

Short Note

N-Benzo[*c*][1,2,5]thiazol-4-yl-3-trifluoromethylbenzamide

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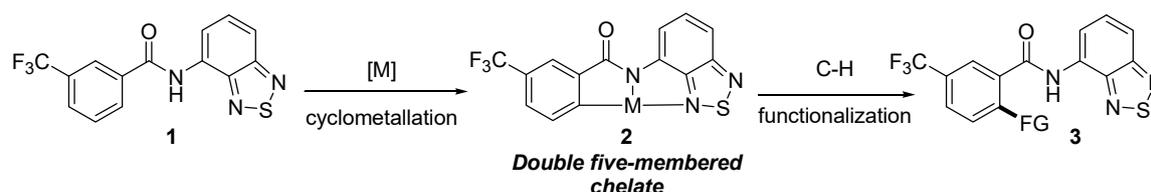


Abstract: The title compound, *N*-benzo[*c*][1,2,5]thiazol-4-yl-3-trifluoromethylbenzamide (**1**) was synthesized by reacting 3-trifluoromethylbenzoyl chloride (**4**) and 4-aminobenzo[*c*][1,2,5]thiadiazole (**5**). The compound was characterized by various spectroscopic methods (¹H NMR, ¹³C NMR, IR, GC-MS) and its composition confirmed by elemental analysis. The importance of this compound lies in its possession of an *N,N*-bidentate directing group. Such a structural motif is potentially suitable for metal-catalyzed C-H bond functionalization reactions.

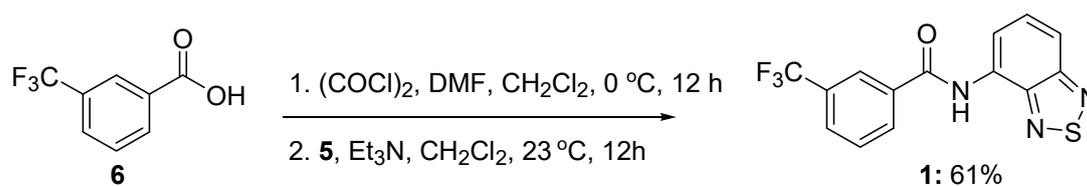
Keywords: benzamide; bidentate directing group; C-H functionalization

1. Introduction

The functionalization of C-H bonds [1,2] transforms an inert nonpolar C-H bond into a reactive/functional one. The strategy can allow the direct access of target molecules, avoiding pre-functionalized materials and/or reagents. Thus materials, reagents, solvents and energy are saved. This concurrently should result in the minimization of waste in a great manifestation of the reduction of waste at the source. Therefore, the functionalization of C-H bonds is atom economical and an environmentally benign approach, and thus green. Site-selectivity or regioselectivity is a major issue in the science of C-H bond functionalization. One approach to improve the site-selectivity is to use directing groups that contain Lewis basic atoms to coordinate the Lewis acidic metal facilitating the C-H bond cleavage. Directing groups can contain one Lewis basic atom, as in monodentate directing groups [3], or two Lewis basic atoms, as in bidentate directing groups [3,4]. The required chelation assistance by directing groups can be designed. The underlying principle is the thermodynamic stability of the intermediate five-membered chelates [4]. Therefore, that was a strong incentive for the synthesis of compounds bearing the more efficient bidentate directing groups. Toward that end, the title compound is synthesized. The title compound, *N*-benzo[*c*][1,2,5]thiazol-4-yl-3-trifluoromethylbenzamide (**1**, Scheme 1), possessing two nitrogen (N) atoms separated by two carbons, represents an example of the *N,N*-bidentate directing group [5]. Thus, it is potentially a substrate for metal-catalyzed C-H bond functionalization. Therefore, the title compound possessing the requisite *N,N*-bidentate directing group can undergo cyclometallation to give an intermediate double-five membered chelate (**2**) followed by a reaction with a suitable electrophile to give the final C-H functionalized product (**3**, Scheme 1).



Scheme 1. Feasibility of the use of the title compound as a bidentate directing group in C-H bond functionalization.



Scheme 4. Synthesis of *N*-benzo[*c*][1,2,5]thiazol-4-yl-3-trifluoromethylbenzamide from the carboxylic acid via the acid chloride.

The benzoic acid-amine coupling method illustrated above (Scheme 3) and the starting acid transformation via the acid chloride (Scheme 4) required longer reaction times and resulted in lower yields. Therefore, the present method, starting from the acid chloride (Scheme 2), outweighs the alternative methods in terms of time and yield and thus efficiency, despite the relatively higher cost of the acid chloride (relative to the benzoic acid).

