

A convenient synthetic approach to 5-(het)arylhydrazine substituted 1,2,4-triazines

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Abstract. A convenient synthesis of 1,2,4-triazines bearing the moieties of (hetero)arylhydrazines at the position of C5 of the 1,2,4-triazine core is reported.

Keywords: 1,2,4-triazines; (hetero)arylhydrazines; 5-cyano-1,2,4-triazines; *ipso*-substitution

Received: 09.09.2020. Accepted: 20.12.2020. Published: 30.12.2020.

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Introduction

1,2,4-Triazines with moieties of (hetero)arylhydrazines at C5 position are of interest as substrates for further heterocyclizations for the synthesis of different condensed triazines, *e.g.*, 2H-pyrazolo[3,4-*e*][1,2,4]triazin-7(6H) — ones, 2,6-dihydro-[1,2,4]triazino[5,6-*d*][1,2,3]triazin-4-amines [1] or 2,6-dihydro-[1,2,4]triazino[6,5-*e*][1,2,4]triazines [2]. As for the methods for the synthesis of similar compounds it was previously proposed *ipso*-substitution of (methyl) sulfanyl group by arylhydrazine [2]. Also, there is a number of heterocyclizations of 1,2,4-triazine ring with the desired substituent at C5 position [1, 3, 4]. In addition, the opening of the condensed furan ring at the positions of C5 and C6 of the triazine ring is possible under the action of arylhydrazine [5].

At the same time, a known approach to the preparation of various 1,2,4-triazines with the residues of various nucleophiles at position C5 is the *ipso*-substitution of the C5-cyano group. This is due to the easy availability of 5-cyano-1,2,4-triazines obtained *via* the nucleophilic substitution of hydrogen process [6]. Thus, the possibility of the substitution of the C5-cyano group by the residues of such nucleophiles as alcohols [7–9], amines [7,10,11], anilines [12–14], lithium-carboranes [15], various CH acid residues [16, 17], hydrazides of carboxylic acids [18, 19] *etc.* was demonstrated earlier. In this article we wish to report the synthesis of 1,2,4-triazines bearing (hetero)arylhydrazine moieties at position C5 by means of *ipso*-substitution of C5-cyano group in 1,2,4-triazines under the action of (het)arylhydrazines.

Experimental part

NMR ^1H and ^{19}F spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz), the internal standard was correspondingly SiMe_4 or CFCl_3 . 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 5-cyano-1,2,4-triazines **1** were obtained according to the described method [8].

A general procedure for the synthesis of 5-(het)arylarlylhydrazinyl substituted 1,2,4-triazines 2

The mixture of corresponding 5-cyano-1,2,4-triazine **1** (1 mmol) and the corresponding (het)arylhydrazine (1.05 mmol) was stirred at 150 °C for 8 h in argon atmosphere. After cooling down the obtained residue was crashed and dissolved in chloroform (5–10 mL). The final products were isolated by flash chromatography on SiO_2 using chloroform as eluent.

2-(2-(3,6-Diphenyl-1,2,4-triazin-5-yl)hydrazinyl)benzo[d]thiazole (2a). Yield 305 mg (0.77 mmol, 77%). NMR ^1H ($\text{DMSO}-d_6$, δ , ppm): 2.42 (s, 3H, Me), 7.02–7.09 and 7.22–7.28 (both m, 1H, H-5,6 (benzothiazole)), 7.43–7.47 (m, 1H, H-7 (benzothiazole)), 7.50–7.60 (m, 5H, Ph), 7.61–7.65 (m, 1H, Ph), 7.66–7.71 (m, 1H, H-4 (benzothiazole)), 8.16–8.22 (m, 2H, Ph), 8.35–8.40 (m, 2H, Ph), 10.84 (s, 1H, NHNH), 13.02 (s, 1H, NHNH). ESI-MS, m/z : 397.12 ($\text{M}+\text{H}$) $^+$.

Results and discussion

The starting 5-cyano-1,2,4-triazines **1** were synthesized as described in literature [8]. *Ipso*-substitution reaction was carried out under the solvent-free condi-

