulted in a Conia-Ene product as the major product. However, the low yields across the board are likely reflective of the instability of the intermediates along the cyclization pathway, and not necessarily product instability (2- and 3-phenyl pyrrole are both isolable species). We have added these results to the Supporting Information and added a comment to the manuscript noting this limitation:

However, monosubstituted isoxazoles afforded low yields of the corresponding pyrrole (see SI for details).

2) To improve clarity for the readers, it would be highly helpful to explicitly draw the structure of the α -methyl propargyl triflate reagent in Figure 4.

We thank the reviewer for identifying this potential point of confusion. We have added the structure of α -methyl propargyl triflate to Figure 4A (shown below), indicating the use of this alternate alkylating agent in the experiment shown:



Reviewer 2

This manuscript presents a synthetically valuable one-pot conversion of isoxazoles into pyrroles via direct O-to-C atom replacement. While numerous strategies for editing the isoxazole skeleton into pyrroles have been reported, achieving this transformation without introducing extraneous functional groups at other positions remains a significant challenge. This work accomplishes a significant O-to-C atom replacement in the isoxazole-to-pyrrole conversion. The authors describe a regioretentive, three-step sequence involving N propargylation, reductive ring opening, and base mediated cyclization. The mechanistic study is thorough, encompassing the identification of a competing Conia ene pathway and development of a predictive steric reaction model. The reaction scope is broad, and several examples were illustrated to show synthetic advantages over traditional pyrrole syntheses. Overall, this work provides a new approach for pyrrole synthesis and in-depth mechanistic insights, and is recommended for publication.

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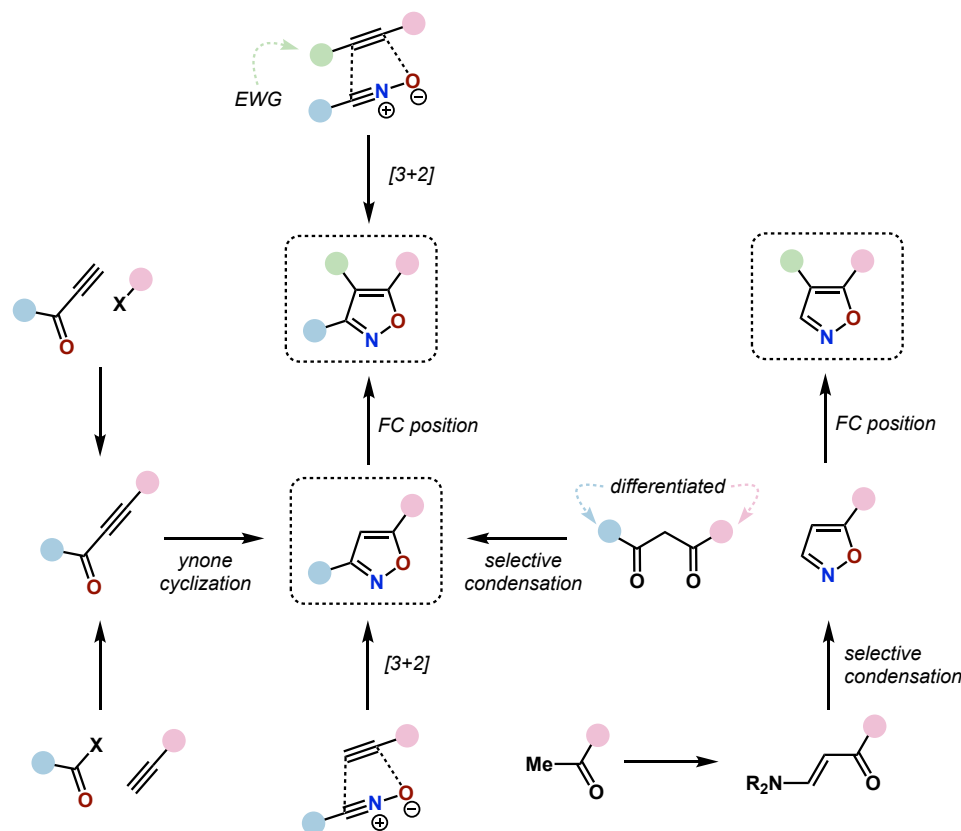
We thank the reviewer for bringing up this point, and we suspect that some of the disagreement here is a matter of perspective regarding the nature of “undesired” substituents. We agree that some

pyrrole syntheses are indeed robust and simultaneously acknowledge that some isoxazole syntheses suffer from their own limitations, particularly regarding regioselectivity.

