

Novel donor-acceptor systems bearing an isoxazol-5-one core

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Dedicated to Prof. Zbigniew Czarnocki on the occasion of his 66th anniversary

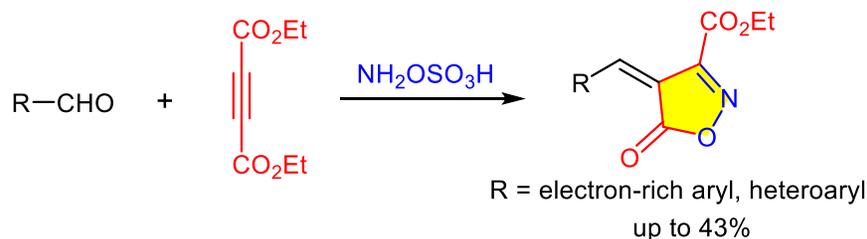
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Abstract

The synthesis of previously unknown esters of 4-(arylmethylene)-5-oxo-4,5-dihydroisoxazole-3-carboxylic acids from aromatic aldehydes, hydroxylamine-*O*-sulfonic acid and diethyl acetylenedicarboxylate *via* a two-step one-pot reaction is presented. The mechanism of the reaction is discussed, and optimization is carried out. The scope and limitations of this multicomponent reaction are described.



Keywords: isoxazol-5-ones, push-pull chromophores, multicomponent reactions, UV/vis absorption, tandem reactions

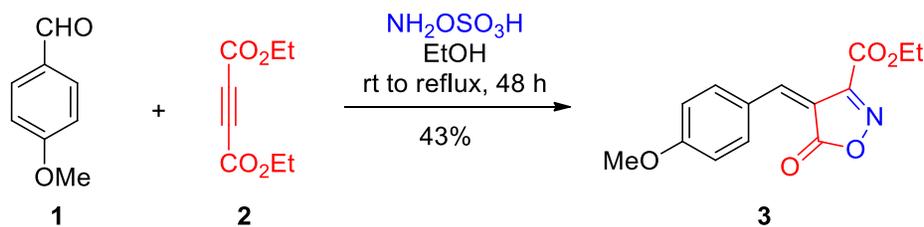
Introduction

The isoxazol-5(4*H*)-one moiety¹ is an important structural motif, present in the number of biologically active compounds,²⁻⁵ natural products^{6,7} and advanced materials.⁸⁻¹⁰ By 1897, Schiff and Betti had already discovered that 4-arylmethylene-isoxazol-5-ones could be prepared by treating acetoacetic ester oxime with various aromatic aldehydes.¹¹ Later, Minnuni and co-workers,¹² as well as Donleavy *et al.*,¹³ obtained the same products from oximes and ethyl acetoacetate. Unsubstituted isoxazolin-5-one was synthesized for the first time by De Sarlo and co-workers from hydroxylamine and ethyl propiolate.¹⁴

Nowadays, molecules bearing the isoxazol-5-one core can be prepared *via* a number of synthetic strategies, often taking the advantage of one-pot protocols. Namely, the multicomponent reactions between ethyl acetoacetate, hydroxylamine and aromatic aldehydes afford the corresponding isoxazol-5-ones in the presence of acid or base, in high yields.¹⁵⁻¹⁷ It is noteworthy that methods leading to products bearing an ester group at position 3 are essentially unknown even though the role of this synthetic handle cannot be underestimated. Thus, there is still a strong need for a new synthetic tool in the preparation of isoxazol-5-ones, allowing for their convenient post-functionalization.

Results and Discussion

During a project aiming at the synthesis of pentasubstituted pyridines, we unexpectedly discovered a new multicomponent reaction leading to compounds bearing the isoxazol-5-one skeleton. In 2011, Sun *et al.* developed the synthesis of tetraesters of *N*-substituted-1,4-dihydropyridine-2,3,5,6-tetracarboxylic acids *via* condensation of diethyl acetylenedicarboxylate with aromatic aldehydes and aryl hydroxylamines.¹⁸ Targeting the *N*-unsubstituted analogue, we decided to modify the original procedure by using a hydroxylamine derivative bearing a good leaving group, that after elimination can directly give an aromatized product. Our first choice was hydroxylamine-*O*-sulfonic acid due to its accessibility. Low substrate conversion was observed when 4-methoxybenzaldehyde (**1**) was treated at room temperature with hydroxylamine-*O*-sulfonic acid and diethyl acetylenedicarboxylate (**2**) in EtOH (Scheme 1).



Scheme 1. Synthesis of isoxazol-5-one **3**.

