

Synthesis of Bromo Substituted-4-biphenyl Acetamide Derivatives

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A number of bromo substituted-4-biphenyl-amides have been synthesized by condensation of 4-biphenyl acetic acid with bromine in acetic acid (in ice-cool media). Bromo substituted-4BPAA is then treated with SOCl_2 in dry benzene to prepare bromo substituted-4-biphenyl acetyl chloride, which is then treated with different aliphatic or aromatic amines to synthesized various bromo substituted-4-biphenyl acetamides. The structure of newly synthesized compounds have been established by analytical and spectral methods.

Key Words: Synthesis, 4-Biphenyl acetic acid, Bromo substituted-4-biphenyl acetamides, Spectral studies.

INTRODUCTION

Biphenyls are the polynuclear aromatic hydrocarbons (PAHs) having more than one aromatic nucleus. The two aromatic nuclei are attached to each other at only one point. Thus, biphenyls with independent benzene ring have been categorized in the class of polyphenyl compounds or isolated polynuclear hydrocarbons.

Biphenyl acetic acid and its derivatives have been found to be effective against many therapeutic diseases. Literature findings have also been shown its various therapeutic uses, such as: antiinflammatory agent¹, as analgesic², antipyretic³, anti-arthritis⁴, antirheumatoid⁵, antihypertensive² and a binder to human blood plasma-prealbumen, *etc.*

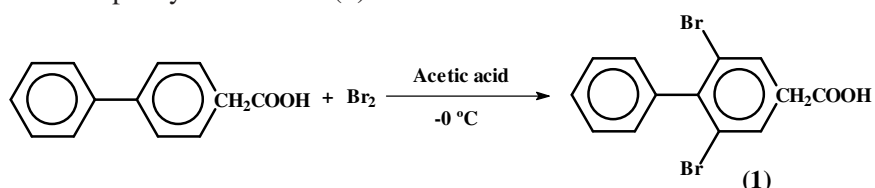
4-Biphenyl acetic acid itself has been reported to possess many effective pharmacological activities, such as antiinflammatory, analgesic, antibacterial⁶ and topical steroidal antiinflammatory activity⁷. The ointment containing 4-biphenyl acetic acid work very effectively as antiinflammatory and analgesic agents⁸. 4-Biphenyl acetic acid cyclodextrin inclusion compounds are reported to show effective mono-nuclear-rogenic antiinflammatory properties and its phenyl alkanamide derivatives have shown agro horticultural bacteriocidal activity⁹. Substituted biphenyls can also be used as antiallergic drugs¹⁰. Biphenyl compounds have stronger analgesic activity along with antiallergic and antiinflammatory activity⁷. Substituted biphenyl-4-acetamide have therapeutic use in the treatment of cancer¹¹. The title compound of biphenyl is also used as an antitumor agent¹².

In view of these observations and in continuation of our research work on biologically active biphenyl analogs, it is proposed to synthesize bromo substituted biphenyl acetamides derived from the condensation of 4-biphenyl acetic acid precursor first with Br_2 (in CH_3COOH at 0°C) and then with different amines (aliphatic as well as aromatic).

EXPERIMENTAL

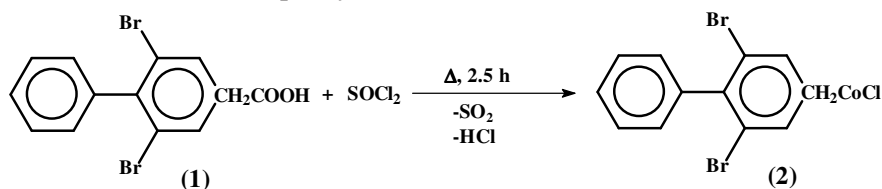
Preparation of 3,3'-dibromo-N-substituted-4-biphenyl acetamide from 4-biphenyl acetic acid

A general procedure for the preparation of 3,3'-dibromo-4-biphenyl acetic acid (a) from 4-biphenyl acetic acid (1).



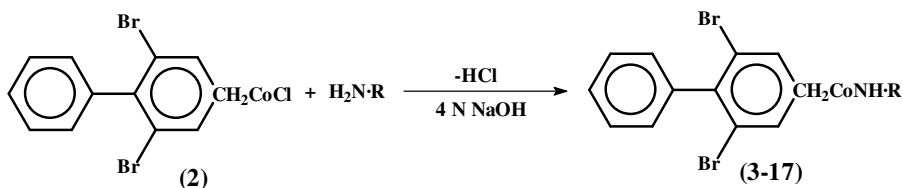
Dissolved 4-biphenyl acetic acid (1 g) in glacial acetic acid (25 mL) and added bromine (1 mL) in acetic acid (1 mL) under constant stirring on magnetic stirrer for 0.5 h in ice-cool medium, then added ice cool water (100 mL) in the reaction mixture. Light yellow crystalline solid was separated out, stirred the reaction mixture again for 15 min at room temperature and filtered through the buchner funnel. Washed the precipitate with ice-cold water to remove the excess of bromine, dried and weighed.

