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One-Pot Synthesis of 2-Acetyl-1*H*-pyrroles from *N*-Propargylic β-Enaminones via Intermediacy of 1,4-Oxazepines

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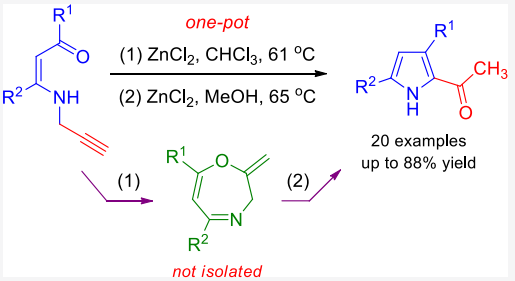
ABSTRACT: A one-pot two-step protocol for the synthesis of 2-acetyl-1*H*-pyrroles from *N*-propargylic β-enaminones was described. When treated with zinc chloride in refluxing chloroform, *N*-propargylic β-enaminones produced in situ 2-methylene-2,3-dihydro-1,4-oxazepines, which, upon further refluxing in methanol with zinc chloride, afforded 2-acetyl-1*H*-pyrroles. The process was found to be general for a wide variety of *N*-propargylic β-enaminones and yielded a diverse range of 2-acetyl-1*H*-pyrroles in good to high yields with large substrate scope and good functional group tolerance. This operationally easy method may provide a rapid access to functionalized 2-acetyl-1*H*-pyrroles of pharmacological interest.



INTRODUCTION

Pyrroles constitute one of the most important classes of heterocyclic compounds found in numerous natural products, pharmaceutical molecules, and functional materials.[1] Indeed, pyrroles are precious scaffolds for pharmaceutical and medicinal research since they possess a broad spectrum of pharmacological and biological properties, including analgesic, antiallergic, anticonvulsant, antidepressant, antidiabetic, anti-hyperlipidemic, anti-inflammatory, antimicrobial, antifungal, antiviral, cholesterol-reducing, and antitumor properties.[2] Admittedly, pyrroles have a profound effect on human health since they are present in a wide range of natural products (e.g., hymenidin, dispacamide B and D, longamide A and B, and spongiacidin B) and drugs (e.g., aloracetam, atorvastatin, elopiprazole, isamoltane, and ketorolac) in order to battle a large number of diseases and pathophysiological conditions.[2,3] Over the years, numerous methods have been developed for their synthesis, and new ones continue to appear since they are crucial intermediates in the synthesis of various drugs and natural products.[4] Thus, in recent years, substantial attention has been paid to develop new and effective methods for the construction of highly functionalized pyrroles.[4,5]

Recently, the rapid assembly of heterocyclic molecules from simple acyclic precursors in a one-pot process has attracted considerable interest of organic chemists. In this regard, *N*-propargylic β-enaminones have proven to be useful since their cyclizations have become a powerful tool in building a broad range of important heterocycles,[6] including pyrroles, 1-pyrrolines, pyridines, 1,2-dihydropyridines, 1,4-oxazepines, and 1,4-thiazepines.[7] With respect to the five-membered ring formation, cyclization of *N*-propargylic β-enaminones mostly afforded pyrrole derivatives. So far, according to the substitution pattern, four kinds of pyrrole derivatives have been obtained from the cyclizations of *N*-propargylic β-enaminones, representative examples of which are given in Scheme 1a. Pioneering studies of Cacchi and Fabrizi and Saito and Hanzawa opened the way for the synthesis of type 1 and 2 pyrrole derivatives, respectively.[8] Later, other research groups were also involved in the synthesis of such pyrrole derivatives.[9] Besides, the Cheng research group reported a ring-closing carbonyl-allene metathesis reaction of *N*-propargyl β-enaminones, which provided 2,4-disubstituted pyrroles, called as type 3, via the intermediacy of dihydropyrrole-fused oxetanes (Scheme 1a, lower left).[10] However, in one case, a minor pyrrole product, called as type 4 here, was also isolated from this reaction in 7% yield (Scheme 1a, lower right). Formation of this byproduct was explained by the ring opening of the oxetane intermediate via C−O bond cleavage.[10] Owing to the presence of a carbonyl group, 2-acetylpyrroles have great potential for further functionalization to construct more complex structures, but their synthesis from *N*-propargylic β-enaminones requires an efficient and high-yielding protocol, possibly via a new synthetic strategy.

Recently, Karunakar and co-workers have reported a gold-catalyzed cyclization of *N*-propargylic β-enaminones, leading to 2-methylene-2,3-dihydro-1,4-oxazepines (Scheme 1b).[11] We have demonstrated that when treated with zinc chloride in halogenated solvents, *N*-propargylic β-enaminones also afforded 2-methylene-2,3-dihydro-1,4-oxazepines via 7-*exo*-*dig* cyclization with high efficiency and large functional group

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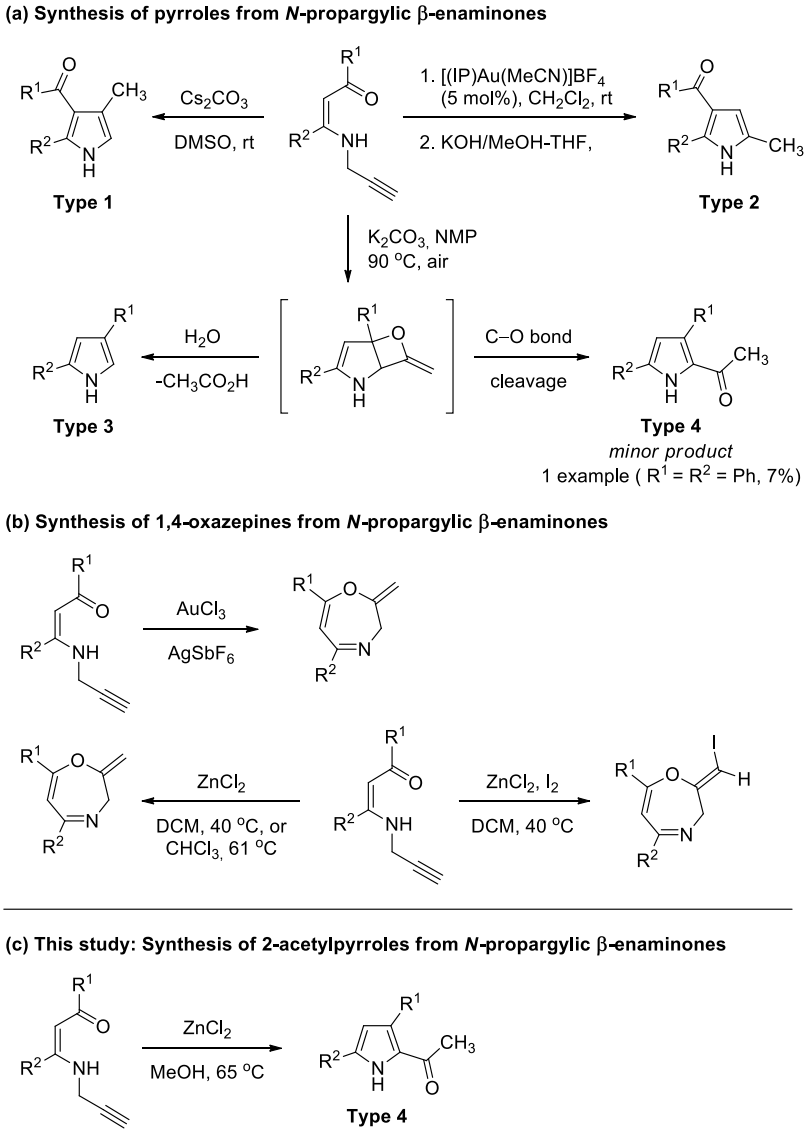
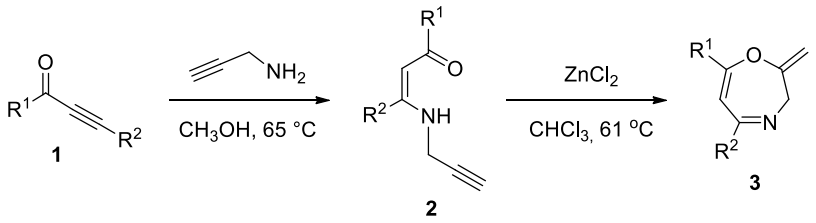
Scheme 1. Strategies for the Synthesis of Pyrroles and 1,4-Oxazepines



Scheme 2. Synthesis of *N*-Propargylic *β*-Enaminones and 1,4-Oxazepines



tolerance (Scheme 1b, lower left).[12] However, with the same reaction in the presence of molecular iodine, it yielded 2-(iodomethylene)-2,3-dihydro-1,4-oxazepines (Scheme 1b, lower right).[13] Our continued interest in the synthesis of new heterocyclic compounds as potential pharmaceuticals and scaffolds has prompted us to investigate new reactivity patterns of *N*-propargylic *β*-enaminones.[14] During these studies, we found an unprecedented method for the synthesis of type 4 pyrrole derivatives. When the zinc chloride-mediated reaction of *N*-propargylic *β*-enaminones was carried out in a polar protic solvent such as methanol, instead of a halogenated solvent such as methylene chloride or chloroform, it led to the formation of 3,5-disubstituted 2-acetylpyrrole [1-(1*H*-pyrrol-2-yl)ethanone] derivatives in good to high yields (Scheme 1c). To the best of our knowledge, the formation of 2-acetylpyrroles by these reactions is without precedent. As part of our ongoing program unveiling the reactivity pathways of *N*-propargylic *β*-enaminones, we herein report a new and novel method for the synthesis of 2-acetylpyrrole derivatives.

RESULTS AND DISCUSSION

As noted before, reactions of *N*-propargylic *β*-enaminones with $ZnCl_2$ in halogenated solvents produced 1,4-oxazepines (Scheme 1b, lower left).[12] By elementary considerations, it

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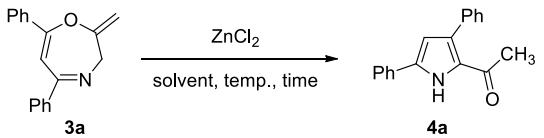
might be expected that 2-acetylpyrroles could arise from intermediate 1,4-oxazepines formed previously during the course of the reaction. Alternatively, 2-acetylpyrroles could result directly from *N*-propargylic β-enaminones without the intermediacy of 1,4-oxazepines. To contribute to a better understanding of the formation of 2-acetylpyrroles from these reactions, we have first prepared 20 derivatives of each of the *N*-propargylic β-enaminones **2** and 1,4-oxazepines **3** from α,β-alkynic ketones **1** according to our previous studies (Scheme 2)[12,14a] and then investigated their reactions (for details, see the Experimental Section).

We next started to explore the reaction of 1,4-oxazepines in protic polar solvents such as alcohols. For this purpose, the reaction of 1,4-oxazepine **3a** was first investigated under different conditions, as shown in Table 1. Initially, compound

Table 1. Optimization of the Reaction Conditions for the Synthesis of 2-Acetylpyrroles from 2-Methylene-2,3-dihydro-1,4-oxazepines[a]



3a **4a**

entry	$ZnCl_2$ (equiv)	solvent	temp (°C)	time (h)	yield of **4a** (%)
1		MeOH	65	35.0	77
2	1.0	MeOH	65	3.0	88
3	1.5	MeOH	65	1.5	84
4	2.0	MeOH	65	1.0	80
5	1.0	EtOH	78	3.0	71
6	1.0	*n*-PrOH	97	3.5	74
7	1.0	*n*-BuOH	116	2.0	63

[a]All reactions were carried out on a scale of 0.30 mmol of 1,4-oxazepine **3a** in 3 mL of solvent under argon under the indicated conditions. For work-up and purification, see the Experimental Section.

3a was refluxed in methanol, which produced 2-acetylpyrrole **4a** in 77% yield (Table 1, entry 1). However, this reaction took long time (35 h) for completion. Then, the same reaction was performed in the presence of 1.0, 1.5, and 2.0 molar equivalents of $ZnCl_2$ (Table 1, entries 2−4). Clearly, the use of $ZnCl_2$ increased the yields of pyrrole **4a** considerably (80−88%) and shortened the reaction times significantly (1−3 h). Although the use of excess $ZnCl_2$, such as 1.5 and 2.0 equiv, decreased the reaction times slightly, it lowered the yields of pyrrole **4a** to some extent. After these results, we decided to continue the reaction with 1.0 equiv of $ZnCl_2$. Subsequently, we carried out the reaction in ethanol, propanol, and butanol under reflux conditions (Table 1, entries 5−7). However, these reactions yielded pyrrole **4a** in relatively lower yields (63−74%). Eventually, the highest yield (88%) of 2-acetylpyrrole **4a** from 1,4-oxazepine **3a** was obtained with 1.0 equiv of $ZnCl_2$ (i.e., under the conditions in entry 2 of Table 1). On the basis of these reactions, we have concluded that formation of 2-acetylpyrroles **4** from *N*-propargylic β-enaminones **2** is a secondary process and occurs from the in situ-formed 1,4-oxazepines **3** during an alcohol-mediated reaction as will be discussed later.

