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Modular Synthesis of Pyrazolones Using an Alkene Aminocarbonylation Reaction

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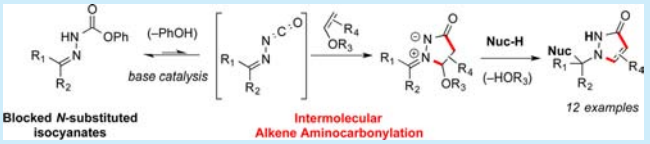
Supporting Information

ABSTRACT: A variety of pyrazolones were synthesized from enol ethers and hydrazones using a reaction sequence involving aminocarbonylation of enol ethers followed by nucleophile-induced aromatization of the azomethine imines intermediates. Using bases to catalyze the in situ formation of imino isocyanates allowed alkene aminocarbonylation to proceed under milder conditions with reactive substrates and enabled aminocarbonylation reactions of sensitive enol ethers. Aromatization of the azomethine imines could be induced by reduction using $NaBH_4$, or by addition of NH_2OH to afford the parent $^{\beta}N-H$ products.



Pyrazolones are valuable compounds that are found in pharmaceuticals,[1a−g] agrochemicals,[2a−c] and dyes and pigments.[3a,b] These aromatic heterocycles have two possible isomers (3- and 5-pyrazolones, Figure 1)[4] and are typically

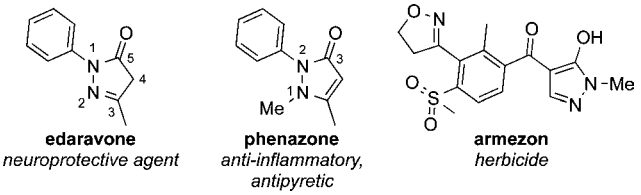
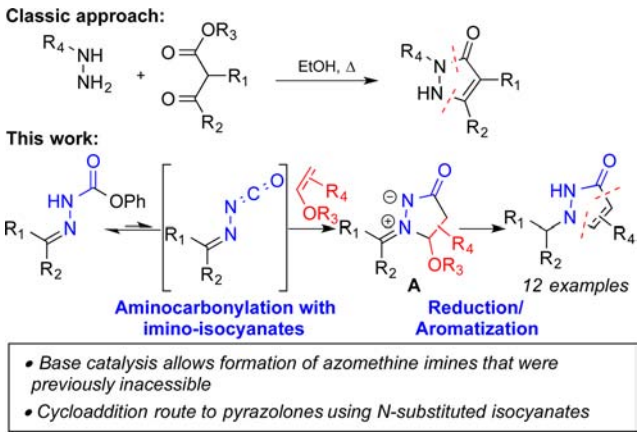


Figure 1. Biologically active pyrazolones.[4]

synthesized by the condensation of hydrazines onto β-keto esters (Scheme 1).[5] This method is very reliable and has many variations. Other routes are available to form the pyrazolones, but these processes generally use similar precursors, and if not, are limited to specific substrates.[6a−e] Synthetic approaches using different disconnections could complement available methods and help with difficult syntheses, for example, when sensitive hydrazines are used or when regioselectivity is required.

Scheme 1. (a) Classic Pyrazolone Synthesis; (b) Aminocarbonylation Route to Pyrazolones



Our group has recently developed alkene aminocarbonylation, using nitrogen-substituted isocyanates to form azomethine imines (**A**) from alkenes and hydrazones.[7,8] Such cycloadditions enable access to a variety of complex azomethine imines, which we derivatized into β-aminocarbonyl compounds.[7b,c] This work also constitutes a rare example of reactivity developed using *N*-substituted isocyanates.[9,10] Given the structural homology between azomethine imines (**A**) and pyrazolones, we were drawn to develop a reaction sequence that would allow for the overall conversion of alkenes into pyrazolones (Scheme 1).[11] Enol ethers undergo facile alkene aminocarbonylation, and we used this feature to access azomethine imines (**A**) in which the 5-membered ring is at the oxidation state needed to form pyrazolones. Herein, we report a two-step route to pyrazolones through the aminocarbonylation of enol ethers, followed by nucleophile-induced aromatization. We also show that base-catalysis can lead to improved aminocarbonylation reactivity.

