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Short Note

5-(4-Fluorophenyl)-3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazole

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Abstract: A new fluorinated 1-naphtyl pyrazoline (**4**) has been successfully synthesized by reacting a fluorinated 1-naphtyl chalcone (**3**) with phenyl hydrazine under microwave irradiation. The structure of compound **4** was characterized by UV-Vis, FTIR, HRMS, 1D NMR and 2D NMR spectroscopies.

Keywords: microwave-assisted synthesis; fluorinated pyrazoline; 1-naphtyl pyrazoline

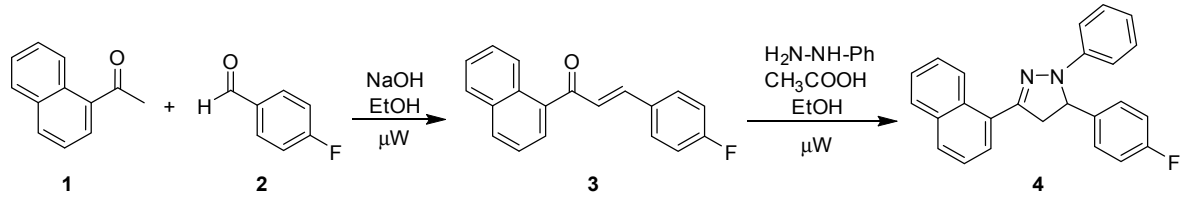
1. Introduction

The substituted pyrazolines can be synthesized via intermolecular cyclization between substituted chalcones and hydrazine derivatives. They are known to have various biological activities including antidepressant [1], antimalarial [2], antitumor [2,3], antibacterial [4,5] and anti-inflammatory [5–8]. Pyrazolines have also shown attractive fluorescents properties to detect some metal cations [9] and are excellent hole transport and emissive layer materials in organic electroluminescence devices [10,11]. In addition, they are also useful in agrochemical research [12]. Therefore, they have been widely synthesized for medication and other purposes.

In this paper, we would like to report the synthesis of a new fluorinated 1-naphtyl pyrazoline derived from a chalcone under microwave irradiation. This method was reported to have a variety of advantages, including shorter reaction time, better yield [13] and environmentally friendly effects [14,15].

2. Results

In this work, we have successfully synthesized a new fluorinated 1-naphtyl pyrazoline under microwave irradiation as shown in Scheme 1.



Scheme 1. The synthesis of 5-(4-fluorophenyl)-3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (**4**).

Compound **4** was obtained as a yellow solid in 71% yield. The melting point was recorded at 158–160 °C uncorr. The UV spectrum (MeOH) showed λ_{max} at 239 and 385 nm. The FTIR spectrum

(KBr) showed the absorption bands (cm^{-1}) at 3058, 1596, 1496, 1341 and 1230. The mass of **4** in HRMS spectrum was found at m/z = 365.4434 (100%), 366.4428 (45%) and 367.4399 (5%). The 1D and 2D NMR spectral data were shown in Table 1.

Table 1. NMR Spectroscopic Data (500 MHz for ^{1}H and 125 Hz for ^{13}C in $CDCl_3$) for **4**.

