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Note

Regioselective [3+2]-Cycloadditions of α,β-Unsaturated Ketones with Hydrazonoyl Chloride-Derived Nitrile Imines for Stereoselective Synthesis of Pyrazolines

Ji Sun Yang and Sung-Gon Kim*
Department of Chemistry, Kyonggi University, Suwon 16227, Korea.
**E-mail: sgkim123@kyonggi.ac.kr*
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Dinitrogen-containing heterocycles are considered highly valuable due to their presence as privileged motifs and crucial components in many natural products and biologically active compounds. Pyrazolines, specially, are five-membered heterocycles containing dinitrogen and have garnered significant attention in the pharmaceutical industry due to their unique biological activity. These pyrazolines display a wide range of biological activities, including anti-inflammatory, antimicrobial, antifungal, analgesic, anti-diabetic, antioxidant, and anticancer properties (*Fig.* 1).[1] For examples, aminopyrine, phenazone, and phenylbutazone are clinically approved drugs that possess potent analgesic, antipyretic and anti-inflammatory properties. Furthermore, the tyrosine kinase inhibitors, ibrutinib and axitinib, have demonstrated excellent anticancer activity. These examples highlight the versatility and potential of pyrazolines in the field of medicinal chemistry.

In light of the importance of pyrazoline heterocycles and their influence on biological systems, considerable efforts have been made towards the development of efficient synthesis methods for a wide range of functionalized pyrazoline heterocycles.[2] Among the various methods available, the most commonly used method for synthesizing pyrazolines is the cyclocondensation reaction between α,β-unsaturated carbonyl compounds and hydrazine or phenyl hydrazine in acidic or basic medium.[3] Additionally, the modified 1,3-dipolar cycloaddition of α,β-unsaturated carbonyl compounds with arylhydrazones has proven to be an effective method for synthesizing pyrazoline derivatives. This reaction involves the oxidative dehydrogenation of the phenyl hydrazone derivative with chloramine-T (CAT) to obtain the nitrile imine intermediate, which leads to the formation of the desired pyrazoline compound in good yields.[4] Recently, the 1,3-dipolar cycloaddition of nitrile imines has been recognized as a highly effective approach for the synthesis of a broad range of dinitrogen-containing heterocycles from relatively simple starting materials.[5] Nitrile imines are typically obtained through the reaction of hydrazonoyl halides with stoichiometric amounts of base. Despite its potential, the [3+2]-cycloaddition of nitrile imine with α,β-unsaturated carbonyls has received limited attention in the literature. In 2005, Sibi and co-workers reported on the asymmetric [3+2]-cycloaddition between 3-acryloyl-2-oxazolidinones and hydrozonoyl halides. The reaction was catalyzed by a chiral Lewis acid complex in combination with a compatible amine base and resulted in the synthesis of chiral dihydropyrazoles (*Scheme* 1-1).[5a] In 2012, Roth et al. reported an Et_3N-mediated [3+2]-cycloaddition between 3-alkylidene oxindoles and hydrazonoyl bromides, resulting in the synthesis of oxindole-based spiro-pyrazoline derivatives with high regioselectivity and diastereoselectivity (*Scheme* 1-2).[5b] The following year, Feng et al. and Stanley et al. independently developed the chiral Lewis acid-catalyzed asymmetric [3+2]-cycloaddition between 3-alkylidene oxindoles and hydrazonoyl halides.[5c,5d] In 2020, Su and co-workers reported a K_2CO_3-mediated [3+2]-cycloaddition of benzoaurones and