While we are confident that our contention in the original manuscript is accurate, in recognition of the nuances raised by the reviewer, we have opted to rephrase this point in the introduction to capture more of the complexity associated with these heterocycle syntheses and their interrelationship. Namely, we have refocused the argument on the fact that isoxazole syntheses can serve as an orthogonal retrosynthetic disconnection for pyrroles, benefiting from their demonstrated modularity – the modified section is reproduced below, with changes highlighted.

Furthermore, though many pyrrole syntheses are robust and can be modified to use more readily accessible carbonyl-derived precursors such as α -halo or amino ketones (Hantzsch, Knorr syntheses)^{25,26} or TosMIC (Van Leusen synthesis),²⁷ these routes are restricted to certain substitution patterns. Indeed, even among more modern developments, starting material accessibility and control of regioselectivity remain central challenges.^{28–31} Conversely, isoxazole syntheses are modular, orthogonal to those of pyrroles, and often employ readily-accessible building blocks. For example, simple condensation of electronically consonant 1,3-dicarbonyls with hydroxylamine, intramolecular cyclization of ynones, and 1,3-dipolar cycloaddition of nitrile oxides with alkynes all readily afford isoxazoles.³² This synthetic ease is a direct consequence of the consonant electronic pattern of the isoxazole backbone and therefore their precursors, such that polarity-matched bond constructions are natural disconnections.

For the benefit of the editor and reviewers, the scheme below shows the last sentence explicitly, demonstrating the synthetic ease of building up complexity in the isoxazole. For example, the 3,5-disubstituted isoxazole has multiple disconnections that are not reliant on either the steric or electronic biases of the starting material. While the simple hydroxylamine condensation onto a 1,3-dicarbonyl is only selective in instances where the substituents are reasonably differentiated, the [3+2] cycloaddition with a terminal alkyne provides the desired isoxazole as the sole product. If the nitrile oxide or terminal alkyne is not readily accessible, ynone cyclization with hydroxylamine is another alternative for regioselective isoxazole synthesis. Furthermore, ynones are attractive synthetic precursors, as they can be accessed from multiple bond disconnections.



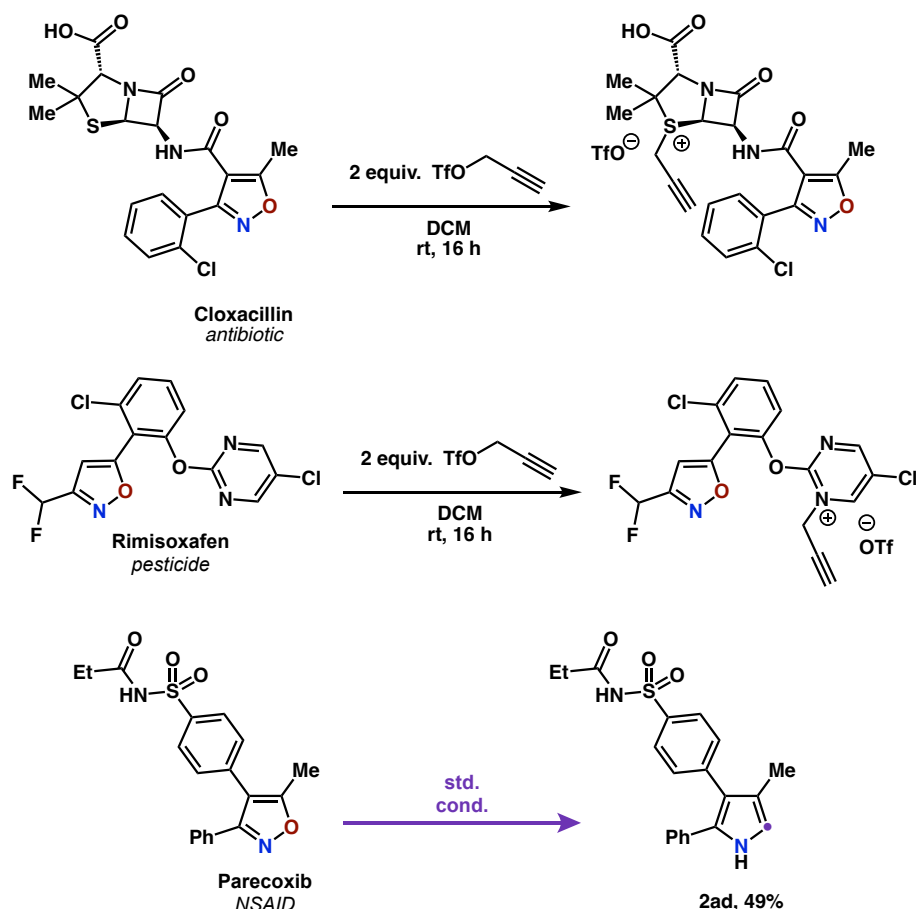
2) It would be beneficial for readers to better understand this area if some recent achievements on atom replacement such as C-to-N and N-to-C replacement, were incorporated into the introduction section.