Position	δ_C (ppm), Type (*J* in Hz)	δ_H (ppm), (*J* in Hz)	HMBC
3	147.3, C	-	-
4	46.1, CH_2	H_{4a}: 3.36, dd (17.0, 7.0) H_{4b}: 4.07, dd (17.0, 12.5)	3, 5, 1′
5	62.6, CH	5.30, dd (12.5, 7.0)	3, 4, 1′, 2′
1′	138.2, d, C (3.8)	-	-
2′	127.6, d, CH (7.5)	7.36, dd (8.5, 5.5)	5, 4′, 6′
3′	116.1, d, CH (22.5)	7.05, t (8.5)	1′, 4′, 5′
4′	162.1, d, C (244.0)	-	-
5′	116.1, d, CH (22.5)	7.05, t (8.5)	1′, 3′, 4′
6′	127.6, d, CH (7.5)	7.36, dd (8.5, 5.5)	5, 2′, 4′
1′′	128.9, C	-	-
2′′	126.7, CH	7.47, d (7.0)	4′′, 9′′
3′′	124.9, CH	7.44, t (7.0)	1′′, 10′′
4′′	129.7, CH	7.84, dd (7.0, 1.0)	2′′, 5′′, 9′′
5′′	128.6, CH	7.91, d (8.5)	4′′, 7′′, 9′′
6′′	126.2, CH	7.59, dt (8.0, 1.0)	8′′, 10′′
7′′	127.4, CH	7.71, dt (8.0, 1.0)	5′′, 9′′
8′′	127.3, CH	9.56, d (8.5)	1′′, 6′′, 10′′
9′′	130.6, C	-	-
10′′	134.2, C	-	-
1′′′	144.6, C	-	-
2′′′	113.5, CH	7.14, d (7.5)	3′′′, 4′′′, 6′′′
3′′′	129.1, CH	7.26, t (7.5)	1′′′, 5′′′
4′′′	119.4, CH	6.85, t (7.5)	2′′′, 3′′′, 5′′′
5′′′	129.1, CH	7.26, t (7.5)	1′′′, 3′′′
6′′′	113.5, CH	7.14, d (7.5)	2′′′

3. Discussion

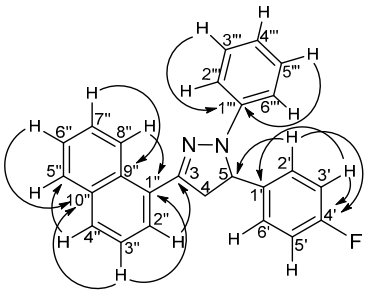
The synthesis of fluorinated 1-naphtyl pyrazoline in this work has been done by two-step reactions. The first step was synthesis of compound **3** via Claisen-Schmidt condensation between **1** and **2** by modification from previously described method [16]. The second step was synthesis of compound **4** via intermolecular cyclization of fluorinated chalcone with phenyl hydrazine using glacial acetic acid as cyclization agent, as shown in Scheme 1. The structure of compound **4** was characterized by UV, FTIR, LCMS, 1D NMR and 2D NMR spectroscopies.

The UV spectrum was recorded in MeOH and showed maxima at 239 and 385 nm. Both absorptions indicated the presence of conjugated double bonds in the naphthalenyl and phenyl rings of **4**. The FTIR spectrum showed the absorption bands (cm^{-1}) at 3058, 1596, 1496, 1341 and 1230, respectively due to the presence of aromatic C-H, C=N, C=C, C-N and C-F vibrations.

The ^{1}H-NMR spectrum of **4** as displayed in Table 1, showing the aliphatic proton signals at δ 3.36 and 4.07. Both signals indicated two aliphatic protons, H_{4a} (eq) and H_{4b} (ax), and coupling at 17.0 Hz due to the geminal coupling, whereas the signal at δ 5.30 indicated H_5 in the pyrazole ring. The aromatic proton signals at δ 9.56–6.85 (16H) were due to the presence of 1-naphthyl, 4′-fluorophenyl and phenyl rings as shown in Table 1. The signals at δ 7.36 (2H) and 7.05 (2H) showed the aromatic protons in 4′-fluorophenyl ring. Both signals not only showed the H-H coupling, but also showed the H-F coupling. Fluorine atom can couple with hydrogen or carbon nuclei in a similar manner as seen between two neighboring hydrogen nuclei [17]. Coupling of an aromatic proton to ^{19}F always gives the AA′BB′ system, an asymmetric appearance [18].

The ^{13}C-NMR spectrum of **4** showed two aliphatic carbon signals at δ 62.6 and 46.1 indicated at C5 and C4 in pyrazole ring, respectively. The signal at δ 147.3 (1H) due to the presence of C3 in pyrazole ring and the aromatic carbon signals at δ 162.1–113.5 was due to the presence of 1-naphthyl, 4′-fluorophenyl and phenyl rings, as shown in Table 1. Four aromatic carbon signals at δ 162.1, 116.1, 112.6, and 138.2, respectively were observed as doublet. The multiplicities due to the 1–4 bonds *J* coupling to ^{19}F. In this case, we obtained the $^{1}J_{C\text{-}F}$ (244 Hz), $^{2}J_{C\text{-}F}$ (22.5 Hz), $^{3}J_{C\text{-}F}$ (7.5 Hz) and $^{4}J_{C\text{-}F}$ (3.75 Hz).

