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A Convenient Method for the Preparation of 2-Aminobenzophenone Derivatives under Ultrasonic Irradiation

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A quick and convenient method for the preparation of 2-aminobenzophenone derivatives is described. This approach consists of the nucleophilic substitution reaction of nitrobenzenes by phenylacetonitrile under conventional and ultrasonic conditions followed by reduction of the produced 2,1-benzisoxazole to 2-aminobenzophenone. This 2-step reaction was studied by changing the reaction parameters (reaction temperature, ultrasound power, and reaction time). The results clearly demonstrated that using ultrasound irradiation results in a high yield within a short reaction time.

Introduction

2-Aminobenzophenone derivatives are important compounds in organic chemistry because of their application in heterocyclic synthesis and medicines.¹ 2-Aminobenzophenones have been used as starting material for the synthesis of a wide variety of heterocyclic systems, such as fluorenones, acridines, acridones, cinnolines, quinazolines, indazoles,^{1,2} and 3-arylindoles.^{3,4} Furthermore, 4-arylquinazolones,^{5,6} 4-arylquinolines,⁷⁻⁹ 4-arylquinoline-2-ones,¹⁰ polyphenylquinolines,¹¹⁻¹⁵ and 1,4-benzodiazepines¹⁶⁻¹⁸ have been prepared from 2-aminobenzophenones. The pharmacological activity of 1,4-benzodiazepines¹⁶⁻²¹ is the most important focus in the study of the preparation of 2-aminobenzophenone derivatives. Several drugs possessing high pharmaceutical activity, such as chlordiazepoxide **1** (clinical psychosis),²² proquazone **2**, and amfenac **3** (anti-inflammatory agents)²³ (Figure 1) have been prepared from 2-aminobenzophenones. Recently, it has been revealed that 2-aminobenzophenone of type **4** (Figure 1) has anti-vascular and cytotoxic effects.²⁴⁻²⁶

There are some general methods for the preparation of 2-aminobenzophenones, such as Friedel-Crafts reaction of anthranilic acid derivatives with aryl compounds,²⁷ Friedel-Crafts acylation of para substituted anilines,²⁸ and reaction of aryl-Grignard reagents with 2-nitro or 2-aminobenzaldehydes.²⁵ These methods are common, but contain several additional steps, such as protecting and deprotecting of the amino group. Moreover, Friedel-Crafts reaction is incompatible with electron withdrawing substituents. Chemical or catalytic reduction of 2,1-benzisoxazole derivatives in a facile and one-step method for the preparation of 2-aminobenzophenones was reported by Simpson²⁹ and Walker.³⁰

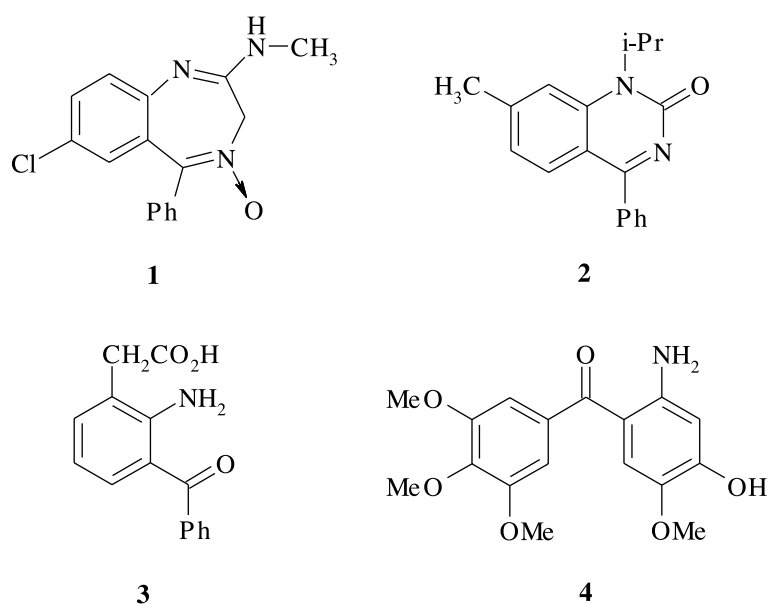


Figure 1. Several drugs prepared from 2-aminobenzophenone derivatives.

