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Synthesis of oxazolines and oxazoles by the reaction of propynals with tosylmethyl isocyanide

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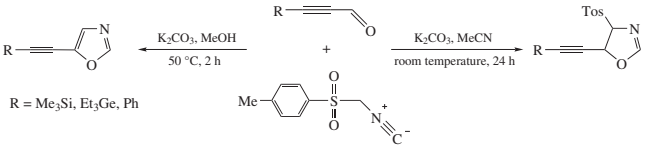
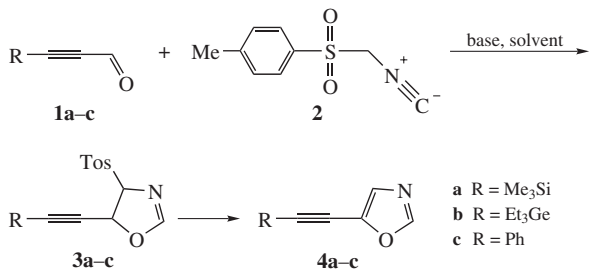
The reaction of 3-(trimethylsilyl)propynal, 3-(triethylgermyl)propynal or 3-phenylpropynal with tosylmethyl isocyanide affords new 5-alkynyl-4-tosyl-2-oxazolines and/or 5-alkynyl-1,3-oxazoles.



Oxazoles and oxazolines are important five-membered heterocycles representing key structural fragments of biologically active substances and drugs.[1] As well, they are used for the preparation of polymers[2] and as chiral ligands for catalytic asymmetric organic syntheses.[3] Numerous methods for the assembling of oxazole and oxazoline heterocycles have been developed to date.[4] One of the common ways for their synthesis is the condensation of tosylmethyl isocyanide with various aldehydes under basic conditions, which was carried out for the first time by the group of van Leusen[5] and has gained widespread currency. However, the use of α,β-unsaturated aldehydes in this strategy is little documented,[6] though in general the acetylenic aldehydes bearing sterically available aldehyde moiety and the activated triple bond are widely utilized in the synthesis of heterocyclic compounds.[7]

In this article, we report on the reaction of substituted propynals, namely 3-(trimethylsilyl)propynal **1a**, 3-(triethylgermyl)propynal **1b** and 3-phenylpropynal **1c**, with tosylmethyl isocyanide **2**. To choose the optimal conditions for the synthesis of heterocycles, we investigated the reaction between compounds **1a** and **2**, varying catalyst, solvent and temperature (Scheme 1, Table 1).

It was found that 3-(trimethylsilyl)propynal **1a** reacted with tosylmethyl isocyanide **2** under conditions of the van Leusen synthesis,[5] namely in the presence of K_2CO_3 in MeOH at room temperature for 24 h, affording oxazole **4a** in a low yield with complete conversion of the starting aldehyde, according to spectral data (Table 1, entry 1). However, an attempt to purify the resulting 5-(trimethylsilylethynyl)-1,3-oxazole **4a** by column chromatography on silica gel led to desilylation and the formation of 5-ethynyl-1,3-oxazole **5** (Scheme 2).



Scheme 1

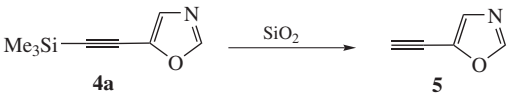
The reactions of propynals **1b** and **1c** with compound **2** under the above conditions furnished chemoselectively the target oxazoles **4b**,**c** in high NMR yields, though the yields were reduced to 58 and 54%, respectively, after purification (Table 1, entries 2 and 3).

When the reaction was carried out at 55 °C, the time needed for the complete conversion of starting aldehydes **1a–c** decreased to 2 h (Table 1, entries 4–6). Under these conditions, propynal **1a** underwent notable resinification, and the target oxazole was produced in a moderate yield (entry 4).

Table 1 Reaction of propynals **1a–c** with tosylmethyl isocyanide **2**.