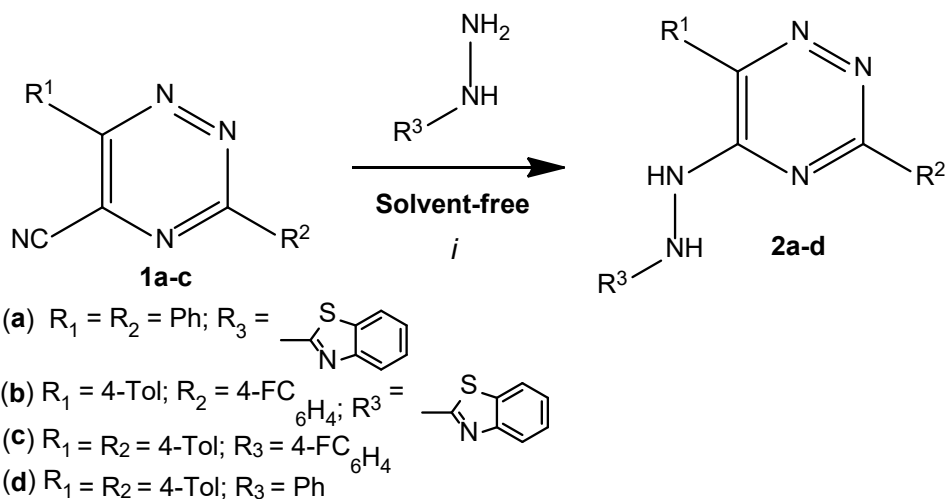
2-(2-(3-(4-Fluorophenyl)-6-(*p*-tolyl)-1,2,4-triazin-5-yl)hydrazinyl)benzo[d]thiazole (2b). Yield 310 mg (0.72 mmol, 72%). NMR ^1H ($\text{DMSO}-d_6$, δ , ppm): 2.42 (s, 3H, Me), 7.07 and 7.28 (both ddd, 3J 7.6, 7.6 Hz, 4J 1.2 Hz, H-5,6 (benzothiazole)), 7.33–7.36 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 7.40–7.45 (m, 2H, $\text{C}_6\text{H}_4\text{F}$), 7.45–7.48 (m, 1H, H-7 (benzothiazole)), 7.77–7.80 (m, 1H, H-4 (benzothiazole)), 8.03–8.06 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 8.49–8.54 (m, 2H, $\text{C}_6\text{H}_4\text{F}$), 11.33 (s, 1H, NHNH), 13.07 (s, 1H, NHNH). ESI-MS, m/z : 429.13 ($\text{M}+\text{H}$) $^+$.

5-(2-(4-Fluorophenyl)hydrazinyl)-3,6-di-*p*-tolyl-1,2,4-triazine (2c). Yield 310 mg (0.80 mmol, 80%). NMR ^1H (CDCl_3 , δ , ppm): 2.43 (s, 3H, Me), 2.45 (s, 3H, Me), 6.90–6.96 (m, 2H, $\text{C}_6\text{H}_4\text{F}$), 6.98–7.02 (m, 2H, $\text{C}_6\text{H}_4\text{F}$), 7.25–7.28 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 7.25–7.28 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 7.29–7.33 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 7.75–7.78 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 7.96–8.00 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 8.79 (s, 1H, NHNH), 9.22 (s, 1H, NHNH). NMR ^{19}F (CDCl_3 , δ , ppm): –126.51 (s, 1F). ESI-MS, m/z : 386.18 ($\text{M}+\text{H}$) $^+$.

5-(2-Phenylhydrazinyl)-3,6-di-*p*-tolyl-1,2,4-triazine (2d). Yield 280 mg (0.76 mmol, 76%). NMR ^1H ($\text{DMSO}-d_6$, δ , ppm): 2.44 (s, 3H, Me), 2.46 (s, 3H, Me), 6.61–6.67 (m, 1H, Ph), 7.03–7.08 (m, 2H, Ph), 7.10–7.16 (m, 2H, Ph), 7.24–7.30 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 7.32–7.37 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 8.00–8.05 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 8.09–8.13 (m, 2H, $\text{CH}_3\text{C}_6\text{H}_4$), 9.10 (s, 1H, NHNH), 12.34 (s, 1H, NHNH). ESI-MS, m/z : 368.19 ($\text{M}+\text{H}$) $^+$.

tions, as reported earlier for anilines and hydrazides [12, 18] (Scheme 1).

The structure of the obtained products **2** was confirmed by using NMR ^1H , mass-



Scheme 1. Reagents and conditions: 150 °C, 8 h, argon atmosphere.

spectrometry and elemental analysis. Thus, NMR ^1H spectra of compound **2** contains two characteristic broadened singlets for N-H-protons in the area of 8.79–13.07 ppm, signals of protons of the substituents at the positions of C3 and C6 of the triazine moiety, as well as the signals of protons of (hetero)aromatic substituents of hydrazines.

Conclusions

In conclusion, we have reported herein a convenient method for the synthesis of 3,6-disubstituted 1,2,4-triazines bearing moieties (het)arylhydrazine residues at the position of C5 of the triazine core

by means of *ipso*-substitution of cyano-group in 1,2,4-triazine-5-carbonitriles by (het)arylhydrazines under the solvent-free conditions. It is worth to mention that, di(het)aryl hydrazine moieties are found in many natural and synthetic biologically active compounds [20–22]. Therefore, further studies are needed to evaluate the reactivity, biological activity and chelating properties of the obtained products **2**.

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