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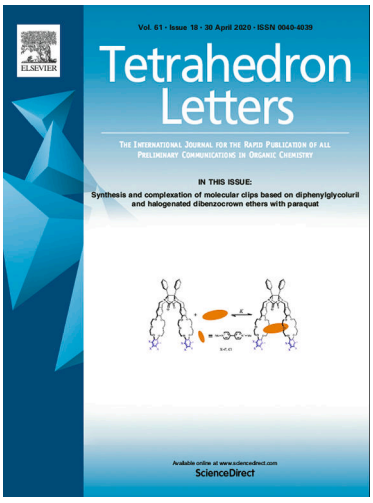

Expedient synthesis of a new class of organic building blocks: *N*-allenylpyrrole-2-carbaldehydes

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PII: S0040-4039(20)31177-1
DOI: https://doi.org/10.1016/j.tetlet.2020.152666
Reference: TETL 152666

To appear in: *Tetrahedron Letters*

Received Date: 25 August 2020
Revised Date: 5 November 2020
Accepted Date: 12 November 2020

Please cite this article as: Martynovskaya, S.V., Shcherbakova, V.S., Ushakov, I.A., Borodina, T.N., Ivanov, A.V., Expedient synthesis of a new class of organic building blocks: *N*-allenylpyrrole-2-carbaldehydes, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152666

Graphical Abstract

Expedient synthesis of a new class of organic building blocks: *N*-allenylpyrrole-2-carbaldehydes

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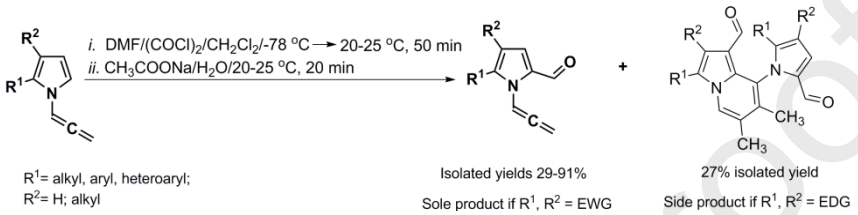

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Expedient synthesis of a new class of organic building blocks: *N*-allenylpyrrole-2-carbaldehydes

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
N-Allenylpyrroles
N-Allenylpyrrol-2-carbaldehydes
Formylation
Vilsmeier–Haack reaction

ABSTRACT

Hitherto unknown *N*-allenylpyrrole-2-carbaldehydes were synthesized *via* the formylation of readily available *N*-allenylpyrroles under the action of the mild formylating complex DMF/$(COCl)_2$. The reaction selectively proceeds in the case of pyrroles with electron-withdrawing substituents to afford the products in good to excellent yields. For pyrroles bearing electron-donating substituents, the reaction proceeds in a cascade manner to deliver unusual complex products, the structure of which was confirmed by X-ray diffraction analysis. The target *N*-allenylpyrrole-2-carbaldehydes represent promising synthons for organic synthesis.

1. Introduction

Functionalized pyrroles represent an important class of versatile building blocks for the directed synthesis of a wide variety of compounds and materials with tailor-made properties. For example, they have found increased applications in the design of pharmaceuticals and congeners of natural compounds[1]. The pyrrole core is a ubiquitous structural unit of new antibiotics, pheromones, toxins, cell fission inhibitors, and immunomodulating agents[2,3]. Pyrrolecarbaldehydes are intermediates and starting materials in organic synthesis, for example, to produce valuable compounds such as carbolines, cyanopyrroles, divinylpyrroles, and various oligopyrrolic systems[4,5]. They are also employed in biomedical chemistry[6] as models for the investigation of multiple sclerosis and expansion of the genetic alphabet[7], ligands for metallocomplexes[8], and conjugated polymers[9,10].

The allene fragment, on the other hand, is a popular structural motif in organic chemistry. Allenes possess unique features and exhibit high reactivity that can significantly improve the biological and pharmacological properties of allene-containing compounds[11]. For example, the allenic prostaglandin analogue enprostil, was reported to be a highly potent inhibitor of gastric acid secretion[12,13]. In addition, enprostil exerts anti-inflammatory activity[14].