2,1-Benzisoxazoles can be prepared by several methods,³¹ including the reduction of *o*-nitrobenzoyl³² or *o*-nitrosobenzoyl³³ compounds, and dehydration of *o*-nitrotulenes.³⁴ Preparation of 2,1-benzisoxazoles, especially those bearing electron withdrawing substituents, from nitrobenzene and phenylacetonitrile in methanolic potassium hydroxide is a convenient one-step method.^{31,35}

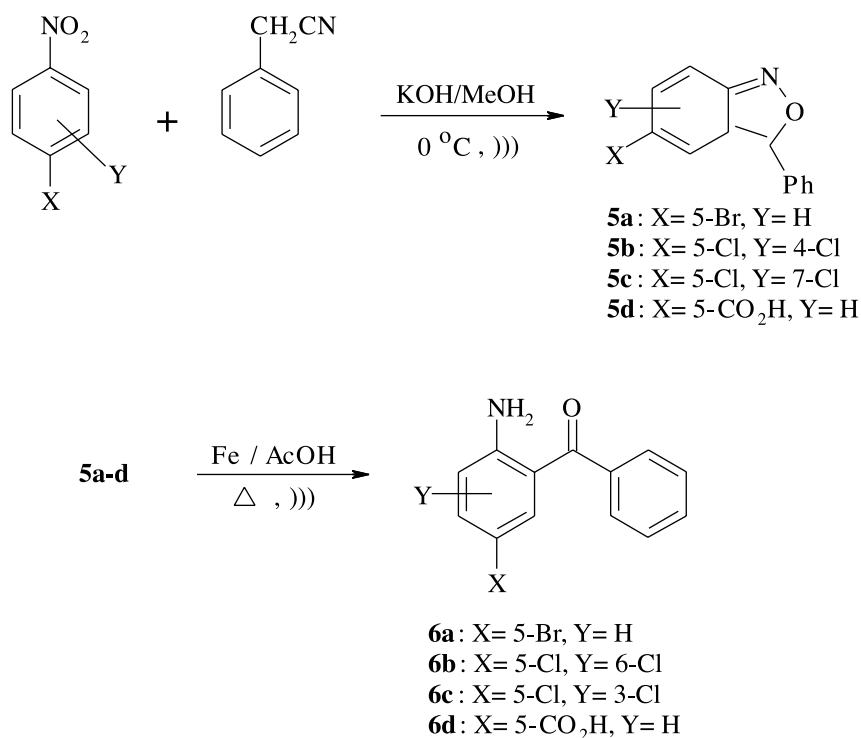


Figure 2. Approach to the preparation of 2-aminobenzophenones.

Herein, we describe a facile approach for the preparation of some new 2-aminobenzophenones in 2 steps (Figure 2). 2,1-Benzisoxazoles **5** were prepared via an aromatic nucleophilic substitution of nitrobenzene derivatives by phenylacetonitrile in methanolic potassium hydroxide. Then, the corresponding 2-aminobenzophenones **6** were produced by reduction of the compounds **5** with an Fe/acetic acid mixture. We also carried out the experiment using ultrasound conditions.

Results and Discussion

A series of 2-aminobenzophenones **6** was prepared by reduction of 2,1-benzisoxazoles **5**. The preparation of compounds **5** was carried out by treatment of nitrobenzene derivatives with phenyl acetonitrile in excess methanolic potassium hydroxide under conventional and ultrasonic conditions.

As seen in Table 1, in the starting condition 2,1-benzisoxazoles were obtained in fair to good yields. Due to the high interest of using ultrasound irradiation for these kinds of reactions, we tested this condition. Although the yields in ultrasonic conditions did not exceed 76%, such results are significant because of the short reaction time.

Table 1. Preparation of 2,1-benzisoxazoles **5** in conventional and ultrasound conditions at 0 °C.