Nevertheless, when the reaction was heated to reflux, the colorless solution changed to deep orange, and after cooling, fine yellow-orange needles of an analytically pure product were formed (Scheme 1). NMR and mass spectrometry analyses excluded the formation of the expected product, suggesting at the same time the formation of a heterocyclic 5-membered ring. To get further insights into the structure of this puzzling product, crystals suitable for X-ray crystallography were obtained by vapor diffusion of hexane into a DCM solution of the compound. X-Ray crystallography supported the presence of the 5-ring and the structure

assigned to compound **3**. The molecule is almost planar with the mean angle between both rings being 177.3° (Figure 1).

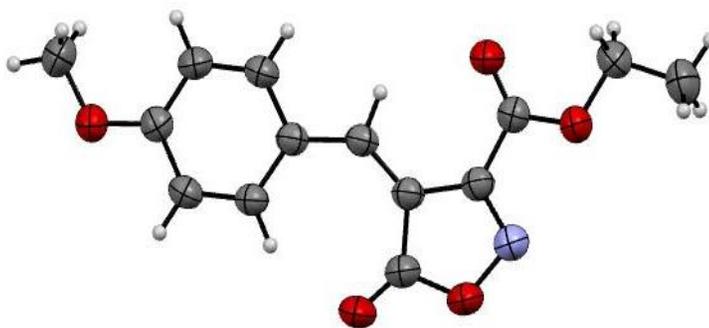


Figure 1. ORTEP X-ray structure of **3**.

A brief study of the literature revealed that such isoxazol-5-ones bearing an ester group at position 3 were described only once before, in a Japanese patent from the 1990s.¹⁹ As the patent described photochemically active materials, we became interested in whether the obtained product exhibits any interesting photophysical properties. Compound **3** has a very intense yellow-orange color, which can be explained by its push-pull structure which resembles products of condensation of 4-methoxybenzaldehyde with barbituric acid.²⁰ The chromophore comprises both the benzene ring and the five-membered isoxazolone moiety and slightly resembles that of green fluorescent proteins.²¹

Table 1. Optimization of synthesis of isoxazol-5-one **3** from hydroxylamine-*O*-sulfonic acid

Entry	Solvent	1 st step ^a (h)	2 nd step ^b (h)	Yield (%)
1	EtOH	48	1.5	43
2	EtOH	48	1.5	1.5 ^c
3	EtOH	0	6.5	29
4	EtOH	18	6	43
5	EtOH	0	26	34
6	THF	0	6.5	26
7	MeCN	0	6.5	24
8	AcOH	0	4.5	traces
9	EtOH	0	4.5	traces ^d
10	EtOH	0	4.5	traces ^e

^a performed at the room temperature; ^b performed at reflux;

^c reaction with hydroxylamine hydrochloride; ^d reaction catalyzed by Fe(OTf)₃ (3 mol%); ^e reaction catalyzed by Cu(OTf)₂ (3 mol %).

Since the yield of the product **3** was moderate, we began the optimization process, testing also another hydroxylamine source, hydroxylamine hydrochloride (Table 1). Surprisingly, the yield of the product **3** was nearly 30 times lower than in the case of hydroxylamine-*O*-sulfonic acid (Table 1, entry 2), for reasons we do not fully understand. We thought that in this case the product could remain in solution as the corresponding

hydrochloride. However, treatment of the reaction mixture with an excess of triethylamine brought no improvement. We also tried to shorten the reaction time, however, stirring at room temperature for at least 16 h was required to reach a satisfactory yield of product **3** (Table 1, entries 3-5). The exploration of other solvents was limited due to the poor solubility of hydroxylamine-*O*-sulfonic acid in non-polar media. Solvents other than ethanol did not afford any particular benefit. On the contrary, the obtained product **3** did not precipitate from the reaction mixture, complicating the product purification (Table 1, entries 6-8). The addition of catalytic amounts of transition metal salts (Table 1, entries 9-10) also did not improve the yields of **3**.