Allene moieties have been systematically introduced into pharmacologically active classes of compounds (e.g. steroids, prostaglandins, amino acids, nucleosides). The functionalized allenes thus obtained often exhibit impressive activities as enzyme inhibitors, cytotoxic, or antiviral agents[15,16,17].

Therefore, the combination of highly reactive aldehyde and allenyl moieties on the biologically important pyrrole core may open up new horizons in this area of research.

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2. Results and Discussion

The most common method for the introduction of a formyl group into the pyrrole ring is the classical Vilsmeier-Haack reaction, which was discovered in the first half of the 20th century[18] and has been employed for the synthesis of a wide variety of pyrrolecarbaldehydes. However, we have previously found that when electron-rich groups (namely, the *N*-vinyl moiety) are incorporated into the initial pyrrole, the classical Vilsmeier-Haack reaction loses its selectivity and proceeds with the formation of various by-products that significantly reduces the applicability of this approach[19]. More intriguingly, the *N*-allenyl group (see above) seems to be even less suitable for Vilsmeier-Haack formylation, since it contains not only the sp^2 carbon atom, but also the sp carbon atom, thus being susceptible to attack of an electrophile.

Furthermore, the allene fragment is more sensitive to acids than the vinyl group, and it is common knowledge that the allene group can undergo various prototropic rearrangements under the influence of acid [20]. We believe that for this reason *N*-allenylpyrroles containing an aldehyde moiety, remain under explored.

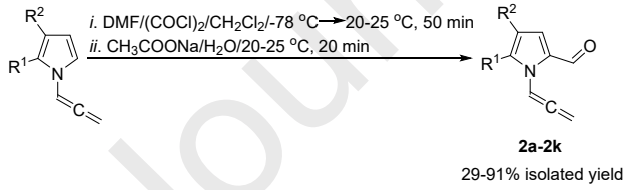
the minor products of reactions. It was reported[21] that indole-2-carbaldehydes functionalized with an *N*-propargyl moiety underwent acetylene-allene isomerization under the action of sodium metal. The isomerization of an unsubstituted propargyl aldehyde into the *N*-allenylpyrrol-2-carbaldehyde in the presence of sodium hydride was also described[22]. The use of sodium metal and sodium hydride makes the method impracticable and environmentally dangerous.

It was previously shown that propargyl chloride was involved in the *N*-alkylation of pyrroles with simultaneous isomerization to the allene in the presence of a superbase medium[23]. In this case, a wide range of *α,β*-substituted pyrroles available *via* the Trofimov reaction (synthesis of pyrroles from ketoximes and acetylene)[24] were employed as the starting compounds. In recent years, the expediency of the Trofimov pyrrole synthesis has been significantly improved due to the replacement of explosive and flammable acetylene with its safer precursor, dichloroethane[25,26,27].

Earlier[28], we developed a modified version of the Vilsmeier-Haack reaction, which allows *N*-vinylpyrroles to be formylated using the milder formylating complex DMF/$(COCl)_2$, with the acid-labile vinyl group being preserved. In the present work, we applied the same approach for the introduction of an aldehyde group into *N*-allenylpyrroles. Consequently, the formyl group was introduced selectively into the 2-position of the pyrrole ring of *N*-allenylpyrrole while preserving the allene function. Finally, substituted *N*-allenylpyrrol-2-carbaldehydes have been synthesized for the first time in 29-91% yield (Scheme 1, Table 1).

