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Short Note

1-(4-Fluorobenzoyl)-9*H*-carbazole

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Abstract: 1-(4-Fluorobenzoyl)-9*H*-carbazole (**1**) was synthesized, starting from 9*H*-carbazole and 4-fluorobenzonitrile, by Friedel–Crafts acylation, using boron trichloride to direct the substitution in 1-position. Single-crystal X-ray diffraction analysis unambiguously revealed the molecular structure of **1**.

Keywords: carbazole; Friedel–Crafts acylation; boron trichloride; structure determination

Citation: Laube, M.; König, J.; Köckerling, M.; Kniess, T. 1-(4-Fluorobenzoyl)-9*H*-carbazole. *Molbank* **2022**, *2022*, M1430. https://doi.org/10.3390/M1430

Academic Editor: Kristof Van Hecke

Received: 30 June 2022
Accepted: 16 August 2022
Published: 19 August 2022

1. Introduction

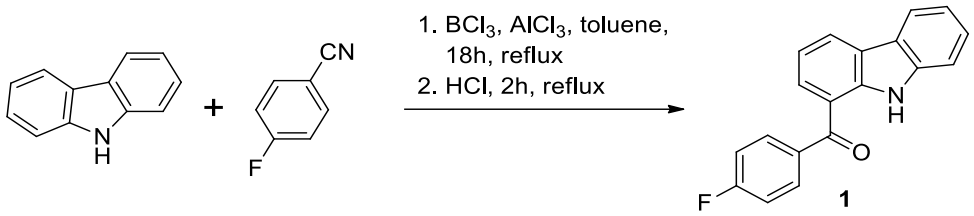
9*H*-Carbazole, an aromatic three-membered heterocycle, is a structural motif that is present in several bioactive natural compounds [1]. Thus, methods for the synthesis and functionalization of this heterocycle are important.

In general, access to 1-aroyl-substituted carbazoles was reported, using lithiation as a key step [2], a Suzuki–Miyaura type coupling reaction starting from 1-(9*H*-carbazole)-boronic acid [3], and ruthenium-catalyzed [4,5] or photochemical [6] rearrangements. The Friedel–Crafts reaction between carbazole and benzoyl chloride was utilized, but resulted in a mix of four benzoylated products with 3,6-di-benzoyl-9*H*-carbazole as the main product [7]. Recently, intramolecular cyclization using metal-free CH-bond activation [8] or palladium-catalyzed oxidative acylations [9], leading to *N*-pyridinyl-protected carbazoles, was reported, offering access to 1-aroyl-substituted carbazoles after deprotection.

Based on our interest in the development of ^{18}F-labeled COX-2 inhibitors [10–12], we were interested in using 1-(4-fluorobenzoyl)-9*H*-carbazole (**1**) as a building block to design a new class of cyclooxygenase-2 inhibitors. We decided to utilize BCl_3-mediated Friedel–Crafts acylation for the synthesis of **1**, because the use of BCl_3 allows for the selective *ortho*-benzoylation of primary and secondary aromatic amines and has been successfully used in the synthesis of 1-cyano- and 1-alkylthiocarbonyl-substituted 9*H*-carbazoles [13]. Herein, we report the synthesis and structural characterization of **1**.

2. Results and Discussion

In analogy to a procedure described by Lo et al. [14], **1** was successfully synthesized by BCl_3-mediated Friedel–Crafts acylation, starting from 9*H*-carbazole and 4-fluorobenzonitrile (Scheme 1). The reaction mechanism is suggested to follow the mechanism known in the literature, which involves (1) the formation of 9-(dichloroboryl)-9H-carbazole and, subsequently, a six-membered complex with the nitrile group of 4-fluorobenzonitrile; (2) the Friedel–Crafts reaction, which leads to 1-aroylation due to the spatial proximity; (3) hydrolysis of the ketimine with HCl [15]. This gave **1** as a crude product, which was purified by column chromatography and finally isolated with a 38% yield. Crystals suitable for single-crystal X-ray diffraction experiments were isolated and analyzed.



Scheme 1. Synthesis of 1-(4-fluorobenzoyl)-9*H*-carbazole (**1**).

The molecular structure of **1** is shown in Figure 1. A moderate intramolecular N1−H···O1 hydrogen bonds with a donor-acceptor distance of 3.055(1) Å causes the orientation of the carbonyl moiety to almost occur in a plane with the carbazole moiety. The fluoro-substituted phenyl ring is twisted out of the plane of the carbazole moiety with a dihedral angle of 54.9°.

