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Direct synthesis of 5-arylethynyl-1,2,4-triazines via direct C-H-functionalization

An efficient synthetic approach towards 5-arylethynyl-1,2,4-triazines via direct C-H-functionalization of 5-*H*-1,2,4-triazines in reaction with lithium acetylenes is reported.

Keywords: C-H-Functionalization, 1,2,4-triazines; acetylenes lithium salts; 5-arylethynyl-1,2,4-triazines

Received: 05.08.2020. Accepted: 01.09.2020. Published: 07.10.2020.

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Introduction

Heterocyclic acetylenes are widely used in various heterocyclization reactions [1], especially via click reactions [2]. Acetylene spacers are presented in a number of conjugated heterocyclic chromophores [3]. Additionally, some heterocyclic acetylenes are known possess with biological activities, for instance as antihypertensive agents [4].

The object of study of this work — 5-arylethynyl-1,2,4-triazines — are promising substrates for the preparation of various classes of compounds with unique applied properties. For example, by the transformation of the 1,2,4-triazine ring into the pyridine one via the aza-Diels-Alder reaction with various dienophiles, the corresponding pyridines can be obtained, including 2,2' — bipyridine ligands [4]. In addition,

arylethynyl substituted 1,2,3-triazoles were obtained in the reaction of the corresponding 3- (2-pyridyl) — 1,2,4-triazines with aryne intermediates [5–6]. Also, by the chemical transformation of 5-arylethynyl the corresponding 5-phenacyl-1,2,4-triazines could be obtained [7–8], which in turn can be transformed into 5-methyl-1,2,4-triazines [9].

Among the reported methods for the synthesis of 5-arylethynyl-1,2,4-triazines, the use of the Sonogashira cross-coupling can be highlighted [10], and in this case 5-iodine or 5-chloro-1,2,4-triazines were used as reactants. In addition, the direct introduction of an arylethynyl moiety via the C-H functionalization of 1,2,4-triazine-4-oxides in the reaction with the lithium salt of acetylene are described by using

deoxygenative aromatization pathway, and the benzoyl chloride was used as an acylating agent [5,11]. The interaction of non-activated 1,2,4-triazines with the lithium salt of arylacetylene is also described, however, the corresponding 5-styryl-1,2,4-triazines were the main reaction products [12–13]. In this aspect, it should be noted the greater availability of 1,2,4-triazines compare

to 1,2,4-triazine-4-oxides; and the preparation of ethynyl derivatives starting from 1,2,4-triazines looks more attractive.

In this article, we wish to report an efficient synthesis of 5-arylethynyl-1,2,4-triazines **1** via direct C-H-functionalization of 5-*H*-1,2,4-triazines **2** with lithium arylacetylenes.

Experimental part

¹H NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz), the internal standard was SiMe₄. Mass spectra (ionization type — electrospray) were recorded on a MicrOTOF-Q II instrument from Bruker Daltonics (Bremen, Germany). Elemental analysis was performed on a Perkin Elmer PE 2400 II CHN analyzer. The starting 1,2,4-triazine **2** was obtained according to the described method [14].

A general procedure for the synthesis of arylethynyl-1,2,4-triazines **1**:

A solution of *n*-BuLi in hexane (2.5 M, 0.8 ml) was added to a solution of the corresponding arylacetylene (2 mmol) in dry THF (4 ml) in a Schlenk flask at a temperature of –78 °C in an argon atmosphere, and the resulting mixture was stirred for 5 min. Then the solution of the corresponding 1,2,4-triazine **1** (1.6 mmol) in dry toluene (35 ml) was added, and a minute later a solution of DDQ (305 mg, 1.34 mmol) in dry toluene (10 ml) was added. The resulting mixture was stirred for 3 h at 78 °C to room temperature. After that methanol (10 ml) was added, and the reaction mixture stirred for 5 min and the solvents were removed under reduced pressure. The resulting oily residue was purified by column chromatography (neutral alumina, eluent: dichloromethane) to afford the desired products.

3- (2-Pyridyl) — 6-phenyl-5-phenylethynyl-1,2,4-triazine (1a). Yield 565 mg (1.7 mmol, 85%). Rf 0.6. M.p. 142–144 °C. NMR ¹H (CDCl₃, δ, ppm): 7.37–7.41 (m, 2H, PhC≡C), 7.43–7.55 (m, 4H, PhC≡C, H-5 (py)), 7.59–7.63 (m, 3H, Ph), 7.94–7.99 (ddd, 1H, ³J 8.0, 8.0 Hz, ⁴J 2.0 Hz, H-4 (py)), 8.19–8.22 (m, 2H, Ph), 8.75 (dd, 1H, ³J 8.0 Hz, ⁴J 1.0 Hz, H-3 (py)), 8.96 (dd, 1H, ³J 4.8 Hz, ⁴J 2.0 Hz, H-6 (py)). ¹³C NMR (CDCl₃, δ, ppm): 86.5 (C-sp), 100.8 (C-sp), 120.8, 124.2, 125.7, 128.5, 128.7, 129.5, 130.7, 132.6, 133.9, 137.2, 142.6, 150.6, 152.4, 157.7, 160.7. ESI-MS, m/z: 335.13 (M + H)⁺. Found, %: C 78.82, H 4.01, N 16.55. C₂₂H₁₄N₄. Calculated, %: C 79.02, H 4.22, N 16.76.

