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One-Pot Oxidation and Rearrangement of Propargylamines and *in Situ* Pyrazole Synthesis

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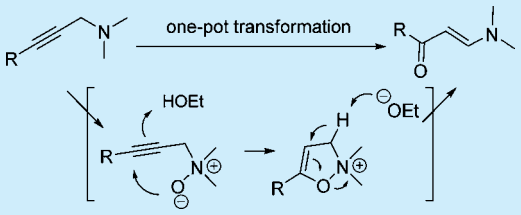
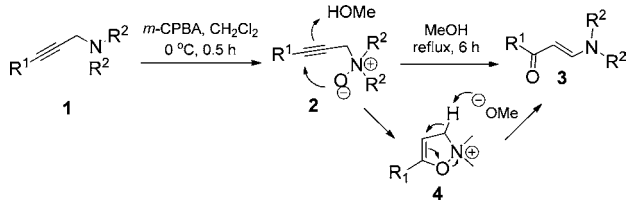
Supporting Information

ABSTRACT: Reported here are procedures for a one-pot oxidation and rearrangement of propargylamines to synthesize enaminones, with supporting mechanistic studies. Also reported are the extended one-pot syntheses of pyrazoles, including celecoxib and various heterocyclic compounds.



Oxidation of propargylamines **1** and subsequent transformation of the isolated propargylamine *N*-oxides **2** to enaminones **3** has been reported (Scheme 1).[1] The literature

Scheme 1. Enaminones from Propargylamines



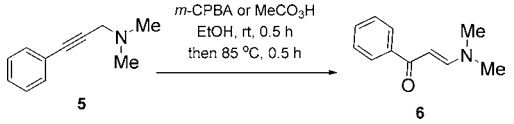
protocols involve two discrete steps: initial oxidation, typically carried out with *m*-CPBA in dichloromethane at 0 °C, and a subsequent thermally induced formation of enaminones in a protic solvent, such as methanol at refluxing temperature for 6 h. Isolation of the propargylamine *N*-oxide intermediate can be complicated as a result of several transformations that lead to spontaneous decomposition at ambient temperature, particularly on silica gel.[2] This may have contributed to the lack of literature reports using this two-step sequence for the synthesis of enaminones beyond the initial report.[3]

A plausible mechanism of this enaminone formation involves formation of isoxazolinium intermediate **4**, generated by addition of the *N*-oxide oxygen to the carbon−carbon triple bond and subsequent proton transfer from a protic solvent, such as methanol. The newly formed methoxide then deprotonates the methylene of isoxazolinium **4**, which triggers fragmentation and isomerization to form enaminone **3**.[1]

Herein we report an *in situ* oxidation and rearrangement protocol to prepare enaminones in one pot from propargylamines,[4] along with experimental evidence that supports the formation of enaminones via isoxazolinium intermediate **4**. In addition, we also describe an extended one-pot process to synthesize pyrazoles, including celecoxib,[5] and other heterocycles *in situ* starting from the corresponding propargylamine precursors.

We sought a protocol to perform the oxidation step in a protic solvent and then carry out the thermal rearrangement *in situ* without the need for a solvent switch or isolation of the intermediate *N*-oxide. This would circumvent the issue of spontaneous decomposition of the *N*-oxide during isolation, in addition to simplifying the overall transformation. We anticipated the oxidation would require a protic solvent because an acidic proton is required for the thermal fragmentation of isoxazolinium intermediate **4**. Thus, a number of oxidizing agents and protic solvent systems were evaluated with **5** as a model substrate in reactions run at 20 °C for 16 h for the oxidation step and 85 °C for 5 h for the rearrangement. This led to the observation of an encouraging 59% conversion to the enaminone **6** when using *m*-CPBA in 95% ethanol and 5% water.[6] Upon further optimization, the oxidation was found to be complete within 30 min at room temperature[7] and rearrangement at 85 °C took only an additional 30 min in absolute ethanol. With shorter reaction times, high molecular weight side products were suppressed[8] and the conversion of **5** to **6** was clean, with an isolated yield of approximately 60% upon column chromatography purification (Scheme 2). Peracetic acid was found to perform similarly to *m*-CPBA in this process.[9]