Table 2. Scope of the investigated reaction

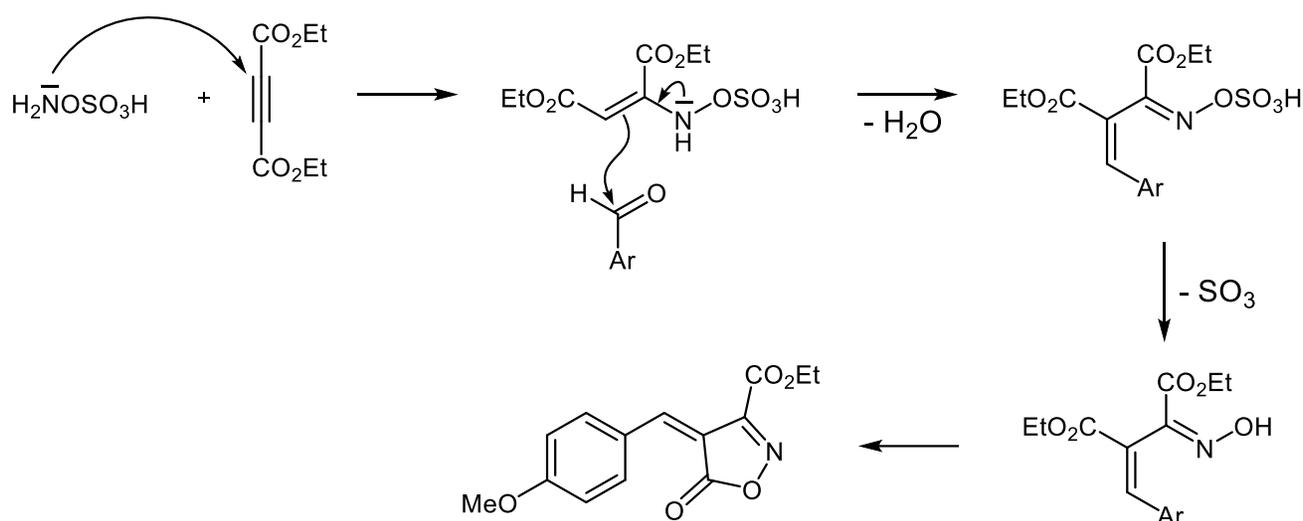
Aldehyde	R	Isoxazolone	Yield (%)	λ_{\max} (nm)	ϵ ($M^{-1} \text{ cm}^{-1}$)
1		3	43	400	25800
4		6	19	491	66000
5		7	14	435	41000

Both 4-dimethylaminobenzaldehyde (**4**) and pyrrole-2-carbaldehyde (**5**) led to the expected products **6** and **7** in low yields, but 2-hydroxybenzaldehyde failed to give the desired heterocycle. Subsequently, we examined electron-poor aldehydes such as pyridine-2-carboxaldehyde, 4-formylbenzotrile and pentafluorobenzaldehyde. Surprisingly, none of these reagents allowed to obtain the expected isoxazolones, which forced us to a more detailed analysis of the composition of the reaction mixtures. Therefore, after crystallization of compound **3**, we submitted the filtrate to chromatographic purification to identify the structure and the distribution of the side products. It is noteworthy that esters of acetylenedicarboxylic acid, owing to their high reactivity, are known to undergo numerous multicomponent reactions. For example, the reaction between diethyl acetylenedicarboxylate and aromatic or aliphatic amines leads to, depending on the conditions, enaminoesters, aminomaleimides,²² 2-pyridones,²³ substituted pyrroles,²⁴ etc. In the presence of amine and aromatic aldehyde, diethyl acetylenedicarboxylate forms products such as 3-amino 1,5-dihydro-2*H*-pyrrol-2-ones and 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones.²⁵ In the above mentioned reaction leading to compound **3**, besides non-reacted 4-methoxybenzaldehyde (20%), we isolated 4-methoxybenzotrile (10% yield) as a side product resulting from oxime formation followed by elimination of sulfuric acid. Taking into account the complexity of the discussed process, it is therefore easier to understand the lack of expected product in reactions with electron-poor aldehydes, since their higher reactivity versus nucleophiles might easily switch the reaction pathway. We also attempted to synthesize the desired heterocycles in a step-by-step manner but the experiments with an aqueous solution of formaldehyde failed to give ethyl 5-oxo-4,5-dihydroisoxazole-3-carboxylate, which we planned to transform into arylmethylene-derivative by condensation with aldehyde in

presence of base. Overall, despite the limited applicability, the cheap starting materials and simple reaction work-up make our method an attractive way of the preparation of arylmethylenisoxazoles.

These new dyes belong to the class of dipolar chromophores (push-pull chromophores) with an aromatic ring acting as donor and the isoxazolone scaffold as electron-acceptor. The presence of the electron-withdrawing CO₂Et group increases the electron-accepting properties of the heterocycle, resulting in a bathochromic shift of absorption maxima of dyes **3**, **6** and **7** compared to analogous isoxazolones lacking this group.¹⁹ The absorption maxima of isoxazolones **6** and **7** is bathochromically shifted in comparison to that of compound **3**, which can be explained by more pronounced electron-donating character of the aryl substituents.²⁶⁻²⁹ For all tested compounds **3**, **6** and **7** no fluorescence was detected, which is probably caused by thermal relaxation via the rotation at a methine bridge.

We believe that from a mechanistic point of view this reaction proceeds via Michael addition of hydroxylamine to diethyl acetylenedicarboxylate, with formation of enamine, which subsequently reacts with aromatic aldehyde. The resulting oxime-*O*-sulfonic acids tend to eliminate sulfur trioxide above room temperature,³⁰ and then the transesterification reaction leads to the final product.