We thank the reviewer for raising this point. To further highlight recent accomplishments in atom replacement chemistry, we have cited the following additional publications, which include two primary literature reports of N-to-C replacement and two reviews on aromatic atom replacement: *Chem.* 2024, 10, 1940-1949; *Org. Lett.* 2024, 26, 4280-4285; *Eur. J. Org. Chem.* 2026, 29, e202501188; and *Chem. Rev.* 2026, *ASAP*, doi: 10.1021/acs.chemrev.5c01009.

3) The late-stage modification of complex molecules including pharmaceuticals and natural products represents a key merit of skeletal editing. Although isoxazole motifs are not widely prevalent in natural products, we encourage the authors to include several representative examples of such applications to further highlight the synthetic utility of this methodology.

We thank the reviewer for their suggestion. While one merit of many skeletal editing methods does involve their applications towards late-stage modifications of natural products or drug compounds, we recognize that a limitation of the present method is some degree of incompatibility with basic functional groups (i.e., competitive alkylation). Nonetheless, we believe our method provides access to many traditionally challenging heterocyclic scaffolds, which is another key merit of skeletal editing (see, for instance, arguments we have made in *Science* 2025, 389, 6757, *Nature* 2025, 641, 646, or *Chem. Rev.* 2026, *ASAP* doi: 10.1021/acs.chemrev.5c01009). Considering the inherent limitations of pyrrole syntheses, the synthetic utility of this method is not undermined.

With this in mind, we would first like to point the reviewer's attention to pyrrole **2ad** in Figure 4E, which is derived from the isoxazole-based NSAID Parecoxib. Second, we have (during this revision period) attempted to apply our method to a small handful of additional isoxazole-based pharmaceuticals, including the antibiotic Cloxacillin and the recently approved pesticide Rimisoxafen (shown below). In both cases, propargyl triflate alkylated other nucleophilic sites in the molecule.



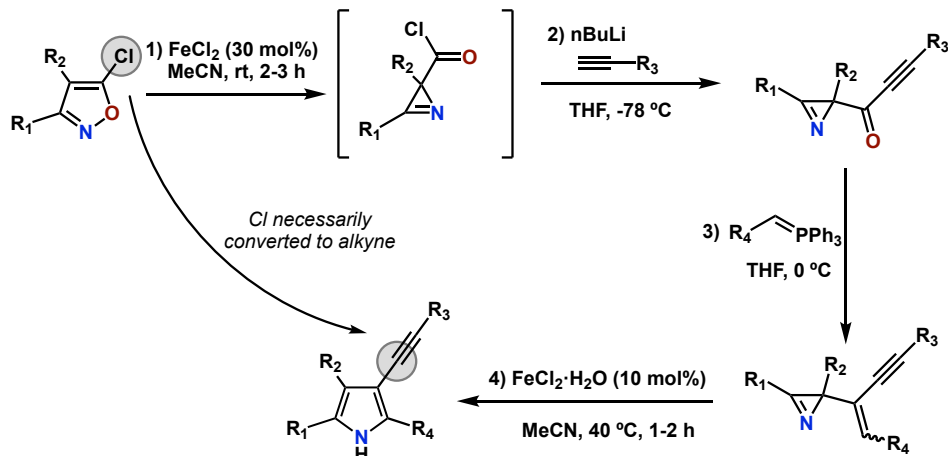
In recognition of these experiments, we have added to the main text a note about the general incompatibility of certain functionalities, namely sites more basic than isoxazole, writing:

More nucleophilic functionalities, including pyridines, pyrimidines, and sulfides are not tolerated in the reaction, as they undergo competitive alkylation.

