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Synthesis of 2-(Hetero)aryl-5-(trimethylsilylethynyl)oxazoles from (Hetero)arylacrylic Acids

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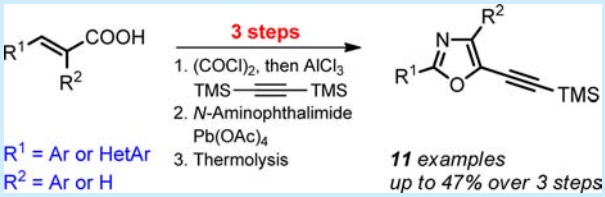
Supporting Information

ABSTRACT: A three-step method for the synthesis of 2-(hetero)aryl-5-(trimethylsilylethynyl)oxazoles is described. Easily accessible bis(trimethylsilyl)acetylene and acrylic acid derivatives are used as starting materials for the preparation of mono- and disubstituted 5-(trimethylsilyl)pent-1-en-4-yn-3-ones. Oxidative phthalimidoaziridination of these enynones provides the key 2-acyl-1-phthalimidoaziridines that are further utilized in the thermal expansion of the three-membered ring to furnish the target functionalizable oxazoles.

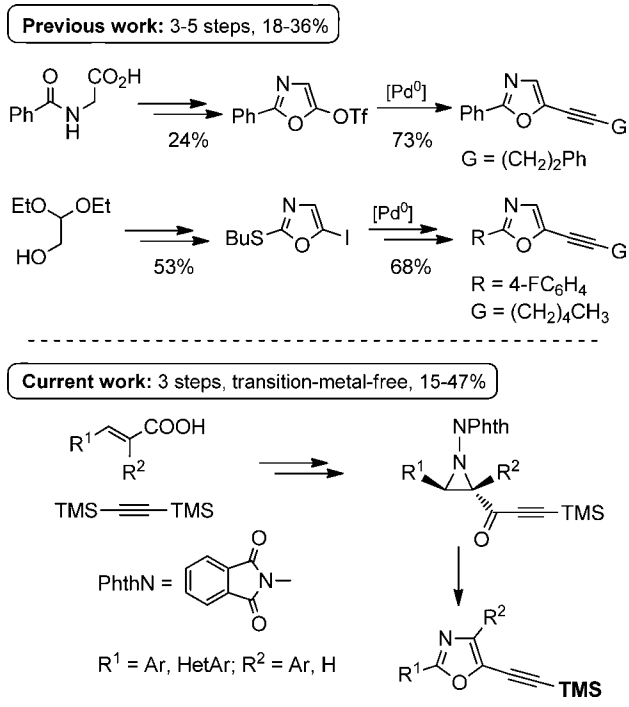


As numerous bioactive natural products contain an oxazole ring, research has focused on the properties and methods of synthesis of these heterocycles.[1] In addition, the scaffold of 2,5-disubstituted oxazole features promising fluorescent properties, which may be used in optical materials, biomolecular probes, and sensor elements.[2] The availability of easily functionalized groups at the oxazole ring plays a key role in the elaboration of this heterocycle, and a terminal triple bond offers a wealth of practical synthetic transformations toward this goal. While several methods for the synthesis of alkynyloxazoles are known,[3] 5-alkynyl substituted oxazoles have primarily been obtained by the Sonogashira reaction (Scheme 1).[4] These catalytic processes use mild reaction conditions and show considerable functional group compatibility. However, the employed halogen or triflate oxazole electrophiles are often not commercially available and their preparation is sometimes tedious, which can increase the total number of synthetic steps and diminish the overall yield of the desired products. As a feasible alternative to known methods, we have developed a novel synthetic route to alkynyloxazoles from easily available compounds and report our results herein.

Earlier we have shown that oxazoles can be prepared in good yields by a two-step procedure involving thermolysis of *N*-phthalimidoaziridines obtained from α,β-unsaturated ketones.[5] It is also known that the acylation of bis(trimethylsilyl)-acetylene (BTMSA) with acyl chlorides is suitable for the preparation of trimethylsilylalkynones.[6] Based on this knowledge, we decided to explore a novel route to 5-(trimethylsilylethynyl)oxazoles from substituted acrylic acids employing an aziridine as the key intermediate (*vide infra*).

