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A Practical Method for Oxazole Synthesis by Cycloisomerization of Propargyl Amides

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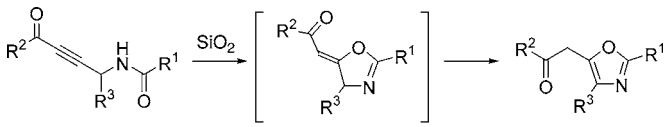
ABSTRACT



2,5-Disubstituted and 2,4,5-trisubstituted oxazol-5-yl carbonyl compounds were prepared in good yields by a mild SiO_2-mediated cycloisomerization of propargyl amides.

Oxazoles are common substructures in numerous biologically active compounds, synthetic intermediates, and pharmaceuticals.[1−3] Accordingly, many strategies have been developed for the preparation of oxazoles.[1] In the classical and widely used Robinson−Gabriel oxazole synthesis,[4] harsh dehydrating reagents (H_2SO_4, P_2O_5, $SOCl_2$, etc.) are usually required, which restricts the range of tolerated functional groups. Milder protocols for cyclodehydration and oxazole ring synthesis have recently become available.[5] In addition, alternatives to the cyclodehydration of hydroxy- or ketoamides such as base-promoted or palladium-catalyzed cycloisomerizations of alkynyl amides have recently been reported by several groups.[6] As part of our studies of oxazole-containing natural products, we are interested in a general approach toward oxazol-5-yl acetates. Agents containing this core functionality possess diverse pharmacological properties, including cardiovascular, antiinflammatory, and antihyperglycemic activities.[7] C(5)-β-Carbonyl-substituted oxazoles **III** are also valuable building blocks in organic synthesis. Herein, we report a practical and mild method for the syntheses of these 2,5-disubstituted and 2,4,5-trisubstituted oxazoles by the silica gel mediated cycloisomerization of alkynyl amides **I**.

Deprotonation of propargyl amides **1** with ^{n}BuLi or LiHMDS, nucleophilic addition to benzaldehyde, and Dess−Martin oxidation provided ready access to keto amides **3** (Scheme 1). In the course of a detailed investigation of the cycloisomerization of alkynyl amide **3a**, we found that treatment with bases such as NaHMDS, Et_3N, and K_2CO_3 provided no desired product (Table 1, entries 1, 2, and 3). The instability of oxazole **4a** under basic conditions led to complex reaction mixtures. Neutral thermal conditions or the presence of a palladium catalyst[8] were similarly unsuccessful

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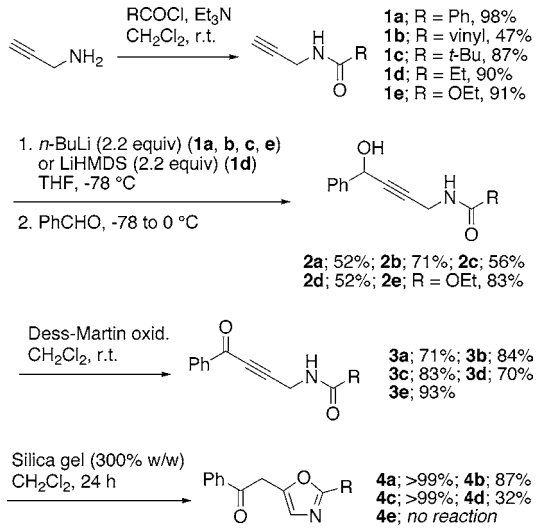
Scheme 1. Silica Gel Mediated Conversion of Propargyl Amides to 2,5-Disubstituted Oxazoles



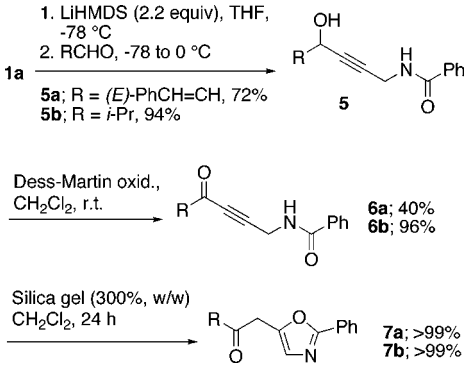
(entries 4 and 5). Acids such as pyridinium *p*-toluenesulfonate (PPTS), $Cu(OTf)_2$, and $Yb(OTf)_3$ were not effective (entries 6, 7, and 9). However, Ag(I)-catalyzed cycloisomerization[9] proceeded to give **4a** in a 57% yield (entry 8). Moreover, a mild silica gel mediated reaction was found to provide oxazolyl ketone **4a** in excellent yield (entry 10).[10,11] These reaction conditions proved general in scope with the exception of ethyl carbamate **3e**, which failed to undergo the heterocyclization process (Scheme 1). In addition, the C(2)-ethyl-substituted oxazole **4d** was isolated in a modest 32% yield, but sterically hindered aliphatic and vinyl groups at the C(2) position were well tolerated.