4) It should be noted that the claim “an O-to-C replacement reaction of heteroaromatic systems has yet to be disclosed” overlooks existing literature. Several transformative approaches for the oxazole-to-pyrrole conversion have been documented, albeit sometimes introducing residual substituents. To ensure a comprehensive and clear perspective for readers, the manuscript would benefit from citing these key developments. Relevant references, for example: *J. Org. Chem.* 2026, 91, 767-779; *Tetrahedron* 2014, 70, 4631-4639; *J. Org. Chem.* 2017, 82, 256-268; *Org. Biomol. Chem.* 2021, 19, 1976–1984; *Org. Lett.* 2015, 17, 5224-5227.

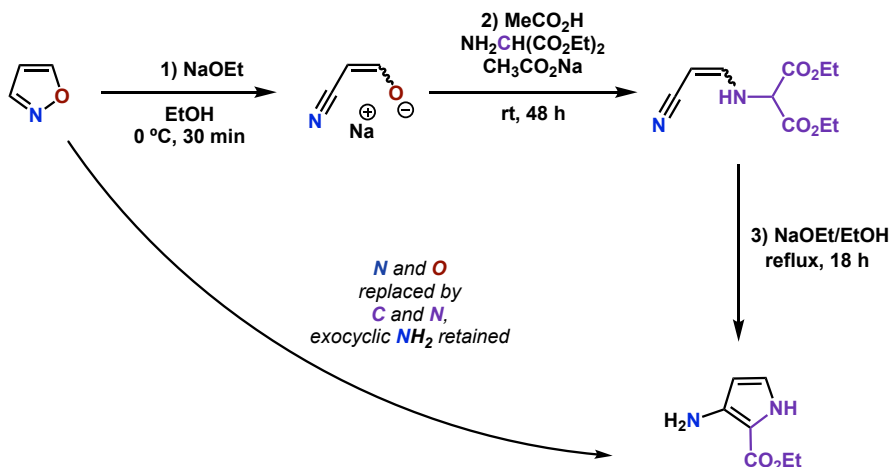
We appreciate this point raised by the reviewer; however, we note that while each of these reports uses isoxazoles (or related heteroarenes) as starting materials, none qualify as single-atom edits. To make this point clearly, we reproduce here each of the noted precedents as schemes:

Khlebnikov, JOC, 2026:



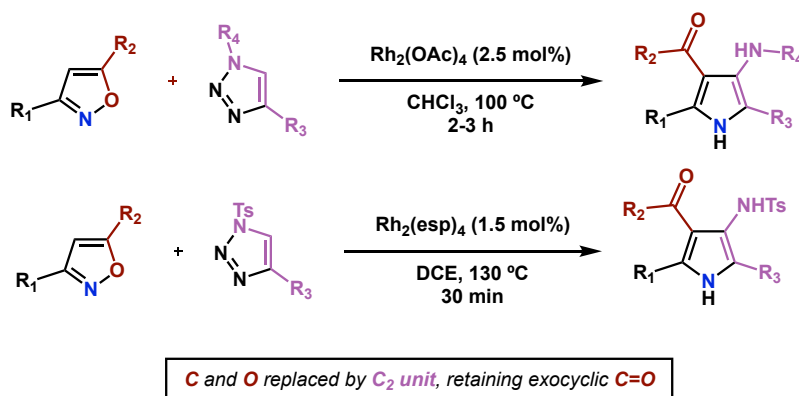
This is the precedent with the most homology to our method, but it requires starting from a 5-Cl isoxazole and necessarily transforms that substituent into an alkynyl group. As such, it is not a single-atom edit by the traditional definition, as it requires changes to the spectator functionality during atom replacement.

Liskowski, Tetrahedron, 2014:



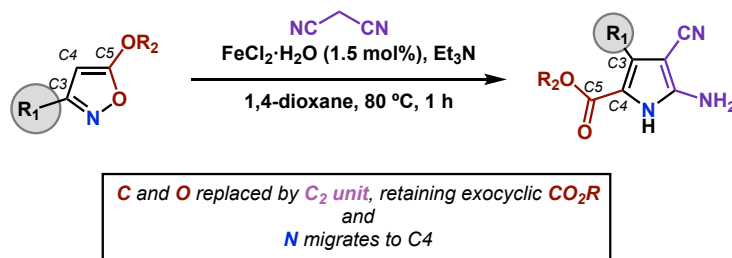
This is a two-atom replacement reaction of an isoxazole, where the original oxygen is replaced by nitrogen, the nitrogen is replaced by a carbon, and the original nitrogen is retained as an exocyclic substituent on the pyrrole. Both the multi-atom replacement and the retention of the replaced atom violate requirements for single-atom editing.