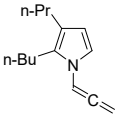
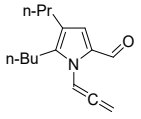
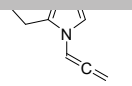
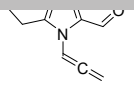
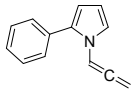
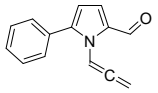
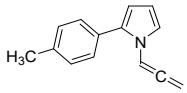
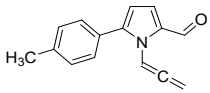
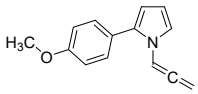
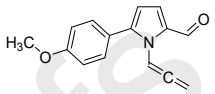
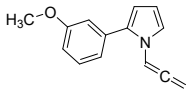
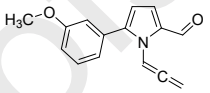
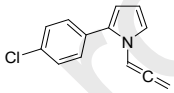
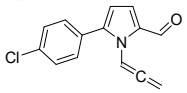
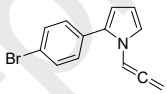
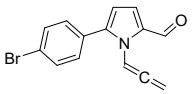
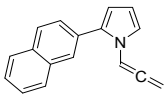
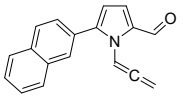
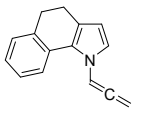
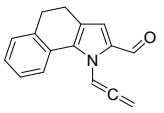
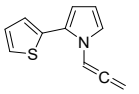
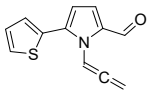
Oxalyl chloride was added dropwise to *N,N*-dimethylformamide in dichloromethane, then a solution of *N*-allenylpyrrole **1** in dichloromethane was added dropwise. After stirring at room temperature, the reaction mixture was treated with an aqueous solution of sodium acetate. Extraction with dichloromethane gave crude product **2**, which was purified by column chromatography.

It should be noted that under these conditions, which were previously successfully applied to the formylation of *N*-vinylpyrroles, the reaction times were shorter (15 min instead of 30 min). It was shown that a prolonged process led to resinification of the reaction mixture, and this, in turn, hindered purification of the crude product and decreased the yields of *N*-allenylpyrrole-2-carbaldehydes **2**.



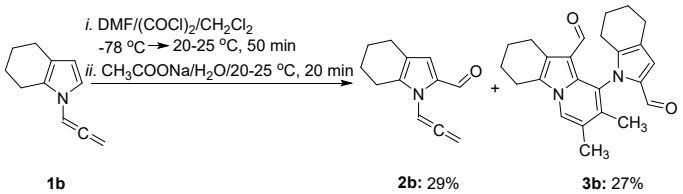
Scheme 1. Synthesis *N*-allenylpyrroles-2-carbaldehydes **2a-k**.

Table 1. Formylation of *N*-allenylpyrroles.

Entry	*N*-Allenylpyrroles **1**	Product **2**	Isolated yield (%)
a			48
b			29
c			85
d			84
e			88
f			91
g			91
h			84
i			73
j			58
k			87

Reagents and conditions: $(COCl)_2$ (11 mmol), DMF (11 mmol), CH_2Cl_2 (13 mL), **1** (10 mmol), CH_3COONa (50 mmol).

As can be seen from Table 1, the selectivity of *N*-allenylpyrrole formylation dramatically depends on the nature of the substituent on the pyrrole ring. *N*-Allenylpyrroles **1** bearing aromatic and heteroaromatic substituents on the pyrrole ring (**2c-2i**, **2k**) exclusively afforded the target *N*-allenylpyrrole-2-carbaldehydes in good to excellent yields (73–91%). In the case of donor substituents (**2a**, **2b**), the yields were only moderate (29–48%), and product **3** was also observed in the reaction mixture, the structure of which was unambiguously proved by X-ray diffraction analysis using the formylation of **1b** as a representative example (Scheme 2, Fig. 1).



