Ruthenium Catalysis

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Ruthenium-Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles**

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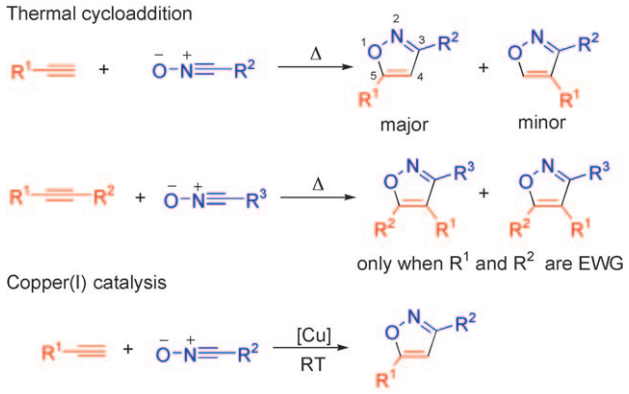
Isoxazoles, a major class of five-membered nitrogen heterocycles, are embedded in a number of pharmaceutically important compounds that have been the focus of numerous biological studies during the last several years.[1] Although a variety of methods for their synthesis have been reported, few are general, regioselective, and high yielding.[2] The cycloaddition of alkynes and nitrile oxides, which is probably the most direct route to access these heterocycles, is rarely used.[3] The reasons for this are simple: in contrast to the reaction with olefins, the uncatalyzed, thermal cycloaddition reactions of nitrile oxides with alkynes are neither chemo- nor regioselective and, as a consequence, are plagued by low yields and the formation of multiple products. These shortcomings are not surprising considering the relatively high reactivity of nitrile oxides, their propensity to dimerize, and the general inert character of alkynes.

Copper(I) acetylides have been shown to react regioselectively with nitrile oxides to generate 3,5-disubstituted isoxazoles.[4] However, there are no reported methods for generating the regiocomplementary 3,4-disubstituted isomers. In fact, even when thermal cycloaddition reactions of nitrile oxides with alkynes are successful, they favor the formation of the 3,5-disubstituted isomer (Scheme 1). Furthermore, examples of reactions of nitrile oxides with internal alkynes are limited to a handful of highly activated alkynes (e.g. acetylene dicarboxylate and related electron-deficient acetylenes). Unactivated, electron-rich, or sterically hindered acetylenes usually fail to react altogether.[5]

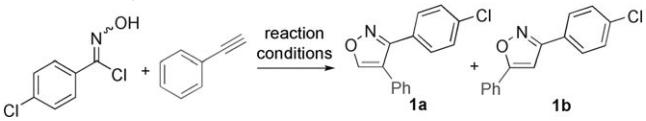
The recent discovery of the ruthenium(II)-catalyzed azide–alkyne cycloaddition reaction,[6] which produces 1,5-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles, prompted us to explore the catalytic activity of ruthenium complexes in nitrile oxide–alkyne cycloaddition reactions. Herein, we report that 3,5-di- and 3,4,5-trisubstituted isoxazoles can be obtained with excellent regioselectivity at room temperature by a ruthenium(II)-catalyzed cycloaddition reaction of nitrile oxides (generated in situ from hydroximoyl chlorides by treatment with Et_3N) and terminal or internal alkynes, respectively.



Scheme 1. Cycloaddition reactions of nitrile oxides and alkynes. EWG = electron-withdrawing group.

Initially, we screened several ruthenium(II) complexes and common solvents for their catalytic activity (Table 1). When phenylacetylene and 4-chloro-*N*-hydroxybenzimidoyl chloride were combined with Et_3N in the absence of a ruthenium catalyst at room temperature, the 3,5-disubstituted regioisomer **1b** was formed exclusively, as determined by GC analysis of the crude reaction mixture (Table 1, entry 1). In contrast, when [Cp*RuCl(cod)] (cod = cycloocta-1,5-diene, Cp* = C_5Me_5) was used, **1a** was formed preferentially, but incomplete conversion was observed in DMF, THF, and $CHCl_3$ (Table 1, entries 2–4) With 5 mol% of [Cp*RuCl(cod)] in 1,2-dichloroethane (1,2-DCE), the starting materials were converted into the 3,4-disubstituted isoxazole **1a** (95:3 **1a**/**1b**; Table 1, entry 5). Other Ru complexes, lower

Table 1: Optimization of ruthenium(II)-catalyzed reactions of nitrile oxides and alkynes.



Entry	Reaction conditions[a]	Conversion [%][b] 1a	1b
1	no catalyst, 1,2-DCE	0	72
2	5 mol% [Cp*RuCl(cod)], DMF	82	5
3	5 mol% [Cp*RuCl(cod)], THF	81	3
4	5 mol% [Cp*RuCl(cod)], $CHCl_3$	78	6
5	5 mol% [Cp*RuCl(cod)], 1,2-DCE	95	3
6	5 mol% [Cp*RuCl(cod)], 1,2-DCE, 0°C	80	6
7	10 mol% [Cp*RuCl(cod)], 1,2-DCE	97	3
8	2 mol% [Cp*RuCl(cod)], 1,2-DCE	53	30
9	5 mol% [Cp*RuCl(PPh_3)$_2$], 1,2-DCE	69	17
10	5 mol% [CpRuCl(PPh_3)$_2$], 1,2-DCE	1	74

[a] Reaction conditions: phenylacetylene (1.0 mmol), hydroximoyl chloride (1.1 mmol), Et_3N (1.25 mmol) in solvent (5 mL) at room temperature for 10 h. [b] Determined by GC analysis.