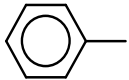
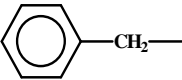
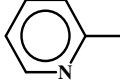
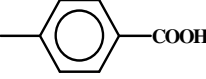
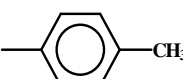
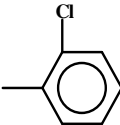
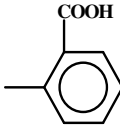
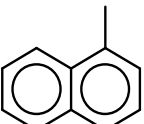
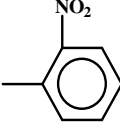
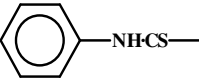
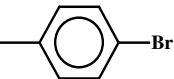
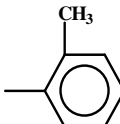
A general method for the preparation of 3,3'-dibromo-4-biphenyl acetyl chloride (2) from 3,3'-dibromo-4-biphenyl acetic acid (1).



3,3'-Dibromo-4-biphenyl acetic acid (1) (500 mg) dissolved in dry benzene (10 mL), added thionyl chloride (0.5 mL) dropwise alongwith constant stirring in a round bottom flask of 50 mL then refluxed the reaction mixture for 2.5 h on water bath at 78-80 °C. The recovered benzene and thionyl chloride from reaction mixture through distillation traces of solvent through vacuum pump. 3,3'-Dibromo-4-biphenyl acetyl chloride (2) obtained as a viscous oil (542 mg, 100 % yield). It was used to form amides in next step without further purification by condensed it with different suitable amines to form different types of bromo substituted acetamides.

A general procedure for the preparation of 3,3'-dibromo-N-substituted-4-biphenyl acetamides (3-17) from 2.