The HSQC spectrum showed that H_{4a} and H_{4b} correlated with the carbon signal at δ 46.1 and H_5 correlated with the carbon signal at δ 63.9. The correlations indicated that C4 is a secondary carbon, whereas C5 is tertiary carbon. In addition, the ^{1}H-^{13}C long range connectivities were also discussed based on HMBC spectral data as displayed in Table 1. The important HMBC in naphthyl, 4′-fluorophenyl, and phenyl rings were illustrated in Scheme 2.



Scheme 2. The important HMBC correlations of **4**.

4. Experimental Section

4.1. General Informations

The materials used in this work include 1-acetylnaphthalene, 4-fluorobenzaldehyde, sodium hydroxide, hydrochloric acid, phenyl hydrazine, glacial acetic acid, universal indicator, and some organic solvents, such as ethanol, *n*-hexane and ethyl acetate, were produced by Merck. The synthesis reactions were carried out in an ace pressure tube using a Samsung ME109F domestic microwave oven. Melting point was determined on a Fisher-Johns apparatus (Fisher Scientific, Waltham, MA, USA) (uncorr). TLC Analysis was carried out using GF_{254} (Merck Millipore, Darmstadt, Germany) under UV Lamp 254/366 nm (Camag™, Camag Chemie-Erzeugnisse & Adsorptionstechnik AG, Muttenz, Switzerland). UV spectrum were recorded on Genesys™ 10S UV-Visible spectrophotometer (Thermo Scientific™, Waltham, MA, USA). FTIR spectra were recorded in KBr powder on a Shimadzu® FT-IR Prestige-21 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Mass spectral data were recorded on LC-HRMS Mariner Biospectrometry™ (Applied Biosystems, Foster City, CA, USA). ^{1}H and ^{13}C-NMR spectral data were recorded on an Agilent® (Agilent Technologies, Santa Clara, CA, USA) at 500 MHz and 125 MHz, respectively.

4.2. Synthesis of 5-(4-Fluorophenyl)-3-(naphthalen-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazole (**4**)

Some 1 mmol compound **3** and 2 mmol phenyl hydrazine were added into an ace pressure tube and dissolved in 10 mL ethanol. Then, three drops of acetic glacial acid was added into the tube and the mixture was irradiated using a domestic microwave oven (180 W) for 10 min. The reaction was monitored every 30 s of irradiation by TLC until the reaction was completed. Then, the mixture was cooled to afford a precipitate. The precipitate was filtered *in vacuo*, washed by cold *n*-hexane and allowed to dry in a desiccator. Then, it was recrystallized in a mixture of ethyl acetate and *n*-hexane to get compound **4**.

Yellow solid (71% yield); m.p. 158–160 °C uncorr; UV (MeOH) λ_{max} (nm): 239 and 385; FTIR (KBr) ν(cm^{-1}): 3058, 1596, 1496, 1341 and 1230. HRMS: m/z = 365.4434 (100%), 366.4428 (45%) and 367.4399 (5%). ^{1}H and ^{13}C-NMR spectral data is provided in Table 1. Copies of HRMS, 1D and 2D spectra of **4** (Figures S1–S7) are provided in the Supplementary Materials.

5. Conclusions

In summary, we have successfully applied the domestic microwave oven to synthesize a new fluorinated 1-naphtyl pyrazoline (**4**). The reaction occurred in a short time and under simple reaction conditions in 71% yield. All the spectroscopic data agreed with the structure of product that we expected.

Supplementary Materials: The MDL molfile and the other supplementary materials are available online at http://www.mdpi.com/1422-8599/2016/2/M891.

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Author Contributions: J.J. and A.Z. designed the whole experiments; J.J. and I.I. performed the experiments and contributed to manuscript; I.I. and H.Y.T. analyzed the HRMS, 1D and 2D NMR spectral data and wrote the manuscript; All authors read and approved the final manuscript.

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

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