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Short Note

6-Nitro-4*H*-benzo[*d*][1,3]thiazin-2-amine

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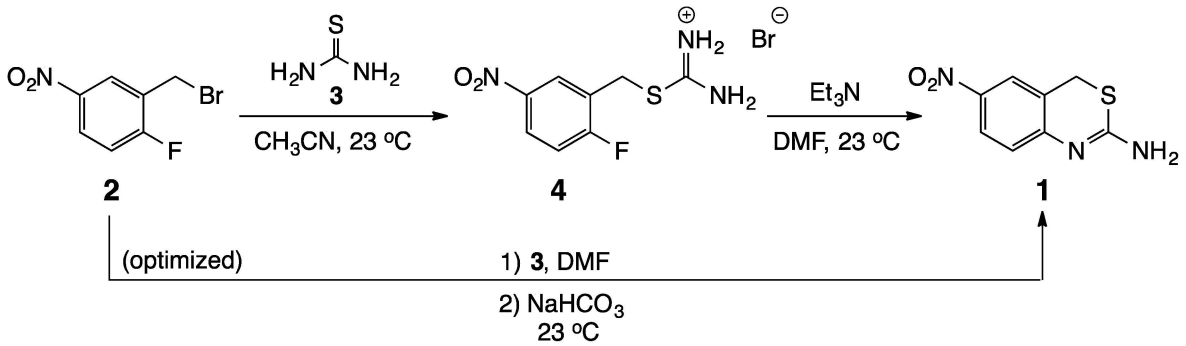
Abstract: An efficient and cost-effective synthesis of 6-nitro-4*H*-benzo[*d*][1,3]thiazin-2-amine based on a sequential S_N2-S_NAr process is reported. The synthesis is accomplished with an overall yield of 80%.

Keywords: sequential S_N2-S_NAr reaction; 1,3-thiazin-2-amine; heterocycle

1. Introduction

The tandem S_N2-S_NAr reaction has proven to be useful for the synthesis of a number of aryl-fused heterocyclic systems [1,2]. The current work describes the application of this strategy to the preparation of 6-nitro-4*H*-benzo[*d*][1,3]thiazin-2-amine (**1**). Ring-fused 1,3-thiazin-2-amines have recently been explored as potential agents for the treatment of Alzheimer's disease and other neurological disorders as they have potent inhibitory activity against amyloid precursor protein (APP) and beta-secretase proteins (BACE1 and BACE2) [3–14]. We planned to incorporate this moiety into compounds of biological interest to our research group.

Many previous syntheses of 1,3-thiazin-2-amines have involved reactions of variously substituted enones with thiourea, and several cases proceeded in a tandem fashion [15–17]. Several others have utilized metal catalysts to promote the heterocyclization [18]. Our synthesis began with 2-fluoro-5-nitrobenzyl bromide (**2**) [1] and represents a potentially new approach to these compounds (see Scheme 1). With a reactive benzylic bromine and an activated fluorine situated ortho to each other on the aromatic ring, **2** is perfectly suited to react with two of the nucleophilic sites in thiourea (**3**) to generate the target heterocycle. It was hoped that this would lead to the title compound **1** by a tandem process, but in practice, the conversion was possible only by a sequential reaction. Nevertheless, it was possible to efficiently perform this transformation in a single reaction vessel in high yield.



Scheme 1. Synthesis of 6-nitro-4*H*-benzo[*d*][1,3]thiazin-2-amine (**1**).

Initially, **2** was reacted with **3** in acetonitrile according to the procedure of Lam, *et al.* [19] to give the isothiouronium salt **4** [20]. The conversion to **1** was then completed by dissolving **4** in *N*,*N*-dimethylformamide (DMF) and treating with an equivalent of triethylamine. While successful, this two-step protocol was inefficient, requiring two set-ups and two product isolations, with an overall yield of only 54%. The use of triethylamine as the base in the second step led to emulsions during the final work-up, which contributed to the low yield and made this route more tedious. Thus, we refined the procedure to streamline the synthesis and simplify the isolation of the target heterocycle. In the optimized scheme, the entire process was performed at room temperature in a single reaction vessel by stirring **2** and **3** in DMF solvent for 1 h, followed by treatment with powdered sodium bicarbonate for 3 h. Product isolation involved diluting the crude reaction mixture with water to precipitate the thiazinamine, collecting and washing the solid with water to remove residual base, and drying under vacuum to remove water. The overall yield for the conversion was 80%.

2. Experimental

6-Nitro-4H-benzo[d][1,3]thiazin-2-amine (**1**)

To a stirred solution of thiourea (**3**, 1.6 g, 21 mmol) in anhydrous DMF (50 mL) under nitrogen was added 2-fluoro-5-nitrobenzyl bromide (**2**, 5.0 g, 21 mmol) and the reaction was stirred for 1 h at room temperature. To this solution was added powdered sodium bicarbonate (1.8 g, 21 mmol) and the reaction was stirred for an additional 3 h. The crude reaction was quenched by addition of 150 mL of distilled water and stirring was continued for 30 min. During this time the product precipitated as a bright yellow solid. The solid was collected by filtration through a Buchner funnel and was washed with distilled water. The product was dried under high vacuum at room temperature to give **1** (3.52 g, 80%) as a bright yellow solid. This material was sufficiently pure for most purposes. An analytical sample was obtained by recrystallization from absolute ethanol, mp 228–230 °C. IR (nujol): 3422, 3294, 1656, 1551, 1339 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.13 (d, J = 2.7 Hz, 1H), 8.05 (dd, J = 8.8, 2.7 Hz, 1H), 7.79 (br s, 2H), 7.98 (d, J = 8.8 Hz, 1H), 4.09 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 153.9, 141.7, 124.2, 123.7, 123.2, 120.9, 28.1. Anal. Calcd for $C_8H_7N_3O_2S$: C, 45.93; H, 3.37; N, 20.08. Found: C, 46.01; H, 3.41; N, 19.97.

Supplementary Materials: The supplementary materials and the molfile can be found at http://www.mdpi.com/1422-8599/2016/2/M899.

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Author Contributions: K.K.G. and J.T.H. optimized the reaction, acquired the spectra, and analyzed the data. R.A.B. designed the synthesis, confirmed the data analysis, and wrote the paper. All of the authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

References and Notes

1. Compound **2** is prepared in three steps from commercial 2-fluorobenzaldehyde by nitration ($NaNO_2$ in H_2SO_4), aldehyde reduction (BH_3· THF in THF or $NaBH_4$ in EtOH), and conversion to the bromide (PBr_3 in Et_2O), see Bunce, R.A.; Rogers, D.; Nago, T.; Bryant, S.A. 4*H*-1-Benzopyrans by a tandem S_N2-S_NAr reaction. *J. Heterocycl. Chem.* **2008**, *45*, 547–550. [CrossRef] Compound **2** is also commercially available from Oakwood Products. Inc. [1-(800)-467-3386. Available online: www.oakwoodchemical.com (accessed on 9 May 2016)], though it is rather expensive.

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