Table 1. Preparation of oxazole **4a** from alkynyl ketone **3a**: Reaction Optimization

entry	conditions	product	yield [%][a]
1	NaHMDS (1.0 equiv), −78 °C, 30 min	complex mixture	ND
2	Et_3N (1.0 equiv), CH_2Cl_2, rt, 4 h	complex mixture	ND
3	K_2CO_3 (6 equiv), DMF, rt, 4 h	complex mixture	ND
4	toluene, reflux, 12 h	no reaction	0
5	$PdCl_2$ (10 mol %), MeCN, rt, 24 h	complex mixture	ND
6	PPTS (1.0 equiv), CH_2Cl_2, rt, 4 d	no reaction	0
7	$Cu(OTf)_2$ (0.2 equiv), CH_2Cl_2, rt, 12 h	no reaction	0
8	AgOTf (20 mol %), CH_2Cl_2, rt, 12 h	**4a**	57
9	$Yb(OTf)_3$ (20 mol %), CH_2Cl_2, rt, 24 h	no reaction	0
10	silica gel (300%, w/w), CH_2Cl_2, rt, 24 h	**4a**	99

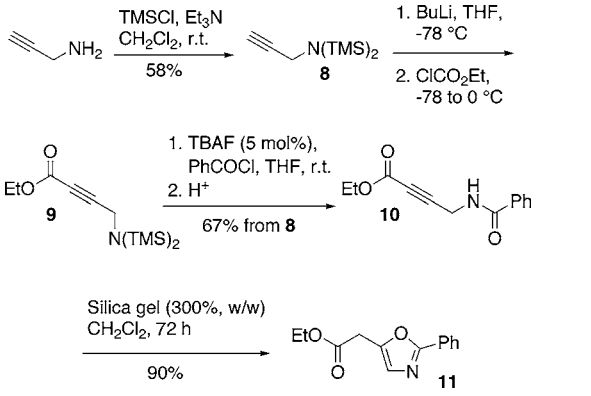
[a] Yields of isolated **4a**; ND = not determined.

Scheme 2. Selective Conversion of Alkyl and Alkenyl Ketones to 2,5-Disubstituted Oxazoles



This methodology was readily extended to alkyl and alkenyl carbonyl oxazoles, oxazol-5-yl acetates, and 2,4,5-trisubstituted oxazoles (Schemes 2, 3, and 4, respectively). Starting with amide **1a**, the preparation of the isopropyl and styryl ketones **7a** and **7b** followed a synthetic pathway analogous to that of oxazoles **4** (Scheme 2). For the synthesis of oxazol-5-yl acetate **11**, propargylamine was converted to the bis-TMS-protected amine **8** (Scheme 3). Treatment of

Scheme 3. Silica Gel Mediated Conversion of Propargyl Amides to Oxazol-5-yl Acetates



the alkynyllithium derivative of **8** with ethyl chloroformate gave ester **9**. Fluoride-catalyzed amidation of $(TMS)_2$-amine **9** with benzoyl chloride afforded alkynyl amide **10** in good yield.[12] Use of the fluoride-catalyzed amidation procedure was crucial since alkynyl amide **10** as well as the desilylated

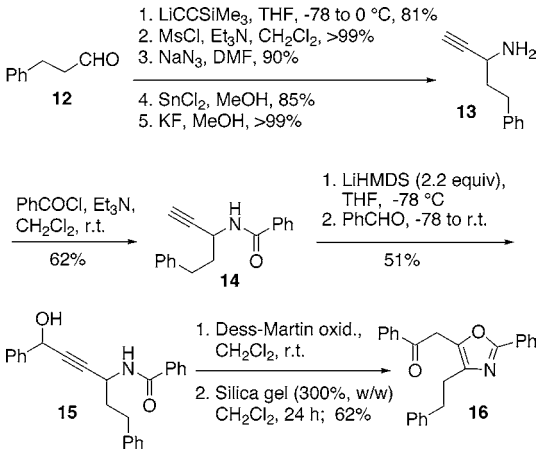
(8) Wipf, P.; Soth, M. J. *Org. Lett.* **2002**, *4*, 1787.

(9) For silver(I)-assisted heterocyclizations of acetylenic compounds, see: (a) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447. (b) Marshall, J. A.; Sehon, C. A. *Org. Synth.* **1999**, *76*, 263. (c) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.