Scheme 2. *In Situ* Propargylamine Oxidation and Rearrangement



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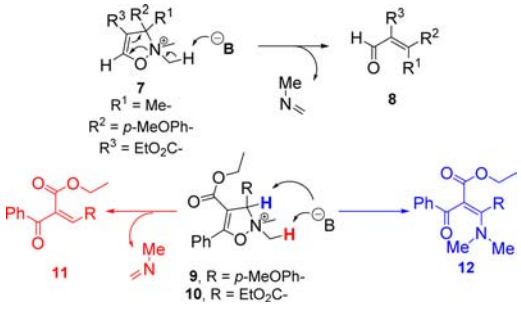
We then turned our attention to mechanistic understanding of the transformation. Literature precedents of isoxazolinium ions are rare. The most relevant examples were reported by Chiacchio and co-workers,[10a−c] involving an isoxazolinium ring formed by [3 + 2]-cycloaddition followed by quaternization of nitrogen with methyl triflate. Compound **7**, a 3,3-disubstituted isoxazolinium triflate with an electron-withdrawing ester functional group attached to the C4 position, underwent base-induced thermal rearrangement to furnish enone **8** as the major product in methanol (Scheme 3).[10a,b] The other two

Scheme 3. Literature Isoxazolinium Chemistry



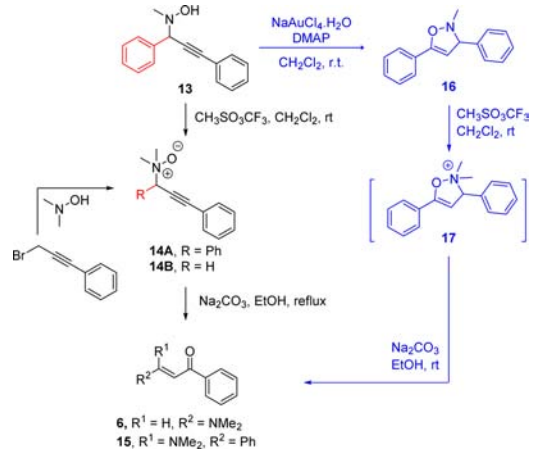
isoxazolinium salts Chiacchio studied, **9** and **10**, both bear an electron-withdrawing group at C3 and a second electron-withdrawing group attached to C4.[10c] When **9** and **10** were subjected to a base at elevated temperature, a mixture of enone **11** and enaminone **12** was obtained. Chiacchio et al.[10c] rationalized the outcome via proton transfer at the methyl-H vs the C3−H during the rearrangement, leading to **11** and **12** respectively (Scheme 3).

Realizing the difference in the electronic nature of the isolated literature isoxazolinium ions **7**, **9**, and **10**, compared with intermediate **4**, we set out to prepare an isoxazolinium ion with electronic and regiochemical properties more in line with **4** (R = Ph), via a synthetic pathway independent of propargylamine oxidation and rearrangement. Such an intermediate, if proven viable as a precursor to enaminones, would provide experimental evidence to support the mechanism outlined in Scheme 1.

Thus, *N*-hydroxypropargylamine **13** was prepared and alkylated with methyl triflate at 20 °C under neutral conditions to furnish propargylamine *N*-oxide **14A** (Scheme 4). When treated with Na_2CO_3 in ethanol at 85 °C, compound **14A** transformed into enaminone **15**, as expected. On the other hand, **13** was also converted into isoxazoline **16** via a cyclization mediated by $NaAuCl_4$.[11] From **16**, we synthesized and isolated isoxazolinium **17** via methylation using methyltriflate in the absence of base. Compound **17** was stable at neutral pH and did not spontaneously rearrange. However, in the presence of Na_2CO_3 in ethanol, **17** underwent a transformation to enaminone **15** at room temperature.[12] Furthermore, **14B** was also synthesized and isolated via alkylation of *N*,*N*-dimethyl hydroxylamine with phenyl propargyl bromide. Compound **14B** was then subjected to Na_2CO_3 in ethanol at 85 °C, with the outcome being the expected enaminone **6**. These observations are consistent with the oxidation and rearrangement mechanism via the isoxazolinium intermediate as outlined in Scheme 1.[13]

