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Short Note

3-(4-(Benzyloxy)-3-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyridine

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Abstract: The [1,2,4]triazolo[4,3-*a*]pyridine derivative 3-(4-(benzyloxy)-3-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyridine was prepared in a 73% isolated yield by means of an oxidative ring closure of a hydrazine intermediate. Sodium hypochlorite was used as the oxidant and ethanol as a solvent, making the process a clean, green approach. The reaction was performed at room temperature for 3 h, and then the heterocycle was isolated in an analytically pure form by extraction, followed by passing the crude product mixture through a small plug of alumina.

Keywords: oxidation; triazolopyridine; ring closure; sodium hypochlorite; green chemistry

1. Introduction

Triazolopyridines are a class of compounds that are currently attracting significant attention [1,2]. These heterocyclic molecules comprise a triazole ring fused to a pyridine ring. There are multiple isomers which differ by the location of the nitrogen atoms and the nature of the ring fusion. The [1,2,4]triazolo[4,3-*a*]pyridine motif (Figure 1) is found in a variety of biologically active compounds, including antibacterial, antithrombotic, anti-inflammatory, antiproliferative, and herbicidal agents [3–8]. They can also be used as molecular chemosensors for metal ions, anions, and amino acids [9,10] as well as in the construction of luminophores [11]. This subset of the triazolopyridine family can be prepared with a number of synthetic routes [2]. Some involve an oxidative ring closure [12–17] and others employ a transition metal catalysis [18,19].

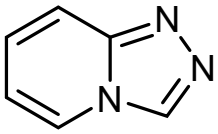

Figure 1. The [1,2,4]triazolo[4,3-*a*]pyridine motif.

Our research group has focused some significant effort on the preparation of heterocyclic compounds, and we have developed a series of methodologies centered around the use of oxoammonium salts and their corresponding nitroxide analogs as reagents and catalysts [20–23]. A theme running through our work is the use of cleaner, greener approaches to preparative chemistry. As such, we became interested in applying some of our methodologies to the synthesis of [1,2,4]triazolo[4,3-*a*]pyridines by means of an oxidative cyclization of hydrazines. Such an approach is not unprecedented but often involves the use of toxic or hazardous reagents such as Cr(VI) salts (Figure 2a) [13] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Figure 2b) [14]. Sodium hypochlorite was used as an oxidant, being more environmentally benign (Figure 2c) [24], and served as a starting point for our method development. Here, we present the synthesis of 3-(4-(benzyloxy)-3-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyridine (**2**) from *N*-[(3-methoxy-4-phenylmethoxyphenyl)methylideneamino]pyridin-2-amine (**1**), serving as a representative example of our approach (Figure 2d).

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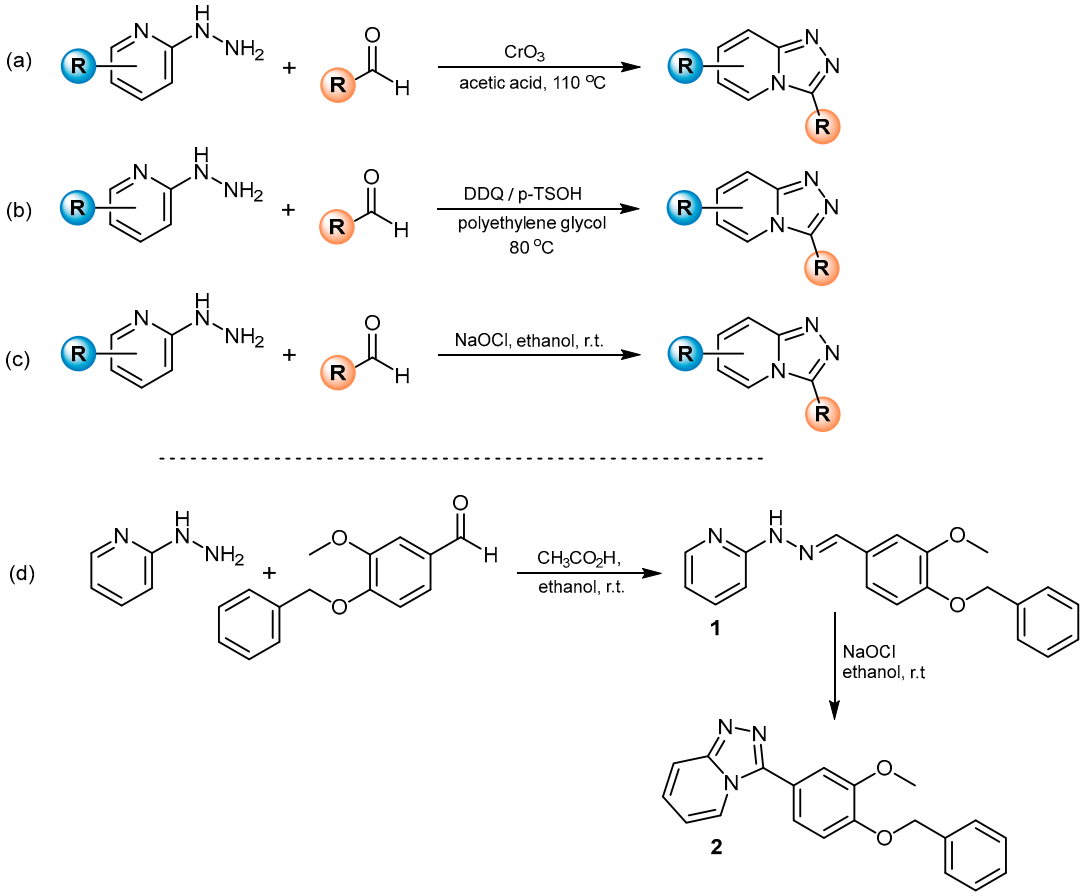