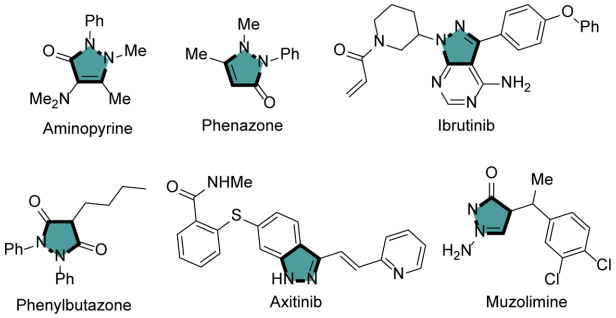
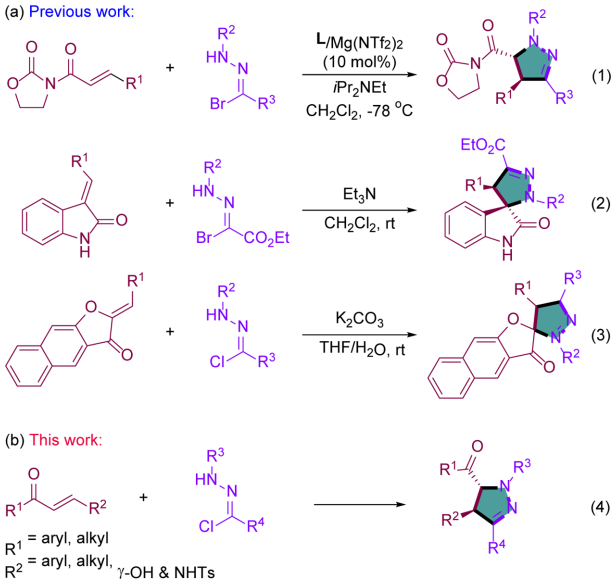
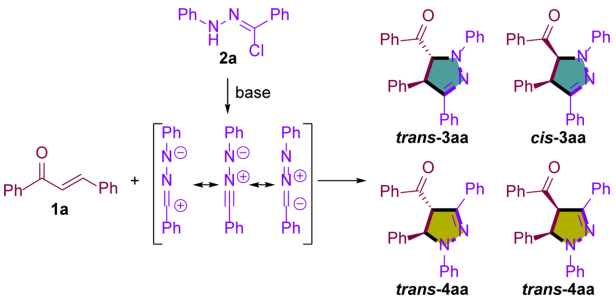


***Figure* 1.** Selected examples of pyrazoline-based clinically used drugs.



***Scheme* 1.** [3+2] Cycloaddition of α,β-unsaturated carbonyls with hydrazonoyl halides.



***Scheme* 2.** Regio- and diasteroslective [3+2]-cycloaddtion of α,β-unsaturated phenyl ketone **1a** and hydrozonoyl chloride **2a**.

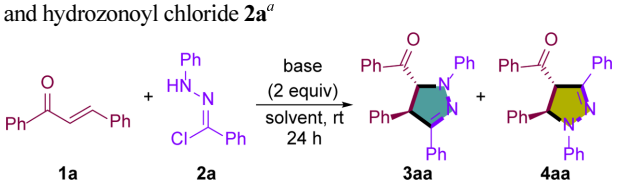
hydrazonoyl chlorides, resulting in the synthesis of spiro naphthofuranone-pyrazoline compounds with good yields (*Scheme* 1-3).[5f] Although there have been several reports on the [3+2]-cycloaddition reaction between various α,β-unsaturated carbonyls and hydrazonoyl halides, limited studies have been conducted on the reaction between β-substituted α,β-unsaturated ketones and hydrazonoyl chlorides. Although one example of this reaction has been reported using chalcone and hydrazonoyl chloride,[6] a comprehensive examination of this reaction has yet to be undertaken. In this work, we present our successful exploration of the [3+2]-cycloaddition reaction between β-substituted α,β-unsaturated carbonyls and hydrazonoyl chlorides, resulting in the synthesis of highly functionalized pyrazoline heterocycles with remarkable regioselectivity and diastereoselectivity (*Scheme* 1-4).

In the presence of a base, hydrazonoyl chlorides are converted into reactive nitrile imines, where both N1 and C3 are nucleophilically activated.[7] The [3+2]-cycloaddition reaction between α,β-unsaturated phenyl ketone **1a** and hydrazonoyl chloride **2a**, in the presence of a base, results in the formation of two potential regioisomers, C-adduct **3aa** and N-adduct **4aa**, each of which can have two diastereomers (*Scheme* 2). In previous literature,[6] the preferred reaction path involved the nucleophilic attack of the carbenoid C3 carbon on the β-position of the chalcone **1a**, resulting in the formation of the *trans*-**3aa** regioselective pyrazoline. However, Reddy and co-workers reported that the [3+2]-cycloaddition reaction between **1a** and the nitrile imine, which was generated in situ from phenylhydrazone with chloramine-T, produced N-adduct **4aa**.[4] With this in mind, we sought to re-examined the [3+2]-cycloaddition reaction between α,β-unsaturated phenyl ketone **1a** and hydrazonoyl chloride **2a** and optimize the conditions for the synthesis of highly functionalized pyrazoline heterocycles in an environmentally friendly manner.