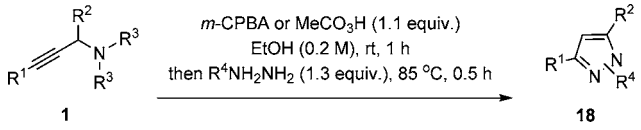
Enaminones are versatile intermediates to access important heterocycles such as pyrazoles, triazoles, pyrimidinones, and pyrimidines. An *in situ* synthesis of these heteroaryls directly

Scheme 4. Isoxazolinium Ion as a Viable Precursor to Enaminones



from propargylamines would be a useful extension of this oxidation rearrangement protocol. To that effect, we developed viable conditions to carry out a three-step sequence in one pot to synthesize pyrazoles. For example, upon oxidation of **1** using *m*-CPBA or peracetic acid, with the introduction of hydrazine or various substituted hydrazines, either before or after thermal rearrangement, we obtained pyrazoles in 36% to 91% isolated or combined yields of the regioisomeric products (Table 1). This protocol was applied to propargylamines with aryl

Table 1. Extended One-Pot Pyrazole Formation



18	R^1	R^2	R^3	R^4	Yield (%)
18a		H	*n*-Pr	H	42
18b		H	*n*-Pr	*i*-Pr	91(19/72)[b]
18c		H	*n*-Pr	Me	59[c]
18d		H	*n*-Pr	Ph	71(26/45)[b]
18e[a]		Ph	*n*-Pr	H	48
18f		H	*n*-Bu	Ph	41[c]
18g		H	*n*-Pr	Ph	43(6/37)[b]
18h		H	*n*-Pr	H	36
18i		H	*n*-Et	H	46
18j		H	*n*-Et	H	40

[a]Compound **18e** was synthesized starting from compound **15**. [b]Regioisomers were separated by column chromatography. [c]Regioisomers could not be separated by column chromatography.

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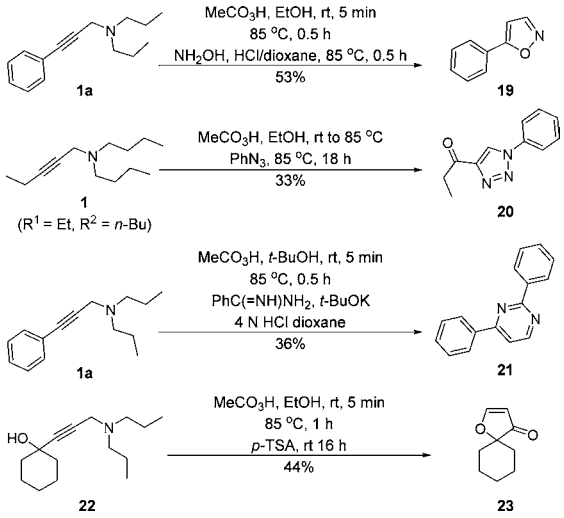
substitution on the terminal acetylene C3 position (**18a** to **18e**[14] 42 to 91% yield),[15] as well as alkyl substitutions (**18f** to **18j** 36% to 46% yield). Aryl and alkyl substitutions on the C1 position of propargylamines were also tolerated (**18e**, 48% yield). In addition, hydrazine, alkyl hydrazines, and aryl hydrazines appeared to participate in this transformation without issue (R_4 = H, Me, *i*Pr, Ph). Although the isolated yields are not consistently high, the method has the potential to rapidly deliver a wide variety of functionalized heterocycles from a single intermediate, something highly valued in the drug discovery synthesis environment. For example, literature syntheses of α-hydroxylated pyrazoles involve metalation of protected pyrazoles followed by trapping the carbanion with a carbonyl electrophile,[16] with the limitations of carbanion chemistry in addition to the requirement of a pyrazole nitrogen protecting group for N-unsubstituted pyrazoles. The propargylamine strategy has no such prerequisite conditions; thus, compound **18h** was prepared using the current strategy in 36% isolated yield in one reaction vessel.