First, we prepared several substituted cinnamic and 3-heteroarylacrylic acids **1a**−**h** from the corresponding aldehydes and malonic acid by the Knoevenagel reaction. In addition, 2-aryl-3-phenylacrylic acids **2a**−**c** and **3a,b** were synthesized from benzaldehyde and arylacetic acids.[7,8] In general, two stereoisomers are obtained in this reaction, but (*E*)-isomer **2** with *cis*-orientation of the aryl rings prevails (Table 1). Mixtures of

Scheme 1. Representative Synthesis of 5-Alkynyloxazoles[4a,b]



isomeric phenylacrylic acids **2** and **3** were separated utilizing their different acidity: treatment of solutions of their salts with acetic acid (pH ∼5) afforded (*E*)-isomers, and further acidification to pH ∼1 with concentrated HCl allowed isolating (*Z*)-isomers (see Supporting Information for details). The reaction with 4-nitrophenylacetic acid gave a better result when triethylamine was replaced with less basic pyridine,[8] and the

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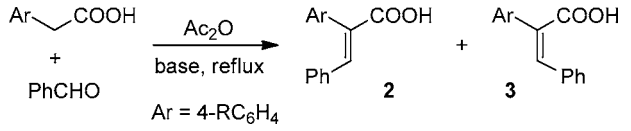
Table 1. Synthesis of Acrylic Acids 2 and 3



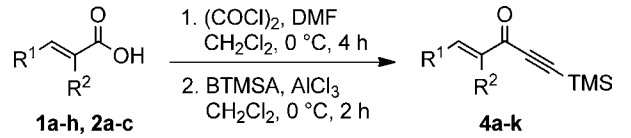
entry	R	base	time (h)	(*E*)-isomer (%)[a]	(*Z*)-isomer (%)[a]
1	H	Et_3N	5	**2a** (55)	**3a** (19)
2	OMe	Et_3N	5	**2b** (61)	**3b** (14)
3	NO_2	Et_3N	5	**2c** (7)	**3c** (–)
4	NO_2	Py	1.5	**2c** (44)	**3c** (–)

[a]Isolated yield.

heating time was reduced (Table 1, entries 3, 4). While this allowed an increase in the yield of **2c** from 7% to 44%, the isolation of the (*Z*)-isomer **3c** using our protocol was not successful.

The acyl chlorides obtained by the treatment of unsaturated acids **1a–h** and **2a–c** with oxalyl chloride were used without purification for the acylation of bis(trimethylsilyl)acetylene to furnish ketones **4a–k** in good yields (Table 2). We also wish to point out that (*Z*)-acrylic acids **3** exhibit varying reactivity under our reaction conditions. Thus, no ketone is formed when **3a** is subjected to the standard protocol, as the corresponding acyl chloride does not react with bis(trimethylsilyl)acetylene instead giving the product of intramolecular cyclization (see Supporting Information for details).

Table 2. Synthesis of Enynones 4a–k



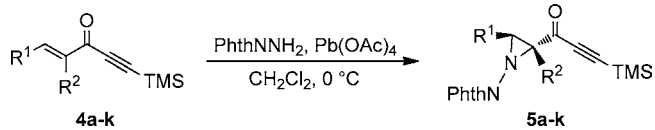
entry	acid	R^1	R^2	enynone	yield (%)
1	**1a**	4-$O_2NC_6H_4$	H	**4a**	73
2	**1b**	4-ClC_6H_4	H	**4b**	84
3	**1c**	Ph	H	**4c**	91
4	**1d**	4-MeC_6H_4	H	**4d**	90
5	**1e**	4-$MeOC_6H_4$	H	**4e**	82
6	**1f**	2-thienyl	H	**4f**	82
7	**1g**	3-thienyl	H	**4g**	89
8	**1h**	1-phenylpyrazol-4-yl	H	**4h**	77
9	**2a**	Ph	Ph	**4i**	84
10	**2b**	Ph	4-$MeOC_6H_4$	**4j**	82
11	**2c**	Ph	4-$O_2NC_6H_4$	**4k**	66

Oxidative aminoaziridination of enynones **4a–k** readily gave previously unknown 1-phthalimidoaziridines **5a–k** in good yields (Table 3). Since the inversion of an endocyclic nitrogen atom is slow on the NMR time scale,[10] disubstituted aziridines **5a–h** exist as mixtures of two invertomers with a significant predominance of one of them at 25 °C. ^{1}H NMR spectra of these compounds contain two pairs of characteristic doublets assigned to the protons of the aziridine ring. While signals of the major invertomers appear at δ 3.84–3.94 and 4.47–4.71 ppm, those for the minor ones are at δ 4.06–4.32 and 4.45–4.76 ppm. The values of the vicinal coupling constants (^3J = 4.7–5.0 Hz for the major invertomers and ^3J = 5.2–5.4 Hz for the minor ones) indicate the *trans*-arrangement of the aziridine protons, which is consistent with the well-known retention of the initial configuration of the double bond in the course of the oxidative aminoaziridination.[11] Carbon atom signals of the aziridine ring are observed at δ 44–54 ppm in the ^{13}C NMR spectra.