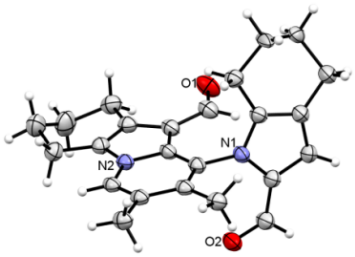
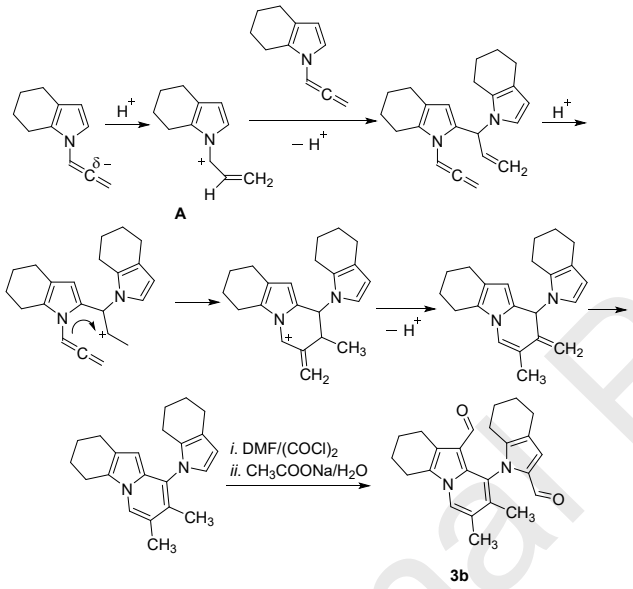


Figure 1. X-ray structure of **3b**.

The formation of product **3b** can be rationalized as a cascade process catalyzed by acid (product of the partial hydrolysis of chloroanhydride with traces of water, Scheme 3).



Scheme 3. Possible mechanism for the formation of **3b**.

The cascade assembly is completed by the formation of the pyrrole rings in the DMF/$(COCl)_2$ system, one of which is assembled at position 3 to give product **3**.

In the case of pyrroles with electron-withdrawing substituents in the α'- and β'-positions of the ring, the decreased electron density on the allene fragment makes this reaction impossible. It is assumed that the reduced yield of compound **2a** is due to the same process. Due to the presence of bulky aliphatic substituents, the expected product **3a** was not isolated by column chromatography. We also believe that the decreased yield of compound **2j** bearing a donating substituent on the pyrrole ring (58%) can be due to a minor side process affording product **3g**, which was not isolated.

3. Conclusion

Despite the high sensitivity of *N*-allenylpyrroles to acidic reagents, they can be selectively formylated by utilizing the modified formylating complex DMF/$(COCl)_2$, thus opening the route to a new class of substituted *N*-allenylpyrrole-2-carbaldehydes, which are promising building blocks and reagents.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The reported study was funded by RFBR, project number 19-33-90051. Experimental work was carried out using the equipment of the Baikal Analytical Centre for Collective Use of the Siberian Branch of the Russian Academy of Sciences. The authors would like to thank Dr.Sc. Rozentsveig I.B. and the employees of the laboratory of unsaturated heteroatomic compounds of Irkutsk Institute of Organic Chemistry SB RAS for the helpful suggestions and fruitful discussion.

Supplementary Material

Supplementary data to this article can be found online at

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Highlights

- Hitherto unknown *N*-allenylpyrrole-2-carbaldehydes have been synthesized
- Mild formylating complex DMF/$(COCl)_2$.
- Promising synthons for fine organic synthesis

Expedient synthesis of a new class of organic building blocks: *N*-allenylpyrrole-2-carbaldehydes

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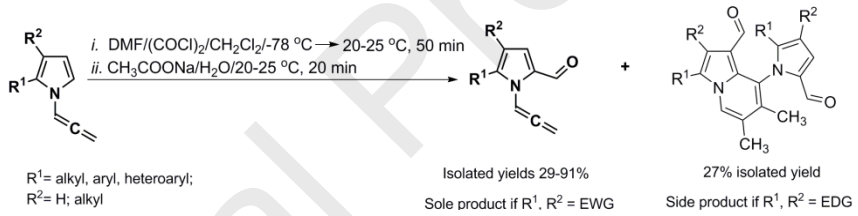

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Graphical Abstract