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Synthesis of 3,4-diarylisoxazoline *N*-oxides from nitrostilbenes and nitroacetates

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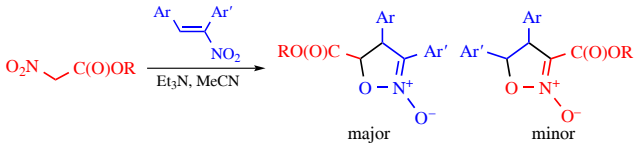
A base-catalyzed reaction of nitrostilbenes with alkyl nitroacetates proceeds regioselectively to afford 3,4-diarylisoxazoline *N*-oxides as sole or major products. In some cases small amounts of 4,5-diarylisoxazoline *N*-oxides were formed as side products.



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Previously a synthesis of 3,4-diarylisoxazoline *N*-oxides (precursors of 3,4-diarylisoxazoles – efficient tubuline inhibitors) from pyridinium ylides and nitrostilbenes was developed (Scheme 1, path A),[1,2] Similar reaction was described for isoquinolinium ylide as well.[3] Notably, modification of the reaction conditions may in principle afford 1,3-dipolar cycloaddition products (indolizines and pyrroloisoquinolines) rather than isoxazoline *N*-oxides[3,4] (see Scheme 1, path B).

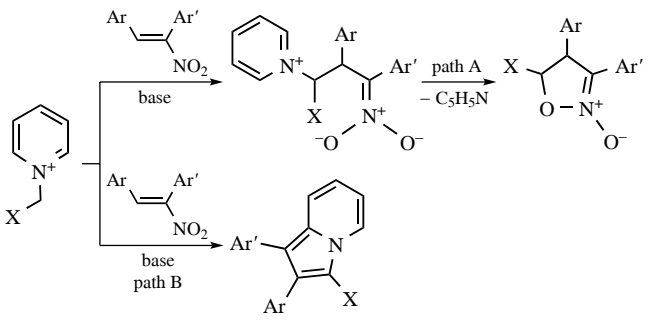
Obviously, the reaction proceeds *via* the initial Michael addition followed by elimination of the pyridine fragment due to nitronate-anion intramolecular attack.[5–8] The second step of this reaction is a special case of isoxazoline *N*-oxide synthesis by the cyclization of nitro compounds containing a leaving group (LG) γ to the nitro substituent[9] (Scheme 2). Our attention was drawn to a possibility of preparation of 3,4-diarylisoxazoline *N*-oxides by reacting nitrostilbenes with nitroacetates (X = COOR; in this case a nitro group rather than pyridine fragment should act as the leaving group LG).

Indeed, a reaction of nitrostilbene **1a** with ethyl nitroacetate **2a** afforded *trans*-5-ethoxycarbonyl-3,4-diarylisoxazoline *N*-oxide **3a** (Scheme 3) identical to that previously produced in the reaction of the same nitrostilbene with the corresponding pyridinium[4] and isoquinolinium[3] ylides. Similar isoxazoline *N*-oxide **3b** was formed from nitrostilbene **1a** and methyl nitroacetate **2b**. This is not a self-evident result: in theory, cyclization of the intermediate Michael adduct could yield regioisomeric 4,5-diarylisoxazoline *N*-oxide **3′** as well (*via* a nitronate **A′**, see Scheme 3). The cyclization outcome in such reactions was previously shown to be highly sensitive to the nature of the substituents in the adduct.[10–13]

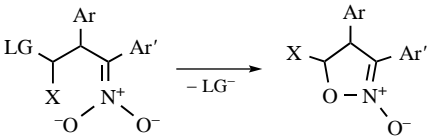
In fact, ^{1}H NMR of the crude **1a** + **2b** reaction mixture, besides the signals for **3b**, revealed also signals of a side product (~10%) assigned as **3′b** (this product was not isolated in pure form; similar impurity was observed in the **1a** + **2a** reaction as well). Two possible explanations for this selectivity of the reaction can be proposed. (1) Initially formed nitronate **A** undergoes cyclization to 3,4-diarylisoxazoline *N*-oxide **3a** *before* it isomerizes to the nitronate **A′**; (2) **A** → **A′** isomerization does take place, in the meantime more nucleophilic nitronate **A** undergoes cyclization more readily than nitronate **A′**.