This strategy was expanded to one-pot syntheses of other heterocyclic systems (Scheme 5). For example, isoxazole **19**

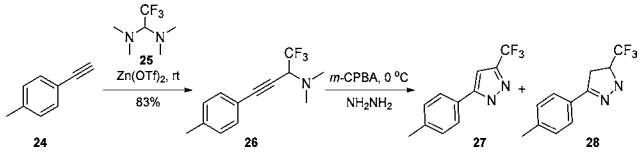
Scheme 5. Additional One-Pot Processes



was synthesized from propargylamine **1** in 53% isolated yield by substitution of hydroxylamine for hydrazine.[17] Triazole **20** was prepared in 33% yield in one pot by cycloaddition of phenylazide and elimination of dibutylamine after the thermal rearrangement.[18] Pyrimidine **21** was similarly obtained in 36% isolated yield by condensation with benzamidine.[19] When α-hydroxylated propargylamine **22** was used in the process and *p*-TSA was introduced after the thermal rearrangement, spirocyclic ether **23** was obtained in 44% yield.[20]

Given the success of the enaminones for the synthesis of pyrazoles, we turned our attention toward developing a novel synthesis of celecoxib[5] using the propargylamine oxidation rearrangement strategy. Trifluoromethylated propargylamine **26** has previously been synthesized via coupling of **24** with 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (**25**) using CuI or ZnI_2. In both cases, 1 equiv of the metal iodide was used and the isolated yields of **26** were <60% after an extended reaction time at elevated temperature.[21] We developed a new and more efficient protocol to synthesize compound **26** where coupling of **24** and **25** was effected by 0.2 equiv of $Zn(OTf)_2$, without the use of any solvent or other additive, at 75 °C for only 0.5 h, which provided **26** in an isolated yield of 83% (Scheme 6). This approach was inspired by the zinc acetylide aldehyde addition pioneered by Carreira and Frantz.[22]

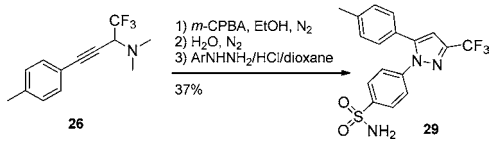
Scheme 6. $Zn(OTf)_2$ Catalyzed Propargylamine Synthesis



Our initial observation appeared to suggest that the oxidation of **26** proceeded unusually slowly, with a substantial amount of **26** remaining upon treatment with *m*-CPBA for 0.5 h. Extending the reaction time or increasing the reaction temperature did not improve conversion. Lowering the oxidation temperature to 0 °C, however, improved the conversion substantially. This may be due to spontaneous hydrolysis of the enaminone to the diketo intermediate in this trifluoromethyl activated species, thus generating Me_2NH which competed for *m*-CPBA. At lower temperature, the hydrolysis was sufficiently suppressed to minimize the interruption of the intended oxidation. When hydrazine was introduced for the formation of pyrazole **27**, two major side products were observed: the hydrated species (M + 18), which was suppressed by introduction of the aryl hydrazine as an HCl/dioxane suspension, and a partially reduced species (M + 2), presumably **28**, formed via the enone pathway similar to the formation of compounds **8** and **11** in Scheme 3. This side product was suppressed when additional water (10% volume) was introduced after the oxidation.

We proceeded with the synthesis of celecoxib **29** using propargylamine **26** and 4-hydrazinylbenzenesulfonamide. The desired product **29** was indeed formed in 37% isolated yield after column purification, in line with the overall yield of all previous syntheses except in the industrial process[5b] (Scheme 7). Importantly, the undesired pyrazole regioismer product

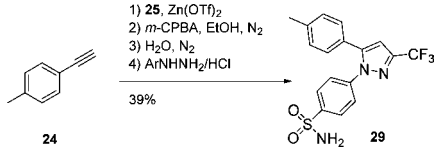
Scheme 7. One-Pot, Three-Step *in Situ* Celecoxib Formation



formed is 2%−3% of the desired regioisomer product **29**, comparable to the ratio observed in the second generation manufacturing process.[2]

Finally, a one-pot, four-step synthesis of celecoxib **29** was realized by incorporating the synthesis of propargylamine **26** into the one-pot, three-step process; thus **29** was prepared directly from **24** in one pot with a 39% yield after chromatography (Scheme 8).

