Tetrahedron 73 (2017) 6728–6735

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 3,4-diaryl-5-carboxy-4,5-dihydroisoxazole 2-oxides as valuable synthons for anticancer molecules

Natalia B. Chernysheva [a], Anna S. Maksimenko [a], Fedor A. Andreyanov [a], Victor P. Kislyi [a], Yuri A. Strelenko [a], Victor N. Khrustalev [b, c], Marina N. Semenova [d], Victor V. Semenov [a, *]

[a] N. D. Zelinsky Institute of Organic Chemistry, RAS, 47 Leninsky Prospect, 119991, Moscow, Russian Federation
[b] Faculty of Science, RUDN University, 6 Miklukho-Maklay Street, 117198, Moscow, Russian Federation
[c] A. N. Nesmeyanov Institute of Organoelement Compounds, RAS, 28 Vavilov Street, 119991, Moscow, Russian Federation
[d] N. K. Koltzov Institute of Developmental Biology, RAS, 26 Vavilov Street, 119334, Moscow, Russian Federation

ARTICLE INFO

Article history:
Received 25 May 2017
Received in revised form
24 September 2017
Accepted 9 October 2017
Available online 13 October 2017

Keywords:
3,4-Diarylisoxazoles
3,4-Diarylisoxazoline oxides
Carbonylmethylpyridinium
Anticancer synthons

ABSTRACT

The convenient regioselective scalable synthesis of 3,4-diaryl-5-carboxy-4,5-dihydroisoxazole 2-oxides was developed based on a condensation of simple starting materials (arylbenzaldehydes, arylnitromethanes, and ethoxycarbonylmethylpyridinium bromide) under mild conditions. The obtained synthons can be applied for the synthesis of 3,4-diarylisoxazole derivatives capable of suppressing malignant growth.

1. Introduction

Isoxazoles and isoxazolines exhibit a broad range of biological effects, including antiviral,[1] anti-inflammatory,[2,3] and anticancer activities.[4–8]

o-Diarylazoles can be considered as *cis*-restricted analogues of combretastatin A-4 (**CA4**, Fig. 1), a highly potent natural cytostatic originally isolated from the bark of African willow tree *Combretum caffrum*.[9] To avoid *cis-trans* isomerization that causes activity decrease, diverse N-containing rings have been introduced to replace the ethene linker, resulting in compounds with antiproliferative antitubulin effects comparable with those of **CA4**.[10] Among them, 5-unsubstituted diaryl-*o*-isoxazole **A** (Fig. 1) effectively inhibited both cancer cell growth and *in vitro* tubulin polymerization.[5,7] Polyoxygenated 3,4-diarylisoxazoles with 5-carboxamide groups (e.g., **B**, Fig. 1) were reported to inhibit Hsp90, a chaperone protein that assists folding of various proteins including those implicated in malignancy.[8]

Several synthetic strategies for diarylisoxazolines and diarylisoxazoles have been reported. Due to the challenges in regioselective functionalization, currently available synthetic routes for 3,4-diarylisoxazoline N-oxides as well as for 3,4-diarylisoxazoles are rather scarce. The known methods require expensive and commercially inaccessible reagents and catalysts, give low yields, and are practically not scalable.[11] Considering the literature evidence, the present study was aimed to the development of an efficient, inexpensive, and scalable procedure for regioselective synthesis of 3,4-diaryl-isoxazoline N-oxides 5-carboxylates (**C**, Fig. 1) from available materials under mild conditions. The ability of isoxazolines to rearrange readily to the respective isoxazoles[12–14] allows for their further use in the preparation of molecules with potential anticancer activity.

2. Results and discussion

Recently it was shown that arylmethylidene nitro acetic esters **1** reacted with ethoxycarbonyl methylpyridinium bromide **2** in the presence of Et_3N to afford 4-aryl-isoxazole-3,5-dicarboxylates **3** in high yields (Scheme 1).[15]

A reproduction of this reaction using 3-(3,4,5-trimethoxyphenyl)-2-nitropropene derivative of **1** showed a formation of intermediate isoxazoline oxide **4a** (Scheme 2). Notably,

* Corresponding author.
E-mail address: vs@zelinsky.ru (V.V. Semenov).