Afterward, we investigated the generality and substrate scope for this reaction, as depicted in Table 2. A variety of 2-methylene-2,3-dihydro-1,4-oxazepines **3** was employed to synthesize a diverse range of 2-acetylpyrroles **4**. All reactions proceeded well and afforded the expected pyrroles **4** in good to high yields (63−88%). By employing these reactions, 20 derivatives of 2-acetylpyrroles **4** were prepared, 19 of which were synthesized for the first time. Notably, a large variety of aromatic and heteroaromatic groups with electron-donating and electron-withdrawing substituents survived in these reactions. Halogenated compounds form a large portion of drugs and drug candidates in clinical development since halogen bonds play important roles in the improvement of drug−target binding affinity.[15] Thus, we synthesized 11 derivatives of halogen-containing 2-acetylpyrroles, **4g−j**, **m**, **n**, and **4p−t**, in 63−88% yields (Table 2), three of which were fluorine-bearing 2-acetylpyrroles, **4g**, **h**, and **t**, obtained in 76−88% yields. Notably, in the pharmaceutical industry, fluorinated drugs are quite popular since fluorination has a positive effect on absorption, distribution, metabolism, and excretion.[16] In a wide range of pharmaceuticals, agrochemicals, and materials science, thiophenes are often employed as building blocks and scaffolds.[17] Therefore, we synthesized three derivatives of 5-(thiophen-3-yl)-substituted 2-acetylpyrroles, **4k**, **o**, and **q**, in 67−85% yields (Table 2).

Next, we turned our attention to one-pot synthesis of 2-acetylpyrroles **4** from *N*-propargylic β-enaminones **2**, as illustrated in Table 3. Initially, *N*-propargylic β-enaminone **2a** was treated overnight with 1.0 equiv of $ZnCl_2$ in methanol under reflux conditions, which furnished 2-acetylpyrrole **4a** in 46% yield (Table 3, entry 1). Subsequently, the reaction was repeated in the presence of 1.5 and 2.0 molar equivalents of $ZnCl_2$ (Table 3, entries 2 and 3). Use of excess $ZnCl_2$ did not increase the yield (51%) of pyrrole **4a** considerably. Then, the same reaction was performed in ethanol and propanol under reflux conditions (Table 3, entries 4 and 5), but these reactions also yielded pyrrole **4a** in low to moderate yields (34−46%). Presumably, in alcohols, intermediate 1,4-oxazepine **3a** does not form in high yields since our previous study has shown that 1,4-oxazepines are obtained in good to high yields when the reactions were carried out in halogenated solvents such as dichloromethane and chloroform.[12] On the other hand, in halogenated solvents, 1,4-oxazepines do not convert into 2-acetylpyrroles. Hence, we have planned this synthesis as a one-pot two-step process, as depicted in Table 3. First of all, on the basis of our previous study,[12] *N*-propargylic β-enaminone **2a** was refluxed in chloroform for 2 h with 1.0 equiv of $ZnCl_2$, which provided in situ formation of intermediate 1,4-oxazepine **3a** in good to high yields. Then, chloroform was replaced with methanol, and the resulting crude mixture was refluxed under the conditions given in entries 6−9 of Table 3. In other words, the second step of the process was optimized. When the crude reaction mixture was just refluxed in methanol in the second step, it yielded 2-acetylpyrrole **4a** in 57% yield (Table 3, entry 6). Subsequently, in the second step, the crude reaction mixture was treated with 0.5, 1.0, and 1.5 molar equivalents of $ZnCl_2$ (Table 3, entries 7−9), which yielded pyrrole **4a** in 75−85% yields. The highest yield (85%) of **4a** from these one-pot two-step reactions was achieved by employing 1.0 equiv of $ZnCl_2$ in the second step (Table 3, entry 8). Notably, the use of excess $ZnCl_2$ such as 1.5 equiv of $ZnCl_2$ in the second step somewhat lowered the yield (75%) of pyrrole **4a** (Table 3, entry 9). In all reactions of the one-pot two-step process, intermediate 1,4-oxazepine **3a** was not isolated. Derivatization studies for one-pot two-step transformation were made according to optimized conditions given in entry 8 of Table 3.

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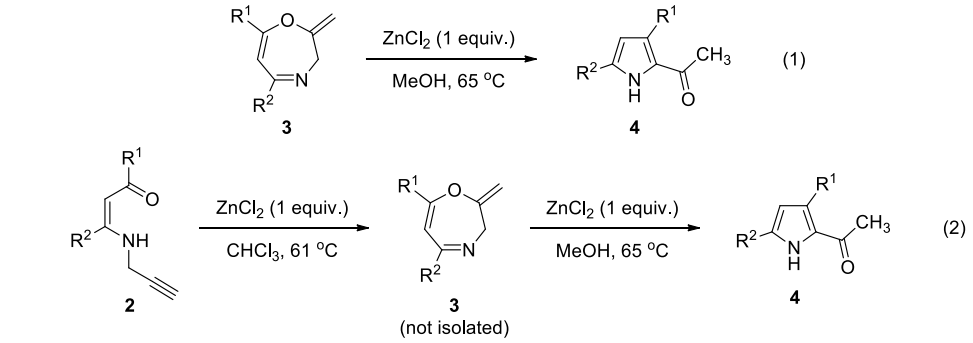
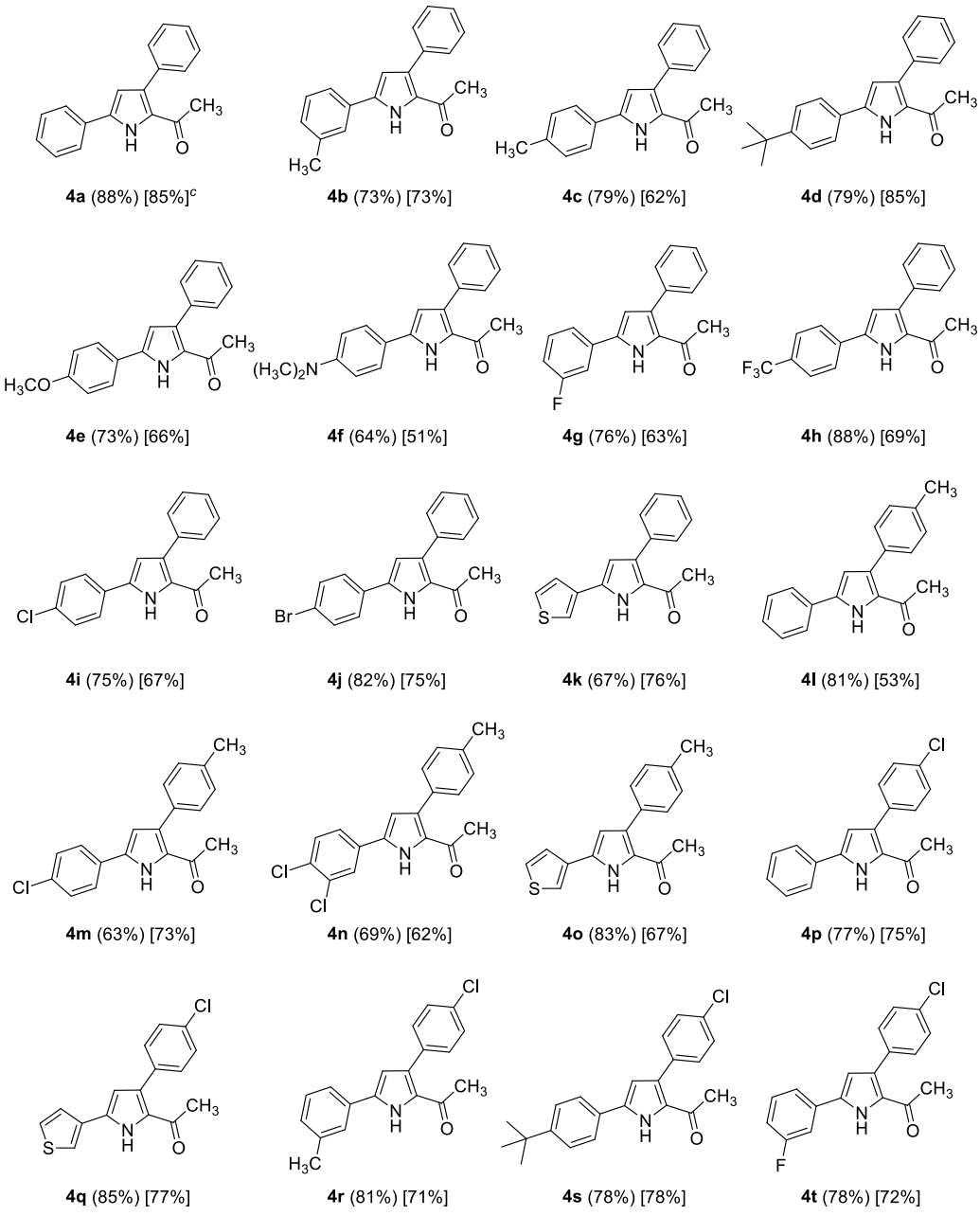
Table 2. Synthesis of 2-Acetylpyrroles from 2-Methylene-2,3-dihydro-1,4-oxazepines and *N*-Propargylic *β*-Enaminones[a,b]





[a]The yields of 2-acetylpyrroles **4** obtained from 2-methylene-2,3-dihydro-1,4-oxazepines **3** according to eq 1 are shown in parentheses. [b]The yields of 2-acetylpyrroles **4** resulted from *N*-propargylic *β*-enaminones **2** via a one-pot two-step process according to eq 2, without isolating intermediate 1,4-oxazepines **3**, are given in square brackets. [c]When the reaction was performed on a 1.60 mmol scale of *N*-propargylic *β*-enaminone **2a**, 2-acetylpyrrole **4a** was obtained in 80% yield (see the Experimental Section).

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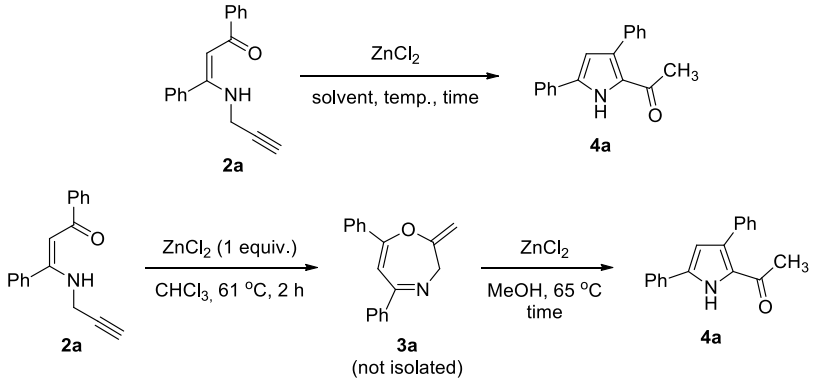
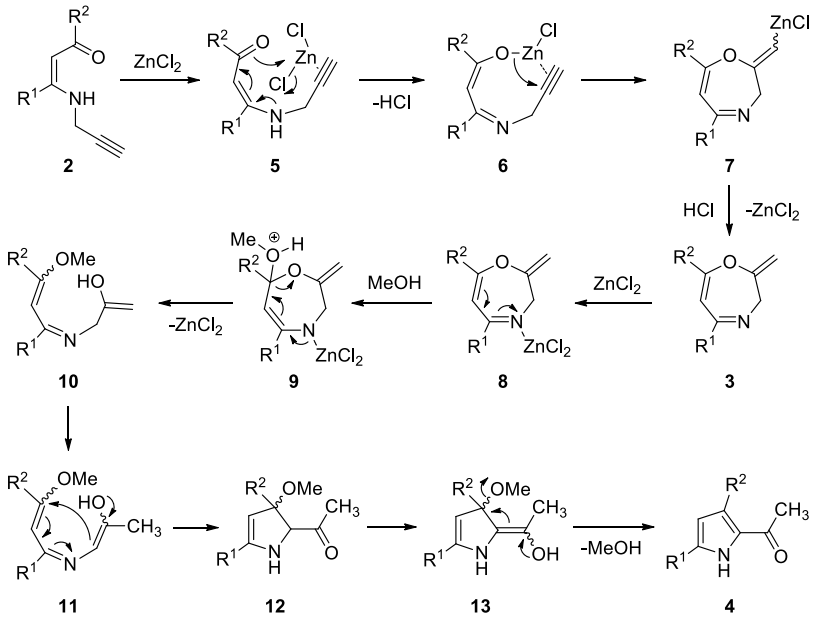
Table 3. Optimization of the Reaction Conditions for the Synthesis of 2-Acetylpyrroles from *N*-Propargylic *β*-Enaminones[a,b]



entry	$ZnCl_2$ (equiv)	solvent	temp (°C)	time (h)	yield of **4a** (%)
1	1.0	MeOH	65	24.0	46
2	1.5	MeOH	65	12.0	51
3	2.0	MeOH	65	11.0	51
4	2.0	EtOH	78	8.0	46
5	2.0	*n*-PrOH	97	5.0	34
entry	$ZnCl_2$ (equiv)[b]		time (h)		yield of **4a** (%)
6			3.0		57
7	0.5		1.5		75
8	1.0		1.0		85
9	1.5		1.0		75

[a]All reactions were carried out on a scale of 0.30 mmol of *N*-propargylic *β*-enaminone **2a** in 3 mL of solvent under argon under the indicated conditions. For work-up and purification, see the Experimental Section. [b]The amount (equiv) of $ZnCl_2$ used in the second step.

