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Efficient and Divergent Synthesis of Fully Substituted 1*H*-Pyrazoles and Isoxazoles from Cyclopropyl Oximes

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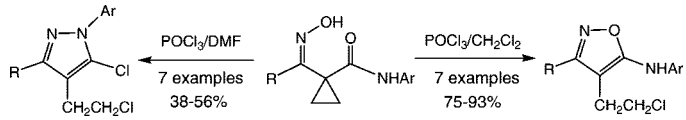
ABSTRACT



Efficient and divergent one-pot synthesis of fully substituted 1*H*-pyrazoles and isoxazoles from cyclopropyl oximes based on reaction conditions selection is reported. Under Vilsmeier conditions ($POCl_3$/DMF), substituted 1*H*-pyrazoles were synthesized from 1-carbamoyl, 1-oximyl cyclopropanes via sequential ring-opening, chlorovinylation, and intramolecular aza-cyclization. In the presence of $POCl_3/CH_2Cl_2$, substituted isoxazoles were obtained from the cyclopropyl oximes via ring-opening and intramolecular nucleophilic vinylic substitution (S_NV) reactions.

Pyrazole motif makes up the core structure of numerous biologically active compounds, including blockbuster drugs such as Celebrex[1] and Viagra,[2] that find a wide range of applications in pharmaceutical and agrochemical industry.[3,4] Many synthetic methods for pyrazoles are available, among which notable methods involve the reactions between 1,3-difunctional compounds with hydrazines or their derivatives,[5] and 1,3-dipolar cycloadditions of diazo compounds onto triple bonds.[6] Isoxazole derivatives represent another important class of nitrogen-containing heterocycles along with diverse useful bioactivities and are widely used as key intermediates in the preparation of natural products and related structures.[7,8] Intensive research has generated numerous approaches for the synthesis of isoxazoles,[9] including reactions of hydroxylamine with 1,3-dicarbonyl compounds,[10] α,β-unsaturated nitriles/carbonyl compounds,[11,12]

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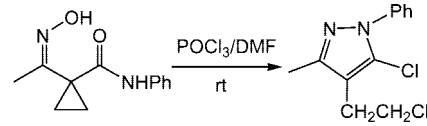
and ynones,[13] reaction of an oxime-derived dianion with an ester/amide,[14] and [3 + 2] cycloaddition reaction between an alkyne and a nitrile oxide.[15]

On the other hand, the utility of cyclopropane derivatives in organic synthesis has been recognized for their ready accessibility and good reactivity originating from the inherent ring strain that can lead to a variety of ring-opening reactions under the influence of a wide range of chemicals, for example, electrophiles, nucleophiles, and radicals.[16,17] In our recent work, we achieved one-pot synthesis of halogenated pyridin-2(1*H*)-ones from 1-acyl, 1-carbamoyl cyclopropanes under Vilsmeier conditions.[18] In connection with this study and our continued interest regarding the synthesis of carbo- and heterocycles from β-oxo amide derivatives,[19] we synthesized a series of cyclopropyl oximes **1** and exploited their synthetic potential. As a result of these studies, we developed an alternative one-pot divergent synthesis of fully substituted 1*H*-pyrazoles and isoxazoles from a single multifunctional reagent, cyclopropyl oximes, in the presence of $POCl_3$/DMF (Vilsmeier reagent, VR) and $POCl_3/CH_2Cl_2$, respectively. Herein, we wish to report our experimental results and present proposed mechanisms involved in the ring-opening/recyclizations.

The substrates, 1-carbamyl, 1-oximyl cyclopropanes **1**, were prepared by the reaction of 1-acyl, 1-carbamyl cyclopropanes[3] with hydroxylamine (NH_2OH·HCl) in the presence of NaOAc in methanol at room temperature in high yields (up to 95%). We then selected 1-(1-(hydroxyimino)ethyl)-*N*-phenyl cyclopropanecarboxamide **1a** from a series of substrates **1** as the model compound to examine its behavior under Vilsmeier conditions.

Upon treatment of **1a** with 5.0 equiv of $POCl_3$/DMF at room temperature for 1.0 h, the reaction proceeded smoothly as indicated by TLC and furnished one product after workup and purification by column chromatography. From the spectral and analytical data, the product was characterized as 5-chloro-4-(2-chloroethyl)-3-methyl-1-phenyl-1*H*-pyrazole **2a** (Scheme 1).