Our investigation was initiated by conducting the [3+2]-cycloaddition reaction between α,β-unsaturated phenyl ketone **1a** and hydrazonoyl chloride **2a**, using either the environmentally-friendly organic base Et_3N or the inorganic base Na_2CO_3, in various solvents at room temperature. The reaction performed with Et_3N in CH_2Cl_2 for 24 hours resulted in the production of [3+2]-cycloaddition compound **3aa** in good yield (86%) with high **3aa**/**4aa** selectivity (7:1) as determined by ^1H NMR analysis of the reaction mixture (*Table* 1, entry 1). Furthermore, the pyrazoline **3a** was also formed with high diastereoselectivity (>20:1). While a slight decrease in yield was observed with toluene as the solvent, the reaction showed increased regioselectivity (entry 2). In CH_3CN, the yield was slightly increased (91%), but the ratio of **3aa**/**4aa** decreased (entry 4). Utilizing EtOH as the solvent maintained the yield while increasing regioselectivity (entry 5). When the reaction was conducted in the presence of Na_2CO_3 as the base, it was found that the reaction hardly proceeded in solvents such as CH_2Cl_2, toluene, and THF (entries 6−7). To our delight, the reaction performed with EtOH as the solvent proceeded smoothly, resulting in the production of **3aa** with a high yield of 92% and excellent selectivity (13:1 ratio **3aa**/**4aa**, >20:1 dr; entry 10).

Following the optimization of the reaction conditions, we explored the versatility and scope of hydrazonoyl chlorides in the [3+2]-cycloaddition reaction. Our results indicate that the reaction is compatible with both electron-donating and electron-withdrawing groups at the *para*-position of the aryl ring in the hydrazonoyl chloride sub-

***Table* 1.** [3+2]-Cycloaddition of α,β-unsaturated phenyl ketone **1a** and hydrozonoyl chloride **2a**[a]



1a **2a** **3aa** **4aa**

Entry	Base	Solvent	Yield (%)[b]	Ratio[c] **3aa/4aa**	Dr[c] **3aa**
1	Et_3N	CH_2Cl_2	86	7:1	>20:1
2	Et_3N	toluene	70	11:1	>20:1
3	Et_3N	THF	37	9:1	>20:1
4	Et_3N	CH_3CN	91	5:1	>20:1
5	Et_3N	EtOH	87	10:1	>20:1
6	Na_2CO_3	CH_2Cl_2	9	-[d]	-d
7	Na_2CO_3	toluene	8’	-[d]	-d
8	Na_2CO_3	THF	5	-[d]	-d
9	Na_2CO_3	CH_3CN	81	5:1	>20:1
10	Na_2CO_3	EtOH	92	13:1	>20:1

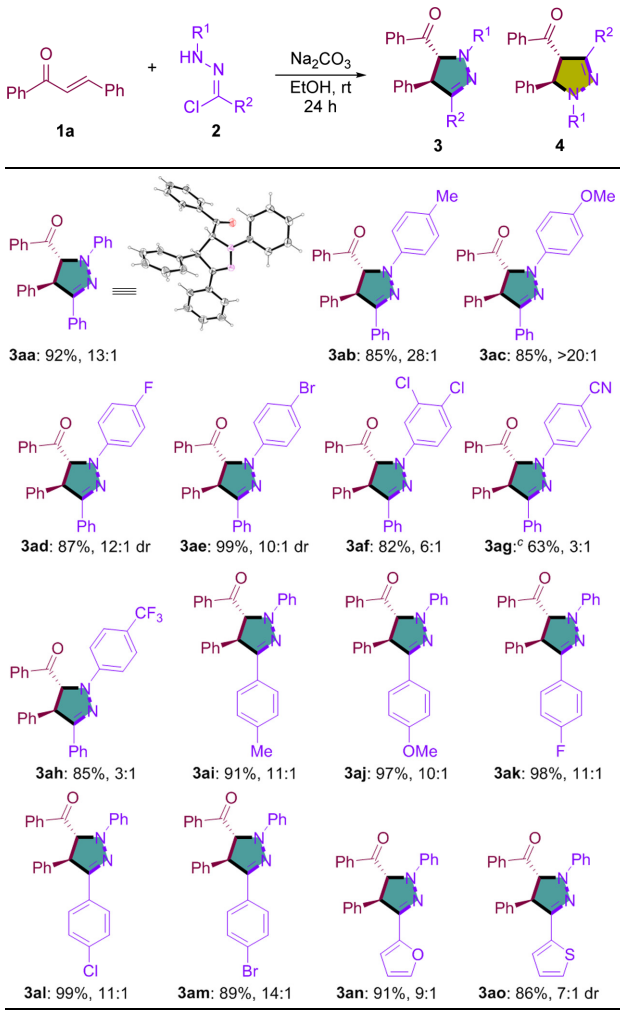
[a]The reactions were carried out in solvent (0.1 M) with **1a** (0.1 mmol), **2a** (0.12 mmol), and base (0.12 mmol).
[b]Isolated yield (**3aa** + **4aa**) after chromatographic purification.
[c]Determined by ^{1}H NMR analysis of the crude product.
[d]Not determined.