Scheme 3. Proposed Mechanism for the Formation of 2-Acetylpyrroles from *N*-Propargylic *β*-Enaminones



Subsequently, we explored the generality and substrate scope for one-pot two-step synthesis of 2-acetylpyrroles **4**, as shown in Table 2. A diverse range of 2-acetylpyrroles **4** was synthesized from *N*-propargylic *β*-enaminones **2** in good to high yields (51−85%). It is noteworthy to mention that the yields (51−85%) of the one-pot two-step process are quite comparable with those (64−88%) obtained from 1,4-oxazepines **3** (see Table 2 for comparison of the yields). In fact, all reactions of one-pot two-step transformation proceeded well and tolerated the presence of a wide variety of aromatic and heteroaromatic groups with electron-donating and electron-withdrawing substituents. The reaction of *N*-propargylic *β*-enaminone **2a** was performed on a relatively larger scale as well, which yielded 2-acetylpyrrole **4a** in 80% yield (Table 2), slightly lower than that (85%) in a small scale, indicating the practical utility of the method as a synthetic tool. We synthesized 11 derivatives of halogen-bearing 2-acetylpyrroles, **4g−j**, **m**, **n**, and **4p−t**, in 62−78% yields (Table 2), three of which were fluorine-containing 2-acetylpyrroles, **4g**, **h**, and **t**, obtained in 63−72% yields. We also synthesized three

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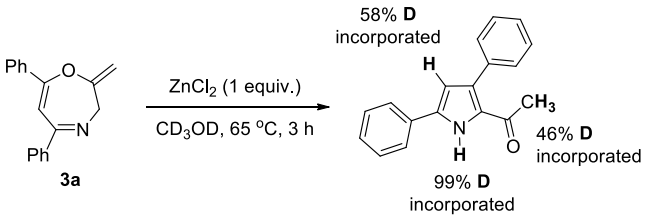
derivatives of 5-(thiophen-3-yl)-substituted 2-acetylpyrroles, **4k**, **o**, and **q**, in 67−77% yields (Table 2). Overall, 20 derivatives of 2-acetylpyrroles **4** were synthesized, 19 of which were prepared for the first time in this study.

The mechanism proposed for the formation of 2-acetylpyrroles **4** is given in Scheme 3, partly based on our previous study.[12] First, the interaction of zinc chloride with the alkyne moiety of **2** yields **5**. Subsequent coordination of carbonyl oxygen to zinc through vinylogous amido−imido tautomerization generates intermediate **6**, bringing the carbonyl and alkyne functionalities in close proximity. Then, intramolecular 7-*exo*-*dig* cyclization occurs to produce vinylzinc intermediate **7**. Hydrolysis with HCl generated in situ affords 1,4-oxazepine derivatives **3**.[12] The interaction of zinc chloride with amine nitrogen of **3** produces **8**, in which the vinylogous imine functionality is activated. This enables conjugate addition of methanol to give ketal **9**. Then, ring opening provides enol **10**, which converts into more stable enol **11**. Subsequently, cyclization takes place to furnish dihydropyrrole **12**. Finally, methanol elimination through enol **13** affords 2-acetylpyrrole derivatives **4** (Scheme 3). It is noteworthy to mention that hydrolysis or rearrangement of 1,4-oxazepines to pyrroles was rarely observed,[12,18] but formation of 2-acetylpyrroles from them is without a precedent.

During the course of the reaction, 2-methylene-2,3-dihydro-1,4-oxazepines **3** undergo a methanol-mediated rearrangement to afford 2-acetylpyrroles **4**, as shown in the proposed mechanism (Scheme 3). To the best of our knowledge, this is a very rare or previously unknown process. In order to provide evidence for the methanol involvement in reaction, we carried out the reaction of 1,4-oxazepine **3a** with 1.0 equiv of $ZnCl_2$ in d_4-methanol (CD_3OD) at reflux for 3 h to see if there is any deuterium (D) incorporation in the final 2-acetylpyrrole product **4a**. The reaction was very clean and generated the partially deuterium-incorporated pyrrole derivative **4a−D** (Scheme 4). From the integration values of the ^1H NMR

Scheme 4. Reaction of 2-Methylene-2,3-dihydro-1,4-oxazepine 3a with Zinc Chloride in CD_3OD



spectrum of the crude reaction mixture (**4a−D**), 46% deuteration of the methyl group, 58% deuteration of the C−H bond of the pyrrole ring, and 99% deuteration of the N−H bond were determined (see the Supporting Information for ^1H and ^{13}C NMR spectra of the crude reaction mixture). In particular, the incorporation of deuterium into methyl and C−H regions of the molecule clearly supports the proposed mechanism. However, during the course of the reaction, if formed, the nondeuterated 2-acetylpyrrole **4a** can also undergo the deuteration process. Thus, we examined the reaction of the pure 2-acetylpyrrole **4a** with 1.0 equiv of $ZnCl_2$ in CD_3OD at reflux for 3 h, but in this reaction, a low level of deuterium incorporation (4−6%) at the methyl and C−H sites of the molecule was observed. This strongly implies that deuterium incorporation mostly occurs during the conversion of 1,4-oxazepine **3a** to 2-acetylpyrrole **4a**.

In order to further prove the methanol involvement in the reaction, particularly via conjugate addition, we performed some control experiments with 1,4-oxazepine **3a**, as depicted in Table 4. First, the reaction of **3a** with $ZnCl_2$ was carried out in acetic acid (Table 4, entry 1), in which the starting 1,4-oxazepine **3a** was recovered in 55% yield, along with some unidentified decomposition products. However, a type 1 pyrrole derivative, namely, (4-methyl-2-phenyl-1*H*-pyrrol-3-yl) (phenyl)methanone (**14a**), was also isolated from this reaction but in very low yield (2%), which possibly resulted from the reaction of 1,4-oxazepine **3a** with trace H_2O existing in acetic acid. This is supported by the reaction conducted in a 1:1 mixture of acetic acid/water, which expectedly yielded pyrrole **14a** in high yield (71%), along with a small amount of 2-acetylpyrrole **4a** (6%) (Table 4, entry 2). As anticipated, an increasing amount of water raises the yield of type 1 pyrrole derivative **14a**. It is worth mentioning that during their purification on silica gel in our previous study,[12] 6-alkyl-substituted 2-methylene-2,3-dihydro-1,4-oxazepines generated the corresponding type 1 pyrrole derivatives in low yields (9−20%) as well, presumably via a similar mechanism. Notably, the reaction in acetic acid did not produce any 2-acetylpyrrole **4a** (Table 4, entry 1). This might be possibly due to the fact that acetic acid is less nucleophilic and basic as compared to methanol and water, as a result of resonance. In other words, acetic acid may not give conjugate addition under reaction conditions, and so it does not catalyze the formation of 2-acetylpyrrole **4a**. However, the reaction in a 1:1 mixture of acetic acid/water produced 2-acetylpyrrole **4a** in low yield (6%) (Table 4, entry 2). This could possibly have occurred as a byproduct from the reaction of 1,4-oxazepine **3a** with water. Subsequently, the same reaction with $ZnCl_2$ was tried in a 1:1 mixture of tetrahydrofuran (THF)/H_2O, which yielded pyrrole **14a** in 26% yield, along with the starting 1,4-oxazepine **3a** recovered in 65% yield (Table 4, entry 3). When a few drops of conc. HCl was used instead of $ZnCl_2$, the same reaction provided pyrrole **14a** in low yield (9%) and most of the starting 1,4-oxazepine **3a** was isolated back (76%) (Table 4, entry 4). Next, the reaction with $ZnCl_2$ was carried out in a 1:1 mixture of ethylene glycol/THF, which afforded 2-acetylpyrrole **4a** in 10% yield along with a new product, a keto−ketal derivative **15a**, in 26% yield (Table 4, entry 5); the formation of the latter provides useful information about the reaction mechanism, as will be discussed later. Finally, the same reaction in a 1:1 mixture of ethylene glycol/1,4-dioxane also yielded the same products, **4a** and **15a**, but in 22 and 20% yields, respectively (Table 4, entry 6).

Like methanol, water catalyzes or mediates the reaction as well, but its reaction produces a type 1 pyrrole derivative such as **14a**, instead of a type 4 pyrrole product such as **4a**. The mechanism proposed for the formation of pyrrole **14a** is depicted in Scheme 5. Similar to the mechanism with methanol in Scheme 3, conjugate addition of water to 1,4-oxazepine **3a** in the presence of $ZnCl_2$ or acid, followed by ring opening, gives bisenol **16a**, which then converts into keto−enol intermediate **17a**. Reaction with water differs at this stage (**16a** to **17a** in Scheme 5) from that with methanol (**10** to **11** in Scheme 3), which causes the formation of different pyrrole products. Afterward, cyclization via an aldol-type reaction furnishes 1-pyrroline (3,4-dihydro-2*H*-pyrrole) **18a**. Water

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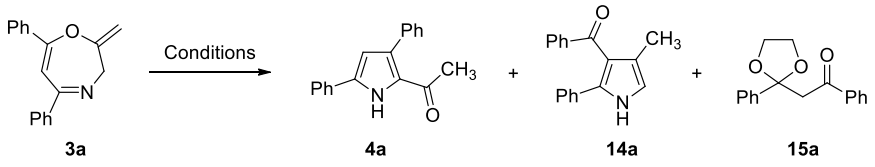
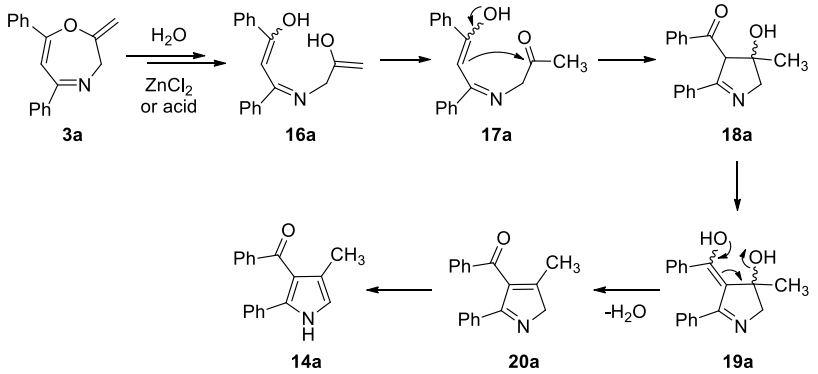
Table 4. Control Experiments for the Formation of 2-Acetylpyrroles from 2-Methylene-2,3-dihydro-1,4-oxazepines



entry	Conditions	products (yield, %)
1	$ZnCl_2$ (1.0 equiv), CH_3CO_2H, 80 °C, 5.5 h	**3a** (55%) + **14a** (2%)
2	$ZnCl_2$ (1.0 equiv), CH_3CO_2H/H_2O (1:1), 80 °C, 5.5 h	**4a** (6%) + **14a** (71%)
3	$ZnCl_2$ (1.0 equiv), THF/H_2O (1:1), 80 °C, 6.0 h	**3a** (65%) + **14a** (26%)
4	THF/H_2O (3:1), conc. HCl (3 drops), 80 °C, 6.0 h	**3a** (76%) + **14a** (9%)
5	$ZnCl_2$ (1.0 equiv), $HOCH_2CH_2OH/THF$ (1:1), 80 °C, 6.0 h	**4a** (10%) + **15a** (26%)
6	$ZnCl_2$ (1.0 equiv), $HOCH_2CH_2OH$/dioxane (1:1), 80 °C, 5.5 h	**4a** (22%) + **15a** (20%)

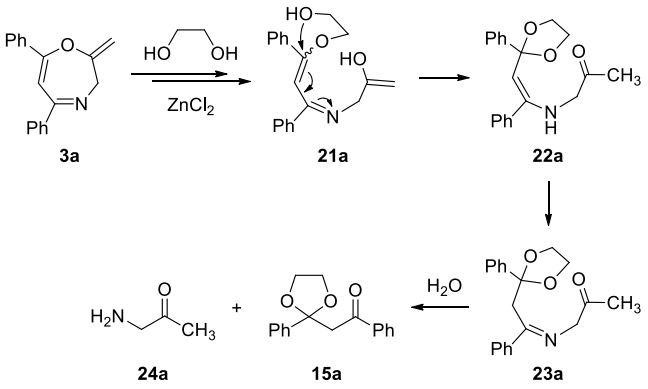
Scheme 5. Proposed Mechanism for the Formation of Pyrrole 14a from *N*-Propargylic *β*-Enaminones



elimination through the intermediacy of enol **19a** provides 2*H*-pyrrole **20a**. Finally, isomerization affords 1*H*-pyrrole **14a** (Scheme 5).

Notably, from the reactions in ethylene glycol, a keto−ketal derivative, **15a**, was obtained in addition to 2-acetylpyrrole **4a**. The suggested mechanism for the formation of **15a** is given in Scheme 6. As in the mechanism with methanol (Scheme 3),

Scheme 6. Proposed Mechanism for the Formation of Keto−Ketal 15a from *N*-Propargylic *β*-Enaminones



tandem conjugate addition of ethylene glycol to 1,4-oxazepine **3a** and ring opening of the resulting ketal yield enol **21a**. Subsequently, second conjugate addition takes place to afford keto−ketal intermediate **22a** with enamine functionality, which then converts into more stable keto−ketal derivative **23a** with imine functionality. At last, hydrolysis of compound **23a** through imine functionality affords the observed keto−ketal derivative **15a** and aminoacetone (**24a**) (Scheme 6). Alternatively, keto−ketal intermediate **22a** with enamine functionality can also directly hydrolyze to keto−ketal **15a** without the intermediacy of keto−ketal **23a**. However, we were unable to isolate aminoacetone (**24a**) from these reactions since it is water-soluble and possibly went into the water phase during the extraction.

In summary, the reactions in the presence of water and ethylene glycol indirectly prove the involvement of methanol in these reactions through conjugate addition. Notably, after the conjugate addition of water, followed by the ring opening of the ketal formed, the reaction pathway changes as compared to that with methanol and the resulting keto−enol intermediate undergoes an aldol-type reaction to afford a different pyrrole product, **14a** (i.e., a type 1 pyrrole), instead of the expected 2-acetylpyrrole **4a** (i.e., a type 4 pyrrole). However, in the reactions with ethylene glycol, conjugate addition occurs twice, which results in the formation of a keto−ketal product, **15a**. Overall, these cumulative results support the involvement of methanol indirectly to catalyze or mediate the reaction.