Figure 2. Preparation of [1,2,4]triazolo[4,3-*a*]pyridines by means of oxidative cyclization of hydrazines using (**a**) Cr(VI) salts, (**b**) DDQ, (**c**) sodium hypochlorite, and (**d**) our approach to prepare **2** from **1**.

2. Results and Discussion

To prepare [1,2,4]triazolo[4,3-*a*]pyridine **2**, we first generated hydrazine **1**. This was achieved by treating a 1:1 stoichiometric mixture of 2-hydrazinopyridine and 4-benzyloxy-3-methoxybenzaldehyde in ethanol with acetic acid. The hydrazine precipitated out of the solution in pure form. Hydrazine **1** was then treated with four equivalents of sodium hypochlorite pentahydrate in ethanol, with the reaction mixture being stirred at room temperature for 3 h. The [1,2,4]triazolo[4,3-*a*]pyridine **2** was isolated by means of an aqueous/organic extraction and purified by passing the material through a plug of alumina, obtaining a 73% isolated yield.

The novel [1,2,4]triazolo[4,3-*a*]pyridine product **2** was characterized by IR and NMR spectroscopy as well as high-resolution mass spectrometry. ^{13}C-NMR spectrum showed 18 signals, which was in agreement with the number of unique carbon environments in **2**. The ^{1}H-NMR showed signals for the aromatic backbone of the [1,2,4]triazolo[4,3-*a*]pyridine as well as the 4-benzyloxy-3-methoxy group in the 3-position of the heterocyclic moiety. The high-resolution mass spectrum confirmed the identity and purity of the product.

3. Materials and Methods

3.1. General Experimental

Chemicals were purchased from Oakwood Chemicals (Estill, SC, USA), Sigma-Aldrich (St. Louis, MO, USA), and Alfa Aesar (Haverhill, MA, USA), with the exception of 4-benzyloxy-3-methoxybenzaldehyde, which was prepared using the literature method. Deuterated dimethyl sulfoxide (DMSO-*d6*) was purchased from Cambridge Isotope Laboratories (Tewksbury, MA, USA). NMR spectra (^{1}H and ^{13}C) were recorded at 300 K on a Brüker Avance Ultra Shield 300 MHz, Bruker DRX-400 400 MHz, or Brüker Avance

500 MHz spectrometer. The ^{1}H-NMR spectra were referenced to residual non-deuterated dimethyl sulfoxide (2.50 ppm) in DMSO-*d6*. ^{13}C-NMR spectra were referenced to DMSO (39.52 ppm). Reactions were monitored with NMR and/or with TLC on alumina plates (60 Å porosity, 250 μm thickness). TLC analysis was performed using dichloromethane and visualized with UV light. Infrared spectra were recorded on a Bruker Alpha FTIR spectrometer using an attenuated total reflection (ATR) diamond crystal. High-resolution mass spectra were collected on an Applied Biosystems QSTAR Elite instrument equipped with an electrospray ionization (ESI) source, calibrated using Agilent LC/MS tuning mix.