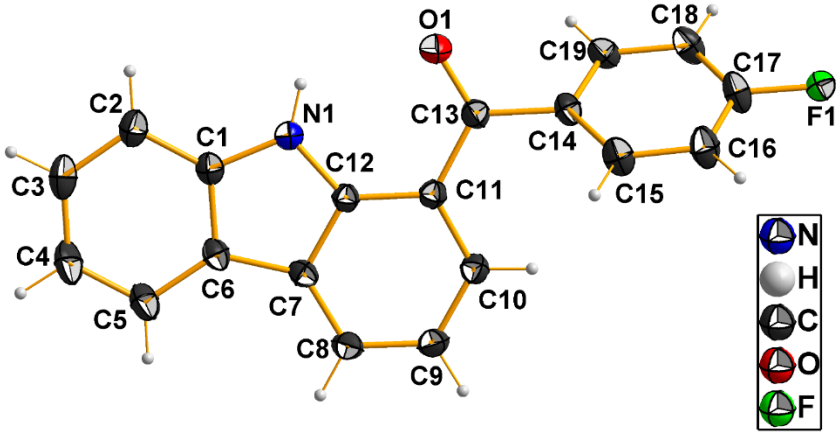


Figure 1. Molecular structure (ORTEP plot at 50% probability) of compound **1**.

In the plane (0,0,1), the molecules are packed in chains along the *a*-axis, which are oriented anti-parallel, in the direction [0,0,1]. This is due to the intermolecular N1−H···O1 hydrogen bonds between the carbonyl and amine groups with D···A = 3.056(1) Å) and π···π-interactions. Further weak hydrogen bonds between fluorine and the C5−H group of the neighboring phenyl ring at a D···A distance of 3.397(1) Å cause binding along the *b*-axis. The weak interactions are shown in Figure 2 as dashed lines.

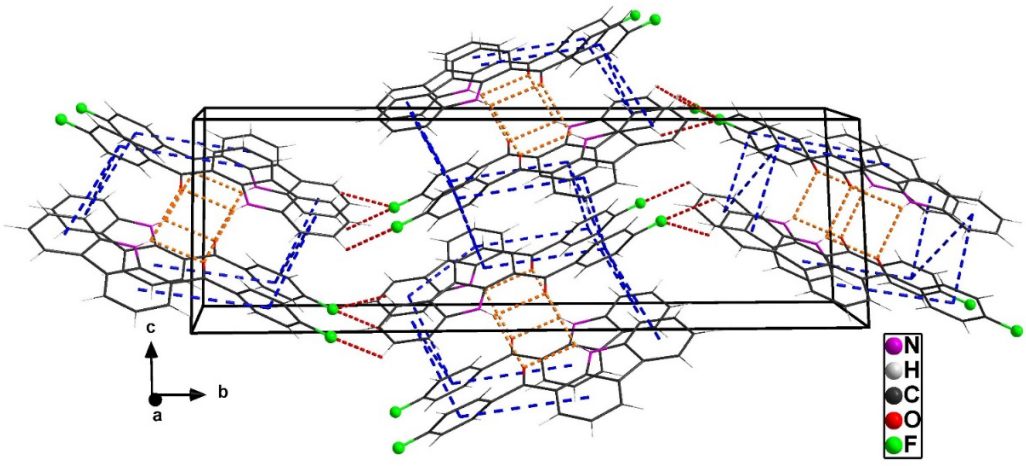


Figure 2. View of the arrangement of the molecules of **1** in and around the unit cell. Blue dashed lines indicate π···π-interactions, orange dashed lines the N1−H···O1 hydrogen bonds and red dashed lines the F1 . . . H−C5 hydrogen bonds.

3. Materials and Methods

3.1. General

All commercial reagents and solvents were used without further purification. NMR spectra were recorded on a Varian Inova-400 and referenced to the residual solvent shifts for ^{1}H and ^{13}C, and to $CFCl_3$ for ^{19}F spectra as internal standard. *J*-Values are given in Hz. Carbazole and phenyl are abbreviated as Ca and Ph, respectively. UPLC-MS was performed using the following system: column Aquity UPLC® BEH C18 column (Waters, 100 × 2.1 mm, 1.7 µm, 130 Å), UPLC *I*-Class (Waters, Milford, MA, USA): binary gradient pump BSM, autosampler FTN, column manager CM, and diode array detector PDAeλ coupled to Waters Xevo TQ-S, flow rate 0.4 mL/min, eluent: (A): 0.1% acetic acid in MeCN/MeOH 1/1/ (B): 0.1% acetic acid in H_2O; gradient: $t_{0\ min}$ 45/55-$t_{0.5\ min}$ 45/55-$t_{5.5\ min}$ 95/5-$t_{7.0\ min}$ 95/5-$t_{8.0\ min}$ 45/55-$t_{8.5\ min}$ 45/55). The crystallographic data were collected with a Bruker-Nonius APEX-II CCD diffractometer with Mo-Kα radiation (λ = 0.71073 Å). The structures were solved using SHELXS-14 and refined against F^2 for all data by full-matrix least squares with SHELXL-14 [16,17]. All non-hydrogen atoms were refined anisotropically; all hydrogen atoms bonded to carbon atoms were placed on geometrically calculated positions and refined using a riding model. CCDC-2178615 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (accessed on 23 July 2022 or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; E-mail: deposit@ccdc.cam.ac.uk).