■ CONCLUSIONS

In summary, we have developed a robust one-pot procedure for the synthesis of 2-acetylpyrroles from *N*-propargylic *β*-enaminones via intermediacy of 1,4-oxazepines. The rearrangement of intermediate 1,4-oxazepines to 2-acetylpyrroles was proved by refluxing the isolated 1,4-oxazepines with zinc chloride in methanol. Interestingly, 1,4-oxazepines undergo a methanol-promoted tandem ring-opening/ring-closing reaction to afford 2-acetylpyrroles. A diverse range of 2-acetylpyrrole derivatives were separately synthesized from both 2-methylene-2,3-dihydro-1,4-oxazepines and *N*-propar-

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gylic β-enaminones in good to high yields. The reaction was general for a variety of both 1,4-oxazepines and *N*-propargylic β-enaminones and demonstrated good tolerance to a variety of aromatic and heteroaromatic groups. We anticipate that the high efficiency and wide reaction scope of the process could make it potentially attractive for the library construction of 2-acetylpyrroles in designing new and novel molecular entities and/or structural leads.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts were given in parts per million (ppm) relative to $CDCl_3$ (7.26 and 77.16 ppm in ^{1}H and ^{13}C{^{1}H} NMR, respectively) or CD_3OD (3.31 and 49.00 ppm in ^{1}H and ^{13}C{^{1}H} NMR, respectively). Coupling constants (*J*) were given in hertz (Hz), and spin multiplicities were shown by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). DEPT ^{13}C NMR information is depicted in parentheses as C, CH, CH_2, and CH_3. Infrared (IR) spectra were obtained using attenuated total reflection. Band position diagnostics for major functional groups were recorded in reciprocal centimeters (cm^{-1}). Mass spectra (MS) and high-resolution MS (HRMS) were obtained using electrospray ionization (ESI) with micro-Tof; *m*/*z* values are reported (for each measurement, the mass scale was recalibrated with sodium formate clusters, and samples were dissolved and measured in MeOH or CH_3CN). Melting points were determined on an automated instrument. Flash chromatography was performed using thick-walled glass columns and "flash-grade" silica gel (230−400 mesh). Thin-layer chromatography (TLC) was accomplished using commercially prepared 0.25 mm silica gel, and visualization was done with a short-wavelength UV lamp (254 nm). The relative proportions of solvents in chromatography solvent mixtures refer to the volume/volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All solvents used in reactions and chromatography were distilled and/or dried properly for purity. The inert atmosphere was created using slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in an oven prior to use.

N-Propargylic β-enaminones **2** and 1,4-oxazepines **3** were synthesized from α,β-alkynic ketones **1** according to our previous studies.[12,14a]

General Procedure for the Synthesis of 2-Methylene-2,3-dihydro-1,4-oxazepines. To a stirred solution of the corresponding *N*-propargylic β-enaminone (1.0 mmol) in $CHCl_3$ (10.0 mL) under argon was added $ZnCl_2$ (1.0 mmol). The resulting mixture was then heated to reflux at 61 °C for approximately 2 h in an oil bath (note that the progress of the reaction was monitored by routine TLC for the disappearance of *N*-propargylic β-enaminone using hexane/ethyl acetate (9:1) as the eluent). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (40 mL) and a saturated aqueous NH_4Cl solution (15 mL) were added. After the layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 35 mL) again. The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding 2-methylene-2,3-dihydro-1,4-oxazepines.

*2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**).* 1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2a**) (287.5 mg, 1.1 mmol) and $ZnCl_2$ (149.9 mg, 1.1 mmol) were used to yield 273.2 mg (95%) of the indicated product as a brownish-orange solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 94.2−95.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85−7.73 (m, 4H), 7.50−7.38 (m, 6H), 6.40 (s, 1H), 4.76 (s, 1H), 4.57 (s, 2H), 4.39 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (C), 158.9 (C), 158.2 (C), 139.8 (C), 135.2 (C), 130.2 (CH), 130.0 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 126.3 (CH), 99.8 (CH), 93.9 (CH_2), 55.6 (CH_2). The spectral data were in agreement with those reported previously for this compound.[12]

*2-Methylene-7-phenyl-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (**3b**).* 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**2b**) (385.5 mg, 1.4 mmol) and $ZnCl_2$ (190.8 mg, 1.4 mmol) were used to yield 285.3 mg (74%) of the indicated product as an orange oil (R_f = 0.48 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86−7.79 (m, 2H), 7.70 (s, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.52−7.45 (m, 3H), 7.38−7.26 (m, 2H), 6.44 (s, 1H), 4.81 (s, 1H), 4.60 (s, 2H), 4.44 (d, *J* = 1.3 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (C), 158.7 (C), 158.2 (C), 139.7 (C), 138.0 (C), 135.1 (C), 130.7 (CH), 130.1 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 126.2 (CH), 124.6 (CH), 99.8 (CH), 93.8 (CH_2), 55.4 (CH_2), 21.4 (CH_3). The spectral data were in agreement with those reported previously for this compound.[12]

*2-Methylene-7-phenyl-5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**3c**).* 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (**2c**) (220.3 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 154.1 mg (70%) of the indicated product as a brownish solid (R_f = 0.48 in 4:1 hexane/ethyl acetate; mp 73.0−75.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78−7.74 (m, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.46−7.41 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.39 (s, 1H), 4.73 (s, 1H), 4.54 (s, 2H), 4.37 (d, *J* = 1.4 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 158.6 (C), 158.3 (C), 140.0 (C), 136.9 (C), 135.1 (C), 130.0 (CH), 129.0 (CH), 128.5 (CH), 127.3 (CH), 126.2 (CH), 99.8 (CH), 93.5 (CH_2), 55.3 (CH_2), 21.3 (CH_3). The spectral data were in agreement with those reported previously for this compound.[12]

*5-[4-(tert-Butyl)phenyl]-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3d**).* 3-[4-(*tert*-Butyl)phenyl]-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2d**) (253.9 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 223.8 mg (88%) of the indicated product as a brownish-orange oil (R_f = 0.58 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.75 (m, 4H), 7.52−7.43 (m, 5H), 6.47 (s, 1H), 4.79 (s, 1H), 4.60 (s, 2H), 4.42 (d, *J* = 1.3 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (C), 158.6 (C), 158.3 (C), 153.3 (C), 137.0 (C), 135.2 (C), 130.1 (CH), 128.6 (CH), 127.2 (CH), 126.3 (CH), 125.3 (CH), 99.9 (CH), 93.7 (CH_2), 55.5 (CH_2), 34.8 (C), 31.3 (CH_3); IR (neat): 2960, 1654, 1622, 1573, 1493, 1448, 1361, 1313, 1291, 1261, 1192, 1106, 1061, 1019, 999, 946, 820, 763, 731, 683, 613 cm^{-1}; MS (ESI, *m*/*z*): 318.19 $[M + H]^+$; HRMS (ESI): calcd for $C_{22}H_{24}NO$, 318.1852 $[M + H]^+$; found, 318.1859.

*5-(4-Methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3e**).* 3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2e**) (203.9 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol) were used to yield 146.8 mg (72%) of the indicated product as a yellow solid (R_f = 0.21 in 4:1 hexane/ethyl acetate; mp 112.0−113.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79−7.73 (m, 4H), 7.46−7.40 (m, 3H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.39 (s, 1H), 4.72 (s, 1H), 4.52 (s, 2H), 4.37 (d, *J* = 1.1 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (C), 161.1 (C), 158.54 (C), 158.49 (C), 135.1 (C), 132.2 (C), 130.0 (CH), 128.8 (CH), 128.5 (CH), 126.2 (CH), 113.5 (CH), 99.8 (CH), 93.3 (CH_2), 55.2 (OCH_3), 55.1 (CH_2). The spectral data were in agreement with those reported previously for this compound.[12]

*N,N-Dimethyl-4-(2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)aniline (**3f**).* 3-(4-(Dimethylamino)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2f**) (334.8 mg, 1.1 mmol) and $ZnCl_2$ (149.9 mg, 1.1 mmol) were used to yield 204.5 mg (61%) of the indicated product as a brownish-yellow oil (R_f = 0.30 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80−7.75 (m, 2H), 7.74−7.69 (m, 2H), 7.49−7.40 (m, 3H), 6.70 (d, *J* = 8.9 Hz, 2H), 6.43 (s, 1H), 4.69 (s, 1H), 4.51 (s, 2H), 4.35 (d, *J* = 1.2 Hz, 1H), 3.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (C), 159.0 (C), 158.5 (C), 151.8 (C), 135.5 (C), 130.0 (CH), 128.8 (CH), 128.6 (CH), 127.2 (C), 126.3 (CH), 111.5 (CH), 100.3 (CH), 93.2 (CH_2), 54.8 (CH_2), 40.3 ($N(CH_3)_2$). The spectral data were in agreement with those reported previously for this compound.[12]

*5-(3-Fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3g**).* 3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)-prop-2-en-1-one (**2g**) (251.4 mg, 0.9 mmol) and $ZnCl_2$ (122.7 mg,

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0.9 mmol) were used to yield 211.3 mg (84%) of the indicated product as an orange solid (R_f = 0.45 in 4:1 hexane/ethyl acetate; mp 67.7−68.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79−7.74 (m, 2H), 7.59−7.56 (m, 1H), 7.55−7.51 (m, 1H), 7.47−7.41 (m, 3H), 7.37 (td, J = 8.0, 5.9 Hz, 1H), 7.13 (ddd, J = 8.3, 5.1, 1.8 Hz, 1H), 6.35 (s, 1H), 4.78 (s, 1H), 4.56 (s, 2H), 4.41 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0 (C), 162.9 (d, ^1J = 246.3 Hz, CF), 159.4 (C), 158.0 (C), 142.1 (d, ^3J = 7.1 Hz, C), 135.1 (C), 130.4 (CH), 130.0 (d, ^3J = 8.0 Hz, CH), 128.7 (CH), 126.4 (CH), 123.2 (d, ^4J = 2.6 Hz, CH), 117.0 (d, ^2J = 21.6 Hz, CH), 114.5 (d, ^2J = 22.7 Hz, CH), 99.2 (CH), 94.4 (CH_2), 55.6 (CH_2). The spectral data were in agreement with those reported previously for this compound.[12]

*2-Methylene-7-phenyl-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1,4-oxazepine (**3h**).* 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**2h**) (230.5 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol) were used to yield 172.9 mg (75%) of the indicated product as a yellowish-orange solid (R_f = 0.67 in 4:1 hexane/ethyl acetate; mp 101.9−103.4 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.1 Hz, 2H), 7.79−7.33 (m, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.50−7.40 (m, 3H), 6.35 (s, 1H), 4.79 (s, 1H), 4.58 (s, 2H), 4.42 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C), 159.6 (C), 157.8 (C), 143.1 (C), 134.9 (C), 131.7 (q, ^2J = 32.4 Hz, C), 130.4 (CH), 128.7 (CH), 127.8 (CH), 126.3 (CH), 125.3 (q, ^3J = 3.7 Hz, CH), 124.1 (q, ^1J = 272.2 Hz, CF_3), 98.9 (CH), 94.5 (CH_2), 55.8 (CH_2). The spectral data were in agreement with those reported previously for this compound.[12]

*5-(4-Chlorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3i**).* 3-(4-Chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)-prop-2-en-1-one (**2i**) (207.0 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol) were used to yield 175.9 mg (85%) of the indicated product as a brown solid (R_f = 0.61 in 4:1 hexane/ethyl acetate; mp 112.9−114.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80−7.66 (m, 4H), 7.46−7.30 (m, 5H), 6.32 (s, 1H), 4.77 (s, 1H), 4.54 (s, 2H), 4.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C), 159.2 (C), 158.0 (C), 138.1 (C), 136.0 (C), 134.9 (C), 130.2 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 126.2 (CH), 99.1 (CH), 94.0 (CH_2), 55.5 (CH_2); IR (neat): 2961, 1660, 1624, 1584, 1559, 1487, 1446, 1397, 1363, 1315, 1290, 1263, 1197, 1115, 1103, 1083, 1062, 1026, 1011, 944, 881, 855, 815, 760, 730, 688, 606 cm^{-1}; MS (ESI, m/z): 296.08 [M + H]$^+$; HRMS (ESI): calcd for $C_{18}H_{15}ClNO$, 296.0837 [M + H]$^+$; found, 296.0842.

*5-(4-Bromophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3j**).* 3-(4-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)-prop-2-en-1-one (**2j**) (204.1 mg, 0.6 mmol) and $ZnCl_2$ (81.8 mg, 0.6 mmol) were used to yield 177.9 mg (87%) of the indicated product as an orange solid (R_f = 0.42 in 4:1 hexane/ethyl acetate; mp 120.3−121.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.74 (m, 2H), 7.69 (t, J = 7.8 Hz, 2H), 7.58−7.51 (m, 2H), 7.50−7.41 (m, 3H), 6.35 (s, 1H), 4.80 (s, 1H), 4.57 (s, 2H), 4.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0 (C), 159.3 (C), 158.0 (C), 138.6 (C), 135.0 (C), 131.5 (CH), 130.3 (CH), 129.0 (CH), 128.6 (CH), 126.3(CH), 124.6 (C), 99.1 (CH), 94.2 (CH_2), 55.6 (CH_2); IR (neat): 2960, 1661, 1623, 1585, 1557, 1483, 1446, 1393, 1363, 1315, 1297, 1262, 1197, 1114, 1102, 1068, 1025, 1008, 949, 883, 855, 826, 814, 760, 723, 688 cm^{-1}; MS (ESI, m/z): 340.03 [M + H]$^+$; HRMS (ESI): calcd for $C_{18}H_{15}{}^{79}BrNO$, 340.0332 [M + H]$^+$; found, 340.0334.

