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Synthesis and Characterization of 2-Benzamido-*N*-Benzoylbenzamide

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Abstract
Anthranilamide or 2-aminobenzamide is imide form of anthranilic acid. Anthranilamide derivatives is used for analgesic, antipyretic, anti-inflammatory, antimicrobial, antiangiogenic, and anticoagulant activity. 2-benzamido-N-benzoylbenzamide was obtained Schotten-Baumann reaction via the acylation of anthranilamide with benzoyl chloride. The structure of the 2-benzamido-N-benzoylbenzamide was purified test by Thin Layer Chromatography (TLC) and melting point range test; confirmed by UV-Vis Spectrophotometry, FT-IR and ^{1}H-NMR. Yield 71%.

KEYWORDS : ***Anthranilamide, Acylation, Benzoyl Chloride, Schotten-Baumann Reaction***

I. INTRODUCTION

Anthranilamide (*o*-aminobenzamides) is a anthranilic acid derivatives that has the potential of biological activity to be developed as new drugs. Some of anthranilamide derivatives had been reported as analgesic, antipyretic, anti-inflammatory, antimicrobial, antiangiogenic, and anticoagulant activity (Heindel, 1971; Kurbatov, 2014; Bashir, 2012; Haberey,2002; Pandya, 2012). Research on the synthesis of 2-benzamido-*N*-benzoylbenzamide from the starting material of anthranilamide was reacted with benzoyl chloride derivatives. The general procedure of synthesis was used tetrahydrofuran as solvent and pyridine as catalyst to obtain 2-benzamido-*N*-benzoylbenzamide (Nevin, 2012). In this research aims to synthesis and characterization of 2-benzamido-*N*-benzoylbenzamide.

II. EXPERIMENTAL

a. Instruments

Reactions were monitored with TLC using pre-coated aluminum sheets with GF254 silica gel, 0.2 mm layer thickness (E. Merck). Eluen for TLC using ethyl acetate : chloroform (1:3); ethyl acetate : n-hexane (2:3), and the spots were visualized in UV chamber. Melting points were determined on Electrothermal melting point apparatus. The IR spectra of the compounds were recorded Perkin Elmer Spectrum One spectrophotometer using KBr disks. :H- NMR spectra were obtained on JEOL JNM-ECS 400 (^{1}H-NMR: 400 MHz, 13C-NMR: 100 MHz) instrument from Institute of Tropical Disease Airlangga University. We used DMSO-d6 as solven for ^{1}H- NMR analysis. The chemical shifts are reported in d scale (ppm) downfield from internal tetramethylsilane (TMS) (chemical shift in δ values).

b. Synthesis of 2-benzamido-N-benzoylbenzamide

To a stirred solution of anthranilamide (2.7 mmol) in tetrahydrofuran (25 ml) and pyridine (1 ml). Benzoyl chloride (5.0 mmol) in THF (10 ml) on was added dropwise, in tetrahydrofuran tetrahydrofuran water bath while stirred by magnetic stirrer. The reaction mixture was stay for another 1h at room temperature. The reaction mixture was refluxed for another 1h, maintaining temperature 60-70 ^{o}C. The reaction mixture was rotavapor until a solid product was formed. The reaction mixture neutralized with saturated sodium bicarbonate solution and white solid which separated was filtered, washed with aquabidest and recrystallized from 96% ethanol and characterized by IR and ^{1}H-NMR. M.P. 216-218 ˚C, Yield 71%.

III. RESULT AND DISCUSSION

In the present work, an attempt has been made to undertake the synthesis of 2-benzamido-*N*-benzoylbenzamide through a multi steps process. For this purpose, a mol ratio is required which is the use of twice the amount of benzoyl chloride toward anthranilic acid using tetrahydrofuran as a solvent and pyridine as a base (Furnis, 1978). When 2-benzamido-*N*-benzoylbenzamide crystals are formed. The product was characterized by IR and its melting point was determined. The reaction is depicted in Figure 1. The mechanism of synhesis is Schotten-Baumann reaction, the first step of the reaction is addition of the nucleophilic amide (-$CONH_2$) Anthranilamide to the electrophilic carbonyl group from acyl chloride. The base is important because it removes the proton from the -NH_2 as it attacks the carbonyl group (McMurry, 1984). The intermediate product will collapses again by an elimination reaction, this time losing chloride ion, and forming the amide compound (Fessenden, 1999). Second step of the reaction is addition of the nucleophilic amine (-NH_2) Anthranilic acid to the electrophilic carbonyl group from acyl chloride. The base is important because it removes the proton from the -NH_2 as it attacks the

carbonyl group. The intermediate product will collapses again by an elimination reaction, this time losing chloride ion, and forming the amide compound.