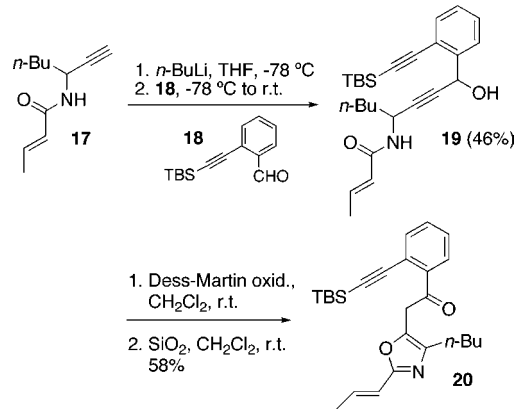
(10) A silica gel mediated furan synthesis has been reported by Marshall's group: (a) Marshall, J. A.; Zou, D. *Tetrahedron Lett.* **2000**, *41*, 1347. (b) Marshall, J. M.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037.

(11) Care should be taken to use "dry" silica gel. Flash chromatography grade silica gel (230−400 mesh) from several suppliers was used as received and gave consistent results for **4a**. However, if 10% w/w H_2O was added to the silica gel, the yield of **4a** dropped by ca. 10% and some starting material **3a** remained after 24 h reaction time.

Scheme 4. Silica Gel Mediated Conversion of a Propargyl Amide to a 2,4,5-Trisubstituted Oxazole



Scheme 5. Chemoselective Heterocyclization To Give a 2,4,5-Trisubstituted Polyunsaturated Oxazolyl Ketone



derivative of **9** were unstable under basic conditions. The silica gel mediated cycloisomerization of **10** led to oxazole **11** in 90% yield. As expected, a longer reaction time (72 h) was necessary for the synthesis of oxazol-5-yl acetate **11** than for oxazoles **4a**−**d** and **7a**,**b** (24 h). The isomerization of oxazoline **II** to oxazole **III** proved to be the rate-limiting step in this conversion.

The addition of substituents at the 4-position of the oxazole heterocycle required the synthesis of α-branched propargylic amines (Scheme 4). Conversion of hydrocinnamaldehyde **12** to the propargylic alcohol, displacement of the corresponding mesylate with azide, and reduction followed by deprotection provided amine **13** in 61% overall yield. Amide formation and subsequent nucleophilic addition to benzaldehyde provided alcohol **15**. The Dess−Martin oxidation followed by the silica gel mediated cycloisomerization led in good yield to the 2,4,5-trisubstituted oxazole **16**.[13]

As a further demonstration of the chemoselectivity and functional group tolerance of this new oxazole synthesis, TBS-protected diyne **19** was converted to the corresponding trisubstituted oxazole **20** (Scheme 5). The dianion of crotyl amide **17** was added to aldehyde **18** to give alcohol **19**. Subsequent Dess−Martin periodinane oxidation and silica gel mediated cyclization led to the desired oxazolyl ketone **20** in 58% yield without significant interference of the additional double and triple bonds in the substrate.[14]

In conclusion, we have developed a new, practical method for the preparation of 2,5-disubstituted and 2,4,5-trisubstituted oxazol-5-yl ketones and esters. The use of silica gel, a cheap and easily removable reagent, facilitates the cycloisomerization process and allows for mild reaction conditions and considerable functional group compatibility. Since appropriately substituted cycloisomerization precursors can be readily obtained from in situ prepared alkynyllithium reagents, this procedure is suitable for diversity-oriented heterocycle synthesis[15,16] as well as natural product synthesis.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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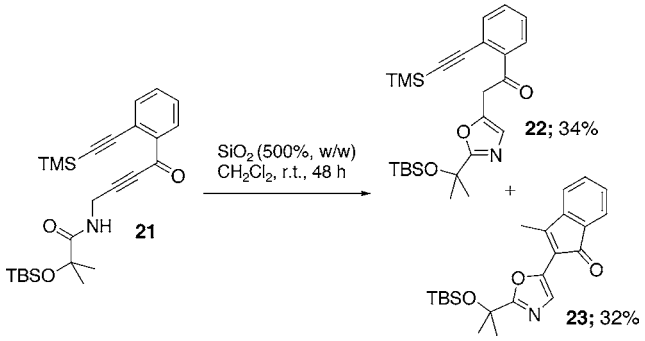
(13) The Dess−Martin oxidation of **15** afforded mixtures of alkynyl ketones and oxazole **16**. After the chromatographic removal of byproducts derived from the Dess−Martin reagent, the mixture was treated with silica gel to complete the conversion to **16**.

(14) Interestingly, the structurally related TMS-protected diyne **21** underwent competitive double cycloisomerization to afford a 1:1 mixture of oxazole **22** and benzindenone **23**.



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