Agafonova, *JOC*, 2016 and Tang, *Org. Lett.* 2015:



These two very similar reports are both two-atom replacement reactions of an isoxazole, where the original oxygen and its adjacent carbon are replaced by a C₂ unit from the triazole, and the carbon and oxygen are retained as an exocyclic carbonyl substituent on the pyrrole. Both the multi-atom replacement and the retention of the replaced atom violate requirements for single-atom editing.

Khlebnikov, *Org. Biomol. Chem.*, 2021:



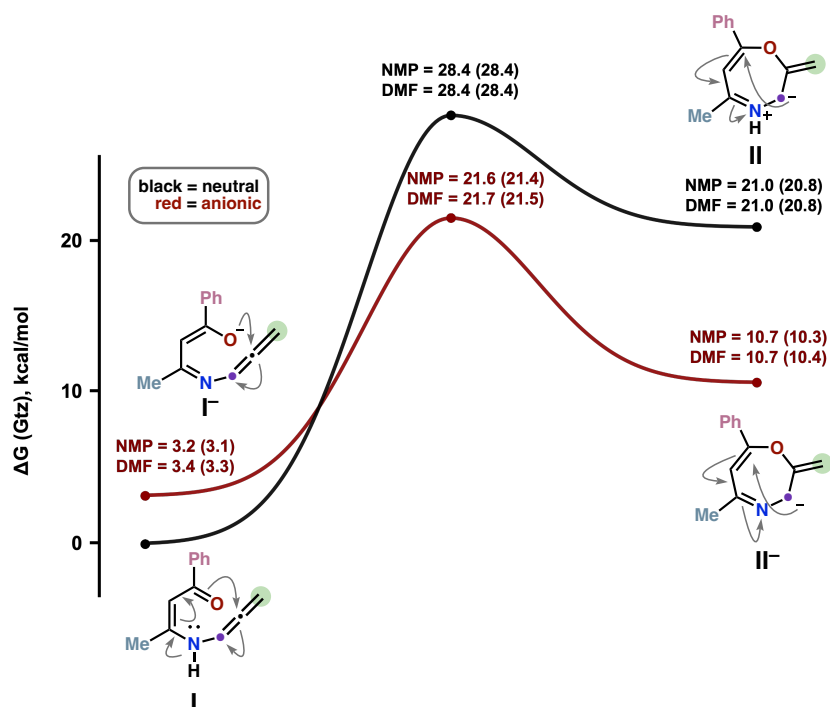
This is a complex rearrangement, wherein not only are two carbons replaced (C and O for a C₂ subunit of the malononitrile) with retention of the CO₂ unit as an exocyclic substituent, but also the nitrogen of the isoxazole migrates during the rearrangement from C₃ to C₄. The multi-atom replacement, the retention of the replaced atom, and the rearrangement of the connectivity of the skeleton violate requirements for single-atom editing.

As should be clear from the above analysis, these reports do not simply modify the aromatic core and therefore do not possess the same retrosynthetic simplicity afforded by our transformation, which, in contrast to the above, changes only the oxygen into a CH and leaves the rest of the core undisturbed. In the spirit of acknowledging the previous work, we have nonetheless included these citations with a new sentence in the manuscript, writing:

Indeed, perhaps because of this challenge, while several reports have converted isoxazoles into pyrrole-containing scaffolds, none achieved this transformation in a single-atom replacement manner.^{19–23}