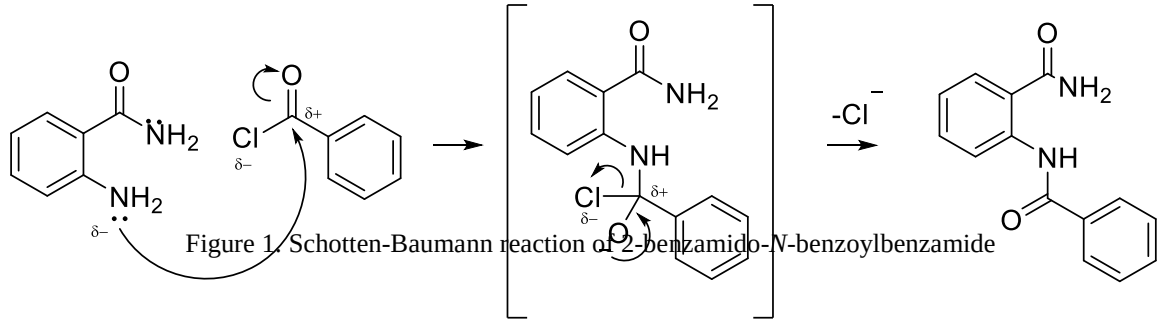
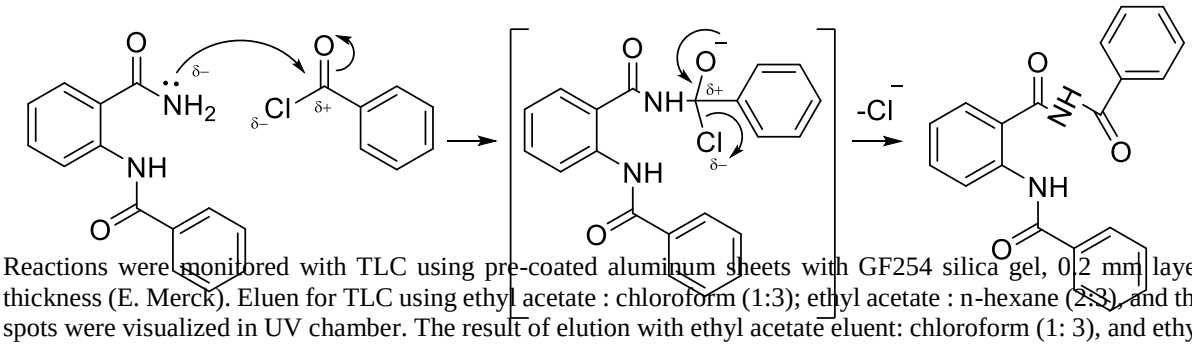


Figure 1. Schotten-Baumann reaction of 2-benzamido-*N*-benzoylbenzamide



Reactions were monitored with TLC using pre-coated aluminum sheets with GF254 silica gel, 0,2 mm layer thickness (E. Merck). Eluen for TLC using ethyl acetate : chloroform (1:3); ethyl acetate : n-hexane (2:3), and the spots were visualized in UV chamber. The result of elution with ethyl acetate eluent: chloroform (1: 3), and ethyl acetate: hexane (2: 3), at compound BB1 obtained a single stain with Rf value of 0.57; and 0,37;

The melting point was determined using electrothermal melting point apparatus. The melting point of 2-benzamido-*N*-benzoylbenzamide was determined to be 216-218 °C. Structural elucidation of compounds was accompanied by UV-Vis, IR, ^{1}H-NMR.