*2-Methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (**3k**).* 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**2k**) (294.1 mg, 1.1 mmol) and $ZnCl_2$ (149.9 mg, 1.1 mmol) were used to yield 241.1 mg (82%) of the indicated product as a yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate; mp 98.0−100.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.75 (m, 2H), 7.70−7.67 (m, 1H), 7.60 (d, J = 5.0 Hz, 1H), 7.46 (s, 3H), 7.35−7.29 (m, 1H), 6.42 (s, 1H), 4.78 (s, 1H), 4.55 (s, 2H), 4.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (C), 158.3 (C), 158.0 (C), 142.7 (C), 135.0 (C), 130.1 (CH), 128.5 (CH), 126.7 (CH), 126.2 (CH), 125.9 (CH), 125.6 (CH), 99.3 (CH), 93.9 (CH_2), 55.2 (CH_2). The spectral data were in agreement with those reported previously for this compound.[12]

*2-Methylene-5-phenyl-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**3l**).* 3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**2l**) (220.3 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 140.6 mg (64%) of the indicated product as a yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate; mp 81.0−83.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.81 (m, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.49−7.43 (m, 3H), 7.27 (d, J = 8.1 Hz, 2H), 6.41 (s, 1H), 4.79 (s, 1H), 4.59 (s, 2H), 4.42 (d, J = 1.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (C), 159.0 (C), 158.2 (C), 140.4 (C), 139.9 (C), 132.3 (C), 130.0 (CH), 129.3 (CH), 128.3 (CH), 127.4 (CH), 126.2 (CH), 99.1 (CH), 93.7 (CH_2), 55.5 (CH_2), 21.4 (CH_3); IR (neat): 3106, 2995, 2837, 1657, 1626, 1588, 1569, 1509, 1445, 1359, 1312, 1292, 1261, 1193, 1113, 1076, 1055, 1028, 952, 926, 908, 882, 813, 765, 705, 692, 616 cm^{-1}; MS (ESI, m/z): 276.14 [M + H]$^+$; HRMS (ESI): calcd for $C_{19}H_{18}NO$, 276.1383 [M + H]$^+$; found, 276.1386.

*5-(4-Chlorophenyl)-2-methylene-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**3m**).* 3-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**2m**) (247.8 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 198.3 mg (80%) of the indicated product as an orange solid (R_f = 0.50 in 4:1 hexane/ethyl acetate; mp 115.4−116.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64−7.60 (m, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.28−7.24 (m, 2H), 7.13 (d, J = 8.1 Hz, 2H), 6.19 (s, 1H), 4.65 (s, 1H), 4.42 (s, 2H), 4.28 (d, J = 1.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (C), 159.5 (C), 158.1 (C), 140.7 (C), 138.3 (C), 136.1 (C), 132.2 (C), 129.4 (CH), 128.8 (CH), 128.6 (CH), 126.3 (CH), 98.5 (CH), 94.1 (CH_2), 55.6 (CH_2), 21.4 (CH_3); IR (neat): 2961, 1650, 1583, 1488, 1409, 1366, 1312, 1260, 1196, 1088, 1060, 1011, 863, 843, 802, 727, 679 cm^{-1}; MS (ESI, m/z): 310.10 [M + H]$^+$; HRMS (ESI): calcd for $C_{19}H_{17}ClNO$, 310.0993 [M + H]$^+$; found, 310.0996.

*5-(3,4-Dichlorophenyl)-2-methylene-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**3n**).* 3-(3,4-Dichlorophenyl)-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**2n**) (275.4 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 220.3 mg (80%) of the indicated product as a yellow solid (R_f = 0.53 in 4:1 hexane/ethyl acetate; mp 119.0−120.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 2.0 Hz, 1H), 7.59−7.52 (m, 3H), 7.39 (d, J = 8.4 Hz, 1H), 7.19−7.14 (m, 2H), 6.18 (s, 1H), 4.69 (s, 1H), 4.45 (s, 2H), 4.32 (d, J = 1.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (C), 159.9 (C), 157.8 (C), 140.8 (C), 139.8 (C), 134.1 (C), 132.7 (C), 132.0 (C), 130.3 (CH), 129.41 (CH), 129.39 (CH), 126.7 (CH), 126.3 (CH), 97.9 (CH), 94.4 (CH_2), 55.7 (CH_2), 21.5 (CH_3); IR (neat): 2915, 1655, 1579, 1469, 1372, 1317, 1264, 1233, 1191, 1062, 1027, 854, 809, 754, 717, 676, 644 cm^{-1}; MS (ESI, m/z): 344.06 [M + H]$^+$; HRMS (ESI): calcd for $C_{19}H_{16}Cl_2NO$, 344.0604 [M + H]$^+$; found, 344.0613.

*2-Methylene-5-(thiophen-3-yl)-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**3o**).* 3-(Prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)-prop-2-en-1-one (**2o**) (225.1 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 188.7 mg (84%) of the indicated product as a yellow solid (R_f = 0.23 in 4:1 hexane/ethyl acetate; mp 88.0−90.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.65 (m, 3H), 7.57 (dd, J = 5.1, 1.1 Hz, 1H), 7.35−7.31 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 6.40 (s, 1H), 4.76 (s, 1H), 4.54 (s, 2H), 4.41 (d, J = 1.1 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (C), 158.7 (C), 158.1 (C), 143.0 (C), 140.5 (C), 132.3 (C), 129.3 (CH), 126.9 (CH), 126.3 (CH), 125.9 (CH), 125.7 (CH), 98.8 (CH), 93.9 (CH_2), 55.4 (CH_2), 21.4 (CH_3); IR (neat): 2196, 1623, 1580, 1409, 1345, 1312, 1266, 1200, 1182, 1110, 1059, 1017, 865, 805, 778, 753, 695, 654 cm^{-1}; MS (ESI, m/z): 282.09 [M + H]$^+$; HRMS (ESI): calcd for $C_{17}H_{16}NOS$, 282.0947 [M + H]$^+$; found, 282.0942.

*7-(4-Chlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**3p**).* 1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)-prop-2-en-1-one (**2p**) (236.6 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 197.9 mg (84%) of the indicated product as a yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate; mp 125.8−127.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83−7.75 (m, 2H), 7.72−7.63 (m, 2H), 7.47−7.35 (m, 5H), 6.35 (s, 1H), 4.75 (s, 1H), 4.54 (s, 2H), 4.40 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz,

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$CDCl_3$): δ 166.7 (C), 158.0 (C), 157.6 (C), 139.6 (C), 136.1 (C), 133.5 (C), 130.0 (CH), 128.8 (CH), 128.3 (CH), 127.5 (CH), 127.3 (CH), 99.8 (CH), 94.1 (CH_2), 55.4 (CH_2); IR (neat): 2953, 2837, 1656, 1625, 1587, 1569, 1488, 1445, 1402, 1362, 1312, 1290, 1258, 1192, 1110, 1088, 1054, 1028, 1010, 885, 858, 820, 769, 714, 691, 601 cm^{-1}; MS (ESI, *m/z*): 296.08 $[M + H]^+$; HRMS (ESI): calcd for $C_{18}H_{15}ClNO$, 296.0837 $[M + H]^+$; found, 296.0842.

*7-(4-Chlorophenyl)-2-methylene-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (**3q**).* 1-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**2q**) (241.5 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 210.6 mg (87%) of the indicated product as a yellow solid (R_f = 0.32 in 4:1 hexane/ethyl acetate; mp 121.0−122.9 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.5 Hz, 3H), 7.55 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.31−7.28 (m, 1H), 6.35 (s, 1H), 4.74 (s, 1H), 4.51 (s, 2H), 4.40 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8 (C), 157.8 (C), 157.1 (C), 142.5 (C), 136.0 (C), 133.4 (C), 128.7 (CH), 127.5 (CH), 126.7 (CH), 125.9 (CH), 125.6 (CH), 99.4 (CH), 94.1 (CH_2), 55.1 (CH_2). IR (neat): 3100, 3952, 2834, 1652, 1621, 1578, 1520, 1488, 1402, 1349, 1312, 1260, 1231, 1194, 1111, 1088, 1055, 1011, 874, 837, 818, 787, 693, 605 cm^{-1}; MS (ESI, *m/z*): 302.04 $[M + H]^+$; HRMS (ESI): calcd for $C_{16}H_{13}ClNOS$, 302.0401 $[M + H]^+$; found, 302.0410.

*7-(4-Chlorophenyl)-2-methylene-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (**3r**).* 1-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**2r**) (247.8 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 214.8 mg (87%) of the indicated product as a pale-yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate; mp 89.0−91.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.7 Hz, 2H), 7.65 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.35−7.25 (m, 2H), 6.38 (s, 1H), 4.77 (s, 1H), 4.57 (s, 2H), 4.42 (d, *J* = 1.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 158.1 (C), 157.6 (C), 139.6 (C), 138.1 (C), 136.2 (C), 133.6 (C), 130.9 (CH), 128.8 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 124.6 (CH), 100.0 (CH), 94.1 (CH_2), 55.5 (CH_2), 21.5 (CH_3); IR (neat): 3053, 2960, 1645, 1624, 1572, 1491, 1404, 1361, 1318, 1262, 1200, 1114, 1087, 1063, 1010, 908, 874, 934, 809, 779, 696, 668, 631, 607 cm^{-1}; MS (ESI, *m/z*): 310.10 $[M + H]^+$; HRMS (ESI): calcd for $C_{19}H_{17}ClNO$, 310.0993 $[M + H]^+$; found, 310.1000.

*5-[4-(tert-Butyl)phenyl]-7-(4-chlorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**3s**).* 3-(4-(*tert*-Butyl)phenyl)-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2s**) (246.3 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol) were used to yield 202.3 mg (82%) of the indicated product as an orange oil (R_f = 0.48 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77−7.70 (m, 4H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 4.76 (s, 1H), 4.57 (s, 2H), 4.41 (d, *J* = 1.3 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C), 158.2 (C), 157.5 (C), 153.4 (C), 136.9 (C), 136.1 (C), 133.7 (C), 128.8 (CH), 127.6 (CH), 127.2 (CH), 125.4 (CH), 100.0 (CH), 94.0 (CH_2), 55.4 (CH_2), 34.8 (C), 31.3 (CH_3); IR (neat): 2960, 1737, 1654, 1623, 1581, 1489, 1405, 1361, 1313, 1260, 1192, 1092, 1059, 1012, 909, 813, 736, 682, 632 cm^{-1}; MS (ESI, *m/z*): 352.15 $[M + H]^+$; HRMS (ESI): calcd for $C_{22}H_{23}ClNO$, 352.1463 $[M + H]^+$; found, 352.1473.

*7-(4-Chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**3t**).* 1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2t**) (219.6 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol) were used to yield 163.0 mg (74%) of the indicated product as an orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate; mp 114.5.0−115.6 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.55−7.47 (m, 2H), 7.40−7.32 (m, 3H), 7.15−7.07 (m, 1H), 6.30 (s, 1H), 4.76 (s, 1H), 4.54 (s, 2H), 4.40 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6 (C), 162.8 (d, ^1J = 246.6 Hz, CF), 158.1 (C), 157.8 (C), 141.9 (d, ^3J = 7.1 Hz, C), 136.4 (C), 133.4 (C), 129.9 (d, ^3J = 8.1 Hz, CH), 128.9 (CH), 127.6 (CH), 123.1 (d, ^4J = 2.6 Hz, CH), 117.0 (d, ^2J = 21.6 Hz, CH), 114.3 (d, ^2J = 22.7 Hz, CH), 99.3 (CH), 94.5 (CH_2), 55.6 (CH_2). The spectral data were in agreement with those reported previously for this compound.[12]

General Procedure for the Synthesis of 2-Acetyl-1*H*-pyrroles from 1,4-Oxazepines. To a stirred solution of the corresponding 2-methylene-2,3-dihydro-1,4-oxazepine (0.5 mmol) in MeOH (5.0 mL) under argon was added $ZnCl_2$ (0.5 mmol), and the resulting mixture was then heated to reflux at 65 °C for approximately 2 h in an oil bath (the progress of the reaction was monitored by routine TLC for the disappearance of 2-methylene-2,3-dihydro-1,4-oxazepine using hexane/ethyl acetate/acetone (19:1:0.2) as the eluent). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (40 mL) and saturated aqueous NH_4Cl (15 mL) were added. After the layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 35 mL). The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator to give a crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding 2-acetyl-1*H*-pyrroles.

*1-(3,5-Diphenyl-1H-pyrrol-2-yl)ethanone (**4a**).* 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**) (130.7 mg, 0.5 mmol) and $ZnCl_2$ (68.1 mg, 0.5 mmol) were used to yield 115.0 mg (88%) of the indicated product as a beige solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 147.0−149.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.17 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.52−7.38 (m, 7H), 7.33 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 2.9 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8 (CO), 136.7 (C), 136.4 (C), 134.6 (C), 130.9 (C), 129.8 (CH), 129.6 (C), 129.0 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 125.3 (CH), 110.9 (CH), 27.6 (CH_3); IR (neat): 3251, 1612, 1597, 1492, 1461, 1438, 1356, 1291, 1269, 1184, 1075, 992, 956, 914, 826, 760, 703, 688, 671, 613 cm^{-1}; MS (ESI, *m/z*): 262.12 $[M + H]^+$; HRMS (ESI): calcd for $C_{18}H_{16}NO$, 262.1226 $[M + H]^+$; found, 262.1232. The spectral data were in agreement with those reported previously for this compound.[10]

*1-[3-Phenyl-5-(m-tolyl)-1H-pyrrol-2-yl]ethanone (**4b**).* 2-Methylene-7-phenyl-5-(*m*-tolyl)-2,3-dihydro-1,4-oxazepine (**3b**) (137.7 mg, 0.5 mmol) and $ZnCl_2$ (68.1 mg, 0.5 mmol) were used to yield 100.9 mg (73%) of the indicated product as an off-white solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 130.0−131.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.38 (s, 1H), 7.58−7.51 (m, 2H), 7.49−7.39 (m, 5H), 7.35−7.28 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 2.9 Hz, 1H), 2.42 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7 (CO), 138.6 (C), 136.9 (C), 136.4 (C), 134.6 (C), 130.8 (C), 129.8 (CH), 129.4 (C), 129.0 (CH), 128.9 (CH), 128.3 (CH), 127.6 (CH), 125.9 (CH), 122.5 (CH), 110.9 (CH), 27.6 (CH_3), 21.5 (CH_3); IR (neat): 3275, 3224, 1625, 1492, 1451, 1358, 1273, 1206, 1109, 994, 956, 909, 822, 786, 768, 694, 613 cm^{-1}; MS (ESI, *m/z*): 276.14 $[M + H]^+$; HRMS (ESI): calcd for $C_{19}H_{18}NO$, 276.1383 $[M + H]^+$; found, 276.1390.