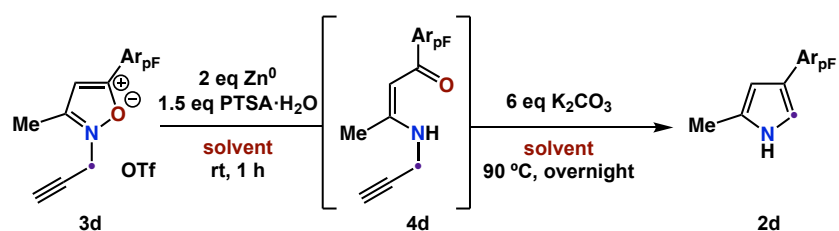
5) The calculations were performed using the PCM model with DMF as the solvent, whereas the experimental cyclization was conducted in NMP. Notably, as shown in Table S5 (solvent screening), DMF afforded only a 13% yield, while NMP gave a significantly higher yield of 76%. This discrepancy raises questions about the suitability of using DMF in the computational model to represent the actual reaction environment. Although DMF and NMP are structurally similar, NMP may exhibit different Lewis basicity or solvation effects. It is recommended that the authors comment on the potential solvent effects or provide single-point calculations in NMP for key transition states to better align the computational and experimental findings.

We thank the reviewer for raising this insightful question, especially given the results of our solvent screen. The PCM model is based on the dielectric constant (ϵ) of the solvent, with $\epsilon = 32.2$ for NMP and $\epsilon = 37.7$ for DMF. While this difference is small, we have performed the requested calculations with the adjusted ϵ value for NMP and found that the results (shown below) are very similar.



It is clear, therefore, that implicit solvation is not sufficient to capture the full range of solvent effects evident from our observed experimental differences. While the extreme computational demands of explicit solvation are outside the scope of the present study, we hypothesize that because NMP is Lewis basic and thus capable of hydrogen-bonding to the enaminone, it is well-equipped to activate the intermediate for 7-endo-dig cyclization.

While NMP and DMF (as well as DMA and DMSO) are similarly polar, high-boiling solvents, they are sufficiently different such that they lead to changes in yield. Quantification of their Lewis basicity using NMR can be found in *J. Org. Chem.* 2021, 86, 5, 4143–4158 (copied below). The authors found that of these four solvents, NMP is the most strongly hydrogen-bond accepting. Despite the ostensible similarity of DMF and NMP, their ability to accept hydrogen bonds greatly impacts their reactivity.

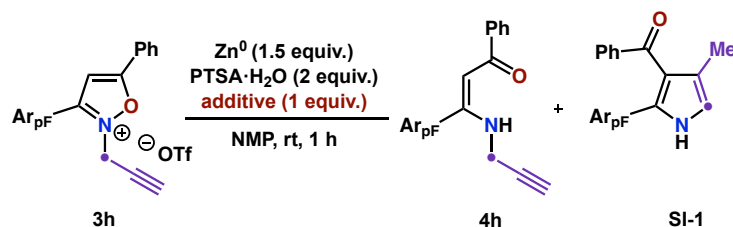


Solvent	H-bond acceptance	2d (%)
NMP	0.76	76
DMSO	0.71	68
DMF	0.69	13
DMA	0.75	3
DMA/H ₂ O (10:1)	-	58

This argument, however, caused us to reevaluate our original result with DMA. Despite its high H-bond acceptance ability, we found that the pyrrole yield was significantly diminished (3%) when using DMA instead of NMP. However, because we had also observed effects from the amount of water present in the solvent mixture (for NMP, we observed that the small amount of water often present in commercial bottles can promote the cyclization, but using dry solvent arrests the reaction), we tested the addition of water to the DMA and observed a meaningful increase in yield. We have also added this result to Table S5 of the SI.

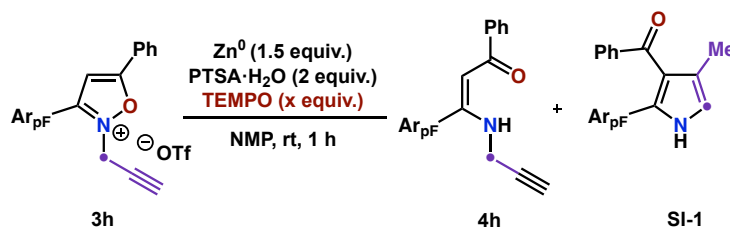
6) The use of TEMPO to inhibit side reactions during the reduction step in synthesizing 2g and 2h raises questions about the nature of these side pathways and the generality of this requirement. Specifically, what by-products are formed without TEMPO, and must other diaryl substrates employ the same precaution? A mechanistic explanation (e.g., radical trapping or oxidation prevention) alongside control experiments omitting TEMPO would be valuable. Such additions would provide deeper insight into the reaction's robustness and guide future substrate selection.

