



Ethynylation of 2-(furan-2-yl)- and 2-(thiophen-2-yl)pyrroles with acylbromoacetylenes in the Al₂O₃ medium: relative reactivity of heterocycles

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ABSTRACT

2-(Furan-2-yl)- and 2-(thiophen-2-yl)pyrroles are readily ethynylated with acylbromoacetylenes in the solid Al₂O₃ medium (no solvent, room temperature, 1 h) to afford 5-(furan-2-yl)- and 5-(thiophen-2-yl)-2-acylethynylpyrroles in 39–74% yields. In the case of 2-(furan-2-yl)pyrroles, an alternative ethynylation of the furan ring takes place, the ratio of the furan and pyrrole ring ethynylation products being 1:5–7. No ethynylation of the thiophene ring as well as ethynylation of both heterocycles in a one molecule has been detected. Thus the reactivity of the heterocycles towards the ethynylation system (acylbromoacetylenes/Al₂O₃) falls in the order: pyrrole>furan>thiophene.

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1. Introduction

Functionalized pyrroles, furans and thiophenes represent a recurring structural motif found in bioactive natural products and pharmaceuticals.¹ Among them, of a particular interest are the functionalized heterocycles bearing acetylenic moieties.² Commonly, ethynylation of heterocycles is implemented via Sonogashira reaction using the corresponding halides and terminal alkynes.³ In 2004, an alternative direct palladium-, copper, and base-free ethynylation of the pyrrole and indole rings with haloacetylenes in the Al₂O₃ medium (room temperature, no solvent) was discovered.⁴ Later, haloacetylenes have been employed for ethynylation of diverse heterocycles using palladium,⁵ nickel,⁶ copper⁷ or gold⁸ catalyst. Simultaneously, the Al₂O₃-promoted ethynylation of pyrroles and indoles keep steadily developing. A number of ethynylpyrroles with alkyl, cycloalkyl and aryl substituents have been successfully synthesized according to this protocol. It has been shown that some other solid metal oxides (MgO, CaO, ZnO, BaO)⁹ and salts (K₂CO₃)¹⁰ can be utilized instead of Al₂O₃ with certain advantages. This methodology has been thoroughly documented in two recent reviews.¹¹

Despite the broad scope of pyrroles and indoles tolerated as substrate in ethynylation reactions with haloacetylenes in the media of solid metal oxides and salts, pyrroles with hetaryl (furyl- and thienyl) substituents remain out of the framework of this reaction. The study of this reaction could clarify the following two essential issues: (i) whether furan and thiophene are capable of this ethynylation and (ii) what is the relative reactivity of these five-membered aromatic heterocycles towards the ethynylation system haloacetylenes/Al₂O₃ (or other metal oxides or salts). Albeit the known data on protonation,¹² trifluoroacetylation^{12,13} and tricyanoethenylation¹² of furan-(thiophene)- and pyrrole-linked molecules implies a superior reactivity of the pyrrole counterpart of these ensembles.

2. Results and discussions

This paper is devoted to the ethynylation of 2-(furan-2-yl)- (1a,b) and 2-(thiophen-2-yl)pyrroles (1c,d), now readily available via corresponding acyl derivatives and acetylene,¹⁴ with acylbromoacetylenes 2a–c in the medium of solid Al₂O₃ (Tables 1 and 2). The reaction has been carried out according to a topochemical/mechanocatalytic protocol: the reactants (1:1 molar ratio) have been ground with 10-fold mass excess Al₂O₃ at room temperature for 1 h. The solid reaction mixtures have been placed

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Table 1
Reaction of 2-(furan-2-yl)pyrroles **1a,b** with acylbromoacetylenes **2a–c** in the solid Al₂O₃ medium (room temperature, 1 h).

Pyrroles 1a,b	Acylbromoacetylenes 2a–c	Products	Yield (%)
			39
			4 ^a
			47
			5 ^b
			55
			5 ^c
			44
			57
			60

^a Isolated in the mixture with pyrrole **3a**.

^b Isolated in the mixture with pyrrole **3b**.

^c Isolated in the mixture with pyrrole **3c**.

into chromatography column (Al₂O₃) and the products have been eluted with appropriate eluent.

As seen from Table 1, the major direction of ethynylation of 2-(furan-2-yl)pyrroles **1a,b** with acylbromoacetylenes **2a–c** is the formation of 2-acylethynyl-5-(furan-2-yl)pyrroles **3a–f**, while the alternative 2-acylethynyl-5-(pyrrol-2-yl)furans **4a–f** are minor products (**3a–f/4a–f** = ~5–7:1). However, the latter fact is key to the understanding of a topochemical ethynylation of five-membered aromatic heterocycles with haloacetylenes since this is the first observation of reactivity of the furan ring to this reaction.

Table 2
Reaction of 2-(thiophen-2-yl)pyrroles **1c,d** with acylbromoacetylenes **2a–c** in the Al₂O₃ medium (room temperature, 1 h)

Pyrroles 1c,d	Acylbromoacetylenes 2a–c	Products	Yield (%)
			72
			66
			70
			74
			72
			65

In some cases, we have managed to isolate 2-acylethynyl-5-(pyrrol-2-yl)furan (compounds **4a–c**) with ~80% purity and 4–5% yield.

Note that the double ethynylation, i.e., ethynylation of each ring of the molecules studied, was not observed in any case. In other words, alternative reaction occurs either across the pyrrole or furan ring. The absence of products of the double ethynylation points to a strong deactivating effect of acyl substituent, that is, transmitted from one ring to the another ring through the system of 10 bonds involving conjugated 1 triple, 4 double and 5 ordinary bonds. The ratio products **3a–f/4a–f** = ~5–7:1 may be considered as an approximate measure of the pyrrole and the furan ring relative reactivity towards acylhaloacetylenes **2a–c**. The reaction of pyrroles with electrophilic acetylenes is commonly treated as nucleophilic addition of electron-rich pyrrole moiety (often as the pyrrolate anion) to the electron-deficient triple bond, which occurs as N- and C-vinylation.¹⁵ This reaction is usually initiated by the single electron transfer to generate the ion-radical pairs as key intermediates, further forming C–C covalent bond with final elimination of hydrogen halide.⁹ Such a mechanism and the experimental isomer ratios are in agreement with a lower ionization potential of pyrrole ring (8.09 eV) compared to that of furan ring (8.69 eV).¹⁶

Since this ethynylation in the media of solid metal oxides and salts can be understood as a kind of a topochemical/mechanochemical process, the influence of the medium nature on the isomer ratio should be expected. However, under the similar

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