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Convenient synthesis of isoxazolines via tandem isomerization of allyl compounds to vinylic derivatives and 1,3-dipolar cycloaddition of nitrile oxides to the vinylic compounds

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ABSTRACT

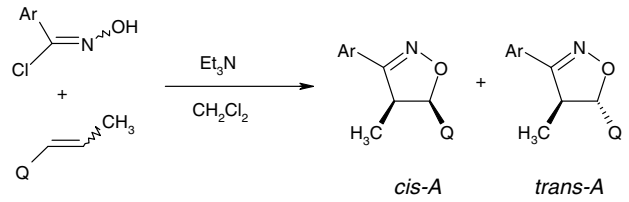
A novel effective method for the synthesis of new isoxazolines via tandem isomerization of QCH(X)CH=CH(Y) to QC(X)=CHCH$_2$(Y) (Q = RO, RS, R$_2$N, R$_3$Si, etc.; X = H, R, OR; Y = H, R; R = alkyl, aryl) catalyzed by ruthenium complexes and 1,3-dipolar cycloaddition of the latter compounds to arenenitrile oxides is presented. The cycloaddition of QCH(X)CH=CH(Y) to 2,6-dichlorobenzonitrile oxide is also described. The regio- and stereoselectivity of the cycloaddition of nitrile oxide to allyl and 1-propenyl (vinylic in general) compounds is discussed.

1,3-Dipolar cycloaddition of nitrile oxides to alkenes or functionalized alkenes (allyl or 1-propenyl, vinyl compounds in general) leading to isoxazolines is an important synthetic transformation.[1–5] Many isoxazolines,[6–9] and their aromatic homologs as well as their aromatic analogs, that is, isoxazoles[10,11] are drugs or potential drugs with, for example, anti-inflammatory,[12] antiplatelet,[13] or antidepressant[14] activity. Isoxazolines are also used in the synthesis of β-aminoalcohols and β-hydroxyketones.[15] The most often studied dipolarophiles are conjugated systems of YCH=CHCOX type (where Y = H, alkyl, aryl; X = H, alkyl, aryl, *O*-alkyl, *O*-aryl, ...),[16,17] simple alkenes,[18] and allyl compounds.[18] In this Letter, we show that the combination of isomerization of allylic systems of the type QCH(X)CH=CH(Y) to vinylic systems QC(X) =CHCH$_2$(Y) via 1,3-dipolar cycloaddition of nitrile oxides to QC(X)=CHCH$_2$(Y) provides a route to synthesize substituted 4,5-dihydroisoxazoles. Allylic systems of type QCH(X)CH=CH(Y) (Q = RO, RCOO, RS, R$_2$N, R$_3$Si, etc.; R = alkyl or aryl; X = H, alkyl, *O*-alkyl; Y = H, alkyl) are easy to synthesize and many catalytic systems are known, which allow isomerization of QCH(X)CH=CH(Y) allylic systems to QC(X) =CHCH$_2$(Y) vinylic systems.[19–26] Importantly, many QC(X)=CHCH$_2$(Y) systems are difficult to obtain by methods other than isomerization of allylic precursors. Transition metal complexes[19–36] are particularly attractive catalysts for double bond migration in allylic systems (because of their chemo-, regio-, and stereoselectivity).

Dipolar cycloaddition of relatively stable nitrile oxides to vinylic systems of QC(X)=CHCH$_2$(Y) type allows simple and convenient synthesis of a series of functionalized 4,5-dihydroisoxazoles containing the Q group (e.g., R$_2$N, RO, RS, R$_3$Si) connected to the heterocyclic ring (Scheme 1 and Table 1). Dihydroisoxazoles of this type are very difficult to obtain by other methods.

The nitrile oxide required was generated in situ from an oximoyl chloride and triethylamine in dichloromethane.[37,38] The starting oximoyl chlorides were synthesized from the respective oximes and NCS in the presence of a catalytic amount of hydrogen chloride.[39]

QC(X)=CHCH$_2$(Y) was obtained separately by isomerization of QCH(X)CH=CH(Y) mediated by the ruthenium complex [RuClH(CO)-(PPh$_3$)$_3$], (Scheme 2, Tables S1 and S2—see Supplementary data).



Scheme 1. Cycloaddition of 2,6-dichlorobenzonitrile oxide to 1-propenylic (vinylic) systems.