*1-[3-Phenyl-5-(p-tolyl)-1H-pyrrol-2-yl]ethanone (**4c**).* 2-Methylene-7-phenyl-5-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**3c**) (110.1 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 87.1 mg (79%) of the indicated product as an off-white solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 164.5−165.9 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.48−7.38 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 2.9 Hz, 1H), 2.38 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6 (CO), 138.3 (C), 136.9 (C), 136.5 (C), 134.6 (C), 129.8 (CH), 129.7 (C), 129.3 (CH), 128.3 (CH), 128.1 (CH), 127.7 (C), 125.2 (CH), 110.5 (CH), 27.6 (CH_3), 21.3 (CH_3); IR (neat): 3299, 3277, 1620, 1495, 1462, 1409, 1287, 1262, 1181, 1100, 1071, 1017, 952, 801, 766, 700, 634, 610 cm^{-1}; MS (ESI, *m/z*): 276.14 $[M + H]^+$; HRMS (ESI): calcd for $C_{19}H_{18}NO$, 276.1383 $[M + H]^+$; found, 276.1391.

*1-{5-[4-(tert-Butyl)phenyl]-3-phenyl-1H-pyrrol-2-yl}ethanone (**4d**).* 5-[4-(*tert*-Butyl)phenyl]-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3d**) (127.0 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 100.0 mg (79%) of the indicated product as a white solid (R_f = 0.47 in 4:1 hexane/ethyl acetate; mp 168.0−169.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.52−7.39 (m, 7H), 6.59 (d, *J* = 2.9 Hz, 1H), 2.16 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6 (CO), 151.5 (C), 136.8 (C), 136.4 (C), 134.6 (C), 129.9 (CH), 129.3 (C), 128.3

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(CH), 128.1 (C), 127.7 (CH), 126.0 (CH), 125.0 (CH), 110.6 (CH), 34.8 (C), 31.3 (CH_3), 27.6 (CH_3); IR (neat): 3273, 2961, 1626, 1494, 1452, 1415, 1289, 1261, 992, 957, 821, 772, 699, 673, 610 cm^{-1}; MS (ESI, *m/z*): 318.19 $[M + H]^+$; HRMS (ESI): calcd for $C_{22}H_{24}NO$, 318.1852 $[M + H]^+$; found, 318.1861.

*1-[5-(4-Methoxyphenyl)-3-phenyl-1H-pyrrol-2-yl]ethanone (**4e**).* 5-(4-Methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3e**) (116.5 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 84.8 mg (73%) of the indicated product as a yellowish-white solid (R_f = 0.25 in 4:1 hexane/ethyl acetate; mp 174.1−177.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 7.66−7.62 (m, 2H), 7.46−7.37 (m, 5H), 6.97−6.92 (m, 2H), 6.47 (d, *J* = 3.0 Hz, 1H), 3.83 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5 (CO), 159.8 (C), 136.9 (C), 136.5 (C), 134.8 (C), 129.8 (CH), 129.1 (C), 128.3 (CH), 127.7 (CH), 126.7 (CH), 123.6 (C), 114.5 (CH), 110.1 (CH), 55.4 (OCH_3), 27.5 (CH_3); IR (neat): 3274, 1612, 1599, 1495, 1463, 1440, 1421, 1387, 1294, 1275, 1245, 1175, 1103, 1071, 1027, 954, 824, 793, 765, 716, 699, 641, 608 cm^{-1}; MS (ESI, *m/z*): 292.13 $[M + H]^+$; HRMS (ESI): calcd for $C_{19}H_{18}NO_2$, 292.1332 $[M + H]^+$; found, 292.1340.

*1-{5-[4-(Dimethylamino)phenyl]-3-phenyl-1H-pyrrol-2-yl}-ethanone (**4f**).* *N*,*N*-Dimethyl-4-(2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)aniline (**3f**) (121.8 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 78.0 mg (64%) of the indicated product as a yellow solid (R_f = 0.22 in 4:1 hexane/ethyl acetate; mp 193.6−195.9 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.56 (d, *J* = 8.9 Hz, 2H), 7.46−7.38 (m, 5H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 3.0 Hz, 1H), 3.00 (s, 6H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9 (CO), 150.4 (C), 137.8 (C), 136.7 (C), 135.0 (C), 129.8 (CH), 128.6 (C), 128.2 (CH), 127.6 (CH), 126.3 (CH), 118.7 (C), 112.4 (CH), 109.3 (CH), 40.4 ($N(CH_3)_2$), 27.4 (CH_3); IR (neat): 3303, 3276, 2802, 1594, 1498, 1463, 1411, 1383, 1353, 1272, 1209, 1184, 1102, 1069, 948, 819, 798, 766, 699, 676, 632, 612 cm^{-1}; MS (ESI, *m/z*): 305.17 $[M + H]^+$; HRMS (ESI): calcd for $C_{20}H_{21}N_2O$, 305.1648 $[M + H]^+$; found, 305.1651.

*1-[5-(3-Fluorophenyl)-3-phenyl-1H-pyrrol-2-yl]ethanone (**4g**).* 5-(3-Fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3g**) (111.8 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 85.0 mg (76%) of the indicated product as a white solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 176.0−177.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 7.48−7.34 (m, 8H), 7.05−6.98 (m, 1H), 6.57 (d, *J* = 3.0 Hz, 1H), 2.12 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2 (CO), 163.4 (d, ^1J = 246.2 Hz, CF), 136.2 (C), 135.5 (C), 134.6 (C), 133.2 (d, ^3J = 8.3 Hz, C), 130.6 (d, ^3J = 8.5 Hz, CH), 129.92 (CH), 129.86 (C), 128.4 (CH), 127.9 (CH), 121.0 (d, ^4J = 1.9 Hz, CH), 115.1 (d, ^2J = 21.3 Hz, CH), 112.4 (d, ^2J = 23.1 Hz, CH), 111.5 (CH), 27.7 (CH_3); IR (neat): 3301, 3288, 3062, 1628, 1489, 1454, 1434, 1414, 1357, 1271, 1206, 1176, 1107, 1076, 991, 977, 957, 892, 848, 814, 784, 766, 729, 704, 680, 613 cm^{-1}; MS (ESI, *m/z*): 280.11 $[M + H]^+$; HRMS (ESI): calcd for $C_{18}H_{15}FNO$, 280.1132 $[M + H]^+$; found, 280.1136.

*1-{3-Phenyl-5-[4-(trifluoromethyl)phenyl]-1H-pyrrol-2-yl}-ethanone (**4h**).* 2-Methylene-7-phenyl-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1,4-oxazepine (**3h**) (131.7 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 115.4 mg (88%) of the indicated product as a yellowish-white solid (R_f = 0.41 in 4:1 hexane/ethyl acetate; mp 196.0−198.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.49−7.38 (m, 5H), 6.64 (d, *J* = 3.0 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.3 (CO), 136.0 (C), 134.9 (C), 134.5 (C), 134.3 (C), 130.3 (C), 130.2 (q, ^2J = 32.4 Hz, C), 129.9 (CH), 128.5 (CH), 128.0 (CH), 126.1 (q, ^3J = 3.5 Hz, CH), 125.4 (CH), 124.2 (q, ^1J = 272.0 Hz, CF_3), 112.1 (CH), 27.8 (CH_3); IR (neat): 3290, 1618, 1465, 1450, 1411, 1318, 1295, 1262, 1159, 1106, 1062, 1017, 957, 841, 815, 767, 704, 676, 626, 612 cm^{-1}; MS (ESI, *m/z*): 330.11 $[M + H]^+$; HRMS (ESI): calcd for $C_{19}H_{15}F_3NO$, 330.1100 $[M + H]^+$; found, 330.1109.

*1-[5-(4-Chlorophenyl)-3-phenyl-1H-pyrrol-2-yl]ethanone (**4i**).* 5-(4-Chlorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3i**) (118.3 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 89.0 mg (75%) of the indicated product as an off-white solid (R_f = 0.40 in 4:1 hexane/ethyl acetate; mp 173.3−175.1 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.57 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.48−7.39 (m, 5H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.55 (d, *J* = 2.9 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0 (CO), 136.2 (C), 135.8 (C), 134.8 (C), 134.0 (C), 129.83 (CH), 129.80 (C), 129.5 (CH), 129.2 (CH), 128.4 (CH), 127.8 (C), 126.7 (CH), 111.2 (CH), 27.7 (CH_3); IR (neat): 3286, 1621, 1488, 1462, 1411, 1355, 1284, 1261, 1086, 1013, 956, 832, 812, 765, 738, 702, 666, 611 cm^{-1}; MS (ESI, *m/z*): 296.08 $[M + H]^+$; HRMS (ESI): calcd. for $C_{18}H_{15}ClNO$, 296.0837 $[M + H]^+$; found, 296.0844.

*1-[5-(4-Bromophenyl)-3-phenyl-1H-pyrrol-2-yl]ethanone (**4j**).* 5-(4-Bromophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**3j**) (102.1 mg, 0.3 mmol) and $ZnCl_2$ (40.9 mg, 0.3 mmol) were used to yield 83.7 mg (82%) of the indicated product as an off-white solid (R_f = 0.43 in 4:1 hexane/ethyl acetate; mp 184.0−186.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.43 (s, 1H), 7.68−7.58 (m, 2H), 7.58−5.51 (m, 2H), 7.50−7.35 (m, 5H), 6.57 (s, 1H), 2.13 (d, *J* = 4.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0 (CO), 136.1 (C), 135.7 (C), 134.7 (C), 132.1 (C), 129.88 (CH), 129.86 (C), 129.8 (CH), 128.4 (CH), 127.8 (CH), 126.9 (C), 122.2 (CH), 111.2 (CH), 27.7 (CH_3); IR (neat): 3854, 3284, 2008, 1618, 1485, 1462, 1408, 1282, 1261, 1068, 1007, 955, 810, 769, 739, 705, 611 cm^{-1}; MS (ESI, *m/z*): 340.03 $[M + H]^+$; HRMS (ESI): calcd for $C_{18}H_{15}{}^{79}BrNO$, 340.0332 $[M + H]^+$; found, 340.0333.

*1-[3-Phenyl-5-(thiophen-3-yl)-1H-pyrrol-2-yl]ethanone (**4k**).* 2-Methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (**3k**) (133.7 mg, 0.5 mmol) and $ZnCl_2$ (68.1 mg, 0.5 mmol) were used to yield 89.9 mg (67%) of the indicated product as a yellow solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 173.9−176.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.32 (s, 1H), 7.72−7.65 (m, 1H), 7.55−7.33 (m, 7H), 6.51−6.40 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8 (CO), 136.4 (C), 134.7 (C), 133.0 (C), 132.6 (C), 129.9 (CH), 128.9 (C), 128.4 (CH), 127.8 (CH), 126.7 (CH), 125.6 (CH), 120.9 (CH), 111.1 (CH), 27.6 (CH_3); IR (neat): 3286, 3092, 1620, 1473, 1450, 1409, 1380, 1266, 1212, 1075, 1021, 992, 957, 851, 818, 788, 764, 705, 679, 606 cm^{-1}; MS (ESI, *m/z*): 268.08 $[M + H]^+$; HRMS (ESI): calcd for $C_{16}H_{14}NOS$, 268.0791 $[M + H]^+$; found, 268.0795.

*1-[5-Phenyl-3-(p-tolyl)-1H-pyrrol-2-yl]ethanone (**4l**).* 2-Methylene-5-phenyl-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**3l**) (110.1 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 89.1 mg (81%) of the indicated product as an off-white solid (R_f = 0.43 in 4:1 hexane/ethyl acetate; mp 148.7−150.1 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 7.76−7.68 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.39−7.33 (m, 3H), 7.30−7.27 (m, 2H), 6.58 (d, *J* = 3.0 Hz, 1H), 2.46 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8 (CO), 137.5 (C), 136.6 (C), 134.6 (C), 133.3 (C), 131.0 (C), 129.7 (CH), 129.6 (C), 129.0 (CH), 128.2 (CH), 125.3 (CH), 111.0 (CH), 27.6 (CH_3), 21.3 (CH_3) (note that two CH peaks overlap on each other); IR (neat): 3281, 3227, 1624, 1497, 1460, 1438, 1358, 1289, 1268, 1106, 1021, 996, 955, 913, 839, 823, 806, 762, 690, 670, 637 cm^{-1}; MS (ESI, *m/z*): 276.14 $[M + H]^+$; HRMS (ESI): calcd for $C_{19}H_{18}NO$, 276.1383 $[M + H]^+$; found, 276.1389.