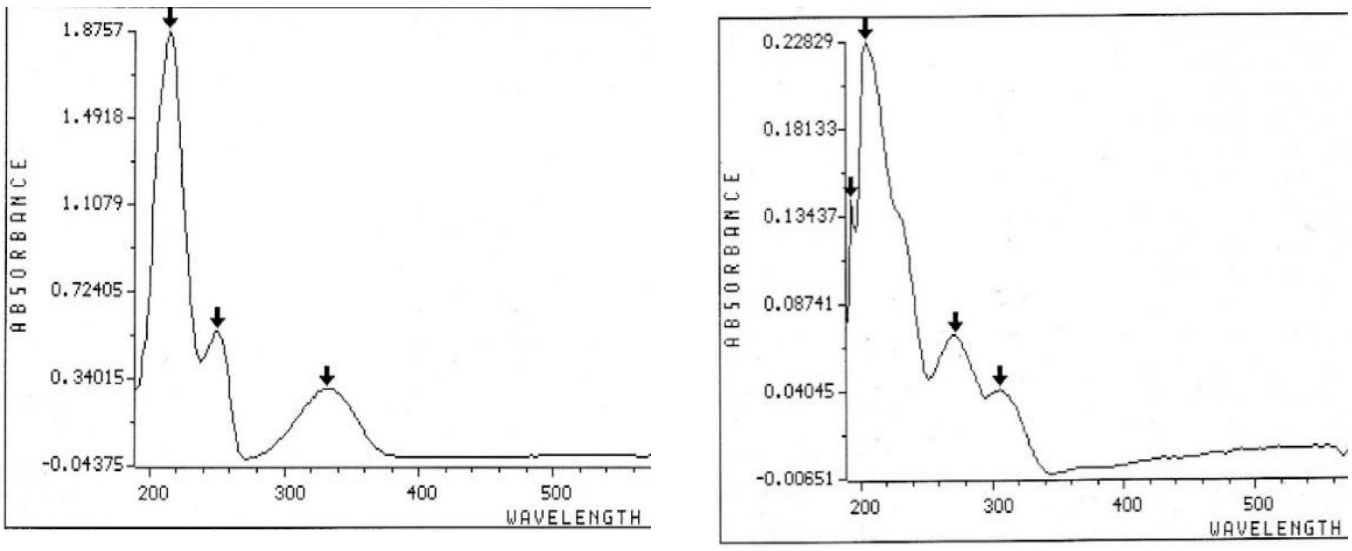


Figure 2 UV-Visible spectroscopy results of anthranilamide (left) and of 2-benzamido-*N*-benzoylbenzamide (right) of ethanol

Table 1 Characteristics of the UV-Visible spectroscopy of absorption peak anthranilamide and 2-benzamido-*N*-benzoylbenzamide

No.	Compound	λ maks (nm)
1.	anthranilamide	214, 250, 332
2.	2-benzamido-*N*-benzoylbenzamide	204, 272, 306

Based on the figure 2, we obtain 2-benzamido-*N*-benzoylbenzamide ultraviolet in ethanol absolute at 1 ppm there are 3 absorption peaks at maximum wavelength 204; 272; 306 nm. 2-benzamido-*N*-benzoylbenzamide ultraviolet in ethanol absolute at 1 ppm there are 3 absorption peaks at maximum wavelength 214; 250; 332 nm. Differences in the spectral pattern of the synthesized compound with the starting material spectral pattern indicating that the starting compound produced the synthesis product.