Product	Conventional conditions		Ultrasound irradiation	
	Time (h)	Yield (%)	Time (h)	Yield (%)
5a	6	65 (66) ³⁶	0.5	60
5b	6	70	0.5	65
5c	6	80	0.5	76
5d	6	50	0.5	50

The reduction of 2,1-benzisoxazoles **5** was carried out by changing the reaction temperatures and also using ultrasound instead of heat. Initially, the best 2,1-benzisoxazoles **5**:acid ratio and the optimum amount of Fe were investigated. The results showed that compound **5**:acid ratio of 1:10 (mmol/mL) and 11 mmol Fe is optimal. The present procedure using Fe resulted in these products being obtained at 90 °C and within shorter reaction times, as indicated in Table 2. In comparison with the literature,³⁶ we reduced the amount of acid to less than one third, which resulted in a better yield in a shorter time. We obtained the same results using ultrasound irradiation for this step with a moderate temperature. Ultrasound effects on organic reactions are attributed to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid.^{37–39} Cavitation induces very high local temperatures and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer.

Table 2. Effects of temperature and ultrasound in the reduction of 2,1-benzisoxazoles **5** to 2-aminobenzophenones **6**.

Product	60 °C		80 °C		90 °C		Ultrasound irradiation (25 °C)	
	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
6a	140	70	120	70	80 (150) ³⁶	75 (70) ³⁶	20	75
6b	120	75	100	83	80	98	30	98
6c	120	80	100	85	80	95	20	95
6d	120	80	100	86	80	90	30	90

In summary, it was determined that ultrasound promoted reactions of nucleophilic substitution of nitrobenzenes and reduction of 2,1-benzisoxazoles to prepare 2-aminobenzophenones. This procedure has the advantage of shorter reaction time relative to common methods with an efficient yield.

Experimental

General: Melting points are uncorrected. FT-IR spectra were recorded on a Nicolet Magna 550 spectrometer (KBr). ^1H NMR and ^{13}C NMR spectra were determined on a Bruker DRX-500 Avance spectrometer (500 MHz) using CDCl_3 and DMSO-d_6 as the solvent and TMS as the internal standard. Mass spectra were obtained on a QP 1100 EX spectrometer. Elemental analysis was determined with a Carlo Erba model EA 1108. Sonication was performed in a LEO-150 ultrasonic cleaner with a frequency of 46 kHz and a nominal power of 200 W.

First step; preparation of 3-phenyl-2,1-benzisoxazole (5a-c). To a solution of 8 g of potassium hydroxide in 10 mL of methanol³⁵ was added 0.65 g (5.5 mmol) of phenylacetonitrile with stirring and cooling in an ice bath. After 30 min, a solution of 5 mmol of nitrobenzene derivatives in 5 mL of methanol-THF (3:1) was added dropwise to the mixture. The mixture was stirred for 4 h at 0 °C and 2 h at room temperature. In the ultrasonic procedure, the flask was located at the maximum energy area, which made more cavitation in solution in the ultrasonic cleaner, and sonicated for the period as indicated in Table 1. Sonication continued until the disappearance of starting materials on TLC. Then, 100 mL of cool water was added with stirring. The precipitate was filtered, washed with 50 mL of a cool mixture of water-methanol (3:1), dried with vacuum, and recrystallized in methanol.

5-Bromo-3-phenyl-2,1-benzisoxazole (5a). 1.01 g (5 mmol) of 4-bromo-nitrobenzene gave 0.85 g (65% yield) of pale yellow needles of 5-bromo-3-phenyl-2,1-benzisoxazole, mp 112-114 °C (lit.³⁶ mp 112 °C). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 7.20 (dd, $J = 9.5, 1.2$ Hz, 1H), 7.50 (dd, $J = 9.5, 2.4$ Hz, 1H), 7.6 (m, 3H), 8.00 (d, $J = 7.1$ Hz, 2H), 8.15 (s, 1H), IR (KBr, cm^{-1}): 1624, 1542, 1444, 1043.