Entry	Aldehyde[a]	Base[a]	Solvent	*T*/°C	*t*/h	Yield (%), by ^{1}H NMR (isolated)	
						3	**4**
1	**1a**	K_2CO_3	MeOH	24	24	–	30
2	**1b**	K_2CO_3	MeOH	24	24	–	93 (58)
3	**1c**	K_2CO_3	MeOH	24	24	–	99 (54)
4	**1a**	K_2CO_3	MeOH	55	2	–	40
5	**1b**	K_2CO_3	MeOH	55	2	–	98
6	**1c**	K_2CO_3	MeOH	55	2	–	97
7	**1a**	K_2CO_3	MeCN	24	24	88 (48)	–
8	**1b**	K_2CO_3	MeCN	24	24	96 (52)	–
9	**1c**	K_2CO_3	MeCN	24	24	99 (60)	–
10	**1a**	K_2CO_3	MeCN	55	2	91	–
11	**1b**	K_2CO_3	MeCN	55	2	96	–
12	**1c**	K_2CO_3	MeCN	55	2	90	–
13	**1a**	DBU	THF	24	20	50	40
14	**1a**	DABCO	THF	24	20	60	30
15	**1a**	Et_3N	THF	24	24	90	–
16	**1a**	Et_3N	MeOH	24	24	–[b]	–[b]
17	**1a**	Et_3N	$CHCl_3$	24	24	97 (67)	–
18	**1a**	Et_3N[c]	$CHCl_3$	24	24	98	–
19	**1b**	Et_3N	$CHCl_3$	24	24	95 (53)	–
20	**1c**	Et_3N	$CHCl_3$	24	24	94 (56)	–
21	**1c**[d]	K_2CO_3	MeOH	55	2	–	99 (71)

[a] A base (1 mmol) was added to a solution of aldehyde **1** (1 mmol) and tosylmethyl isocyanide **2** (1 mmol) in a solvent (6 ml); the products were isolated by column chromatography. [b] Reaction products were not detected due to a strong resinification. [c] Two equiv. Et_3N were used. [d] Gram scale reaction (10 mmol aldehyde).



4a **5**

Scheme 2

The use of acetonitrile as a solvent in combination with K_2CO_3 at room temperature allowed us to obtain the intermediate oxazolines **3a**–**c** in moderate to high yields (Table 1, entries 7–9). When the temperature was elevated to 55 °C, the reaction was complete in 2 h, affording selectively oxazolines **3a**–**c** (entries 10–12).

Testing the bases chosen initially from Et_3N, DBU and DABCO revealed that triethylamine was the best reagent for the preparation of oxazolines **3a**–**c** (Table 1, entries 15 and 17–20). A higher amount of Et_3N did not affect the synthesis outcome (entry 18). The use of chloroform together with triethylamine ensured the highest isolated yield of product **3a** (entry 17). With THF as a solvent in the presence of DBU or DABCO, the reaction proceeded non-selectively, resulting in oxazoline **3a** accompanied by the corresponding oxazole **4a** (entries 13 and 14). For the combination Et_3N/MeOH, a strong resinification occurred and products **3a** or **4a** were not detected in the reaction mixture by ^{1}H NMR (entry 16).

To illustrate the potential of our method, we also synthesized oxazole **4c** on a gram scale in 71% isolated yield (Table 1, entry 21).

The structures of oxazolines **3a**–**c** and oxazoles **4b**,**c** were confirmed by ^{1}H and ^{13}C NMR spectroscopy data. Note, that all the ^{1}H NMR spectra of oxazolines **3a**–**c** contain signals of the tosyl moiety as well as the three signals of equal intensity assigned to the heterocyclic ring, namely the singlet at ~7 ppm and two doublets at 5.17–5.30 and 5.60–5.88 ppm. For oxazoles **4a**–**c**, these signals are absent, while the signals of the alkynyl moieties are preserved, and an additional singlet appears in a weaker field at 7.79–7.89 ppm.

In summary, it has been established that the reaction of 3-(trimethylsilyl)propynal, 3-(triethylgermyl)propynal and 3-phenylpropynal with tosylmethyl isocyanide proceeds chemoselectively at the carbonyl group, affording hitherto unknown oxazolines and oxazoles in good yields. The introduction of the triple bond as well as Si or Ge heteroatom into the products would potentially broaden the synthetic and biological applications of the resulting heterocycles.

The main results were obtained using the equipment of Baikal Analytical Center of Collective Using, Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.015.

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