*1-[5-(4-Chlorophenyl)-3-(p-tolyl)-1H-pyrrol-2-yl]ethanone (**4m**).* 5-(4-Chlorophenyl)-2-methylene-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**3m**) (123.9 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 78.1 mg (63%) of the indicated product as a white solid (R_f = 0.58 in 4:1 hexane/ethyl acetate; mp 199.1−201.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.56−7.52 (m, 2H), 7.30−7.26 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.42 (d, *J* = 3.0 Hz, 1H), 2.33 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0 (CO), 137.7 (C), 135.5 (C), 134.8 (C), 134.0 (C), 133.1 (C), 129.8 (C), 129.7 (CH), 129.5 (C), 129.3 (CH), 129.1 (CH), 126.5 (CH), 111.2 (CH), 27.7 (CH_3), 21.4 (CH_3); IR (neat): 3290, 1631, 1493, 1443, 1356, 1284, 1260, 1181, 1087, 1011, 955, 831, 817, 799, 729, 656 cm^{-1}; MS (ESI, *m/z*): 310.10 $[M + H]+$; HRMS (ESI): calcd for $C_{19}H_{17}ClNO$, 310.0993 $[M + H]^+$; found, 310.1001.

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*1-[5-(3,4-Dichlorophenyl)-3-(p-tolyl)-1H-pyrrol-2-yl]ethanone (**4n**).* 5-(3,4-Dichlorophenyl)-2-methylene-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**3n**) (137.7 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 95.0 mg (69%) of the indicated product as a white solid (R_f = 0.50 in 4:1 hexane/ethyl acetate; mp 224.0−226.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.21 (s, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.45−7.37 (m, 2H), 7.23 (pseudo d, J = 8.3 Hz, 2H), 7.18 (pseudo d, J = 8.3 Hz, 2H), 6.46 (d, J = 3.0 Hz, 1H), 2.35 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0 (CO), 137.8 (C), 134.8 (C), 134.2 (C), 133.4 (C), 132.9 (C), 132.1 (C), 131.14 (C), 131.06 (CH), 130.2 (C), 129.7 (CH), 129.2 (CH), 127.1 (CH), 124.5 (CH), 111.8 (CH), 27.8 (CH_3), 21.4 (CH_3); IR (neat): 3271, 1617, 1485, 1442, 1417, 1359, 1281, 1180, 1134, 1107, 1027, 993, 954, 870, 814, 758, 697, 655 cm^{-1}; MS (ESI, m/z): 344.06 $[M + H]^+$; HRMS (ESI): calcd for $C_{19}H_{16}Cl_2NO$, 344.0604 $[M + H]^+$; found, 344.0601.

*1-[5-(Thiophen-3-yl)-3-(p-tolyl)-1H-pyrrol-2-yl]ethanone (**4o**).* 2-Methylene-5-(thiophen-3-yl)-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**3o**) (112.5 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 93.2 mg (83%) of the indicated product as a yellow solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 167.0−169.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, 1H), 7.76−7.72 (m, 1H), 7.46 (dd, J = 5.0, 0.8 Hz, 1H), 7.39−7.32 (m, 3H), 7.27 (d, J = 7.9 Hz, 2H), 6.46 (d, J = 2.8 Hz, 1H), 2.45 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9 (CO), 137.5 (C), 134.8 (C), 133.3 (C), 133.0 (C), 132.7 (CH), 129.7 (C), 129.1 (CH), 128.9 (C), 126.6 (CH), 125.7 (CH), 120.8 (CH), 111.1 (CH), 27.6 (CH_3), 21.4 (CH_3); IR (neat): 3286, 3100, 2917, 1667, 1573, 1486, 1369, 1277, 1178, 1132, 1058, 1016, 768, 653 cm^{-1}; MS (ESI, m/z): 282.09 $[M + H]^+$; HRMS (ESI): calcd for $C_{17}H_{16}NOS$, 282.0947 $[M + H]^+$; found, 282.0956.

*1-[3-(4-Chlorophenyl)-5-phenyl-1H-pyrrol-2-yl]ethanone (**4p**).* 7-(4-Chlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**3p**) (118.3 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 91.1 mg (77%) of the indicated product as a yellowish-white solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 173.0−174.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 7.72−7.67 (m, 2H), 7.45−7.31 (m, 7H), 6.53 (d, J = 3.0 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5 (CO), 136.9 (C), 134.8 (C), 133.8 (C), 133.1 (C), 131.1 (CH), 130.7 (C), 129.5 (C), 129.1 (CH), 128.6 (CH), 128.4 (CH), 125.3 (CH), 110.8 (CH), 27.7 (CH_3); IR (neat): 3282, 3227, 1623, 1488, 1460, 1433, 1396, 1359, 1289, 1267, 1086, 1016, 994, 953, 914, 837, 809, 759, 688, 671, 632, 610 cm^{-1}; MS (ESI, m/z): 296.08 $[M + H]^+$; HRMS (ESI): calcd for $C_{18}H_{15}ClNO$, 296.0837 $[M + H]^+$; found, 296.0842.

*1-[3-(4-Chlorophenyl)-5-(thiophen-3-yl)-1H-pyrrol-2-yl]-ethanone (**4q**).* 7-(4-Chlorophenyl)-2-methylene-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (**3q**) (120.7 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 102.9 mg (85%) of the indicated product as a pale-yellow solid (R_f = 0.34 in 4:1 hexane/ethyl acetate; mp 195.1−196.3 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.35 (s, 1H), 7.69−7.66 (m, 1H), 7.44−7.33 (m, 6H), 6.42 (d, J = 2.9 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5 (CO), 134.8 (C), 133.9 (C), 133.2 (C), 132.4 (C), 131.2 (CH), 128.9 (C), 128.6 (CH), 126.8 (CH), 125.6 (CH), 121.0 (CH), 111.0 (CH), 27.7 (CH_3) (note that two C peaks overlap on each other); IR (neat): 3310, 3217, 3088, 2349, 2027, 1617, 1533, 1492, 1467, 1446, 1377, 1266, 1216, 1086, 1015, 993, 973, 952, 854, 829, 782, 735, 672, 648, 635, 605 cm^{-1}; MS (ESI, m/z): 302.04 $[M + H]^+$; HRMS (ESI): calcd for $C_{16}H_{13}ClNOS$, 302.0401 $[M + H]^+$; found, 302.0409.

*1-[3-(4-Chlorophenyl)-5-(m-tolyl)-1H-pyrrol-2-yl]ethanone (**4r**).* 7-(4-Chlorophenyl)-2-methylene-5-(*m*-tolyl)-2,3-dihydro-1,4-oxazepine (**3r**) (123.9 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol) were used to yield 100.2 mg (81%) of the indicated product as an off-white solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 178.8−179.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.14 (s, 1H), 7.51−7.46 (m, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 6.53−6.50 (m, 1H), 2.40 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.4 (CO), 138.8 (C), 137.0 (C), 134.8 (C), 133.8 (C), 133.0 (C), 131.1 (CH), 130.6 (C), 129.4 (C), 129.2 (CH), 129.0 (CH), 128.6 (CH), 125.9 (CH), 122.5 (CH), 110.8 (CH), 27.7 (CH_3), 21.6 (CH_3); IR (neat): 3303, 3220, 1624, 1440, 1270, 1086, 1016, 952, 905, 837, 808, 782, 726, 694, 634, 613 cm^{-1}; MS (ESI, m/z): 310.10 $[M + H]^+$; HRMS (ESI): calcd for $C_{19}H_{17}ClNO$, 310.0993 $[M + H]^+$; found, 310.1001.

*1-{5-[4-(tert-Butyl)phenyl]-3-(4-chlorophenyl)-1H-pyrrol-2-yl}-ethanone (**4s**).* 5-[4-(*tert*-Butyl)phenyl]-7-(4-chlorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**3s**) (105.6 mg, 0.3 mmol) and $ZnCl_2$ (40.9 mg, 0.3 mmol) were used to yield 82.4 mg (78%) of the indicated product as an off-white solid (R_f = 0.46 in 4:1 hexane/ethyl acetate; mp 222.0−224.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 6.51 (d, J = 3.0 Hz, 1H), 2.12 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3 (CO), 151.7 (C), 137.0 (C), 134.9 (C), 133.8 (C), 133.1 (C), 131.2 (CH), 129.3 (C), 128.5 (CH), 127.9 (C), 126.0 (CH), 125.1 (CH), 110.5 (CH), 34.8 (C), 31.3 (CH_3), 27.7 (CH_3); IR (neat): 3279, 2947, 1619, 1491, 1460, 1413, 1358, 1290, 1259, 1185, 1085, 1016, 994, 954, 832, 812, 757, 723, 671, 634, 610 cm^{-1}; MS (ESI, m/z): 352.15 $[M + H]^+$; HRMS (ESI): calcd for $C_{22}H_{23}ClNO$, 352.1463 $[M + H]^+$; found, 352.1472.

*1-[3-(4-Chlorophenyl)-5-(3-fluorophenyl)-1H-pyrrol-2-yl]-ethanone (**4t**).* 7-(4-Chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**3t**) (94.1 mg, 0.3 mmol) and $ZnCl_2$ (40.9 mg, 0.3 mmol) were used to yield 73.5 mg (78%) of the indicated product as an off-white solid (R_f = 0.40 in 4:1 hexane/ethyl acetate; mp 199.0−201.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.42 (s, 1H), 7.51−7.44 (m, 2H), 7.44−7.39 (m, 2H), 7.39−7.34 (m, 3H), 7.05−6.98 (m, 1H), 6.54 (d, J = 3.0 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0 (CO), 163.4 (d, ^1J = 246.0 Hz, CF), 135.7 (C), 134.6 (C), 134.0 (C), 133.1 (C), 133.0 (d, ^3J = 8.2 Hz, C), 131.2 (CH), 130.7 (d, ^3J = 8.4 Hz,CH), 129.9 (C), 128.7 (CH), 121.0 (d, ^4J = 2.5 Hz, CH), 115.19 (d, ^2J = 21.3 Hz, CH), 112.38 (d, ^2J = 23.2 Hz, CH), 111.4 (CH), 27.8 (CH_3); IR (neat): 3294, 3060, 1631, 1491, 1432, 1356, 1274, 1204, 1175, 1089, 1014, 977, 955, 887, 841, 805, 777, 737, 720, 683, 627 cm^{-1}; MS (ESI, m/z): 314.08 $[M + H]^+$; HRMS (ESI): calcd for $C_{18}H_{14}ClFNO$, 314.0743 $[M + H]^+$; found, 314.0752.

General Procedure for the Synthesis of 2-Acetyl-1*H*-pyrroles from *N*-Propargylic *β*-Enaminones. To a stirred solution of the corresponding *N*-propargylic *β*-enaminone (0.5 mmol) in $CHCl_3$ (5.0 mL) under argon was added $ZnCl_2$ (0.5 mmol), and the resulting mixture was heated to reflux at 61 °C for approximately 2 h in an oil bath (the progress of the first step was monitored by routine TLC for the disappearance of *N*-propargylic *β*-enaminone using hexane/ethyl acetate (9:1) as the eluent). After the mixture was allowed to cool to room temperature, the solvent was removed on a rotary evaporator, and methanol (5 mL) and $ZnCl_2$ (0.5 mmol) were added. The resulting mixture was then refluxed with stirring at 65 °C for approximately another 2 h under argon in an oil bath (the progress of the second step was monitored by routine TLC for the disappearance of 2-methylene-2,3-dihydro-1,4-oxazepine using hexane/ethyl acetate/acetone (19:1:0.2) as the eluent). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (40 mL) and saturated aqueous NH_4Cl (15 mL) were added. After the layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 35 mL). The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator to give a crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding 2-acetyl-1*H*-pyrroles.

*1-(3,5-Diphenyl-1H-pyrrol-2-yl)ethanone (**4a**).* 1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2a**) (130.7 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol) were used to yield 111.1 mg (85%) of the indicated product as a beige solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 147.0−149.0 °C).

When the reaction was carried out on a relatively larger scale by employing 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2a**) (418.1 mg, 1.6 mmol) and $ZnCl_2$ (436.1 mg, 3.2 mmol), the indicated product (**4a**) was obtained in 334.5 mg (80%).

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*1-[3-Phenyl-5-(m-tolyl)-1H-pyrrol-2-yl]ethanone (**4b**).* 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**2b**) (137.7 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol) were used to yield 100.7 mg (73%) of the indicated product as an off-white solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 130.0−131.0 °C).

*1-[3-Phenyl-5-(p-tolyl)-1H-pyrrol-2-yl]ethanone (**4c**).* 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (**2c**) (110.1 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 67.9 mg (62%) of the indicated product as an off-white solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 164.5−165.9 °C).

*1-{5-[4-(tert-Butyl)phenyl]-3-phenyl-1H-pyrrol-2-yl}ethanone (**4d**).* 3-[4-(*tert*-Butyl)phenyl]-1-phenyl-3-(prop-2-yn-1-ylamino)-prop-2-en-1-one (**2d**) (127.0 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 108.5 mg (85%) of the indicated product as a white solid (R_f = 0.47 in 4:1 hexane/ethyl acetate; mp 168.0−169.0 °C).

*1-[5-(4-Methoxyphenyl)-3-phenyl-1H-pyrrol-2-yl]ethanone (**4e**).* 3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2e**) (145.7 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol) were used to yield 96.4 mg (66%) of the indicated product as a yellowish-white solid (R_f = 0.25 in 4:1 hexane/ethyl acetate; mp 174.1−177.0 °C).

*1-{5-[4-(Dimethylamino)phenyl]-3-phenyl-1H-pyrrol-2-yl}-ethanone (**4f**).* 3-[4-(Dimethylamino)phenyl]-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2f**) (152.2 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol) were used to yield 77.7 mg (51%) of the indicated product as a yellow solid (R_f = 0.22 in 4:1 hexane/ethyl acetate; mp 193.6−195.9 °C).

*1-[5-(3-Fluorophenyl)-3-phenyl-1H-pyrrol-2-yl]ethanone (**4g**).* 3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2g**) (139.8 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol) were used to yield 88.1 mg (63%) of the indicated product as a white solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 176.0−177.0 °C).