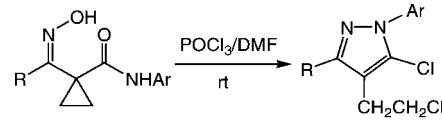
Scheme 1. Reaction of **1a** with $POCl_3$/DMF



1a **2a**

The reaction conditions, including reaction temperature and the ration of **1a** to $POCl_3$/DMF, were then investigated. A series of experiments revealed that 2.0 equiv of $POCl_3$/DMF was sufficient for the synthesis of **2a**, and the optimal results were obtained when the reaction of **1a** was performed with 3.0 equiv of $POCl_3$/DMF at room temperature (~20 °C) for 0.5 h, whereby the yield of **2a** reached 38% (Table 1, entry 1). It should be mentioned that side products were obtained from the reaction system as an inseparable mixture by column chromatography over silica gel.

Table 1. Reactions of Cyclopropyl Oximes **1** under Vilsmeier Conditions[a]



1 **2**

entry	**1**	R	Ar	**2**	yield[c] (%)
1	**1a**	Me	C_6H_5	**2a**	38
2	**1b**	Me	4-MeC_6H_4	**2b**	41
3	**1c**	Me	4-$MeOC_6H_4$	**2c**	44
4	**1d**	Me	4-ClC_6H_4	**2d**	39
5	**1e**	Me	2-$MeOC_6H_4$	**2e**	45
6	**1f**	Me	2,4-$Me_2C_6H_3$	**2f**	47
7[b]	**1g**	C_6H_5	C_6H_5	**2g**	56

[a] Reagents and conditions: 1 (1.0 mmol), $POCl_3$/DMF (3.0 mmol), rt, 0.5–1.5 h. [b] Reaction time, 6.0 h. [c] Isolated yield.

Having established the optimal conditions for the ring-opening/recyclization process, we intended to determine its scope with respect to the amide motif. Thus, a series of cyclopropyl oximes **1b**−**g** were subjected to $POCl_3$/DMF (3.0 equiv) at room temperature, and some of the results are summarized in Table 1. The efficiency of the protocol proved to be suitable for **1b**−**g** bearing variable aryl amide groups affording the corresponding 1*H*-pyrazoles **2b**−**g** in moderate yields (Table 1, entries 2–7).

On the basis of the obtained results and our previously reported work,[18] a plausible mechanism for the synthesis of

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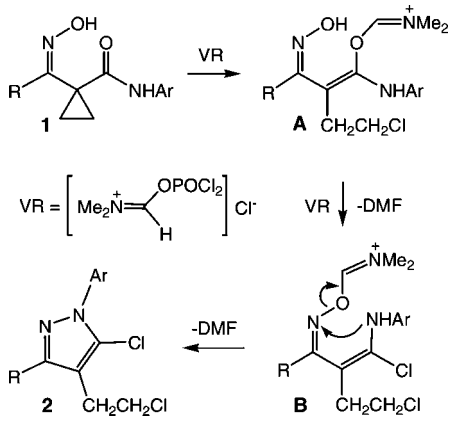
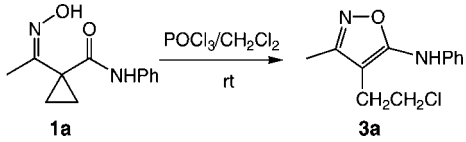
Scheme 2. Plausible Mechanism for the Reaction of Cyclopropyl Oximes **1** under Vilsmeier Conditions



substituted 1*H*-pyrazoles **2** is presented in Scheme 2. The transformation commences from the ring-opening reaction of cyclopropyl oxime **1** mediated by Vilsmeier reagent to generate iminium intermediate **A** followed by a halogenation reaction to give iminium intermediate **B**,[20] which undergoes an intramolecular aza-cyclization to **2**.

Encouraged by the results that cyclopropyl oximes can undergo a ring-cleavage reaction under Vilsmeier conditions, we subsequently examined the reaction behavior of cyclopropyl oximes **1** toward $POCl_3$ in absence of DMF. Thus, the reaction of **1a** was performed with $POCl_3$ (3.0 equiv) in CH_2Cl_2 at room temperature. The substrate was consumed within 1.0 h as shown by TLC monitoring of the reaction. After workup and purification by column chromatography, the reaction furnished a white solid, which was characterized as 4-(2-chloroethyl)-3-methyl-*N*-phenyl isoxazol-5-amine **3a** instead of a 1*H*-pyrazole on the basis of its spectral and analytical data (Scheme 3). The structure of **3a** was further

Scheme 3. Reaction of **1a** with $POCl_3$ in CH_2Cl_2



confirmed by the X-ray single-crystal analysis (Figure 1).