We thank the reviewer for identifying this point requiring clarification. We found that diaryl substrates can form 3-benzoyl pyrroles during the Zn/PTSA reduction reaction. This is behavior unique to this substrate sub-class—other substitution patterns are not observed to form these products during the reduction step. Through empirical additive screening, we found that TEMPO minimizes this side-reactivity in favor of the 2° enaminone, leading to a greater yield of desired pyrrole upon subjection to the cyclization conditions (see optimization tables below).

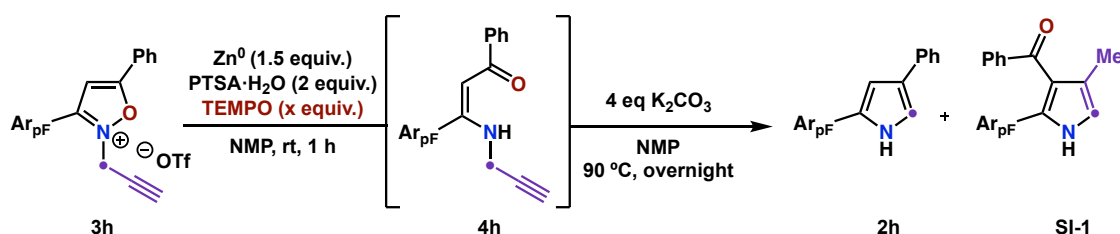


Entry	Additive	4h (%)	SI-1 (%)
1	None	19	22
2	TEMPO	53	10
3	BHT	23	22

4	ABNO	27	17
5	galvinoxyl	40	16
6	TEMPOL	51	11

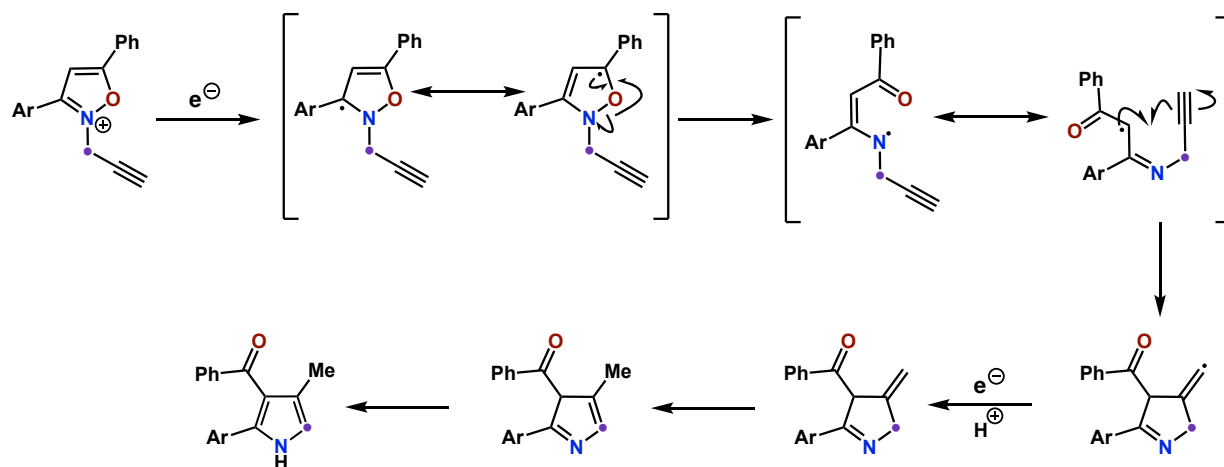


Entry	TEMPO equiv.	4h (%)	SI-1 (%)
1	1	51	12
2	2	51	3
3	4	60	0
4	10	66	0

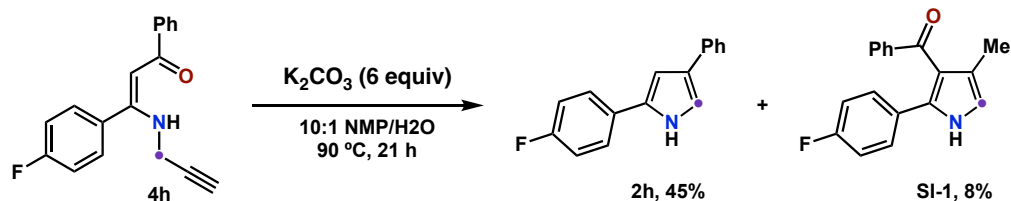


Entry	TEMPO equiv.	2h (%)	SI-1 (%)
1	1	35	20
2	2	28	6
3	4	27	0
4	10	15	0

Though this side-product pyrrole matches the substitution pattern of the Conia-Ene-type pyrroles that we observe under the base-mediated cyclization conditions (i.e., Figure 4), it is uniquely formed during the reduction step for this substrate sub-class. We therefore hypothesize that two different mechanisms are operative, one under the polar conditions of the base-mediated cyclization and a different mechanism for this specific sub-class under the reduction conditions. Given the influence of TEMPO, we suspect that a $1e^-$ mechanism is responsible for the formation of the undesired pyrrole upon treatment with Zn (shown below). Given also that this is specific to substrates with aryl substituents at the 3 and 5 positions, we hypothesize that the radical species formed after the first reduction of the isoxazolinium species (and subsequent ring opening) is sufficiently stabilized to undergo cyclization before the second reduction event. We propose that the following intermediates are plausible for the formation of the 3-benzoyl pyrrole. TEMPO may intercept these species covalently prior to subsequent reduction to the desired anion or otherwise prevent a chain mechanism (not shown) from propagating.



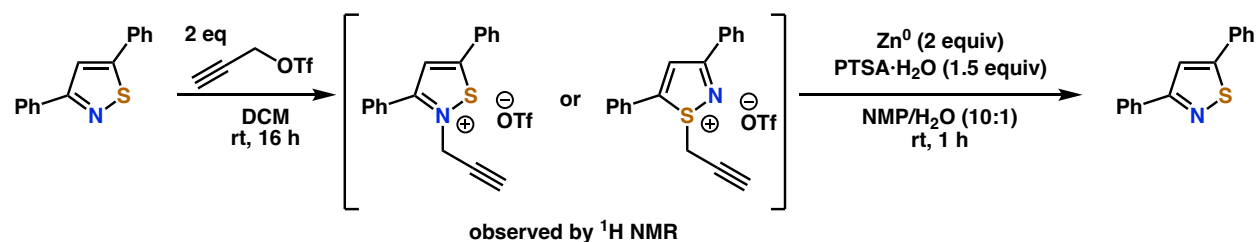