First, we focused on the synthesis of a variety of azomethine imines derived from vinyl and enol ethers. Our previously reported conditions for alkene aminocarbonylation typically require high temperatures (100−150 °C) to proceed.[7b] Unfortunately, some enol ethers decomposed at these temperatures or underwent a second [3 + 2] cycloaddition with the azomethine imine; this prompted us to investigate milder reaction conditions. We anticipated that with reactive alkenes we might be able to decrease the reaction temperature by using bases to catalyze the formation of the *N*-substituted isocyanate intermediate.[12] Based on this hypothesis, several bases were screened using dihydrofuran as the enol ether. Encouragingly,

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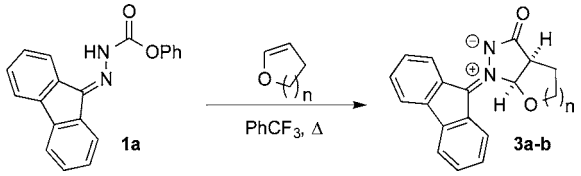
Table 1. Optimization of Alkene Aminocarbonylation with Basic Additives[a]



entry	*n*	temp (°C)	base	equiv of **1a**	equiv of alkene	yield[b] (%)
1[c]	1	70	none	1	2	24
2	1	70	none	1	2	31
3[c]	1	70	Et_3N	1	2	61
4	1	70	Et_3N	1	2	68
5	1	70	Et_3N	1.5	1	>95
6	2	70	none	1.5	1	20
7	2	70	Et_3N	1.5	1	38
8	2	100	Et_3N	1.5	1	87

[a]Conditions: hydrazone, alkene, base (3 mol %) in $PhCF_3$ (0.1 M), heated at 70 or 100 °C (sealed vial, oil bath). [b]Isolated yield. [c]0.05 M.

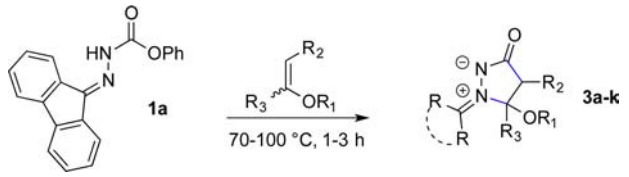
when a loading of 3 mol % of Et_3N was used, we observed a 3-fold yield increase compared to the control reactions (Table 1, entries 3−4 vs 1−2). In contrast, having the alkene as the limiting reagent gave a dramatic increase in yield (entry 5). With less reactive alkenes such as dihydropyran, basic additives did not lead to a significantly higher yield. This suggests that bases are only effective when the rate-determining step is the formation of the imino-isocyanate and not the cycloaddition step (Scheme 1).

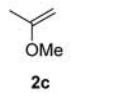
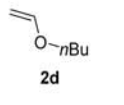
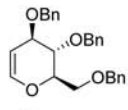
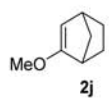
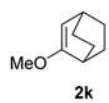
With these conditions we expanded the scope of azomethine imines synthesized from enol ethers (Table 2). Base catalysis at 70 °C permitted the synthesis of **3c** (entry 3), which we were unable to access with the previously reported conditions, as well as **3a** (entry 1) and **3d** (entry 4) in higher yields than previously reported.[7b] A variety of structures were obtained using acyclic (entry 9), cyclic (entries 2, 5−8), and bicyclic (entries 10−11) enol ethers by heating at 100 °C without base catalysis. Notably, aminocarbonylation was possible with a glucal derivative to afford product **3e** (entry 5). Further calibration on the scope of this aminocarbonylation reaction to other substrates is included in the Supporting Information (Figure S1).