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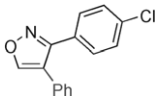
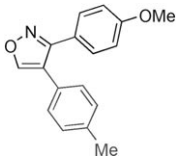
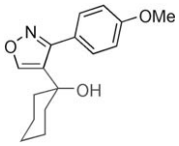
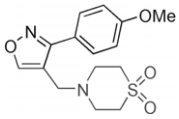
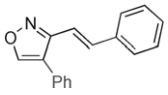
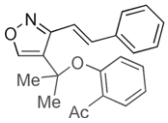
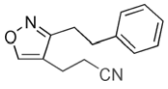
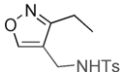
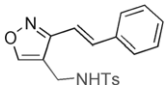
catalyst loadings, and different temperature profiles gave lower conversion and regioselectivity (Table 1, entries 6–10).

To determine the scope of this new reaction, a series of hydroximoyl chlorides were combined with various terminal alkynes in the presence of 5 mol% of [Cp*RuCl(cod)] and 1.25 equivalents of Et_3N and stirred for 2–10 h at room temperature (Table 2). Typically, complete consumption of the alkyne was observed after less than 2 h, very little by-products were formed, and usually only the 3,4-disubstituted isoxazole was observed by GC and ^1H NMR analysis. These reactions were relatively insensitive to the electronic and steric properties of the nitrile oxide. Terminal alkynes bearing a wide variety of functional groups (Table 2), as well as sterically encumbered substrates (Table 2, entries 3 and 6), were competent reactants. When performed on a 20 mmol scale with 2 mol% [Cp*RuCl(cod)] at 0 °C, regioisomerically pure isoxazoles were obtained in high yields (Table 2, entry 9).

Table 2: Ruthenium-catalyzed reactions of nitrile oxides with terminal alkynes.

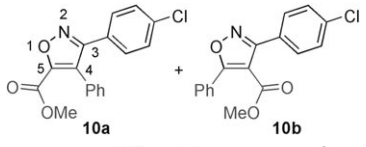
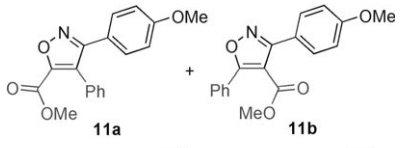
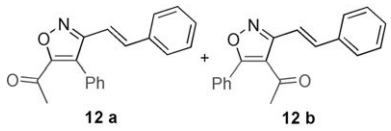
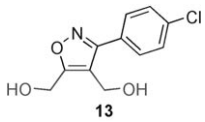
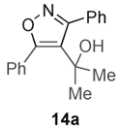
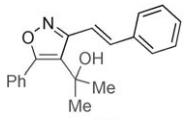
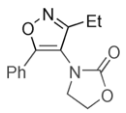
Entry	Product	Compound	Yield [%]
1		**1a**	86
2		**2a**	87[a]
3		**3a**	67
4		**4a**	77
5		**5a**	87
6		**6a**	93
7		**7a**	72
8		**8a**	85
9		**9a**	93[b]

[a] Isolated as a 15:1 regioisomeric mixture. [b] Prepared on 20 mmol scale (alkyne) with 2 mol% [Cp*RuCl(cod)] (see the Supporting Information for details). Ts = 4-toluenesulfonyl.

Importantly, these ruthenium-mediated processes are not restricted to terminal alkynes. In contrast to the copper-catalyzed isoxazole synthesis, where copper(I) acetylides are bona fide intermediates, internal alkynes were effective cycloaddition partners as well. The major regioisomers obtained when [Cp*RuCl(cod)] was used with internal alkynes were opposite to those observed in the analogous thermal reactions, as was the case with the terminal alkynes (Table 3).[7] Notably, when alkynes containing a hydrogen-bond donor were employed, the cycloaddition reactions were especially regioselective and efficient (Table 3, entries 4–6). In fact, the minor regioisomer was not detectable by GC-MS or LC-MS analysis. X-ray crystallographic analysis of **15a** unambiguously confirmed its regiochemistry. The corresponding thermal cycloaddition reactions, even after extended heating with such alkynes, failed to give any isoxazole products. The regioselectivity of these processes is predictable: the more electronegative carbon center of the alkyne becomes C4 of the isoxazole ring unless a hydrogen-bond donor is present, in which cases the hydrogen-bond donor always ends up at C4.

Currently we do not have complete understanding of the mechanism of this new isoxazole synthesis. We hypothesize

Table 3: Isoxazoles produced from internal alkynes.

