

Short Note

(7E)-3-(4-Methoxyphenyl)-7-[(4-methoxyphenyl)methylidene]-4,5,6,7-tetrahydro-3aH-indazole

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Abstract: Indazole derivatives are well known to have various pharmacological activities. We synthesized a novel derivative of indazole, namely (7E)-3-(4-methoxyphenyl)-7-[(4-methoxyphenyl)methylidene]-4,5,6,7-tetrahydro-3aH-indazole by condensation reaction between 3-(4-methoxyphenyl)-3,3a,4,5,6,7-hexahydro-2H-indazole and 4-methoxy-benzaldehyde in good yield (61%).

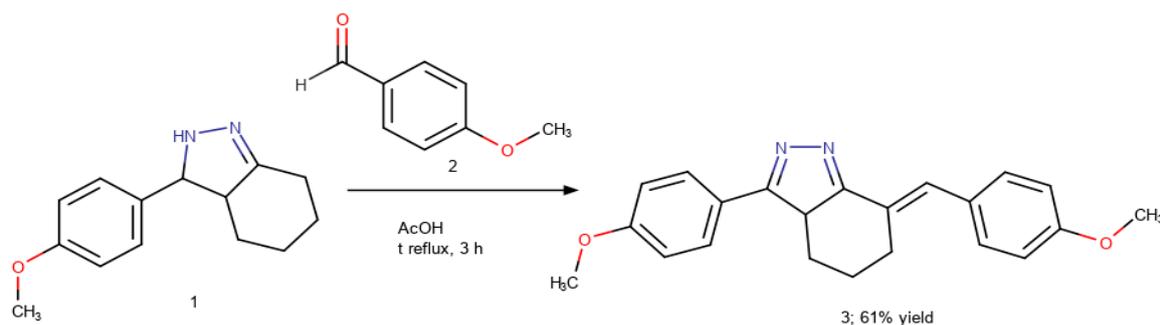
Keywords: indazole derivatives; hexahydro-indazole; tetrahydro-indazole; *p*-methoxybenzaldehyde; condensation

1. Introduction

Indazole derivatives are well known to have various pharmacological activities such as antitumor, anti-inflammatory, antioxidant, antiplatelet, anti-HIV, antihypertensive, serotonin 5-HT₃ receptor antagonist, and others. They are rarely obtained from nature, but most of them are synthetic compounds [1–4]. Due to the importance of the indazole ring in drug development, many chemists were motivated to take the initiative to develop different methods for this heterocycle synthesis. In the present time, there are more than 30 synthesis methods for indazole derivatives, most of them for 1H and 2H indazole derivatives [1–3]. Conversion of the benzene ring of 2H-indazole structure with cyclohexane ring afforded 3,3a,4,5,6,7-hexahydro-2H-indazoles. The general synthesis method for the compounds was by condensation of α,β -unsaturated carbonyl with hydrazine in ethanol as a solvent. These modified indazoles also showed various biological activities [3,5–7]. Attracting our interest in their anti-cancer activities, herein, we report the synthesis of a novel derivative of indazole, (7E)-3-(4-methoxyphenyl)-7-[(4-methoxyphenyl)methylidene]-4,5,6,7-tetrahydro-3aH-indazole.

2. Results and Discussion

The starting material, 3-(4-methoxyphenyl)-3,3a,4,5,6,7-hexahydro-2H-indazole (1), was prepared by the condensation of 2-benzylidenecyclohexanone and 4-methoxy-benzaldehyde according to the reported method [6]. The condensation reaction between 1 and 4-methoxy-benzaldehyde (2) in glacial acetic acid at 120 °C (reflux) for 3 h found compound 3, (7E)-3-(4-methoxyphenyl)-7-[(4-methoxyphenyl)methylidene]-4,5,6,7-tetrahydro-3aH-indazole (3) (Scheme 1).



Scheme 1. Synthesis of the title compound.

The Fourier transform infrared (FTIR) indicated that the NH peak of the title compound (**3**) disappeared. In the $^1\text{H-NMR}$ spectrum, protons of NH and HC-N at about 5.00 and 5.32 ppm were not observed either [7]. Meanwhile, six protons of the two methoxy groups in the two aromatic rings appeared as two peaks at 3.85 ppm (s, 3H) and 3.84 ppm (s, 3H). Protons of CH connecting the two C=N of indazole nucleus and ethylenic (CH=C) appeared as a triplet at 3.84–3.85 ppm (1H) and as singlet peak at 7.10 ppm (1H), respectively. While the eight protons of the two di-substituted phenyl rings at para position appeared as doublet peaks at 7.53 ppm (2H), 7.32 ppm (2H), and as a double doublet peak at 6.89 ppm (4H). The disappearance of CH_2 protons adjacent to the C=N group (C7) indicated the substitution of phenylmethylened moiety occurred at that position. The $^{13}\text{C-NMR}$ spectrum showed the presence of two carbon of C=N (peaks at 158.9 and 157.8 ppm) and carbon of C=C (ethylenic) (peaks at 130.0 and 114.7 ppm) [8,9]. The spectroscopic data of the structure were supported by the high-resolution mass spectrum (HR-MS). The peak of the molecular ion was found at m/z 347.17514 ($[\text{M} + \text{H}]^+$). Those values are fully in accordance with the structure of compound **3**. The FTIR, NMR and HR-MS spectra can be seen in "Supplementary Materials."