Having various azomethine imines at hand, we tested our initial hypothesis: that suitable nucleophiles would trigger aromatization of the aminocarbonylation products to form pyrazolones.[13] We were delighted when the desired pyra-zolone **4d** (Table 3) was obtained in near quantitative yield upon treatment of **3a** with sodium borohydride. Presumably a pyrazolidinone intermediate is formed in which the restored electron density on the nitrogen atom allows ejection of the alcohol and aromatization to the desired pyrazolone (Scheme 2, path **A**). These conditions allowed for the synthesis of pyrazolones bearing substituents at the 4-position (**4c−e**, **4k−l**) and the 5-position (**4a**). These reactions are usually complete in less than 1 h and give good to excellent yields (Table 3). However, these reduction conditions were unsuitable for the formation of bicyclic pyrazolones (**4f**, **4h−j**).

For the bicyclic substrates the aromatization was slow, resulting in incomplete reactions and formation of products derived from the reduction of **I** (Scheme 2). To achieve aromatization of these challenging substrates we developed a two-step process. First, by lowering the temperature to −20−0 °C during the reduction, it was possible to isolate intermediate **I**. Then, aromatization of **I** was induced using a catalytic amount of

Table 2. Aminocarbonylation of Enol Ethers[a]



entry	enol ether	product	yield (%)
1	n = 1, **2a**	**3a**	95
2	n = 2, **2b**	**3b**	81
3	 **2c**	 **3c**	69
4	 **2d**	 **3d**	68
5	 **2e**	 **3e**	76
6	n = 1, **2f**	**3f**	63
7	n = 2, **2g**	**3g**	25
8	n = 3, **2h**	**3h**	57
9	 **2i**	 **3i**	69
10	 **2j**	 **3j**	98
11	 **2k**	 **3k**	86

[a]Conditions: hydrazone (1 mmol, 1.5 equiv), alkene (1 equiv), Et_3N (3 mol %) in $PhCF_3$ (0.1 M), heated to 70 (entries 1, 3, and 4) or 100 °C (sealed vial, microwave reactor or oil bath).

p-TsOH and heating to 60 °C. Gratifyingly, these modified conditions allowed access to pyrazolones **4f** and **4h−j** (Table 3).

Overall, using the two sets of conditions shown in Table 3, we were able to access pyrazolones with fluorenyl and benzyl protecting groups at the N^1 position. Such protecting groups can be removed using reductive conditions as illustrated for the

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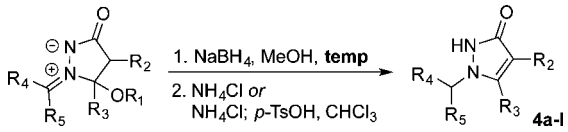
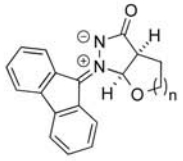
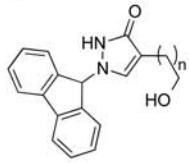
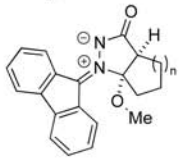
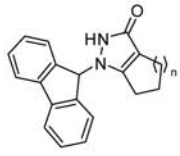
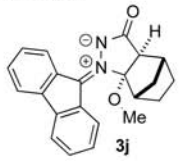
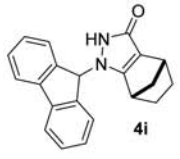
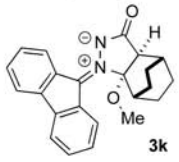
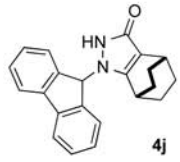
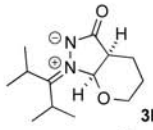
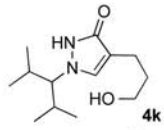
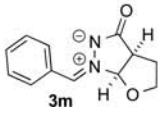
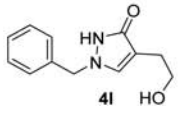
Table 3. Transformation of Adducts into Pyrazolones[a]