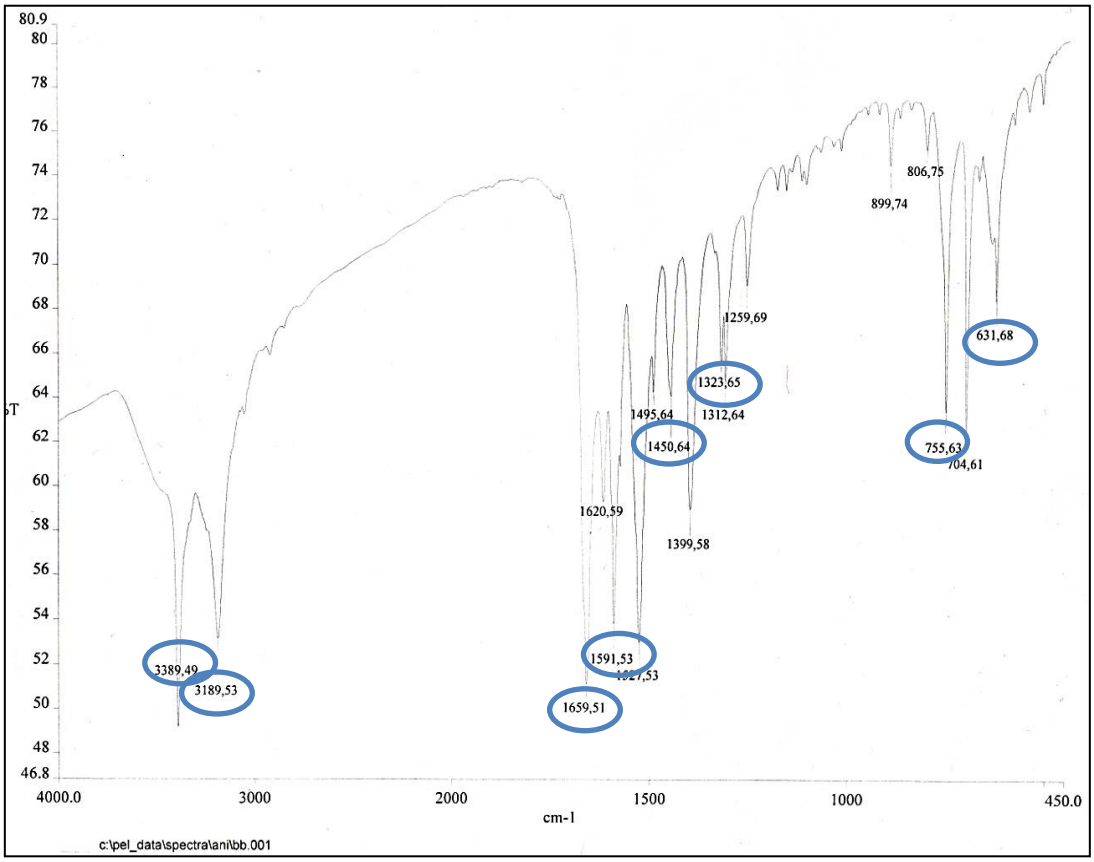


Figure 3. Spectra FTIR of 2-benzamido-*N*-benzoylbenzamide

Table 2. Absorption peak of of 2-benzamido-*N*-benzoylbenzamide on FT-IR Spectra (Pavia, 1990)

Functional Group	Absorption peak (cm^{-1})	Intensity	Theoretic absorption peak (cm^{-1}) *
N-H secondary amine	3389	strong	3500-3100
N-H wag (broad)	631	moderate	900-605
C=C aromatic	1591 and 1450	moderate	1600 and 1475
C=O amide	1659	strong	1680-1620
C-H aromatic	3189	moderate	3110-3000
C-N (amine aromatic)	1323	moderate	1350-1000
1,2 aromatic disubstituted	755	strong	750

The strong absorption at about 1659 cm^{-1} is due to the C=O stretching vibration and the moderate intensity absorption at 1323 cm^{-1} corresponds to a C-N stretching vibration. Formation of the product was confirmed by a sharp band at 1659 cm^{-1} for C=O group along with a band at 3389 cm^{-1} for N-H secondary amine in IR spectra. Also, there were moderate intensity absorption at 3189 cm^{-1} corresponds to a C-H aromatic; moderate intensity absorption at 1591 dan 1450 cm^{-1} corresponds to a C=H aromatic; strong absorption at about 755 cm^{-1} is due to the 1-2 aromatic disubstituted; and moderate intensity absorption at 631 cm^{-1} corresponds to a C=C aromatic.

Appearance of bands near 3389 cm^{-1} for N-H secondary amine also helped in assigning the structure of ^{1}H-NMR were confirmed the structure of 2-benzamido-*N*-benzoylbenzamide (Silverstain, 1981).