4,5-Dichloro-3-phenyl-2,1-benzisoxazole (5b). 0.96 g (5 mmol) of 3,4-dichloronitrobenzene gave 0.93 g (70% yield) of pale yellow needles of 4,5-dichloro-3-phenyl-2,1-benzisoxazole, mp 146-147 °C, $^1\text{H-NMR}$ (500 MHz, CDCl_3): 7.38 (d, $J = 9.4$ Hz, 1H), 7.56 (d, $J = 9.4$ Hz, 1H), 7.6 (m, 3H), 7.85 (dd, $J = 7.8, 1.5$ Hz, 2H), $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 114, 116, 123.5, 127.5, 129, 130.5, 131, 131.5, 133.5, 157, 167, MS (EI) m/z (relative intensity): 268 (4), 266 (50), 264 (78), 228 (10), 164 (40), 105 (16), 77 (100), 52 (55), IR (KBr, cm^{-1}): 1629, 1542, 1444, 1114, Anal. Calcd. for $\text{C}_{13}\text{H}_7\text{Cl}_2\text{NO}$: C 59.12, H 2.67, N 5.30. Found C 59.20, H 2.51, N 5.43.

5,7-Dichloro-3-phenyl-2,1-benzisoxazole (5c). 0.96 g (5 mmol) of 2,4-dichloronitrobenzene gave 1.06 g (80% yield) of yellow needles of 5,7-dichloro-3-phenyl-2,1-benzisoxazole, mp 119-120 °C, $^1\text{H-NMR}$ (500 MHz, CDCl_3): 7.37 (d, $J = 1$ Hz, 1H), 7.61 (m, 3H), 7.8 (d, $J = 1$ Hz, 1H), 8 (d, $J = 7$ Hz, 2H), $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 115.5, 118, 118.5, 123, 127, 128, 129.8, 130.2, 131.5, 155, 166, MS (EI) m/z (relative intensity): 268 (6), 266 (32), 264 (50), 228 (54), 164 (62), 105 (50), 77 (100), 52 (98), 51 (98), IR (KBr, cm^{-1}): 1619, 1542, 1434, 1071, Anal. Calcd. for $\text{C}_{13}\text{H}_7\text{Cl}_2\text{NO}$: C 59.12, H 2.67, N 5.30. Found C 59.21, H 2.75, N 5.12.

3-Phenyl-2,1-benzisoxazole-5-carboxylic acid (5d). Following the procedure described above, after addition of 100 mL of water, a green solution was obtained, which was neutralized with hydrochloric

acid. Yield, 0.61 g (50%) yellow needles of desired product, mp 225 °C dec. ¹H-NMR (500 MHz, DMSO-d₆): 7.67 (m, 3H), 7.75 (d, J = 9.4 Hz, 1H), 7.88 (d, J = 9.4 Hz, 1H), 8.14 (d, J = 7 Hz, 2H), 8.65 (s, 1H), 13.28 (s, 1H), ¹³C-NMR (125 MHz, DMSO-d₆): 114, 116, 126, 127.6, 127.8, 128.5, 130.5, 131.2, 132.2, 158, 167, 168, EI-MS m/z (relative intensity): 238 (40), 194 (25), 149 (8), 136 (38), 105 (45), 77 (100), 52 (65), IR (KBr, cm⁻¹): 2500-3200 (broad peak), 1685, 1629, 1542, 1439, 1242, Anal. Calcd. For C₁₄H₉NO₃: C 70.29, H 3.79, N 5.85. Found C 70.18, H 3.81, N 5.77.

Second step. Preparation of 2-aminobenzophenones (6a-d). 0.5 mmol of 2,1-benzisoxazole derivative (**5a-d**) was dissolved in 5 mL of acetic acid³⁶ in a water bath and 0.1 g (5.5 mmol) of Fe powder was added in 3 portions with stirring over approximately 40 min. During this time, 1 mL of water was added. After completion of reduction, which was indicated with TLC, the reaction mixture was filtered while it was hot. In the ultrasonic procedure the reaction mixture was irradiated by ultrasound in the ultrasonic cleaner and sonicated for the period as indicated in Table 2. Sonication continued until 2,1-benzisoxazoles disappeared by TLC. The reaction mixture was filtered. Then, 100 mL of water was added to the solution. The precipitate was filtered and washed with water, and recrystallized from methanol.