The condensation reaction between the hexahydro-indazole **1** and aromatic aldehyde **2** occurred because the methylene group at position 7 of **1** has alpha hydrogen and adjacent to the azomethine (C=N) group having carbonyl properties [10]. The reaction conditions with glacial acetic acid as a solvent and reflux temperature caused dehydration to obtain α,β -unsaturated imine moiety accompanied by dehydrogenation of heterocycle: 3,3a,4,5,6,7-hexahydro-2H-indazole to be 4,5,6,7-tetrahydro-3aH-indazole. Probable dehydrogenation of the pyrazoline ring of 3,3a,4,5,6,7-hexahydro-2H-indazole was due to aerobic aromatization. The released H_2O was then dehydrated by glacial acetic acid.

A similar product, its tautomeric enamine form, has already been prepared but with a different procedure. The compound was obtained by oxidation of (7E)-3-(4-methoxyphenyl)-7-[(4-methoxyphenyl)-methylidene]-3,3a,4,5,6,7-hexahydro-2H-indazole with a Fe(III)-based reagent in alkaline condition [11]. In the H-NMR spectrum, the main difference in the structure of the two compounds is clearly observed. In compound **3**, the proton peak of 3a-H appears at 3.84–3.85 ppm and lacks proton NH at 9.91 ppm, while in the tautomer form, the NH proton appears at 9.91 ppm and lacks the proton peak at 3.85 ppm [11].

3. Materials and Methods

3.1. General

All chemicals (synthesis or analytical grade) used are purchased commercially. The TLC method was used to evaluate the purity of synthesized compounds. The melting point (uncorrected) was measured by the melting point device (Bibby Sterilin, Staffordshire, UK). Infrared (IR), proton/carbon nuclear magnetic resonance ($^1\text{H}/^{13}\text{C-NMR}$) spectra were recorded on an FTIR spectrophotometer (8400S, Shimadzu, Kyoto, Japan) and a JEOL spectrometer (JNM-ECZ500R/S1, Peabody, MA, USA),

respectively. Meanwhile, the mass spectra (MS) were analyzed by LC-MS/MS (UNIFI-Waters, Milford, MA, USA) with ESI (+) mode.

3.2. Synthesis of (7E)-3-(4-Methoxyphenyl)-7-[(4-methoxyphenyl)methylidene]-4,5,6,7-tetrahydro-3aH-indazole (3)

The synthesis of the title compound (3) was performed according to synthesis method of styryl quinazolinones derivatives reported earlier [12,13]. A mixture of 3-(4-methoxyphenyl)-3,3a,4,5,6,7-hexahydro-2H-indazole (115 mg, 0.5 mmol) and 4-methoxy-benzaldehyde (68 mg, 0.5 mmol) was dissolved in glacial acetic acid (10 mL) and refluxed at 120 °C for 3 h until completion (TLC monitoring). Then, the mixture was poured onto crushed ice, filtered off and washed with cold water to obtain a solid product. Recrystallization from ethyl acetate afforded the pure compound (3) as a pale-yellow powder in 61% yield (106 mg) and mp 252–254 °C. FT-IR (KBr), ν (cm⁻¹): 3053 (Ar-H), 2953 (C-H), 1605 and 1580 (C=N), 1512 and 1450 (C=C), 1250 and 1178 (Ar-O and C-O ether). ¹H-NMR (500 MHz, CDCl₃) δ , ppm: 7.53 (d, *J* = 8 Hz, 2H, H-Ar), 7.32 (d, *J* = 8 Hz, 2H, H-Ar), 7.10 (s, 1H, CH=), 6.89 (dd, *J* = 8 Hz, 4H, H-Ar), 3.84–3.85 (t, *J* = 2–4 Hz, 1H, 3a-H, little overlap with protons of OCH₃), 3.84 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 2.77–2.79 (m, 4H, 4-H and 6-H), 1.86–1.88 (m, 2H, 5-H). ¹³C-NMR: (500 MHz, CDCl₃) δ , ppm: 158.9 (1C), 157.9 (1C), 145.1 (1C), 144.4 (1C), 131.0 (2C), 130.0 (1C), 129.4 (1C), 128.6 (2C), 114.7 (1C), 114.2 (2C), 113.8 (2C), 55.5 (2C), 55.4 (1C), 27.1 (1C), 24.5 (1C), 22.0 (1C). ESI-MS+ (*m/z*): found 347.17514 [M + H]⁺; calc for neutral mass of C₂₂H₂₂N₂O₂ = 346.16813; Mass Error = -0.3 mDa.

Supplementary Materials: The following are available online, Figure S1: FTIR of 3-(4-methoxyphenyl)-3,3a,4,5,6,7-hexahydro-2H-indazole (1); Figure S2: FT-IR spectrum of compound 3; Figure S3: ¹H-NMR spectrum of compound 3; Figure S4: ¹³C-NMR spectrum of compound 3; Figure S5: HR-MS spectrum of compound 3.

Author Contributions: H.H. (Hariyanti Hariyanti) conducted the experiment; H.H. (Hayun Hayun), A.Y., and K.K. supervised the experiment; H.H. (Hariyanti Hariyanti) and H.H. (Hayun Hayun) wrote and revised the manuscript. All authors agreed to the final version of this manuscript.

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

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