Scheme 2. Plausible mechanism of formation of esters of 4-(arylmethylene)-5-oxo-4,5-dihydroisoxazole-3-carboxylic acids.

Conclusions

We have developed a new method for the preparation of isoxazole-5-ones in one-pot two-step protocol, from electron-rich aromatic aldehydes, diethyl acetylenedicarboxylate and hydroxylamine-*O*-sulfonic acid. The reaction is straightforward, giving rise to a new type of dye strongly absorbing green light and possessing ester group as a convenient synthetic handle.

Experimental Section

General. ^1H and ^{13}C NMR were recorded on a Varian VNMRS 500 (^1H : 500 MHz, ^{13}C : 126 MHz) The chemical shifts (δ) and coupling constants (J) are expressed in ppm and Hertz, respectively. UV-vis spectra were recorded on a Perkin-Elmer Lambda 25 spectrophotometer.

(Z)-Ethyl 4-(4-methoxybenzylidene)-5-oxo-4,5-dihydroisoxazole-3-carboxylate (3) (Typical procedure). To a stirred mixture of hydroxylamine-*O*-sulfonic acid (0.46 g, 4.11 mmol) in ethanol (10 mL), under nitrogen, diethyl acetylenedicarboxylate (0.7 mL, 4.11 mmol) was added. After 10 minutes of vigorous stirring to the solution was added a mixture of 4-methoxybenzaldehyde (0.5 mL, 4.11 mmol) in ethanol (4 mL). The reaction mixture was stirred at rt overnight and then heated to reflux for 4 h. After 24 h in rt, the precipitate was filtered, washed with ice-cold ethanol and dried to give the analytically pure *title compound 3* (0.41 g, 43%) as yellow-orange needles. Mp 112-115 °C. IR (KBr): ν_{max} 1715, 1605, 1436, 1257, 1207, 1149, 901, 752 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} 8.51 (d, J 9.0 Hz, 2H), 8.48 (s, 1H), 7.19 (d, J 9.0 Hz, 2H), 4.42 (q, J 7.1 Hz, 2H), 3.93 (s, 3H), 1.36 (t, J 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $\text{DMSO-}d_6$) δ_{C} 168.2, 165.8, 159.3, 155.4, 155.0, 138.4, 126.1, 115.5, 111.6, 62.8, 56.5, 14.3. Anal. calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_5$: C 61.09, H 4.76, N 5.09. Found: C 60.95, H 4.59, N 5.13. HRMS [EI] anal. calcd for 275.0794. Found 275.0797. Crystals of compound **3** were grown by vapor diffusion of hexane into a DCM solution. CCDC 904023 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(Z)-Ethyl 4-[4-(dimethylamino)benzylidene]-5-oxo-4,5-dihydroisoxazole-3-carboxylate (6). Similarly, the use of 4-(dimethylamino)benzaldehyde (**4**, 0.61 g, 4.11 mol) gave the *title compound 6* as orange-red needles (0.22 g, 19%). Mp 136-139 °C (decomp.). IR (KBr): ν_{max} 1739, 1720, 1566, 1541, 1522, 1506, 1380, 1185, 1177, 819 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} 8.44 (br s, 2H), 8.23 (s, 1H), 6.91 (d, J 9.4 Hz, 2H), 4.39 (q, J 7.1 Hz, 2H), 3.20 (s, 6H), 1.34 (t, J 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $\text{DMSO-}d_6$) δ_{C} 169.9, 160.1, 155.8, 155.1, 153.3, 139.3, 121.7, 112.7, 104.1, 62.4, 40.3, 14.3. HRMS [EI] Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$: 288.1110. Found 288.1109.

(Z)-Ethyl 4-[(1H-pyrrol-2-yl)methylene]-5-oxo-4,5-dihydroisoxazole-3-carboxylate (7). Similarly, the use of pyrrole-2-carboxaldehyde (**5**, 0.39 g, 4.11 mol) gave the *title compound 7* as orange needles (0.13 g, 14%). Mp 161-164 °C. IR (KBr): ν_{max} 1743, 1720, 1575, 1549, 1521, 1282, 1173, 1087, 1022 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} 12.79 (s, 1H), 8.42-7.50 (m, 3H), 6.68-6.66 (m, 1H), 4.40 (q, J 7.1 Hz, 2H), 1.35 (t, J 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $\text{DMSO-}d_6$) δ_{C} 172.4, 159.8, 154.7, 138.7, 137.6, 132.3, 131.3, 116.2, 102.3, 62.6, 14.3. Anal. calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_4$: C 56.41, H 4.30, N 11.96. Found: C 56.63, H 4.28, N 11.74. HRMS [EI] anal. calcd for: 234.0640, Found 234.0644.

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