3.2. Preparation of N-[(3-Methoxy-4-phenylmethoxyphenyl)methylideneamino]pyridin-2-amine (**1**)

In a 6 dram (18.5 mL) vial equipped with a stir bar, 2-hydrazinopyridine (5 mmol, 0.546 g) was dissolved in ethanol (10 mL). After, 4-benzyloxy-3-methoxybenzaldehyde (5 mmol, 1.211 g) was added to the vial, and the mixture was stirred for 1 min before adding approximately 10 drops of acetic acid. The precipitate formed was isolated using vacuum filtration; it was first washed with water and then with methanol to afford pure *N*-[(3-methoxy-4-phenylmethoxyphenyl)methylideneamino]pyridin-2-amine (**1**) as a white solid (1.523 g, 91% yield).

MP 175–176 °C. FTIR (ATR 4000–400 cm^{-1}) 3198 w, 2986 w, 2933 w, 1596 s, 1539 m, 1509 s, 1438 vs. 1382 w, 1306 m, 1261 s, 1229 s, 1165 s, 1131 vs. 1087 m, 1019 m cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-*d6*) δ 10.72 (s, 1H), 8.09 (dd, *J* = 4.8, 0.9 Hz, 1H), 7.95 (s, 1H), 7.66–7.58 (m, 1H), 7.49–7.31 (m, 6H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.12–7.02 (m, *J* = 15.9, 5.0 Hz, 2H), 6.73 (dd, *J* = 6.5, 5.2 Hz, 1H), 5.11 (s, 2H), 3.84 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-*d6*) δ 157.16, 149.40, 148.48, 147.70, 138.94, 137.79, 136.95, 128.63, 128.39, 127.86, 127.81, 119.72, 114.60, 113.38, 108.25, 106.21, 69.90, 55.48. HRMS (ESI) *m/z* calculated for $C_{20}H_{20}N_3O_2$ $[M + H]^+$ 334.1556, found 334.1553.

3.3. Preparation of 3-(4-(Benzyloxy)-3-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (**2**)

In a 100 mL capacity round-bottom flask equipped with a stir bar, **1** (2 mmol, 0.666 g), sodium hypochlorite pentahydrate (8 mmol, 1.316 g), and ethanol (40 mL) were added. The flask was sealed with a rubber septum, then the contents were allowed to stir at room temperature for 3 h. The septum was then removed from the flask, and the contents were left open to air overnight, after which time the remaining ethanol was removed in vacuo from the product mixture. The resultant material was dissolved in dichloromethane and gently added atop an aluminum oxide plug. The desired product was eluted off the plug with chloroform. The eluent was collected, and the solvent was removed in vacuo to afford the pure 3-(4-(benzyloxy)-3-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyridine (**2**) as a white solid (0.481 g, 73%).

MP 136-139 °C. FTIR (ATR 4000-400 cm^{-1}) 3232 w, br, 2931 w, br, 1605 w, 1527 m, 1479 m, 1370 m, 1256 vs. 1228 s cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-*d6*) δ 8.55 (d, *J* = 7.0 Hz, 1H), 7.83 (d, *J* = 9.3 Hz, 1H), 7.53–7.47 (m, *J* = 7.2 Hz, 2H), 7.46–7.32 (m, 6H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.00 (t, *J* = 6.6 Hz, 1H), 5.21 (s, 2H), 3.88 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-*d6*) δ 149.78, 149.43, 149.15, 145.96, 136.80, 128.45, 127.94, 127.82, 127.62, 123.93, 120.66, 119.21, 115.54, 114.19, 113.65, 111.85, 69.93, 55.73. HRMS (ESI) *m/z* calculated for $C_{20}H_{18}N_3O_2$ $[M + H]^+$ 332.1399, found 332.1402.

4. Conclusions

A [1,2,4]triazolo[4,3-*a*]pyridine derivative was prepared simply and rapidly in a 73% isolated yield by means of an oxidative ring closure of a hydrazine intermediate. The product could be isolated in an analytically pure form by extraction followed by passing the crude product mixture through a small plug of alumina.

Supplementary Materials: Copies of the ^{1}H- and ^{13}C-NMR as well as the IR spectra of **1** and **2**.

Author Contributions: Conceptualization, K.E.D.; methodology, K.E.D., A.L.S. and E.T.M.; validation, K.E.D., A.L.S. and E.T.M.; formal analysis, K.E.D., A.L.S. and E.T.M.; resources, N.E.L.; data

curation, K.E.D., A.L.S. and E.T.M.; writing—original draft preparation, N.E.L.; writing—review and editing, K.E.D., A.L.S., E.T.M. and N.E.L.; supervision, A.L.S. and N.E.L.; project administration, N.E.L.; funding acquisition, N.E.L. All authors have read and agreed to the published version of the manuscript.

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