A choice between these two options was made due to a control experiment (see Scheme 3) involving methyl α-nitrocinnamate **4**[14] and arylnitromethane **5**. In this case an initially formed nitronate should possess the structure ot type **A′**, so its cyclization should afford 4,5-diarylisoxazoline *N*-oxide **3′b**. However, this was not the case and again 3,4-diarylisoxazoline *N*-oxide **3b** was the major product while its regioisomer **3′b** was observed as a minor impurity (though in somewhat higher amount of ~14%). Thus, of the two abovementioned explanations the option (2) is preferable. ^{1}H NMR study of the **4** + **5** reaction mixture after column chromatography, besides characteristic signals of the major isomer **3b** (two doublets with J = 1.8 Hz at 4.77 and 4.99 ppm for the H^4 and H^5 protons), also revealed two doublets with J = 5.1 Hz at 4.60 (H^4) and 5.41 ppm (H^5) corresponding to the minor isomer **3′b** (these values perfectly fit the literature data[15] for *trans*-4,5-diaryl-3-(alkoxycarbonyl)isoxazoline *N*-oxides).

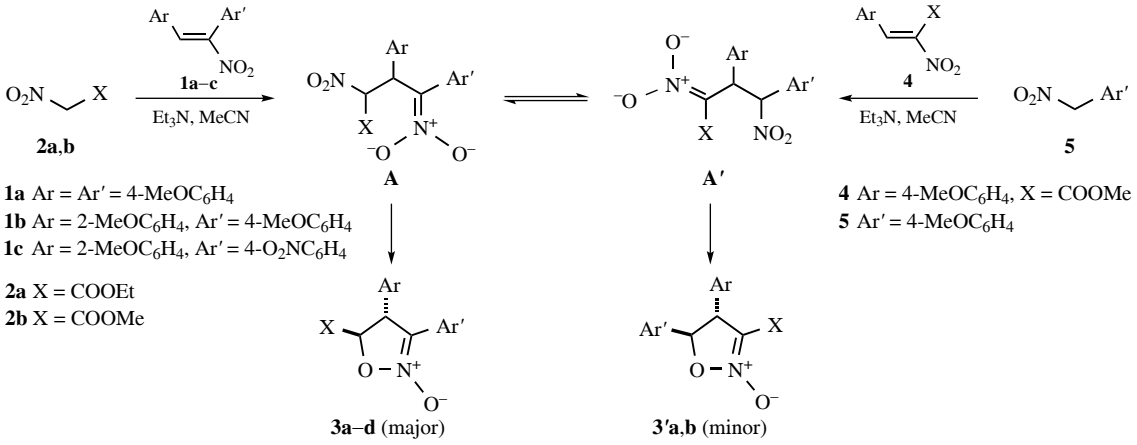
Also, good yields were observed for the reactions of the nitro ester **2b** with nitrostilbenes **1b**,**c** affording isoxazoline *N*-oxides **3c**,**d**, respectively (in the latter case the above impurity



Scheme 1



Scheme 2



Scheme 3

signals typical for **3′** were not observed even in the crude product). Thus, the reaction smoothly occurs both with donor and acceptor substituents in nitrostilbenes.

In general, the conditions and yields of isoxazoline *N*-oxides in the reactions of nitrostilbenes with nitro esters **2** are comparable with those in the previously described reactions of nitrostilbenes with pyridinium ylides.[1,2] Noteworthy, nitro esters **2a**,**b** are commercially available, while the corresponding pyridinium salts need to be prepared in advance; if necessary, compounds **2a**,**b** can be easily prepared as well.[16]

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Online Supplementary Materials

Supplementary data associated with this article (synthetic procedures, characterization data and copies of ^{13}C and ^{1}H NMR spectra for compounds **1c** and **3a**–**d**) can be found in the online version at doi: 10.71267/mencom.7584.

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