3. Materials and Methods

3.1. General Methods

All chemicals, reagents and solvents were purchased from chemical companies (Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany) and were used as received without prior purification. Reactions that required dry conditions were performed in an inert atmosphere with Ar gas. Syringes and needles for the transfer of reagents were oven dried and cooled in a desiccator over silica gel before use. The reaction's progress was monitored by thin-layer chromatography (TLC) on glass plates pre-coated with Merck silica gel. TLC plates were examined under UV lamplight (UVGL-58 Handheld 254/365 nm). Büchi-USA rotary evaporators were used to evaporate solvents using appropriate temperatures. Flash column chromatography was performed using silica gel (Kieselgel) (70–230) mesh as an adsorbent. The purified products were characterized using analyses NMR (^1H NMR, ^{13}C NMR), IR, mass spectra and melting points. Melting points were recorded on the Gallenkamp-MPd350.bm2.5 melting point apparatus (Gallenkamp, Kent, UK). Attenuated total-reflectance IR spectra were recorded on pure samples on Agilent Technologies Cary 630 FTIR (Agilent, Santa Clara, CA, USA). ^1H NMR spectra were recorded in CDCl_3 on JEOL ECX-400 spectrometers (JEOL Ltd., Tokyo, Japan). ^1H NMR chemical shifts (δ) were assigned in part per million (ppm) downfield using an internal standard trimethylsilane (TMS) and were referenced to CDCl_3 , $\delta = 7.24$. Abbreviations s, d, t, q, quin, sept and m refer to singlet, doublet, triplet, quartet, quintet, septet and multiplet, respectively. Chemical shifts in ^{13}C spectra (175 MHz) were quoted in ppm and referenced to the central line of the CDCl_3 triplet, $\delta \text{ C } 77.0$. Coupling constants (*J*) were recorded in hertz (Hz). GC-MS spectra were obtained using an Agilent mass spectrometer (Agilent, Santa Clara, CA, USA). Elemental analysis was performed using an EuroEA Elemental Analyzer (configuration CHN (EuroVector Instruments & Software, Milano, Italy) with a calibration type of K-factor.

3.2. Synthesis of *N*-benzo[*c*][1,2,5]thiazol-4-yl-3-trifluoromethylbenzamide (1)

3-Trifluoromethylbenzoyl chloride (4) (1.00 mL, 6.63 mmol) was added dropwise under an atmosphere of N_2 into a cold ($0 \text{ }^\circ\text{C}$ ice-water bath) solution of 4-aminobenzo[*c*][1,2,5]thiadiazole (5) (1.11 g, 7.34 mmol), in CH_2Cl_2 (50 mL). Et_3N (3.00 mL, 21.5 mmol) was then added to the $0 \text{ }^\circ\text{C}$ mixture under N_2 . The mixture was stirred for 1 h at $0 \text{ }^\circ\text{C}$, allowed to warm up to room temperature and then stirred for an additional 5 h. To the reaction mixture, aqueous saturated NaHCO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 ($3 \times 50 \text{ mL}$). The combined organic extracts were dried over anhydrous MgSO_4 and filtered. The evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2) using Petroleum ether:Et $_2$ O (9:1) gave the title compound (1) as a silver crystalline solid after recrystallization from CH_2Cl_2 :hexane (1.92 g, 90%). $R_f = 0.63$ (Pet. Ether:EtOAc (1:1)), mp = 99–101 $^\circ\text{C}$. ^1H NMR (700 MHz, CDCl_3): $\delta = 9.21$ (s, 1H), 8.59 (d, $J = 7.3 \text{ Hz}$, 1H), 8.25 (s, 1H),

8.16 (d, $J = 7.8$ Hz, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.64 (m, 2H). ^{13}C NMR (176 MHz, CDCl_3): $\delta = 164.0, 154.7, 147.9, 135.0, 131.8$ ($q, J_{\text{C-F}} = 271$ Hz), 131.0, 130.2, 129.6 ($q, J_{\text{C-F}} = 14$), 128.9 ($q, J_{\text{C-F}} = 4$), 124.9, 124.5 ($q, J_{\text{C-F}} = 9$ Hz), 122.2, 116.4, 115.5. IR(film): $\nu_{\text{max}}/\text{cm}^{-1}$: 3293, 1651, 1545, 1522, 1482, 1434. MS (EI) m/z (relative intensity): 323 (16), 173 (100), 145 (67), 125 (6), 95 (12), 75 (6). Elemental analysis, calculated: C (52.01), H (2.49), N (13.00), found (average of two runs): C (51.822), H (2.339), N (12.700).

Supplementary Materials: The following are available online, Figure S1: ^1H NMR of the title compound, Figure S2: ^{13}C NMR of the title compound, Figure S3: IR of the title compound, Figure S4: GC-MS of the title compound, Figure S5: Elemental analysis report of title compound.

Author Contributions: N.A.A., Y.A.L. carried out all experimental work under the supervision of H.H.A.M.

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Conflicts of Interest: Authors declare no conflict of interest.

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