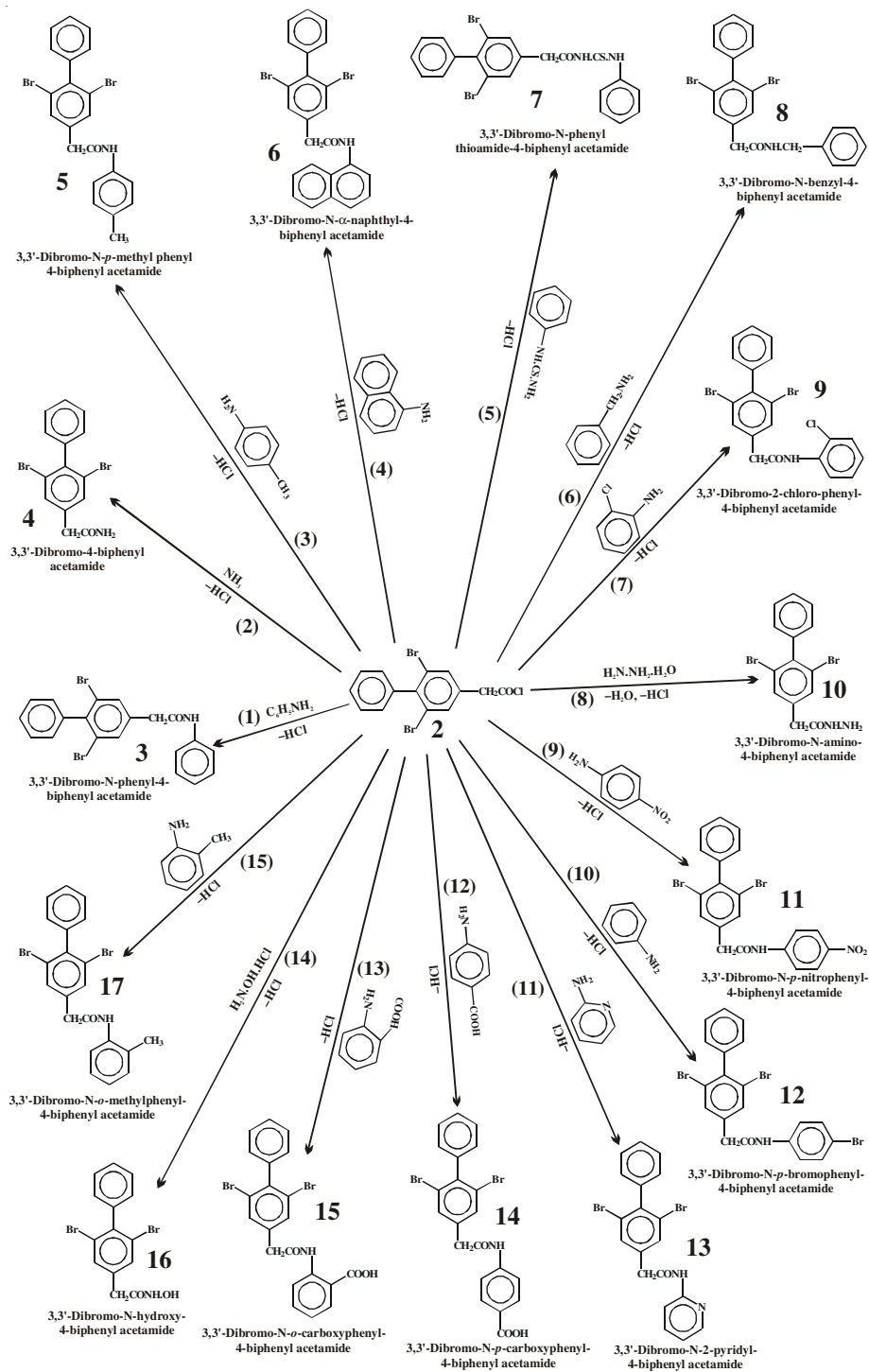


Compd. No.	R	Compd. No.	R	Compd. No.	R
3		8		13	
4	-H	9	-NH ₂ ·H ₂ O	14	
5		10		15	
6		11		16	-OH·HCl
7		12		17	

Dissolved the aliphatic or aromatic primary amine in calculated amount of pyridine and added this mixture in to round bottom flask containing **2**. Dry benzene was added slowly dropwise at room temperature under constant stirring. The TLC of reaction mixture showed that the reaction becomes complete, stirring continue upto the completion of the reaction and then work up the reaction mixture with suitable solvent after *ca.* 20 h. Reaction mixture was taken in saperatory-funnel along with distilled water. Compound dissolved in the solvent, washed the solvent with water about 3-4 times to remove the basic nature of the solvent layer. The solvent layer becomes neutral, solvent layer was taken in conical flask and added MgSO₄ (to absorb the moisture of solvent layer), waited for 5-10 min. Filtered the solution in round bottom flask and recovered the solvent from reaction mixture by distillation and traces of solvent with the help of vacuum pump. Concentrated residue was treated with *n*-hexane for complete precipitation. White or coloured crystalline solid obtained, filtered through Whatman-filter paper (No. 42), washed the precipitation with *n*-hexane about 3-4 times to remove coloured impurities of solid compound, dried and weighed.

Characterization of compounds

3,3'-Dibromo-N-phenyl-4-biphenyl acetamide (3): Pale yellow crystalline solid; m.p. 155-156 C; yield 0.27 g (47.36 %); TLC: R_f 0.353 (20 % EtOAc: hexane); Elemental analysis (%): C 51.11, H 3.16, N 3.14; Br 34.51, ¹H NMR (DMSO-*d*₆) δ: 7.54 (12H-C₆H₅), 6.66 (1H-NH), 1.21 (2H-alicyclic CH₂); IR-1650 cm⁻¹ (>C=O), 3232 cm⁻¹ (>N-H).



Scheme

3,3'-Dibromo-4-biphenyl acetamide (4): White crystalline solid; m.p. 148-150 °C; yield: 0.29 g (60 %); TLC: R_f 0.523 (10 % EtOAc; hexane); elemental analysis (%): C 43.31, H 2.91, N 3.58, Br 41.11; $^1\text{H NMR}$ (DMSO- d_6) δ : 7.40 (7H- C_6H_5), 3.91 (2H-NH₂), 1.13 (2H-alicyclic CH_2); IR-1640 cm^{-1} ($>\text{C}=\text{O}$), 3357 cm^{-1} ($>\text{NH}$).

3,3'-Dibromo-N-paramethylphenyl-4-biphenyl acetamide (5): Yellow crystalline solid; m.p. 158-160 °C; Yield: 0.47 g (80.34 %); TLC: R_f 0.685 (20 % EtOAc; hexane); elemental analysis (%): C 52.16, H 3.43 %, N 2.293; Br 33.67; $^1\text{H NMR}$ (DMSO- d_6) δ : 7.64 (11H- C_6H_5), 7.24 (1H-NH), 1.10 (2H-alicyclic CH_2), 2.11 (3H-alicyclic- CH_3).