*1-{3-Phenyl-5-[4-(trifluoromethyl)phenyl]-1H-pyrrol-2-yl}-ethanone (**4h**).* 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**2h**) (131.7 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 91.0 mg (69%) of the indicated product as a yellowish-white solid (R_f = 0.41 in 4:1 hexane/ethyl acetate; mp 196.0−198.0 °C).

*1-[5-(4-Chlorophenyl)-3-phenyl-1H-pyrrol-2-yl]ethanone (**4i**).* 3-(4-Chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2i**) (118.3 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 79.7 mg (67%) of the indicated product as an off-white solid (R_f = 0.40 in 4:1 hexane/ethyl acetate; mp 173.3−175.1 °C).

*1-[5-(4-Bromophenyl)-3-phenyl-1H-pyrrol-2-yl]ethanone (**4j**).* 3-(4-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2j**) (136.1 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 102.3 mg (75%) of the indicated product as an off-white solid (R_f = 0.43 in 4:1 hexane/ethyl acetate; mp 184.0−186.0 °C).

*1-[3-Phenyl-5-(thiophen-3-yl)-1H-pyrrol-2-yl]ethanone (**4k**).* 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**2k**) (133.7 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol) were used to yield 101.7 mg (76%) of the indicated product as a yellow solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 173.9−176.0 °C).

*1-[5-Phenyl-3-(p-tolyl)-1H-pyrrol-2-yl]ethanone (**4l**).* 3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**2l**) (110.1 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 58.9 mg (53%) of the indicated product as an off-white solid (R_f = 0.43 in 4:1 hexane/ethyl acetate; mp 148.7−150.1 °C).

*1-(5-(4-Chlorophenyl)-3-(p-tolyl)-1H-pyrrol-2-yl)ethanone (**4m**).* 3-(4-Chlorophenyl)-1-(*p*-tolyl)prop-2-yn-1-one (**2m**) (123.9 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 90.1 mg (73%) of the indicated product as a white solid (R_f = 0.58 in 4:1 hexane/ethyl acetate; mp 199.1−201.0 °C).

*1-(5-(3,4-Dichlorophenyl)-3-(p-tolyl)-1H-pyrrol-2-yl)ethanone (**4n**).* 3-(3,4-Dichlorophenyl)-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)-prop-2-en-1-one (**2n**) (137.7 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 85.4 mg (62%) of the indicated product as a white solid (R_f = 0.50 in 4:1 hexane/ethyl acetate; mp 224.0−226.0 °C).

*1-[5-(Thiophen-3-yl)-3-(p-tolyl)-1H-pyrrol-2-yl]ethanone (**4o**).* 3-(Prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-en-1-one (**2o**) (112.5 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 75.3 mg (67%) of the indicated product as a yellow solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 167.0−169.0 °C).

*1-[3-(4-Chlorophenyl)-5-phenyl-1H-pyrrol-2-yl]ethanone (**4p**).* 1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2p**) (118.3 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 89.1 mg (75%) of the indicated product as a yellowish-white solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 173.0−174.0 °C).

*1-[3-(4-Chlorophenyl)-5-(thiophen-3-yl)-1H-pyrrol-2-yl]-ethanone (**4q**).* 1-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**2q**) (120.7 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 93.3 mg (77%) of the indicated product as a pale-yellow solid (R_f = 0.34 in 4:1 hexane/ethyl acetate; mp 195.1−196.3 °C).

*1-[3-(4-Chlorophenyl)-5-(m-tolyl)-1H-pyrrol-2-yl]ethanone (**4r**).* 1-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**2r**) (123.9 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 88.3 mg (71%) of the indicated product as an off-white solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 178.8−179.6 °C).

*1-{5-[4-(tert-Butyl)phenyl]-3-(4-chlorophenyl)-1H-pyrrol-2-yl}-ethanone (**4s**).* 3-(4-(*tert*-Butyl)phenyl)-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2s**) (140.7 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 109.6 mg (78%) of the indicated product as an off-white solid (R_f = 0.46 in 4:1 hexane/ethyl acetate; mp 222.0−224.0 °C).

*1-[3-(4-Chlorophenyl)-5-(3-fluorophenyl)-1H-pyrrol-2-yl]-ethanone (**4t**).* 1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**2t**) (125.5 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol) were used to yield 90.7 mg (72%) of the indicated product as an off-white solid (R_f = 0.40 in 4:1 hexane/ethyl acetate; mp 199.0−201.0 °C).

Reaction of 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (3a) with $ZnCl_2$ in CD_3OD. To a stirred solution of 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**) (104.0 mg, 0.4 mmol) in methanol-d_4 (CD_3OD) (4.0 mL) under argon was added $ZnCl_2$ (54.5 mg, 0.4 mmol), and the resulting mixture was then heated to reflux at 65 °C for approximately 3 h in an oil bath. After the reaction was over, it was allowed to cool to room temperature, and ^1H and ^{13}C NMR spectra were taken directly from the crude reaction mixture.

*Deuterium-Incorporated 1-(3,5-Diphenyl-1H-pyrrol-2-yl)-ethanone (**4a−D**).* ^1H NMR (400 MHz, CD_3OD): δ 11.32 (s, **0.01H**), 7.77 (d, J = 7.4 Hz, 2H), 7.46−7.36 (m, 7H), 7.36−7.30 (m, 1H), 6.58 (d, J = 2.2 Hz, **0.42H**), 2.08−2.00 (m, **1.62H**). From the integration values, the level of deuterium incorporation (% D) was determined as 46% at 2.08−2.00 ppm, 58% at 6.58 ppm, and 99% at 11.32 ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 190.3 (CO), 138.8 (C), 137.9 (C), 136.6 (C), 132.4 (C), 130.8 (CH), 130.5 (C), 129.9 (CH), 129.2 (CH), 129.1 (CH), 128.6 (CH), 126.6 (CH), 111.8 (CH), 27.5 (t, J_{C-D} = 19.7 Hz, CH_3).

General Procedure for the Reactions of 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (3a) (Table 4). To a stirred solution of 1,4-oxazepine **3a** (0.4 mmol) in 4.0 mL of the indicated solvent or solvent mixture was added $ZnCl_2$ (0.4 mmol), except that in one case, three drops of conc. HCl were used instead of $ZnCl_2$. The resulting mixture was then heated at 80 °C for approximately 5.5−6.0 h in an oil bath. After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (40 mL) and saturated aqueous NH_4Cl (15 mL) were added. After the layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried over $MgSO_4$ and evaporated on a rotary evaporator to give a crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (19:1, 9:1, and 4:1) as the eluent to afford the indicated products.

*Reaction of 1,4-Oxazepine **3a** with $ZnCl_2$ in CH_3CO_2H (Table 4, Entry 1).* 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**)

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(104.0 mg, 0.4 mmol) and $ZnCl_2$ (50.0 mg, 0.4 mmol) in CH_3CO_2H (4 mL) were used. After chromatographic purification, two fractions were isolated. The first fraction yielded 57.0 mg (55%) of the starting material 1,4-oxazepine **3a** as a brownish-orange solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 94.2−95.9 °C). The second fraction afforded 2.0 mg (2%) of (4-methyl-2-phenyl-1*H*-pyrrol-3-yl)(phenyl)methanone (**14a**) as a brownish-orange solid (R_f = 0.22 in 4:1 hexane/ethyl acetate; mp 118.5−120.0 °C).

*(4-Methyl-2-phenyl-1H-pyrrol-3-yl)(phenyl)methanone (**14a**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 7.71−7.64 (m, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.21−7.16 (m, 4H), 7.12−7.09 (m, 3H), 6.65 (s, 1H), 2.19 (d, J = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0 (CO), 139.6 (C), 136.4 (C), 132.4 (CH), 131.9 (CH), 129.9 (C), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.4 (CH), 122.4 (CH), 120.5 (C), 117.4 (C), 11.7 (CH_3); IR (neat): 3161, 2945, 2852, 1733, 1716, 1588, 1569, 1488, 1455, 1424, 1400, 1352, 1286, 1236, 924, 898, 843, 772, 742, 694 cm^{-1}; MS (ESI, m/z): 262.12 $[M + H]^+$; HRMS (ESI): calcd for $C_{18}H_{16}NO$, 262.1226 $[M + H]^+$; found, 262.1232. The spectral data were in agreement with those reported previously for this compound.[19]

*Reaction of 1,4-Oxazepine **3a** with $ZnCl_2$ in CH_3CO_2H/H_2O (Table 4, Entry 2).* 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**) (85.0 mg, 0.33 mmol) and $ZnCl_2$ (40.0 mg, 0.33 mmol) in a 1:1 mixture of CH_3CO_2H/H_2O (4 mL) were used. After chromatographic purification, two fractions were isolated. The first fraction afforded 5.4 mg (6%) of 1-(3,5-diphenyl-1*H*-pyrrol-2-yl)ethanone (**4a**) as a beige solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 147.0−149.0 °C). The second fraction yielded 60.4 mg (71%) of (4-methyl-2-phenyl-1*H*-pyrrol-3-yl)(phenyl)methanone (**14a**) as a brownish-orange solid (R_f = 0.22 in 4:1 hexane/ethyl acetate; mp 118.5−120.0 °C).

*Reaction of 1,4-Oxazepine **3a** with $ZnCl_2$ in THF/H_2O (Table 4, Entry 3).* 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**) (132.0 mg, 0.51 mmol) and $ZnCl_2$ (70.0 mg, 0.51 mmol) in a 1:1 mixture of THF/H_2O (4 mL) were used. After chromatographic purification, two fractions were isolated. The first fraction yielded 86.0 mg (65%) of the starting material 1,4-oxazepine **3a** as a brownish-orange solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 94.2−95.9 °C). The second fraction afforded 35.0 mg (26%) of (4-methyl-2-phenyl-1*H*-pyrrol-3-yl)(phenyl)methanone (**14a**) as a brownish-orange solid (R_f = 0.22 in 4:1 hexane/ethyl acetate; mp 118.5−120.0 °C).

*Reaction of 1,4-Oxazepine **3a** with Conc. HCl in THF/H_2O (Table 4, Entry 4).* 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**) (104.0 mg, 0.4 mmol) and three drops of conc. HCl in a 3:1 mixture of THF/H_2O (4 mL) were used. After chromatographic purification, two fractions were isolated. The first fraction yielded 79.0 mg (76%) of the starting material 1,4-oxazepine **3a** as a brownish-orange solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 94.2−95.9 °C). The second fraction afforded 9.0 mg (9%) of (4-methyl-2-phenyl-1*H*-pyrrol-3-yl)(phenyl)methanone (**14a**) as a brownish-orange solid (R_f = 0.22 in 4:1 hexane/ethyl acetate; mp 118.5−120.0 °C).

*Reaction of 1,4-Oxazepine **3a** with $ZnCl_2$ in $HOCH_2CH_2OH$/THF (Table 4, Entry 5).* 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**) (101.0 mg, 0.39 mmol) and $ZnCl_2$ (50.0 mg, 0.39 mmol) in a 1:1 mixture of $HOCH_2CH_2OH$/THF (4 mL) were used. After chromatographic purification, two fractions were isolated. The first fraction yielded 35.0 mg (26%) of 1-phenyl-2-(2-phenyl-1,3-dioxolan-2-yl)ethanone (**15a**) as a purple oil (R_f = 0.34 in 4:1 hexane/ethyl acetate). The second fraction afforded 10.0 mg (10%) of 1-(3,5-diphenyl-1*H*-pyrrol-2-yl)ethanone (**4a**) as a beige solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 147.0−149.0 °C).

*1-Phenyl-2-(2-phenyl-1,3-dioxolan-2-yl)ethanone (**15a**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 7.1 Hz, 2H), 7.57 (d, J = 6.8 Hz, 3H), 7.45 (t, J = 7.6 Hz, 2H), 7.35 (dt, J = 14.1, 7.1 Hz, 3H), 3.98 (t, J = 6.9 Hz, 2H), 3.79 (t, J = 6.9 Hz, 2H), 3.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3 (CO), 142.2 (C), 137.9 (C), 133.0 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 125.7 (CH), 108.6 (C), 64.8 (CH_2), 48.8 (CH_2) (note that two CH peaks overlap on each other); IR (neat): 3059, 3028, 2891, 1677, 1597, 1580, 1472, 1447, 1321, 1177, 1078, 1024, 1000, 947, 862, 809, 763, 699, 688, 603 cm^{-1}; MS (ESI, m/z): 269.12 $[M + H]^+$; HRMS (ESI): calcd for $C_{17}H_{17}O_3$, 269.1172 $[M + H]^+$; found, 269.1178. The spectral data were in agreement with those reported previously for this compound.[20]

*Reaction of 1,4-Oxazepine **3a** with $ZnCl_2$ in $HOCH_2CH_2OH$/1,4-Dioxane (Table 4, Entry 6).* 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**3a**) (100.0 mg, 0.4 mmol) and $ZnCl_2$ (50.0 mg, 0.4 mmol) in a 1:1 mixture of $HOCH_2CH_2OH$/1,4-dioxane (4 mL) were used. After chromatographic purification, two fractions were isolated. The first fraction yielded 21.0 mg (20%) of 1-phenyl-2-(2-phenyl-1,3-dioxolan-2-yl)ethanone (**15a**) as a purple oil (R_f = 0.34 in 4:1 hexane/ethyl acetate). The second fraction afforded 22.0 mg (22%) of 1-(3,5-diphenyl-1*H*-pyrrol-2-yl)ethanone (**4a**) as a beige solid (R_f = 0.26 in 4:1 hexane/ethyl acetate; mp 147.0−149.0 °C).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00077.

Copies of ^{1}H NMR and ^{13}C{1H} NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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