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

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Abstract

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

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 posses 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 vatusious dienophiles, the corresponding pyridines can be obtained, including 2,2'-bipyridine ligands [4]. In addition, arylythenyl substituted 1,2,3-triazoles were obtained in the reaction of the corresponding 3- (2-pyridyl) -1,2,4-triazines with arynie 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 arylythenyl 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 ary lethynyl-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.
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.

![Scheme 1. Mechanism of reaction of 5-H-1,2,4-triazines 2 with lithium-acetylenes](image)

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 σH-adduct A need to be treated with an 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, ^13C spectroscopy, mass spectrometry, and elemental analysis. Thus, in the ^13C 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].
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 reported. This method could serve as a possible Pd-free alternative to the Sonogashira cross-coupling.

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