3,3'-Dibromo-N- α -naphthyl-4-biphenyl acetamide (6): Mustard crystalline solid; m.p. 178-180 °C; Yield: 0.57 g (90.48 %); TLC: R_f 0.352 (30 % EtOAc; hexane); elemental analysis (%): C 55.60, H 3.27, N 2.61 %; Br 31.09; $^1\text{H NMR}$ (DMSO- d_6) δ : 7.76 (14H- C_6H_5), 7.48 (1H-NH), 1.05 (2H-alicyclic CH_2); IR: 1657 cm^{-1} ($>\text{C}=\text{O}$), 3234 cm^{-1} ($>\text{NH}$).

3,3'-Dibromo-N-phenylthioamide-4-biphenyl acetamide (7): Mustard crystalline solid; m.p. 188-190 °C; Yield: 0.50 g (78.12 %); TLC: R_f 0.488 (20 % EtOAc; hexane); elemental analysis (%): C 49.62, H 3.32, N 5.35, S 6.23, Br 31.56; $^1\text{H NMR}$ (DMSO- d_6) δ : 7.66 (12H- C_6H_5), 7.13 (2H-NH), 1.09 (2H-alicyclic- CH_2); IR: 1612 cm^{-1} ($>\text{C}=\text{O}$), 3421 cm^{-1} ($>\text{NH}$).

3,3'-Dibromo-N-benzyl-4-biphenyl acetamide (8): Pale yellow crystalline solid; m.p. 150-152 °C; Yield: 0.78 g (88.64 %); TLC: R_f 0.30 (30 % EtOAc; hexane); elemental analysis (%): C 52.92, H 3.43, N 2.61, Br 35.55; $^1\text{H NMR}$ (DMSO- d_6) δ : 7.69 (12H- C_6H_5), 6.48 (1H-NH), 1.15 (4H-alicyclic- CH_2); IR: 1634 cm^{-1} ($>\text{C}=\text{O}$), 3285 cm^{-1} ($>\text{NH}$).

3,3'-Dibromo-N-2-chlorophenyl-4-biphenyl acetamide (9): White shiny crystalline solid; m.p. 152-155 °C; Yield: 0.18 g (30.50 %); elemental analysis (%): C 50.04, H 2.73, N 2.37, Br 33.20, Cl 7.29; $^1\text{H NMR}$ (DMSO- d_6) δ : 7.79 (11H- C_6H_5), 6.78 (1H-NH); 1.08 (2H-alicyclic- CH_2); TLC: R_f 0.465 (20 % EtOAc; hexane); IR: 1590 cm^{-1} ($>\text{C}=\text{O}$), 3194 cm^{-1} ($>\text{NH}$).

3,3'-Dibromo-N-amino-4-biphenyl acetamide (10): Cream crystalline solid; m.p. 148-150 °C; Yield: 0.50 g (96.15 %); TLC: R_f 0.643 (chloroform); elemental analysis (%): C 39.85, H 3.90, N 6.23, Br 37.81; $^1\text{H NMR}$ (DMSO- d_6) δ : 6.98 (7H- C_6H_5), 6.42 (1H-NH), 3.52 (2H-NH₂), 1.20 (2H- CH_2); IR: 1665 cm^{-1} ($>\text{C}=\text{O}$), 3247 cm^{-1} ($>\text{NH}$).

3,3'-Dibromo-N-para-nitro-phenyl-4-biphenyl acetamide (11): Yellow crystalline solid; m.p. 158-160 °C; Yield: 0.22 g (36.67 %); elemental analysis (%): C 48.86, H 2.80, N 5.56, Br 32.71; TLC: R_f 0.747 (50 % CHCl_3 :benzene); $^1\text{H NMR}$ (DMSO- d_6) δ : 7.89 (11H- C_6H_5), 7.12 (1H-NH); 1.03 (2H-alicyclic- CH_2); IR: 1631 cm^{-1} ($>\text{C}=\text{O}$), 3360 cm^{-1} ($>\text{NH}$).

3,3'-Dibromo-N-para-bromophenyl-4-biphenyl acetamide (12): Pale yellow crystalline solid; m.p. 152-154 °C; Yield: 0.52 g (94.5 %); TLC: R_f 0.477 (25 %

EtOAc:benzene); elemental analysis (%): C 45.76, H 2.80, N 2.8, Br 45.46; ^1H NMR (DMSO- d_6) δ : 7.82 (1H-C₆H₅), 7.15 (1H-NH); 1.07 (2H-alicyclic-CH₂); IR: 1637 cm⁻¹ (>C=O), 3268 cm⁻¹ (>NH).