strate. The resulting pyrazoline products, **3aa**–**3ae**, were obtained in yields ranging from 63-99%, with the highest yield obtained for the *para*-bromo-substituted substrate **3ag** (99% yield). Our findings also reveal that electron-donating substituents result in higher levels of regioselectivity compared to electron-withdrawing substituents. Moreover, strong electron-withdrawing groups, such as CN and CF_3, further reduce regioselectivity.

We then extended our study to the R^2 position of the hydrazonoyl chlorides. Regardless of the electronic nature of the substituents on the aromatic ring, the reactions with hydrazonoyl chlorides resulted in the corresponding pyrazoline products **3ai**–**3am** with outstanding yields (89-99%) and high regioselectivities. The reaction was also successful with heteroaromatic substituted hydrazonoyl chlorides, such as 2-furyl and 2-thiophenyl, yielding high-quality products **3an** and **3ao** (with yields of 91% and 86%, respectively). The relative stereochemistry of pyrazoline **3** was confirmed through X-ray crystallographic analysis of **3aa**.[8]

Expanding our study, we also explored the reactivity of various β-substituted α,β-unsaturated ketones **1** in the [3+2]-cycloaddition reaction. The reaction between β-aryl-α,β-unsaturated ketones **1** with an aryl substituent at R^2 and hydrazonoyl chloride **2** was productive and efficient. The reaction was compatible with both electron-

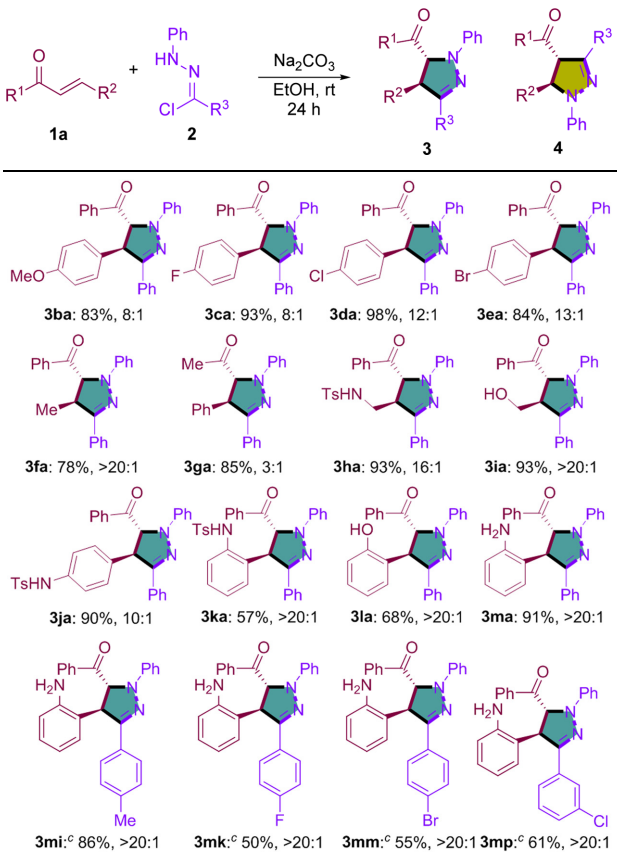
***Table* 2.** Substrate scope of hydrazonyl chlorides[a,b]



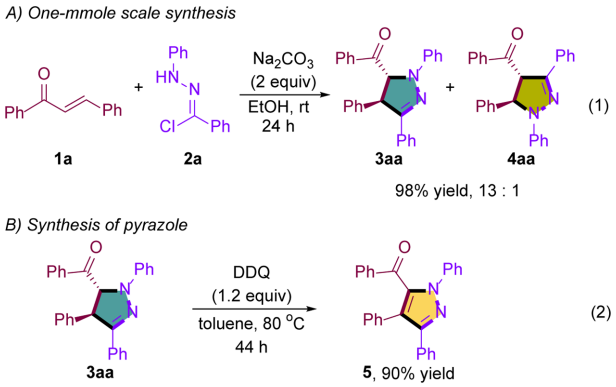
[a]The reactions were carried out with **1a** (0.10 mmol), **2** (0.15 mmol), and Na_2CO_3 (0.20 mmol) in EtOH (0.1 M) at r.t.
[b]Isolated yield after chromatographic purification.
[c]With Et_3N (0.20 mmol) in CH_3CN (0.1 M).