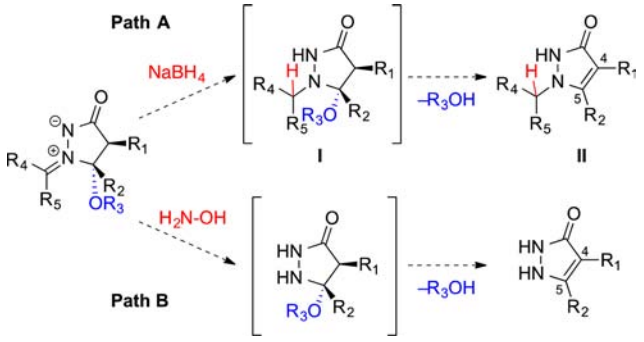
entry	azomethine imine	pyrazolone	yield (%)
1	**3c** $R_1 = R_3 = Me$; $R_2 = H$; $R_4,R_5 = Flu$	**4a** $R_2 = H$; $R_3 = Me$; $R_4,R_5 = Flu$	95
2	**3d** $R_1 = n$-Bu; $R_2,R_3 = H$; $R_4,R_5 = Flu$	**4b** $R_2,R_3 = H$; $R_4,R_5 = Flu$	95
3	**3i** $R_1,R_2 = Et$; $R_3 = H$; $R_4,R_5 = Flu$	**4c** $R_2 = Et$; $R_3 = H$; $R_4,R_5 = Flu$	95
			
4	n = 1, **3a**	**4d**	95
5	n = 2, **3b**	**4e**	94
			
6[b]	n = 1, **3f**	**4f**	59
7	n = 2, **3g**	**4g**	69
8[b]	n = 3, **3h**	**4h**	82
9[b]			72
10[b]			45
11			84
12			84

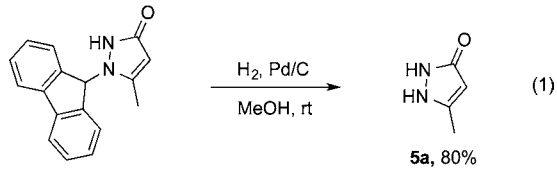
[a]Conditions: Azomethine imine (1 equiv), $NaBH_4$ (1−5 equiv) in MeOH (0.5 M), −20 °C to rt; NH_4Cl quench. [b]Similar conditions but −20 to 0 °C; NH_4Cl quench; then *p*-TsOH (0.5 mol %), $CHCl_3$ (0.05 M), 60 °C, 3 h.

fluorenyl group in eq 1. Consequently, the ability to *selectively* form N^1-functionalized pyrazolones allows the installation of a variety of substituents since reactions for the functionalization at the N^2 position are well established.[14]

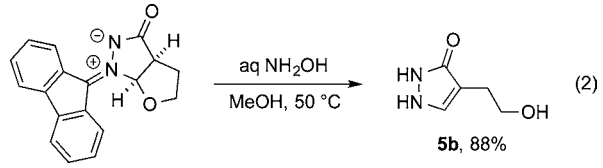
In contrast, we were also interested in developing a more efficient access to N^1,N^2-unsubstituted pyrazolones. In this regard, we developed a one-step reaction to access unprotected pyrazolones directly from azomethine imines (Scheme 2, path **B**).

Scheme 2. Proposed Mechanism for Formation of Pyrazolones from Azomethine Imines





The use of hydroxylamine as a nucleophile allowed for deprotection (via formation of fluorenone oxime) and concurrent aromatization to the pyrazolone eq 2.[15]



In summary, we have significantly expanded the scope and reactivity of azomethine imines derived from enol ethers. We have also shown that it is possible to use basic additives to access milder reaction conditions for alkene aminocarbonylation, provided that the rate-determining step is the generation of the imino-isocyanate. This allowed for the formation of azomethine imines that were previously inaccessible. These azomethine imines were used to form a variety of pyrazolones, with different protecting groups at N^1 and substituents at the 4- and 5-positions. Unprotected pyrazolones could also be obtained in one step from the azomethine imines using hydroxylamine. Overall, this methodology provides a new disconnection for synthesizing pyrazolones by taking advantage of imino-isocyanates as intermediates, allowing the synthesis of pyrazolones that are not easily accessible using literature methods.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01719.

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Notes

The authors declare no competing financial interest.

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