To further support this hypothesis, the isolated 2° enaminone (4h), under the cyclization conditions, forms the desired pyrrole 2h in a 45% NMR yield, along with a minor amount (8%) of the 3-benzoyl pyrrole (SI-1). Given the difference in product ratios between the reduction and cyclization conditions, this is further support that the Cona-Ene-type pyrrole is forming via an alternative mechanism during the reduction step.



While we have included the above data in the supporting information, we have refrained from including this specific mechanistic proposal because we do not feel sufficiently confident in the particulars to responsibly justify its inclusion.

7) Isothiazole is another widely prevalent heterocyclic scaffold. Could the author's methodology be extended to achieve S-to-C replacement for the synthesis of pyrroles from isothiazoles?

We thank the reviewer for this interesting suggestion and have conducted the requested experiment using 3,5-diphenylisothiazole as a model system. We found that the substrate was amenable to alkylation, giving a propargylated isothiazolium salt as a single isomer. While we could not unequivocally assign the structure to discern whether *N*- or *S*-alkylation occurred, upon subjection to our standard reduction conditions, this intermediate dealkylated to return the starting isothiazole.



While an isothiazole-to-pyrrole transformation would be a mechanistically useful comparison to our work, we note that the synthetic utility of such a potential reaction is lower than that for isoxazole starting materials. That is, isothiazoles are more challenging to access and accordingly much less well represented than isoxazoles as heterocyclic building blocks. Therefore, (in accordance with our introduction) the corresponding conversion to pyrroles would likely not represent a similar improvement in accessing novel chemical space, though we may choose to explore this reaction in the future. To acknowledge this concept, we have added a new sentence to the manuscript, writing:

Alkylation reactivity was also observed with isothiazoles, though reduction returned the starting isothiazole.

8) To ensure the professionalism and consistency of the manuscript, all NMR spectra should be processed and presented using a uniform template. It is recommended that the integral values be added to the ^1H NMR spectrum on page S198.

We thank the reviewer for raising this point and have reprocessed the NMR spectra using a uniform template. We have also added the integral values to the ^1H NMR on page S198.