Scheme 8. One-Pot, Four-Step Celecoxib Formation



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In summary, we have established a one-pot protocol to synthesize enaminones directly from propargylamines via oxidation and rearrangement. We demonstrated experimentally that isoxazolinium ions are viable precursors for the formation of enaminones, which is consistent with the proposed oxidation rearrangement mechanism. One-pot, three-step synthetic protocols for functionalized pyrazoles and other heterocycles were also presented. Although the yields were mostly moderate, this method can provide rapid access to functionalized and structurally diverse heterocycles. As a demonstration of this, we developed a one-pot, four-step synthesis of celecoxib starting from commercially available reagents. Considering the ease of synthetic access of propargylamines, this method constitutes a useful alternative to existing methods to access these heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) Oxone was among the oxidizing agents evaluated initially. Water was included as a cosolvent to facilitate solubilization.

(7) In most cases, N-oxidation of propargylamines was completed within minutes at 20 °C.

(8) Enaminones are known to self-condense when subjected to an elevated temperature. Enaminone **6** undergoes a trimeric condensation to form 1,3,5-trisubstituted benzene at 110 °C in high yield. See for example: Al-Zaydi, K. M.; Nhari, L. M.; Borik, R. M.; Elnagdi, M. H. *Green Chem. Lett. Rev.* **2010**, *3*, 93−99.

(9) Throughout our studies, no oxidation of the proparyl sp^1 carbons was observed under our conditions. In addition, a 1:1 mixture of 1-phenyl-1-propyne and triethylamine was subjected to the oxidation conditions employed in our process and the result was again oxidation of the amine instead of 1-phenyl-1-propyne.

(10) (a) Chiacchio, U.; Rescifina, A.; Chiacchio, M. A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **2003**, *68*, 3718−3720. (b) Chiacchio, U.; Liguori, A.; Rescifina, A.; Romeo, G.; Rossano, F.; Sindona, G.; Uccella, N. *Tetrahedron* **1992**, *48*, 123−132. (c) Chiacchio, U.; Casuscelli, F.; Liguori, A.; Rescifina, A.; Romeo, G.; Sindona, G.; Uccella, N. *Heterocycles* **1993**, *36*, 585−600.

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(12) A small quantity of the enone byproduct (M + 1 = 209.07) was observed by LCMS but not isolated. Compound **13** was directly transformed into **18e** in a one-pot three-step process in 36% yield. Similarly, **14b** was converted to **18a** in a one-pot process in 41% yield.

(13) Propargylamine *N*-oxides have been reported to rearrange to *o*-allenyl ethers; see: Szabo, A.; Galambos-Farago, A.; Mucsi, Z.; Timari, G.; Vasvari-Debreczy, L.; Hermecz, I. *Eur. J. Org. Chem.* **2004**, 687. Yet, under our reaction conditions, the *o*-allenyl converts to an unidentified product that is not the enamine.

(14) Compound **18e** was synthesized starting from compound **15**.

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(17) Compound **19** was previously prepared in a two-step sequence starting from acetophenone in 57% isolated yield. See: Nakamura, T.; Sato, M.; Kakinuma, H.; Miyata, N.; Taniguchi, K.; Bando, K.; Koda, A.; Kameo, K. *J. Med. Chem.* **2003**, *46*, 5416−5427.

(18) Structure of **20** was confirmed by 2D NMR.

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(23) (a) A ratio of ∼2:98 was observed based on ELSD detection using Waters Acquity HSS T3, 2.1 mm × 50 mm, C18, 1.7 micron column with a column temperature of 60 °C and gradient method of 5% B for 0.1 min followed by a linear ramp to 95% B 0.1 to 2.6 min, hold at 95% B 2.6 to 2.95 min, and finally return to initial conditions 2.95 to 3.0 min at a flow rate of 1.25 mL/min. (b) A ratio of ∼3:100 was observed based on ^{19}F NMR. See ELSD chromatogram and ^{19}F NMR in the Supporting Information.