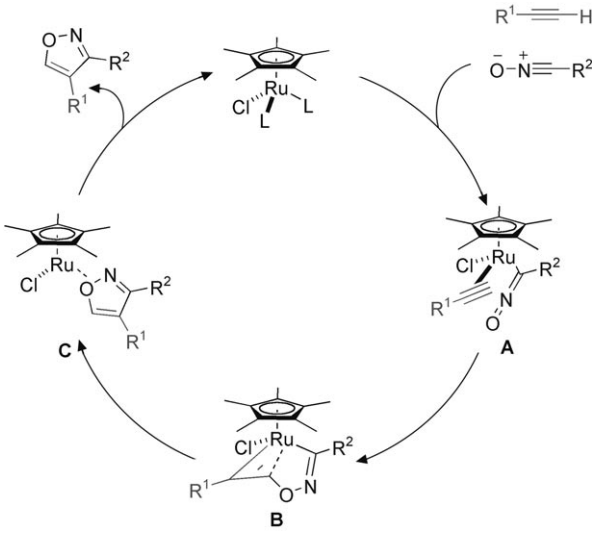
Entry	Products	Yield [%] a	Yield [%] b
1	 **10a** **10b**	71	5
2	 **11a** **11b**	89 (6.6:1 **a**/**b**)	
3	 **12 a** **12 b**	68	16
4	 **13**		78
5	 **14a**	83	–
6	 **15a**	99	–
7	 **16a**	39	–

that like the ruthenium-catalyzed azide–alkyne cycloaddition, these processes may be related to the catalytic cyclotrimerization of alkynes.[8] However, there are several significant differences between the two reactions, which stem from the intrinsically higher reactivity of nitrile oxides and, as a consequence, a tendency to give by-products. In the first step of the proposed mechanism (Scheme 2), displacement of the spectator cyclooctadiene ligand from the [Cp*RuCl(cod)] catalyst by an alkyne and nitrile oxide produces the activated complex **A**, which mediates the oxidative coupling of a nitrile oxide and alkyne, resulting in ruthenacycle **B**.[9]

The oxidative coupling step controls the regioselectivity of the overall process. It appears that the new carbon–oxygen bond is formed between the more electronegative carbon center of the alkyne and the oxygen atom of the nitrile oxide, which represents an unexpected mode of activation of nitrile oxides—normally, their carbon center is electrophilic and readily reacts with nucleophiles.[10] Thus, coordination to the ruthenium atom effectively changes the polarity of the nitrile oxide. Ruthenacycle **B** undergoes reductive elimination giving **C**, and release of the isoxazole product, then completes the catalytic cycle. The observation that Cp*-based catalysts are especially catalytically active is consistent with the lability of the spectator ligands in such ruthenium complexes.[11]

Notably, suppression of common side reactions, such as dimerization of nitrile oxides to form furoxans, and the generally high reactivity of nitrile oxides observed in the ruthenium(II)-catalyzed cycloaddition indicate that the catalytic cycle turns over at least as fast as the nitrile oxide is formed from the hydroximoyl chloride precursor. Detailed kinetic studies of this novel ruthenium(II)-catalyzed cycloaddition reaction are currently underway and should provide further insight into the mechanistic underpinnings of this process.

In summary, 3,4- and 3,4,5-subtituted isoxazoles are now readily accessible from alkynes and hydroximoyl chlorides by an experimentally simple and general catalytic method. Together with the copper(I)-catalyzed process,[4] the ruthenium(II)-catalyzed synthesis allows regioselective and efficient preparation of all isomers of isoxazoles. In addition to the immediate practical benefits, this transformation suggests that different dipoles can be activated and engaged in catalysis by ruthenium complexes.



Scheme 2. Proposed catalytic cycle.

Experimental Section

Ruthenium(II)-catalyzed synthesis of isoxazoles as exemplified for the preparation of 3-(4-chlorophenyl)-4-phenylisoxazole (**1a**). A screw top vial (20 mL) purged with dry nitrogen was charged with 4-chloro-*N*-hydroxybenzimidoyl chloride (208 mg, 1.1 mmol) and phenylacetylene (110 μL, 1.0 mmol). At room temperature, degassed 1,2-dichloroethane (10 mL) was added followed by [Cp*RuCl(cod)] (19 mg, 0.05 mmol) and triethylamine (176 μL, 1.25 mmol) and the vial was capped. After 10 h, the reaction mixture was passed through a plug of silica gel (CH_2Cl_2). The resulting solution was concentrated and the residue was purified by column chromatography on silica gel (pure hexanes to 10:1 hexanes/EtOAc) to provide the indicated compound as a yellow oil (219 mg, 86%). $R_f = 0.41$ (10:1 hexanes/EtOAc); IR (neat): $\tilde{\nu} = 3060$, 1601, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.52$ (s, 1H), 7.47–7.45 (m, 3H), 7.38–7.34 (m, 4H), 7.27–7.24 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.4$, 156.72, 156.70, 136.0, 130.2, 129.2, 129.12, 129.09, 128.9, 127.3, 120.5 ppm; LCMS (ES): *m*/*z* 256 [M^++H]; HRMS calcd for $C_{15}H_{11}ClNO$ [M^++H]: 256.0529; found: 256.0525.

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