As the phthalimide substituent deshields the *syn*-located aziridine proton,[10] assignment of the spatial structure of invertomers can be based on their ^{1}H NMR spectra. The low-field proton doublet of the major invertomer is slightly broadened as compared to the high-field doublet due to the long-range interaction with *ortho*-protons of the aromatic substituent. It indicates that in the major invertomer the phthalimide group and R^1-substituent are in the *anti*-position which appears to be sterically more favorable. The increasing amount of the minor invertomer for heteroarylaziridines **5f–h** is likely due to the smaller size of the five-membered rings as compared to the six-membered phenyl ring. Trisubstituted aziridines **5i–k** exist as single invertomers, and a *syn*-orientation of the phthalimide group and the aziridine proton is supported by the characteristic singlet of the latter at δ 5.03–5.19 ppm. Signals of the methine and quaternary carbons of the aziridine ring are found at δ ~56 and ~63 ppm, respectively.

Finally, we have examined the key thermal transformation of aziridines **5a–k** into targeted azoles **6a–k**. All experiments

Table 3. Synthesis of 1-Phthalimidoaziridines 5a–k



entry	enynone	R^1	R^2	aziridine	ratio of invertomers	isolated yield (%)
1	**4a**	4-$O_2NC_6H_4$	H	**5a**	1:0.02	89
2	**4b**	4-ClC_6H_4	H	**5b**	1:0.05	76
3	**4c**	Ph	H	**5c**	1:0.05	72
4	**4d**	4-MeC_6H_4	H	**5d**	1:0.06	76
5	**4e**	4-$MeOC_6H_4$	H	**5e**	1:0.07	72
6	**4f**	2-thienyl	H	**5f**	1:0.17	65
7	**4g**	3-thienyl	H	**5g**	1:0.12	62
8	**4h**	1-phenylpyrazol-4-yl	H	**5h**	1:0.25	66
9	**4i**	Ph	Ph	**5i**	1:0	78
10	**4j**	Ph	4-$MeOC_6H_4$	**5j**	1:0	74
11	**4k**	Ph	4-$O_2NC_6H_4$	**5k**	1:0	81

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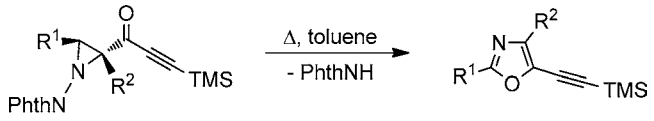
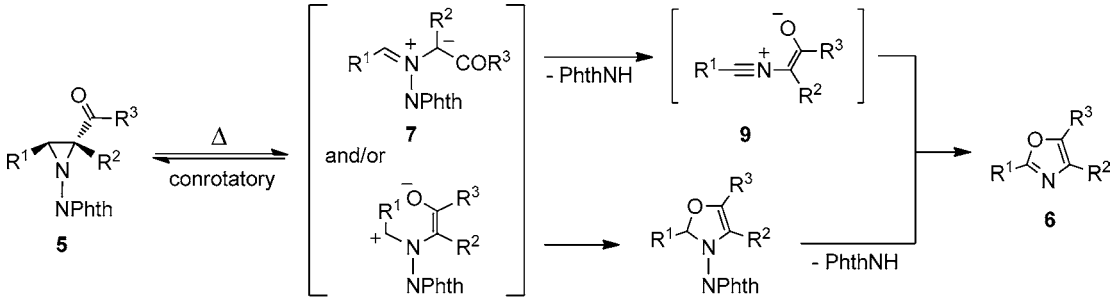
Table 4. Synthesis of Oxazoles 6a–k