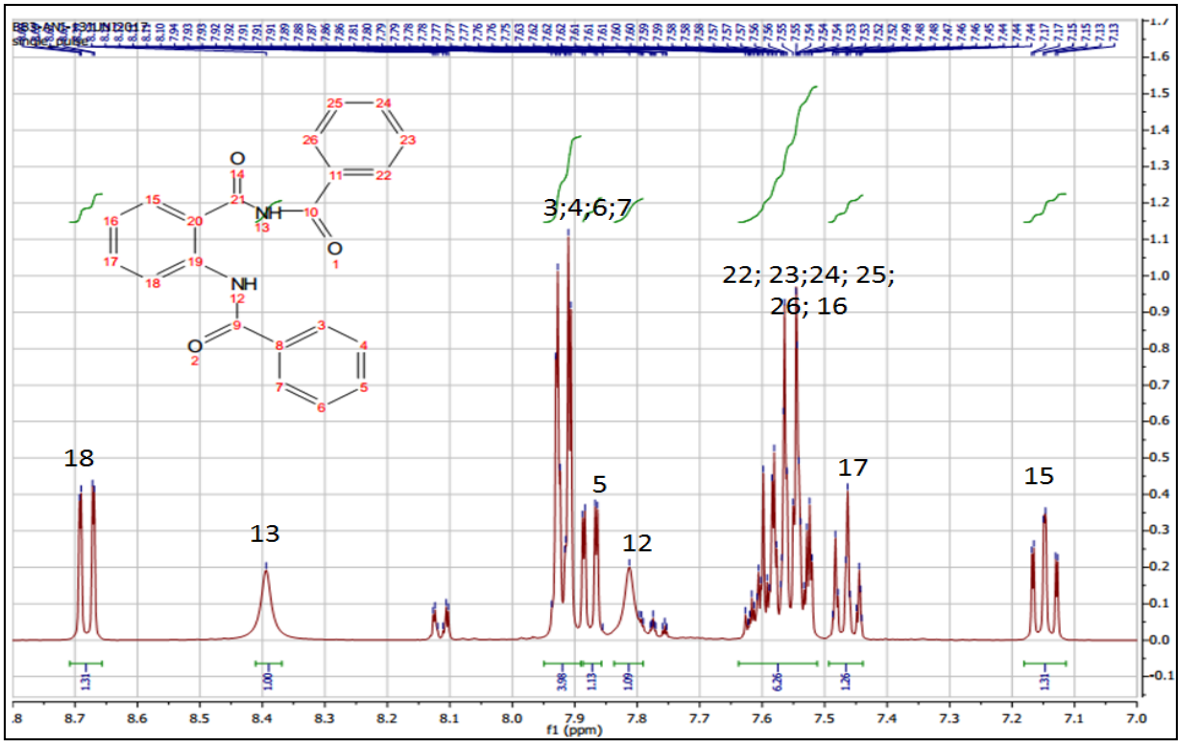


Table 3 Interpretation of ^{1}H-NMR spectra data 2-benzamido-*N*-benzoylbenzamide

Peak of Frequency (ppm)	Peak Multiplicity (s,d, etc)	Peak integration (Number of Protons)	Proton(s) in Molecule
8,68	dd, J=8,4 Hz; 1,2 Hz	1	18
8,39	s	1	13
7,92	d, J=1,2 Hz	2	3;7
7,90	d, J=2,0 Hz	2	4;6
7,88	dd, J=8,0 Hz; 1,5 Hz	1	5
7,09	s	1	12
7,63-7,52	m	6	22; 26; and 23;25 and 26;16
7,49-7,44	t, J= 7,6 Hz	1	17
7,15	t, J= 7,6 Hz	1	15
Total		16	18

(Pavia, 1990)

Based on figure 4 and table 3 the result of ^{1}H-NMR spectra analysis of 2-benzamido-*N*-benzoylbenzamide obtained the peaks which are in the aromatic H atomic area of about 6.5-8 ppm. There are 14 H atoms in the region of 8.68-7.15 ppm is the absorption of H aromatic atoms. The peak of this aromatic atom is doubledoblet at 8.68 ppm with an integration ratio of 1 (H at atom C number 18); doblet at 7.92 ppm with an integration ratio of 2 (H on atom C numbers 3 and 7); doblet at 7.90 ppm with an integration ratio of 2 (H on atom C numbers 4 and 6); doubledoblet area 7.88 ppm with an integration ratio of 1 (H of atom C number 5); multiplet area 7,63-7,52 ppm with integration ratio 6 (H of atom C number 16; 22; 23; 24; 25; 26); triplet area 7,49-7,44 ppm with comparison of integration 1 (H of atom C number 17); and a regional triplet of 7.15 ppm with an integration ratio of 1 (H from atom C number 15). There are 2 H atoms which are the absorption of H atoms from -NH amide which is theoretically according to Pavia (2009) is in the region of 5-9 ppm. The atomic absorption peaks H of -NH amide include singlet at 8.39 ppm region with an integration ratio of 1 (-NH at number 13); and singlet at 7.09 ppm with the integration ratio of 1 (-NH at number 12).

IV. CONCLUSION

The lead compounds of 2-benzamido-*N*-benzoylbenzamide were characterized by melting point, TLC, UV-Vis, IR and 1HNMR spectral studies.

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