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3-(Arylamino)-1,2,4-triazin-5-one: A Novel Synthesis and Its Use[‡]

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Dedicated to the memory of Dr. Paul Janssen

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An optimized procedure is given for the synthesis of novel 3-(arylamino)-1,2,4-triazin-5-one building blocks from commercially available material. By employing these building blocks, a practical protocol is described for the functionalization of the 5-position of the triazine core with anilines or phenols.

Introduction

3-(Arylamino)-1,2,4-triazin-5-ones of general structure **C** (Figure 1) are useful building blocks for further elaboration on the triazine core, analogously to the standard repertoire in the chemistry of 2-hydroxy-N-heterocycles.[2]

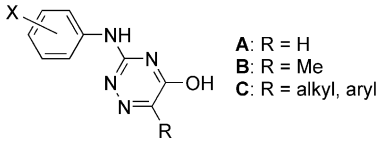
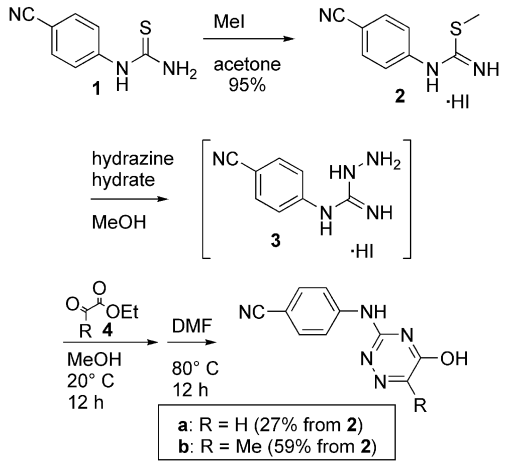


Figure 1. 1,2,4-triazin-5-ones.

These 3-(arylamino)-1,2,4-triazin-5-ones with general structure **A** or **B** (Figure 1), or their tautomeric forms, are not described in the literature,[3] whereas triazines of general structure **C**, where the R group is not H or Me, are very scarcely described, mainly in papers dating back more than 35 years.[4] One letter reports a solid-phase synthesis of structures **C** with various R groups being aryl.[5]

Results and Discussion

As part of our continuing interest in HIV-inhibiting pyrimidines,[6] triazines,[1,7] and purines,[8] we devised a novel route to 3-(arylamino)-1,2,4-triazin-5-ones. These building blocks were further functionalized in the 5-position with either anilines or phenols (see Scheme 2) to furnish products that act as non-nucleoside reverse transcriptase inhibitors (NNRTIs). In this paper we present a practical synthesis of triazines **A** and **B** with X = 4-CN.[9] (Scheme 1) and further functionalization of the 5-position.



Scheme 1. Synthesis of 1,2,4-triazin-5-one **5**.

In the first step, commercial thiourea **1** is *S*-methylated in 92% yield to give the hydroiodide salt **2**,[10] which precipitates from the reaction mixture and is filtered off. For the next step it is essential to keep the isourea in its salt form as use of the free base gave a yield at least 10 times lower. From **2** in an optimized procedure, intermediate hydrazinecarboximidamide **3** was prepared, and in a one-pot process with the appropriate oxo ester **4a** or **4b**, 5-hydroxy-1,2,4-triazines **5a** and **5b** were synthesized and purified by trituration. Triazines **5a** and **5b** were thus obtained in 90+%

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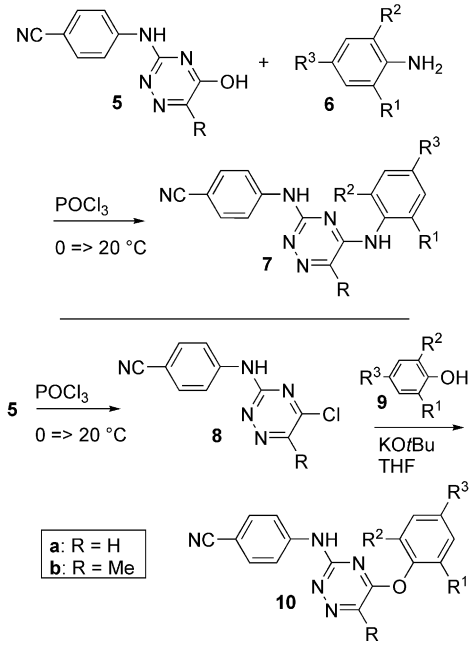
purity in 34% and 41% overall yield, respectively, without the need of column chromatography.[11]

In a further modification towards our products, triazin-5-ones **5a** and **5b** were functionalized with 2,4,6-trisubstituted anilines and phenols. The very reactive 5-chloro-1,2,4-triazines **8** were prepared and coupled to a deprotonated phenol to yield products **10** (Scheme 2). In the aniline series, however, intermediates **8** did not react with **6**. In an alternative one-pot process, however, where the aniline is added to a stirred suspension of **5** in neat phosphoryl chloride, products **7** were obtained from **8** generated in situ. A detailed general procedure for these transformations is given in the Supporting Information.



Scheme 2. Coupling of anilines **6** and phenoles **9** to 1,2,4-triazines **5**.

Conclusions

We have described an optimized procedure for the synthesis of 1,2,4-triazine building blocks **5a** and **5b** without the need for column chromatography and their functionalization of the 5-position with anilines and phenols.