*3.2. Synthesis of 1-(4-Fluorobenzoyl)-9H-carbazole (**1**)*

The synthesis followed the procedure described by Lo et al. [14]. Under nitrogen atmosphere, in this order, carbazole (809.6 mg, purity 95%, 4.6 mmol) in 2.0 mL toluene, 4-fluorobenzonitrile (676 mg, 5.6 mmol) and anhydrous $AlCl_3$ (676 mg, 5.1 mmol) were added to a solution of 1 M BCl_3 in toluene (5.06 mL, 5.06 mmol). The mixture was heated to reflux for 18 h. After that, water (0.25 mL) and 10% HCl (5.1 mL) were added at a temperature of 0 °C and the mixture was heated to reflux for 2 h. The mixture was cooled to 0 °C and the resulting precipitate was filtered by vacuum filtration. The solid was suspended in 2.5% NaOH (11.5 mL) and stirred for 1 h at RT. Filtration and drying in vacuo gave the crude product, which was purified by Dry Column Vacuum Chromatography [18] (MERCK Silica Gel (mesh size 40–63 µm); 1. PE/ EtOAc 90:10→50:50; fractions containing impurities were purified with: 2. PE/ EtOAc 100:0→90:10). **1** was obtained as a pale-yellow solid (505 mg, 38%). mp (Galen III (Cambridge Instruments) melting points apparatus (Leica, Vienna, Austria); uncorrected) 151–153°C; R_f = 0.35 (Merck silica gel F-254 aluminum plates; PE/ EtOAc 85:15); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22 (t, 2H, $^{3}J_{2,3}$ 8.6, $^{3}J_{H,F}$ 8.6, $H_{Ph\ H3/H5}$), 7.26* (t, 1H, $^{3}J_{2,3}$ 7.8, $^{3}J_{3,4}$ 7.6, $H_{Ca\ H3}$), 7.32 (t, 1H, $^{3}J_{5,6}$ 7.9, $^{3}J_{6,7}$ 7.0, $^{3}J_{6,8}$ 1.0, $H_{Ca\ H6}$), 7.51 (t, 1H, $^{3}J_{7,8}$ 8.1, $^{3}J_{6,7}$ 7.1, $^{4}J_{5,7}$ 1.0, $H_{Ca\ H7}$), 7.58 (d, 1H, $^{3}J_{7,8}$ 8.1, $H_{Ca\ H8}$), 7.78 (d, 1H, $^{3}J_{5,6}$ 7.7, $^{4}J_{4,6}$ 1.0, $H_{Ca\ H5}$), 7.85 (dd, 2H, $^{3}J_{2,3}$ 8.8, $^{4}J_{H,F}$ 5.4, $H_{Ph\ H2/H6}$), 8.14 (d, 1H, $^{3}J_{2,3}$ 7.8, $H_{Ca\ H2}$), 8.34 (d, 1H, $^{3}J_{3,4}$ 7.6, $H_{Ca\ H4}$), 10.47 (br. s., 1 H, NH) ppm, *signal overlay with solvent signal; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 111.5 (CH), 115.6 (d, $^{2}J_{C,F}$ 22, $CH_{Ph\ C3/C5}$), 118.2 (CH), 118.5 (C), 120.4 (CH), 120.6 (CH), 122.4 (C), 125.3 (C), 126.2 (CH), 126.8 (CH), 130.6 (CH), 132.0 (d, $^{3}J_{C,F}$ 9, $CH_{Ph\ C2/C6}$), 135.3 (d, $^{4}J_{C,F}$ 3, $C_{Ph\ C1}$), 140.1 (C), 140.3 (C), 165.0 (d, $^{1}J_{C,F}$ 253, $C_{Ph\ C4}$), 196.6 (CO) ppm; ^{19}F-NMR (376 MHz, $CDCl_3$): δ = −107.9 ppm; UPLC: t_R = 4.64 min (99%, monitored at 254 nm); MS (ESI^+, M calculated for $C_{19}H_{12}N_3FNO$ = 289.09) *m*/*z* (%): 290.25 (100) $[M + H]^+$. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of **1** in DCM layered with petroleum ether. For copies of ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra, HPLC chromatogram and MS spectrum see Supplementary Material.

4. Conclusions

The synthesis of 1-(4-fluorobenzoyl)-9*H*-carbazole (**1**) was achieved by BCl_3-mediated Friedel–Crafts acylation which represents a novel and site-specific entry to 1-aroyl-substituted carbazoles that lack the need to protect aromatic amine before synthesis.

Supplementary Materials: Copies of ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra, HPLC chromatogram and MS spectrum.

Author Contributions: Conceptualization, M.L.; methodology, M.L.; validation, M.L., J.K., M.K. and J.K.; formal analysis, M.L. and M.K.; investigation, M.L. and J.K.; resources, M.K. and T.K.; data curation, M.L. and M.K.; writing—original draft preparation, M.L.; writing—review and editing, M.L. and M.K.; visualization, M.L. and M.K.; supervision, T.K.; project administration, T.K.; funding acquisition, M.L. and T.K. All authors have read and agreed to the published version of the manuscript.

Funding: The authors are also thankful to the Deutsche Forschungsgemeinschaft (DFG) for supporting this work with the project 'Development of carborane-based COX-2 inhibitors for therapeutic diagnostic applications' (PI 304/7-1; M.L.).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The excellent technical assistance of Uta Lenkeit, Peggy Nehring, and Juliane Meyer is greatly acknowledged.

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

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