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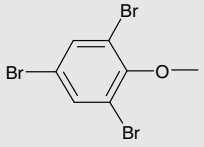
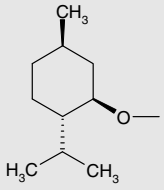
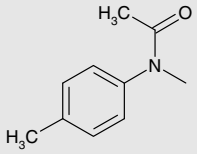
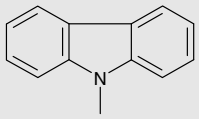
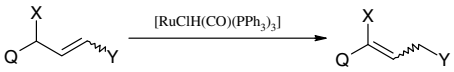
Table 1
Synthesis of isoxazolines via 1,3-dipolar cycloaddition of 2,6-$Cl_2C_6H_3CNO$ to $QCH{=}CHCH_3$[a]

Entry	Q	(*E*/*Z*)[b]	*cis*-A[c]	*trans*-A[c]
1	PhO–	2.2	57	43
2		*Z*	50	50
3		0.4	64	36
4	*n*-BuO–	1.3	34	66
5	*t*-BuO–	0.4	66	34
6	Me_3SiO–	0.2	64	36
7	$(i\text{-Pr})_2N$–	*E*	76	24
8		*E*	83	17
9	H_2NCOHN–	1.0	88	22
10		0.1	28[d]	28[d]
11	*t*-BuS–	*Z*	95	5
12	Ph_3CS–	10	—	—
13	Ph_3Si–	5.9	19[d]	12[d]

[a] Reaction conditions: rt, 24 h, 2,6-$Cl_2C_6H_3CNO$/$QCH{=}CHCH_3$/Et_3N = 1:1:3; conversion: 100% in all cases.
[b] (*E*/*Z*) for $QCH{=}CHCH_3$.
[c] Isolated yields.
[d] Regioisomers B (its structure is presented in Scheme 6) were also formed (25% *cis*-B and 19% *trans*-B for entry 10 and 29% *cis*-B and 40% *trans*-B for entry 13).



Scheme 2. Synthesis of $QC(X){=}CHCH_2(Y)$ via isomerization of $QCH(X)CH{=}CH(Y)$.

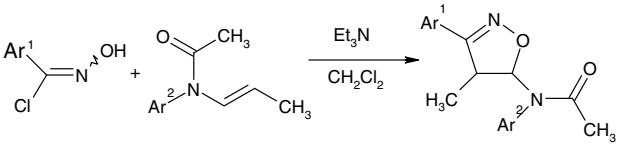
It was important that we used $QC(X){=}CHCH_2(Y)$ (mainly $QCH{=}CHCH_3$) without removing the isomerization catalyst. The complexes of ruthenium were removed only during isolation of the dihydroisoxazoles by adsorption on active carbon or particularly on mesoporous foams functionalized with groups able to coordinate Ru ($\equiv SiCH_2CH_2CH_2NHCH_2CH_2NH_2$). We have previously applied functionalized MCF (Mesoporous Cellular Foam) to remove Ru from the isomerization products of allylic compounds.[30,35] The results of our studies on the synthesis of functionalized isoxazolines from allyl compounds via tandem isomerization of allyl systems ($QCH_2CH{=}CH_2$ type) to 1-propenyl systems ($QCH{=}CHCH_3$) and cycloaddition of nitrile oxide (represented by 2,6-dichlorobenzenenitrile oxide) are collected in Table 1 (for details of the reaction conditions and selected spectral data see Supplementary data).

We have also verified that 4-chlorobenzonitrile oxide (which is less stable than 2,6-dichlorobenzonitrile oxide) as well as 2,4,6-trimethylbenzonitrile oxide and 2,4,6-trimethoxybenzonitrile oxide (which are more stable than 2,6-dichlorobenzonitrile oxide) easily undergoes cycloaddition to (*E*)-*p*-$MeC_6H_4N(COMe)$-$CH{=}CHCH_3$ (Scheme 3).

Also, cycloaddition of 2,6-$Cl_2C_6H_3CNO$ to 1-propenylic systems of type $QCH{=}CHCH_2(Y)$ ($QY = -OCH_2OCH_2-$) and to systems of type $QC(X){=}CHCH_3$ ($QX = -OCH_2CH_2CH_2O-$) was carried out successfully, and the corresponding bicyclic oxepine derivative and spiro orthoester were obtained (Schemes 4 and 5).

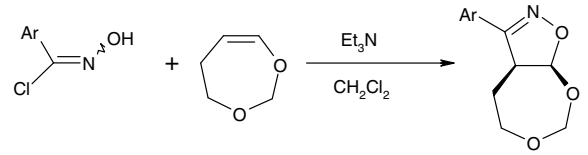
The starting systems $QCH{=}CHCH_2(Y)$ and $QC(X){=}CHCH_3$ (6,7-dihydro-1,3-dioxepine and 2-ethylidene-1,3-dioxane) were prepared in quantitative yield via isomerization of the respective allyl systems mediated by $[RuClH(CO(PPh_3)_3]$ (0.5 mol % Ru, 100 °C, 2 h, without solvent)—see Scheme 2 (and Table S3 see Supplementary data).

The results obtained indicate unequivocally that the regioselectivity of the addition of ArCNO to $QC(X){=}CHCH_2(Y)$ (and to $QCH(X)CH{=}CH(Y)$—see Scheme 7) is controlled by the electron density distribution on the carbon atoms in the allylic or 1-propenylic systems. If the Q group is conjugated with the double bond, as in 1-propenyl ethers, sulfides, enamides, and other vinylic systems (entries 1–9 and 11, Table 1), the cycloaddition product is regioisomer A (*cis*-A and *trans*-A) only. Analogous regioselectivity was observed in the cycloaddition reactions of 4,5-dihydrofuran[40] and 4,5-dihydrothiophene[40] to nitrile oxides. Formation of regioisomers B (*cis*-B and *trans*-B) together with regioisomers A (*cis*-A and *trans*-A) were observed only in the cases of cycloaddition to 9-(1-propenyl)carbazole and triphenyl(1-propenyl)silane (entries 10 and 13, Table 1, Scheme 6).