Experimental Section

Intermediate 2: 1-(4-Cyanophenyl)thiourea (**1**) (4.81 g, 27.2 mmol) was suspended in acetone (100 mL), and MeI (1.78 mL, 28.5 mmol, 1.05 equiv.) was added. The reaction mixture was stirred at room temp. for 2 d, then placed in a cooler for 2 h, and then the solid was filtered off. The filtrate was washed with acetone and dried. Yield: 8.26 g (25.9 mmol 95.3%) of intermediate **2** as its HI salt. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 2.71 (s, 3 H, SMe), 7.55 (d, J = 8.6 Hz, 2 H, ArH), 8.00 (d, J = 8.6 Hz, 2 H, ArH), 9.67 (br. s, 3 H, 2 NH + HI) ppm.

3-[(4-Cyanophenyl)amino]-1,2,4-triazin-5-one (5a): To HI salt **2** (3.80 g, 11.91 mmol) was added hydrazine hydrate (0.69 mL, 14.29 mmol, 1.2 equiv.) and methanol (50 mL). The reaction mixture was stirred at room temp. for 2 d, in a flask with a gas outlet to release the formed thiomethanol. After that time, LCMS indicated 98% conversion to **3**. To the methanolic solution of intermediate **3** was added ethyl glyoxalate (**4a**) (50% in toluene, 4.72 mL, 23.81 mmol, 2 equiv.), and the reaction mixture was stirred at room temp. overnight. The MeOH was evaporated, and the residue was stripped twice with dry toluene (50 mL). Dry DMF (100 mL) was added, and the mixture was heated at 80 °C over 48 h. The DMF was evaporated (40 °C, 2.0 mbar). The yellow-orange solid residue was stirred in methanol (30 mL), filtered off and dried. Yield: 0.868 g (4.07 mmol) of triazine **5a**, 34.2% from intermediate **2**. An analytical sample was prepared by dissolving the compound in hot DMSO and precipitating it in water. ^{1}H NMR (400 MHz, [D$_6$]-DMSO, 22 °C): δ = 7.50 (1 H, triazine-H), 7.77 (d, J = 8.9 Hz, 2 H, ArH), 7.81 (d, J = 8.9 Hz, 2 H, ArH), 9.86 (br. s, 1 H, NH), 12.57 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 22 °C): δ = 162.4, 152.7, 142.4, 140.1, 133.1, 120.4, 119.0, 104.7 ppm. M.p. 351–353 °C. HRMS: calcd. for [MH$^+$] 214.0729, found 214.0718 (–4.89 ppm). FT-IR: $\tilde{\nu}$ = 665.4, 713.6, 736.7, 842.8, 1180.4, 1340.4, 1506.3, 1519.8 cm^{-1}.

6-Methyl-3-[(4-cyanophenyl)amino]-1,2,4-triazin-5-one (5b): To HI salt **2** (3.80 g, 11.91 mmol) was added hydrazine hydrate (0.69 mL, 14.29 mmol, 1.2 equiv.) and methanol (50 mL). The reaction mixture was stirred at room temp. for 2 d, in a flask with a gas outlet to release the formed thiomethanol. After that time, LCMS indicated 97.5% conversion to **3**. To the methanolic solution of intermediate **3** was added methyl pyruvate (**4b**) (2.15 mL, 23.8 mmol, 2 equiv.), and the reaction mixture was stirred at 20 °C overnight. The MeOH was evaporated, and the residue was stripped twice with dry toluene (50 mL). Dry DMF (100 mL) was added, and the mixture was heated at 80 °C over 48 h. The DMF was evaporated (40 °C, 2.0 mbar). The sticky brown residue was stirred in methanol (50 mL), filtered off and dried. Yield: 1.121 g, 4.93 mmol of triazine **5b**, 41.4% from intermediate **2**. An analytical sample was prepared by dissolving the compound in hot DMSO and precipitating it in water. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 2.10 (s, 3 H, Me), 7.78 (t, J = 9.9 Hz, 4 H, ArH), 9.75 (br. s, 1 H, NH), 12.31 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 22 °C): δ = 152.9, 147.8, 142.7, 133.1, 120.0, 119.1, 104.3, 16.9 ppm. M.p. >380 °C (dec.). HRMS: calcd. for [MH$^+$] 228.0885, found 228.0877 (–3.81 ppm). FT-IR: $\tilde{\nu}$ = 1126.4, 1178.4, 1199.6, 1517.9, 1635.5 cm^{-1}.

Supporting Information (see footnote on the first page of this article): Characterization data for compounds **5a** and **5b** (^{1}H NMR, ^{13}C NMR, FT-IR and HRMS); general procedure to prepare products **7** and **10**; table of all products **7** and **10** prepared this way and their yields.

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[2] This hydroxy function can be functionalized after chlorination, triflation, mesylation etc. with or without palladium catalysis; alkylated; used in the Mitsunobu reaction etc.
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[6] See: R. Leenders, J. Heeres, J. Guillemont, P. Lewi, *Tetrahedron Lett.* **2010**, *51*, 543–544 and the literature cited there under references [1] and [2].
[7] G. J. C. Hoornaert, A. Kilonda, J. Heeres, P. J. Lewi, M. R. de Jonge, F. F. D. Daeyaert, H. M. Vinkers, L. M. H. Koymans, P. A. J. Janssen, WO2006015985, **2006**.
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[9] We also successfully used anilines with X = 4-CH=CHCN; 4-CH_2CH_2CN, 4-CH_2CN.
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[11] These compounds have a very adverse solubility making column chromatography impossible.

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