The optimization of reaction conditions, including reaction temperature and the ration of **1a** to $POCl_3$ were then investigated. A series of experiments revealed that 1.0 equiv of $POCl_3$ was sufficient for the synthesis of **3a**, and the

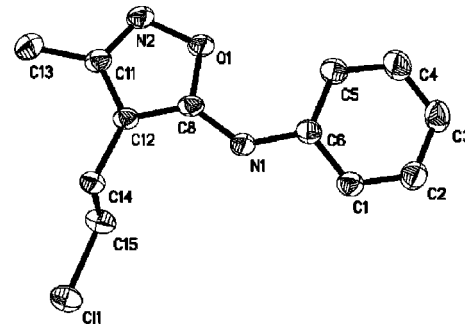
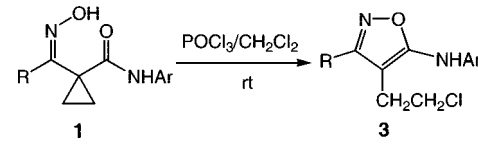


Figure 1. ORTEP drawing of **3a**.

Table 2. Reaction of Cyclopropyl Oximes **1** with $POCl_3$ in CH_2Cl_2[a]



entry	1	R	Ar	3	yield[b] (%)
1	**1a**	Me	C_6H_5	**3a**	90
2	**1b**	Me	4-MeC_6H_4	**3b**	88
3	**1c**	Me	4-$MeOC_6H_4$	**3c**	93
4	**1d**	Me	4-ClC_6H_4	**3d**	87
5	**1e**	Me	2-$MeOC_6H_4$	**3e**	81
6	**1f**	Me	2,4-$Me_2C_6H_3$	**3f**	78
7	**1g**	C_6H_5	C_6H_5	**3g**	75

[a] Reagents and conditions: **1** (1.0 mmol), $POCl_3$ (1.5 mmol), CH_2Cl_2, rt, 0.5–1.5 h. [b] Isolated yield.

optimal results were obtained when **1a** was treated with 1.5 equiv of $POCl_3$ in CH_2Cl_2 at room temperature (~20 °C) for 1.0 h, whereby the yield of **3a** reached 90% (Table 2, entry 1) and **2a** was not even detectable.

Under the optimal conditions as for **3a**, a range of reactions of **1b**−**g** with $POCl_3$ (1.5 equiv) were carried out in CH_2Cl_2 at room temperature, and some of the results are summarized in Table 2. All the reactions proceeded smoothly to afford the corresponding fully substituted isoxazoles **3b**−**g** in good to high yields (Table 2, entries 2–7). The results suggested that $POCl_3$, being a reagent,[21] showed different reaction behavior from Vilsmeier reagent, $POCl_3$/DMF. It was assumed that the formation of substituted isoxazoles **3** involved the ring-opening reaction of cyclopropyl oximes **1** mediated by $POCl_3$ and subsequent intramolecular nucleophilic vinylic substitution (S_NV) reaction,[22] as depicted in Scheme 4.

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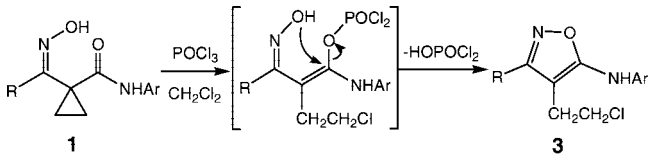
Scheme 4. Plausible Mechanism for the Reaction of Cyclopropyl Oximes **1** with $POCl_3$ in CH_2Cl_2



In summary, an efficient and divergent one-pot synthesis of fully substituted 1*H*-pyrazoles **2** and isoxazoles **3** has been developed from readily available 1-carbamoyl, 1-oximyl cyclopropanes **1** based on approporiate reaction conditions. Thus, a series of cyclopropyl oximes underwent sequential ring-opening, chlorovinylation, and intramolecular aza-cyclization under Vilsmeier conditions ($POCl_3$/DMF), to afford substituted 1*H*-pyrazoles. In the presence of $POCl_3$/CH_2Cl_2, they underwent tandem ring-opening and intramolecular S_NV reactions to yield the corresponding isoxazoles in high yields. This protocol is associated with readily available starting materials, mild conditions, dense and flexible substitution patterns, important synthetic potential of the final products, and easy control of the reaction orientation by reaction conditions selection.

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Supporting Information Available: Experimental details and spectral characterization data for **1–3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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