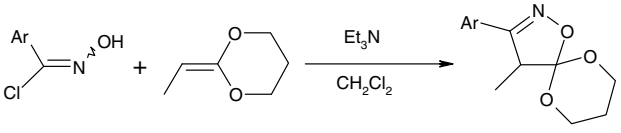


Ar (% isolated yields, *cis*/*trans*) = *p*-chlorophenyl (40, 40/60), 2,4,6-trimethoxyphenyl (70, 50/50), 2,4,6-trimethylphenyl (75, 60/40)

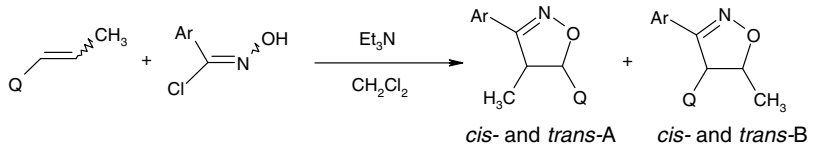
Scheme 3. Cycloaddition of arenenitrile oxides to (*E*)-*N*-(*p*-methylphenyl)-*N*-(1-propenyl)ethanamide.



Scheme 4. Cycloaddition of 2,6-dichlorobenzonitrile oxide to dihydrodioxepine.

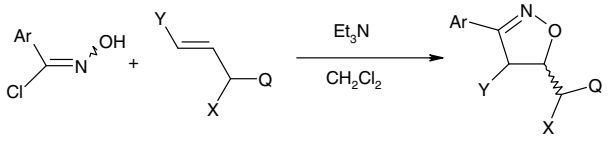


Scheme 5. Cycloaddition of 2,6-dichlorobenzonitrile oxide to 2-ethylidene-1,3-dioxane.



Q = 9-carbazolyl, Ph_3Si

Scheme 6. Cycloaddition of 2,6-dichlorobenzonitrile oxide to 9-(1-propenyl)carbazole and triphenyl(1-propenyl)silane.



a) Q = PhO, *t*-BuO, Me_3SiO, Me_2N, $(i\text{-}Pr)_2N$, *p*-$MeC_6H_4N(COMe)$, 9-carbazolyl, *t*-BuS, Ph_3CS, Me_3Si, Ph_3Si; X ,Y = H

b) Q, X = -$OCH_2CH_2CH_2O$-, Y = H (2-vinyl-1,3-dioxane)

c) Q, Y = -$OCH_2OCH_2OCH_2$-; X = H (4,7-dihydrodioxepine)

Scheme 7. Reagents and conditions: rt, 24 h, ArCNO/Q-allyl/Et_3N = 1:2:3. Conversion: 100% (in all cases); isolated yields: 60–80%. Synthesis of isoxazolines via cycloaddition of 2,6-$Cl_2C_6H_3CNO$ to allylic systems.

The failure of the reaction in the case of trityl-(1-propenyl) sulfide (Q = Ph_3CS, entry 12) probably results from steric interactions. If the trityl group is located further from the reaction center, as in allyl trityl sulfide, cycloaddition proceeds unhindered (Scheme 7). A strong steric effect, which controlled the regioselectivity, was observed previously in the reactions of cycloaddition reactions of benzonitrile oxide to MeCH=CHCO(Y) systems.[16] We have observed that regioisomer A was also the only product of dipolar cycloaddition to allylic systems—Scheme 7.

In these cases, the regioselectivity is controlled by the inductive effect of Q strengthened by the hyperconjugation effect. In the case of allyl systems, even if Q is an electron donor (Q = Me_3Si) and therefore counteracts the hyperconjugation effect, the formation of one regioisomer is observed (thus the CH_3 hyperconjugation effect is dominant). Importantly, our results show that there are no exceptions to the above interpretation, the regioselectivity of the cycloadditions of all 14 systems of type QC(X)=$CHCH_2Y$ and 13 systems of type QCH(X)CH=CHY we studied can be explained with resonance and Q inductive effects and the hyperconjugation effects of the $–CH_2–$ or $–CH_3$ groups. Interestingly, the formation of the mixture of cis (*cis*-A and/or *cis*-B in Schemes 1 and 6) and trans (*trans*-A and/or *trans*-B on Schemes 1 and 6) isomers independently of (*E*)- or (*Z*)-configuration of the QCH=$CHCH_3$ substrate used (entries 2, 7, and 8) indicates that the cycloaddition of ArCNO to these systems cannot be a concerted reaction. This means that this is a two-step reaction and rotation around the QC–CCH_3 bond is possible in the intermediate. As a result, both stereoisomers are formed and not just one, as expected in concerted reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.176.

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