5 - ((4-Methoxyphenyl) ethynyl) — 3- (pyridin-2-yl) — 6-phenyl-1,2,4-triazine (1b). Yield 515 mg (1.41 mmol, 88%). NMR ¹H (CDCl₃, δ, ppm): 3.85 (m, 3H, OCH₃), 6.89 (m, 2H, C₆H₄), 7.45–7.54 (m, 3H, C₆H₄, H-5 (py)), 7.55–7.64 (m, 3H, Ph), 7.95 (ddd, 1H, ³J 7.6 Hz, 7.6 Hz, ⁴J 1.6 Hz, H-4 (py)), 8.17–8.23 (m, 2H, Ph), 8.74 (d, 1H, ³J 8.0 Hz, H-3 (py)), 8.94 (d, 1H, ³J 4.8 Hz, H-6 (py)). ESI-MS, m/z: 365.14 (M + H)⁺. Found, %: C 75.70, H 4.30, N 15.25. C₂₃H₁₆N₄O. Calculated, %: C 75.81, H 4.43, N 15.37.

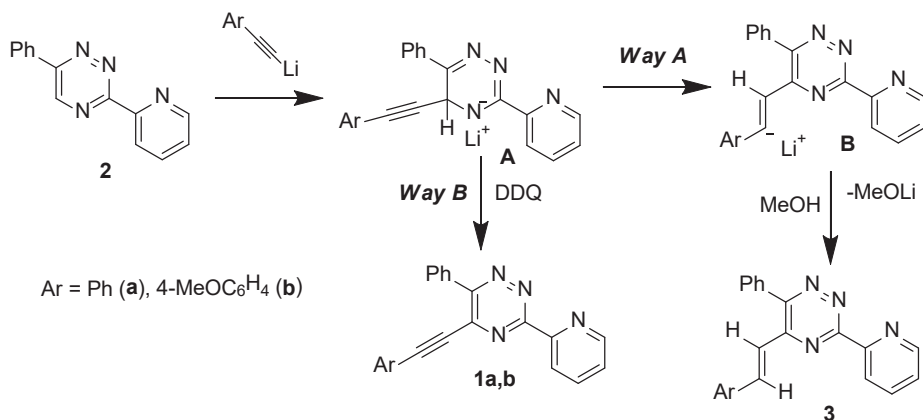
Results and discussion

The previously proposed mechanism [14] for the reaction of 1,2,4-triazines and lithium-acetylenes is presented on the scheme 1.

According to the mechanism, at the first stage, the corresponding σ^H -adduct **A** is formed, which further undergoes a 1,2-hydride shift affording the formation of the corresponding styryl substituent. And the treatment of the reaction mixture with methanol at the final stage leads to the products **3**. Obviously, to block the pathway A for the reaction, the σ^H -adduct **A** need to be treated with and oxidant to form 5-ethynyl-1,2,4-triazine **1**, which no longer turn into 5-styryl derivative **3**. Indeed, it was found that the addition of an oxidizing agent, such

as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), 10 minutes after the initiation of the reaction between 1,2,4-triazine and the arylacetylene lithium salt allowed us to obtain the corresponding 5-phenylethynyl-1,2,4-triazines **1** in up to 88% yields (way **B**), and they were isolated using column chromatography.

The structure of products **1** was confirmed based on the data of NMR ^1H , ^{13}C spectroscopy, mass spectrometry, and elemental analysis. Thus, in the ^{13}C NMR spectra, the signals of *sp*-hybrid carbon atoms in the range of 86.5–100.8 ppm can be observed. The spectral data of compound **1a** correspond to those previously published during its synthesis by an alternative method [5].



Scheme 1. Mechanism of reaction of 5-H-1,2,4-triazines **2** with lithium-acetylenes

Conclusions

An efficient synthetic approach towards 5-arylethynyl-1,2,4-triazines via direct C-H-functionalization of 5-H-1,2,4-triazines in reaction with lithium-acetylenes was re-

ported. This method could serve as a possible *Pd-free* alternative to the Sonogashira cross-coupling.

Acknowledgements

This work was supported by the Russian Science Foundation (Grant # 20-13-00142) and Grants Council of the President of the Russian Federation (no. NSh-2700.2020.3).

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