donating and electron-withdrawing groups at the *para*-position of the aryl ring of R^2, producing the corresponding pyrazoline derivatives **3ba**–**3ea** with high yields (83-98%). The [3+2]-cycloaddition between 1-phenylbut-2-en-1-one (**1f**) and hydrazonoyl chloride **2a** was successfully performed, resulting in the formation of pyrazoline **3fa** with a high yield of 78% and outstanding regioselectivity (>20:1). On the other hand, the reaction between 4-phenylbut-3-en-2-one (**1g**) and hydrazonoyl chloride **2a** still proceeded efficiently, yielding product **3ga** with a yield of 85%, though with a slightly lower regioselectivity (3:1). Furthermore, γ-NHTs- and γ-OH-α,β-unsaturated ketones also showed excellent reactivity in the [3+2]-cycloaddition reaction with hydrazonoyl chloride **2a**, provid-

***Table* 3.** Substrate scope of α,β-unsaturated carbonyls[a,b]



[a]The reactions were carried out with **1a** (0.10 mmol), **2** (0.15 mmol), and Na_2CO_3 (0.20 mmol) in EtOH (0.1 M) at r.t.
[b]Isolated yield after chromatographic purification.
[c]In *i*-PrOH (0.1 M).



***Scheme* 3.** Reaction utility.

ing the desired products in high yields with outstanding regioselectivities.

Additionally, we expanded the versatility of the [3+2]-cycloaddition reaction to include other types of β-aryl-α,β-unsaturated ketones. We found that the reaction is able to handle the presence of a TsNH group at the *para*-position of the aryl ring of the substituent (R^2), leading to the formation of pyrazoline product **3ja** with a high yield of 90%. However, when the TsNH group was located at the *ortho*-position, the yield of the corresponding pyrazoline product **3ka** was moderate at 57%. To our delight, the reaction between β-(*o*-hydroxy)phenyl-α,β-unsaturated ketone **1l** and β-(*o*-amino)phenyl-α,β-unsaturated ketone **1m**, without any protective groups, proceeded smoothly and efficiently, resulting in the formation of the respective pyrazoline products **3la** and **3ma** with good to high yields and excellent regioselectivities. We also investigated the reactivity of various hydrazonoyl chlorides **2** in the [3+2]-cycloaddition reaction with β-(*o*-amino)phenyl-α,β-unsaturated ketone **1m**, which produced the corresponding pyrazoline products (**3mi**, **3mk**, **3mm**, and **3mp**) in moderate to good yields ranging from 50% to 86%.

To further showcase the versatility of the [3+2]-cycloaddition reaction, we performed a one-mole scale synthesis of pyrazoline product **3aa** (*Scheme* 3-1). The reaction between **1a** and **2a** was conducted on a larger scale, under the optimized conditions, and produced pyrazoline **3aa** with a slightly improved yield of 98% and excellent selectivity (13:1 **3a**/**4a** ratio). Additionally, the oxidation reaction using DDQ was smoothly carried out and led to the formation of pyrazole **5** with a yield of 90% (*Scheme* 3-2).

In summary, we have successfully established an environmentally-friendly approach to synthesize highly functionalized pyrazolines through the [3+2]-cycloaddition of α,β-unsaturated ketones and hydrazonoyl chloride-derived nitrile imines using Na_2CO_3 as the base and EtOH as the solvent. This approach was applied to the [3+2]-cycloaddition of various β-substituted-α,β-unsaturated ketones, making it a versatile and practical method for the synthesis of biologically relevant pyrazolines frameworks. Further investigation is underway to explore the potential of this reaction in an asymmetric manner.

EXPERIMENTAL

General Procedure for the [3+2]-Cycloaddition of α,β-Unsaturated Ketones 1 with Hydrazonoyl Chlorides 2; To a solution of α,β-unsaturated ketone 1 (0.10 mmol) and hydrazonyl chloride 2 (0.15 mmol, 1.5 equiv) in EtOH (1.0 mL, 0.10 M) was added Na_2CO_3 (0.20 mmol, 2.0 equiv) at room temperature. After stirring for 24 h at room temperature, the resulting mixture was filtered through the plug of celite, and concentrated in vacuo. The crude residue was

purified by flash column chromatography with EtOAc/hexanes as eluent to afford desired product 3.

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Supporting Information. Detailed experimental procedures, characterization data, and X-ray crystallographic analysis of **3aa** are available online.

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8. CCDC 2248469 (**3aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.