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Synthesis of new alkoxy/alkylthiovinylated oxazoles using tosylmethyl isocyanide

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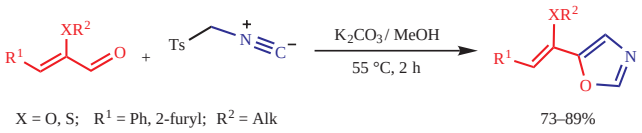
The reaction of 2-alkoxy- and 2-alkylthio-3-(het)arylpropenals with tosylmethyl isocyanide affords oxazoles bearing the corresponding 5-positioned 1-alkylchalcogenyl-2-(het)arylvinyl groups.



X = O, S; R^1 = Ph, 2-furyl; R^2 = Alk — 73–89%

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Functionalized oxazole derivatives are found in nature and are employed as building blocks in medicinal chemistry and drug discovery.[1] Many compounds containing oxazole core exhibit biological activity, for example, possess cytotoxic, antitubulin, and antitumor properties, as well as act as agonists of β_3 adrenergic[2] and dopamine receptors.[3] Some oxazoles are potent PTP-1B inhibitors thus exerting antihyperglycemic action.[4]

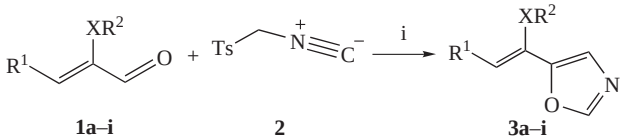
In this regard, the development of new syntheses of oxazole systems is an urgent challenge of modern heterocyclic chemistry, as evidenced by a number of publications.[5] A convenient approach to 5-substituted oxazoles based on tosylmethyl isocyanide ($TsCH_2N{\equiv}C$) was proposed in 1972.[6] A wide range of heterocyclic compounds was obtained on the basis of isocyanides[7] whose chemistry continues to develop.[8] However, to the best of our knowledge, the preparation of oxazoles from α,β-unsaturated aldehydes with the use of $TsCH_2N{\equiv}C$ is scarcely documented,[9] while the application of aldehydes bearing 2-positioned functional substituents are lacking.

Meanwhile, 2-alkoxy- or 2-alkylthio-substituted alk-2-enals represent a structural motif of many biologically active natural compounds.[10] In addition, they are valuable reagents for obtaining a variety of heterocyclic derivatives.[11] Therefore, the introduction of chalcogenoalkenyl groups to the oxazole core can afford new 'hybrid' compounds with useful properties.

Recently, our group has performed the reaction of some substituted propynals with tosylmethyl isocyanide to afford the corresponding alkynyl-equipped oxazolines and oxazoles in good yields.[9(a)] The reaction proceeded chemoselectively at the carbonyl group of aldehydes. Based on this our previous experience,[9(a)] we have assumed that 2-alkoxy- and 2-alkylthio-3-aryl(hetaryl)propenals could also participate in this reaction. Herein, we report on the reaction of 2-alkoxy- and 2-alkylthio-3-(het)arylpropenals **1a**–**i** with tosylmethyl isocyanide **2** (Scheme 1).

We started our study with optimization of the reaction conditions using 2-propylthio-3-phenylpropenal **1a** as a substrate (Table 1). The reaction progress was monitored using ^{1}H NMR by the decrease in the intensity of the characteristic singlet at 9.56 ppm for the starting aldehyde. In fact, in the presence of an equimolar amount of K_2CO_3 in MeOH at 55 °C, the desired product **3a** was obtained in 20% yield (see Table 1, entry 1). In this case, in the ^{1}H NMR spectrum of the reaction mixture, the signals of $TsCH_2N{\equiv}C$ **2** were absent, while the starting aldehyde was retained in significant amounts.

The increase in **1a**:**2**:K_2CO_3 ratio to 1:1.1:1.1 allowed us to raise the content of the target product **3a** to 31% (entry 2). The best results were achieved at 1:1.1:1.4 ratio of **1a**:**2**:K_2CO_3 (entry 5) when the yield approached 97% (^{1}H NMR data) and 89% after column chromatography. Attempts to carry out the



1a–i **2** **3a–i**

a R^1 = Ph, R^2 = Pr, X = S, 89%
b R^1 = Ph, R^2 = Bu, X = S, 87%
c R^1 = 2-furyl, R^2 = Bu, X = S, 81%
d R^1 = R^2 = Ph, X = S, 73%
e R^1 = Ph, R^2 = Bn, X = S, 87%
f R^1 = Ph, R^2 = *n*-C_8H_{17}, X = S, 68%
g R^1 = Ph, R^2 = *n*-$C_{12}H_{25}$, X = S, 63%
h R^1 = 2-furyl, R^2 = Me, X = O, 75%
i R^1 = Ph, R^2 = Me, X = O, 86%

Scheme 1 *Reagents and conditions*: i, K_2CO_3, MeOH, 55 °C, 2 h.

Table 1 Optimization of the reaction conditions on model 3-phenyl-2-propylthiopropenal **1a**.

Entry	**1a**:**2**:K_2CO_3 ratio [a]	*T*/°C	*t*/h	^{1}H NMR yield (%)
1	1:1:1	55	2	20
2	1:1.1:1.1	55	2	31
3	1:1.1:1.2	55	2	54
4	1:1.1:1.3	55	2	72
5	1:1.1:1.4	55	2	97 (89[b])
6	1:1.1:1.4	24	2	–
7	1:1.1:1.4	24	20	–

[a] Aldehyde (1 mmol), $TsCH_2N{\equiv}C$ **2**, K_2CO_3 MeOH (6 ml). [b] Isolated yield after column chromatography.

reaction at room temperature for 2 h were unsuccessful; according to ^{1}H NMR, the target oxazole **3a** was not formed (entries 6, 7) despite the prolongation of the reaction time to 20 h. Hence, the optimal reaction conditions for the synthesis of oxazoles **3** were as follows: **1**:**2**:K_2CO_3 ratio of 1:1.1:1.4, MeOH, 55 °C, 2 h.

With these optimized conditions in hand, we have studied the scope of this reaction applying various substituted 2-propenals **1b**–**g** to deliver the corresponding oxazoles **3b**–**g** in 63–89% yields (see Scheme 1).

The method developed turned out to be effective also for 2-alkoxy-3-(het)arylpropenals **1h**,**i** when oxazoles **3h**,**i** were obtained in 75–86% yields. Obviously, the mechanism of the formation of oxazoles **3a**–**i** is similar to that described previously.[6]

The structures of the obtained compounds were confirmed by ^{1}H, ^{13}C, ^{15}N NMR spectroscopy. In the ^{1}H NMR spectra of compounds **3a**–**i**, the signals for the oxazole C^{2}H and C^{4}H protons are observed in the region of 7.83–7.89 and 7.16–7.36 ppm, while the signals for these carbon atoms are present in the ^{13}C NMR spectra at 150.4–150.8 and 123.9–134.6 ppm, respectively. The ^{15}N {^{1}H–^{15}N} HMBC 2D NMR spectra of compounds **3a**–**i** contain cross-peaks of the nitrogen atom with C^{2}H and C^{4}H protons in the region of 119.8–122.6 ppm.

In summary, new 5-[1-alkylchalcogeno-2-(het)arylethenyl]-1,3-oxazoles **3** comprising new combination of functional groups have been synthesized in high-to-moderate yields using van Leusen reagent, tosylmethyl isocyanide **2**.[6]

The main results were obtained using the equipment of Baikal Analytical Center of Collective Usage SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.05.030.

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