https://doi.org/10.1016/j.tet.2017.10.016
0040-4020/

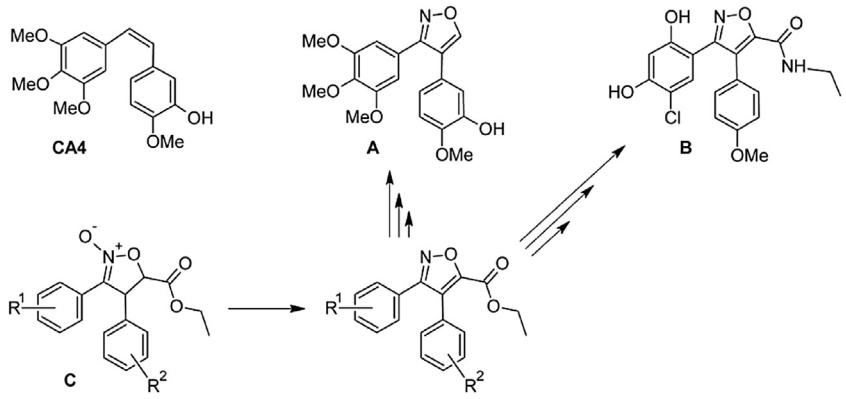
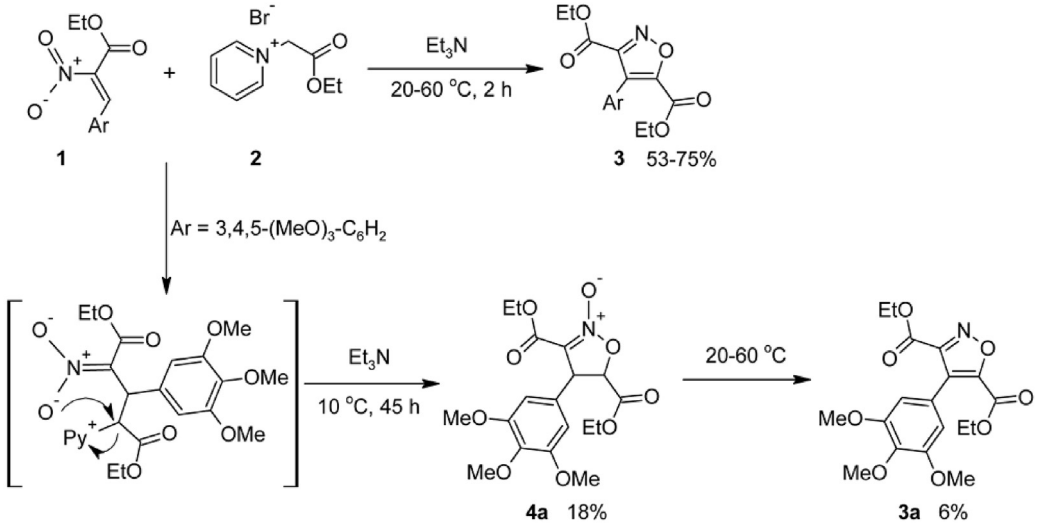


Fig. 1. Chemical route to anticancer combretastatin A-4 (**CA4**) analogs with 3,4-diarylisoxazole fragments. **A** Inhibitor of tubulin polymerization. **B** Hsp90 inhibitor.



Scheme 1. Synthesis of diethyl 4-(aryl)isoxazole-3,5-dicarboxylates **3**.

isoxazole **3a** was the only product at the reaction temperature of 20–60 °C, whereas at 10 °C both **3a** and **4a** were found in the reaction mixture. Isoxazoline N-oxide **4a** was separated, and its structure was confirmed by ^{1}H-NMR-, MS-, and X-ray analyses (Fig. 2). This result led to a proposal that 3,4-diaryl-5-ethoxycarbonyl-4,5-dihydroisoxazole 2-oxides **8** could be obtained selectively by the reaction of diarylnitrostilbenes **7** with pyridinium salt **2.** Corresponding starting nitrostilbenes **7a**–**j** were easily synthesized by condensation of phenylnitromethanes **5** with aldehydes **6**.[16,17] Isoxazolines **8a**–**j** were formed as single products under the mild conditions at different temperatures and reaction times: 20 °C, 100–200 h, or 60 °C, 4–5 h. Importantly, the starting pyridinium bromide **2** and nitrostilbenes **7** can be readily obtained in an amount of 10–20 g, affording isoxazolines **8** in multi-gram scale. The structures of **8** were proved by ^{1}H-, ^{13}C-NMR-, and MS-analyses.

The rearrangement of 3,4-diarylisoxazoline oxides to isoxazoles is well documented in the literature.[12–14] As an example, we selected a procedure in water solution of 2% NaOH at room temperature[12] for the rearrangement of **8a** (Scheme 3).

4-(4-Chlorophenyl)-5-(ethoxycarbonyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole 2-oxide (**8a**) was quantitatively hydrolysed to the corresponding 3,4-diaryl-4,5-dihydroisoxazole 2-oxide (**9a**) in acidic medium. Then **9a** was rearranged in alkaline medium with simultaneous decarboxylation directly to unsubstituted isoxazole **10a** at 20 °C (200 h) or 60 °C (6 h). **10a** was easily separated in alkaline media in good yield over two steps (67%).

Isoxazoline N-oxide **4a** was characterized by single-crystal X-ray diffraction study. The structure is shown in Fig. 2 along with the atomic numbering schemes. The geometrical parameters for **4a** are available in the Supplementary Data. The central isoxazoline ring adopted an *envelope* conformation, with the C5 carbon atom deviating from the mean plane passed through the other atoms of the ring by 0.222(2) Å. The 4-phenyl and 5-ethoxy carbonyl substituents were located in *gauche (trans)* configuration (−127.86(10)°). Thus, the crystal of **4a** consisted of enantiomeric pairs with the (4***RS***,5***RS***)-relative configuration of the asymmetric centers. The 3-carboxylate fragment lay within the basal plane of the isoxazoline ring (the dihedral angle is 4.16(7)°). The ethoxy group of the 3-carboxylate substituent had *gauche* conformation relative to the carbonyl group (the C6–O4–C7–C8 torsion angle is −78.47(14)°), while the ethoxy group of the 5-carboxylate substituent was *trans* arranged to the carbonyl group (the C18–O9–C19–C20 torsion angle is 174.99(10)°). The 3- and 5-methoxy groups in 4-(3,4,5-trimethoxyphenyl) substituent were coplanar to the plane of the benzene ring (the C10–C11–O5–C15 and C14–C13–O7–C17 torsion angles are −3.31(17) and 0.23(17)°, respectively), whereas the 4-methoxy group in 4-(3,4,5-