2-Amino-5-bromo-benzophenone (6a). Yellow crystals, mp 105-106 °C (lit.³⁶ 105 °C), ¹H-NMR (500 MHz, CDCl₃): 5.90 (s, 2H), 6.52 (d, J = 9.2 Hz, 1H), 7.30 (dd, J = 9.2, 2 Hz, 1H), 7.45 (m, 2H), 7.50 (m, 2H), 7.61 (d, J = 8.7 Hz, 2H), IR (KBr, cm⁻¹): 3411, 3314, 1613, 1585, 1532, 1400, 1314, 1142.

2-Amino-5,6-dichloro-benzophenone (6b). Yellow crystals, mp 107-108 °C, ¹H-NMR (500 MHz, CDCl₃): 4 (s, 2H), 6.70 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.5 (m, 2H), 7.6 (t, J = 7.37 Hz, 1H), 7.9 (d, J = 7.4 Hz, 2H), ¹³C-NMR (125 MHz, CDCl₃): 117, 122, 125, 129, 130, 130.3, 132, 134.5, 137, 145, 196, EI-MS m/z (relative intensity): 266 (16), 265 (62), 263 (66), 230 (98), 228 (98), 164, (60), 139 (16), 111 (15), 105 (74), 77 (100), 52 (99), IR (KBr, cm⁻¹): 3462, 3365, 1665, 1619, 1460, 1403, 1314, Anal. Calcd. For C₁₃H₉Cl₂NO. C 57.67, H 3.41, N 5.26, Found C 57.75, H 3.62, N 5.32.

2-Amino-3,5-dichloro-benzophenone (6c). Yellow crystals, mp 93-94 °C, ¹H-NMR (500 MHz, CDCl₃): 6.58 (s, 2H), 7.42 (s, 1H), 7.48 (s, 1H), 7.53 (m, 2H), 7.62 (m, 1H), 7.67 (d, J = 7.3 Hz, 2H), ¹³C-NMR (125 MHz, CDCl₃): 119.57, 119.72, 121.5, 128.8, 129.6, 132.3, 132.56, 133.8, 139.3, 146, 198, EI-MS m/z (relative intensity): 270 (8), 268 (16), 266 (76), 265 (80), 264 (100), 229 (8), 189 (15), 124 (18), 105 (35), 77 (60), 52 (20), IR (KBr, cm⁻¹): 3462, 3344, 1608, 1573, 1439, 1314, 1153, Anal. Calcd. For C₁₃H₉Cl₂NO. C 57.67, H 3.41, N 5.26, Found C 57.52, H 3.60, N 5.37.

2-Aminobenzophenone-5-carboxylic acid (6d). Yellow crystals, mp 220 °C dec. ¹H-NMR (500 MHz, DMSO-d₆): 6.9 (d, J = 8.8 Hz, 1H), 7.6 (m, 5H), 7.75 (s, 2H), 7.8 (dd, J = 8.8, 1.9 Hz, 1H), 7.96 (d, J = 1.9 Hz, 1H), 12.47 (s, 1H), ¹³C-NMR (125 MHz, DMSO-d₆): 116.19, 116.84, 117.5, 129.2, 129.4, 132, 135.4, 137.6, 140.3, 155.8, 167.6, 198.5, EI-MS m/z (relative intensity): 242 (6), 241 (30), 240 (36), 196 (10), 167(8), 136 (8), 105 (96), 77 (100), 51 (22), IR (KBr, cm⁻¹): 3436, 3324, 2500-3300, 1680, 1629, 1599, 1528, 1428, 1314, 1239, 1157, Anal. Calcd. For C₁₄H₁₁NO₃ C 69.70, H 5.81, N 4.59, Found C 69.90, H 5.90, N 4.65.

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