5a-k 6a-k

entry	aziridine	R^1	R^2	temp (°C)	time, h	oxazole	isolated yield (%)
1	**5a**	4-$O_2NC_6H_4$	H	140	6	**6a**	66
2	**5b**	4-ClC_6H_4	H	140	2.5	**6b**	62
3	**5c**	Ph	H	130	3	**6c**	61
4	**5d**	4-MeC_6H_4	H	110	7	**6d**	49
5	**5e**	4-$MeOC_6H_4$	H	110	4.5	**6e**	50
6	**5f**	2-thienyl	H	100	5	**6f**	46
7	**5g**	3-thienyl	H	120	6	**6g**	28
8	**5h**	1-phenylpyrazol-4-yl	H	130	6	**6h**	30
9	**5i**	Ph	Ph	110	7	**6i**	72
10	**5j**	Ph	4-$MeOC_6H_4$	110	7	**6j**	69
11	**5k**	Ph	4-$O_2NC_6H_4$	110	7	**6k**	72

Scheme 2. Plausible Mechanism for the Ring Expansion of 2-Acyl-1-phthalimidoaziridines into Oxazoles



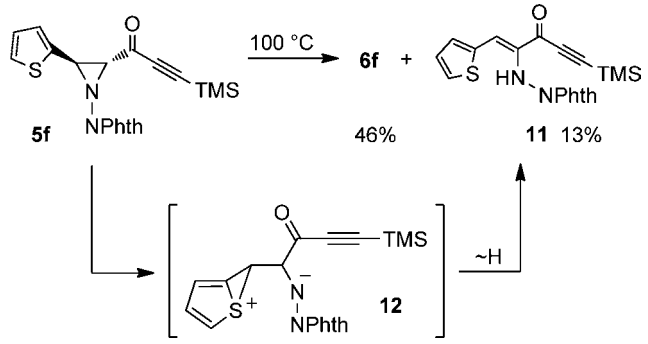
were carried out in toluene solution in sealed vials under TLC control, and products were isolated by column chromatography in good yields (Table 4). The structure and composition of obtained oxazoles **6a–k** are in agreement with their NMR and HRMS data. Importantly, the trimethylsilyl substituted triple bond remained intact in all isolated products. For disubstituted compounds **6a–h**, the signal of the H^4 proton is observed at δ 7.29–7.41 ppm and its corresponding carbon atom resonates at ~133 ppm. Trisubstituted oxazoles **6i–k** feature a signal of the C^4 at lower field (δ ~142–144 ppm).

The transformation of disubstituted aziridines into oxazoles proceeded under milder conditions if substituent R^1 was an electron-rich aromatic ring or a 2-thienyl substituent (Table 4, entries 4–6). This can be explained by a more effective stabilization of the cationic center in the intermediate azomethine ylides (*vide infra*). At the same time, yields of oxazoles **6a–c** with NO_2, Cl, and H substituents were slightly higher even at more elevated temperatures. Conversion of trisubstituted aziridines **5i–k** into oxazoles **6i–k** appears to be insensitive to the electronic character of the substituent at the C^2 atom of the aziridine (Table 4, entries 9–11).

Although the mechanism of the ring expansion of 2-acylaziridines **5** into oxazoles **6** has not been fully elucidated, one can speculate about the likely steps involved in this transformation (Scheme 2). Upon heating, the conrotatory ring opening of the C–C bond in the aziridine gives azomethine ylides **7** and/or **8**. Then two pathways are possible: an elimination of the phthalimide molecule with the formation of nitrile ylide **9** followed by its cyclization into oxazole **6**, or the initial formation of oxazoline **10** with the consequent loss of the phthalimide.[5]

Surprisingly, 2-thienyl-substituted aziridine **5f** underwent a competitive isomerization and gave a mixture of oxazole **6f** and enhydrazine **11** (Scheme 3). The structure of the latter product was confirmed by 2D NMR spectroscopy including $^{13}C-^{1}H$ and $^{15}N-^{1}H$ HSQC, $^{13}C-^{1}H$ HMBC, and NOESY spectra.

Scheme 3. Thermolysis of Aziridine 5f



Nucleophilic ring opening via the C–N bond cleavage is very typical for aziridines.[12] In our case, the observed regioselectivity can be explained by the influence of the neighboring sulfur atom whose lone pair can push out the aziridine nitrogen with the formation of an intermediate zwitter-ion **12**. In addition, a

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similar enhydrazine was not obtained for 3-thienyl analog **5g** supporting our hypothesis.

In summary, we have developed a new synthetic route to 5-alkynyl-1,3-oxazoles via 2-acylaziridines providing an attractive alternative to the known methods. Readily available starting materials and reagents and only three simple steps with good yields are the main advantages of our synthetic protocol. Moreover, this method is applicable for various substituent patterns of the initial compounds that allows introducing one or two groups into the oxazole ring. Lastly, we note that the ethynyl substituent with an easily removable TMS group offers various routes for further useful transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of the 1D and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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