3,3'-Dibromo-N-2-pyridyl-4-biphenyl acetamide (13): Pale brown crystalline solid; m.p.: 148-150 °C; Yield: 0.18 g (32.73 %); TLC: R_f 0.420 (50 % EtOAc: benzene); elemental analysis (%): C 50.09, H 3.75, N 6.17, Br 35.52; ^1H NMR (DMSO- d_6) δ : 7.89 (1H-C₆H₅), 7.31 (1H-NH); 1.04 (2H-alicyclic-CH₂); IR: 1637 cm⁻¹ (>C=O), 3168 cm⁻¹ (>NH).

3,3'-Dibromo-N-*para*-carboxyphenyl-4-biphenyl acetamide (14): Pale yellow crystalline solid; m.p. 158-160 °C; Yield: 0.515 g (85.83 %); TLC: R_f 0.590 (10 % MeOH:CHCl₃); elemental analysis (%): C 51.28, H 3.17, N 2.68, Br 32.35; ^1H NMR (DMSO- d_6) δ : 7.77 (1H-C₆H₅), 7.24 (1H-NH); 12.01 (1H-COOH) 1.14 (2H-alicyclic-CH₂); IR: 1660 cm⁻¹ (>C=O), 2921 cm⁻¹ (>NH).

3,3'-Dibromo-N-*ortho*-carboxyphenyl-4-biphenyl acetamide (15): White crystalline solid; m.p.: 160-162 °C; Yield: 0.26 g (43.33 %); TLC: R_f 0.50 (30 % EtOAc: hexane); elemental analysis (%): C 51.28, H 3.27, N 2.35, Br 32.68; ^1H NMR (DMSO- d_6) δ : 7.81 (1H-C₆H₅), 6.72 (1H-NH); 11.91 (1H-COOH), 1.23 (2H-alicyclic-CH₂); IR: 1666 cm⁻¹ (>C=O), 3307 cm⁻¹ (>NH).

3,3'-Dibromo-N-hydroxy-4-biphenyl acetamide (16): Pale yellow crystalline solid; m.p.: 158-160 °C; Yield: 0.19 g (35.18 %); TLC: R_f 0.477 (70 % EtOAc: hexane); elemental analysis (%): C 38.76, H 2.71, N 3.22, Br 36.41, Cl 8.30; ^1H NMR (DMSO- d_6) δ : 7.70 (7H-C₆H₅), 6.68 (1H-NH); 3.79 (1H-OH), 1.11 (2H-alicyclic-CH₂); IR: 1633 cm⁻¹ (>C=O), 3196 cm⁻¹ (>NH).

3,3'-Dibromo-N-*ortho*-methylphenyl-4-biphenyl acetamide (17): Mustard crystalline solid; m.p. 168-170 °C; Yield: 0.31 g (54.27 %); TLC: R_f 0.159 (70 % EtOAc:hexane); elemental analysis (%): C 54.94, H 3.50, N 3.07, Br 34.68; ^1H NMR (DMSO- d_6) δ : 7.88 (1H-C₆H₅), 6.86 (1H-NH); 1.01 (2H-alicyclic-CH₂), 2.29 (3H-alicyclic-CH₃); IR: 1688 cm⁻¹ (>C=O), 2924 cm⁻¹ (>NH).

RESULTS AND DISCUSSION

Commercially available 4-biphenyl acetic acid (white crystalline solid) was used for the preparation of bromo-substituted-4-biphenyl acetamide derivatives. 4-Biphenyl acetic acid was treated with Br₂ dissolved in acetic acid (in ice-cool). Brominated 4-biphenyl acetic acid (pale yellow crystalline solid) was then treated with thionyl chloride in dry benzene on water bath for 2-3 h. After 1 h, the colour of reaction mixture changes from pale yellow to orange and then on completion of reaction, it changes from orange to brown.

This oily mass of brominated-4-biphenyl acetyl chloride is then treated with different types of aliphatic and aromatic amines in 4 N NaOH to synthesize a variety of amides. These synthesized brominated-4-biphenyl acetamides were treated with *n*-hexane for crystallization. Pure compounds were then analyzed by measured m.p., TLC, NMR, IR and elemental analysis.

Biological activities: Synthesized brominated-4-biphenyl amides have been studied for their antifungal activity against *Fujenum udum* and *Curvalaria lunata*. The culture of each species was incubated at 12 ± 3 °C and the zone of the inhibition was measured after 120 h. Most of these compounds were found to be active against these fungi.

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