Asian Journal of Chemistry Vol. 18, No. 2 (2006), 1055–1060

Synthesis of Biologically Active N-Substituted (Biphenyl) Amides

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A number of N-substituted (biphenylyl) amides have been synthesized by condensation of parent compound, 2-amino biphenyl and different acid chlorides. The acid chlorides, both aliphatic and aromatic ones, were prepared from their corresponding acids using $SOCl_2/PCl_5$ in appropriate solvents. The structures of the newly synthesized compounds have been established by analytical and spectral methods.

Key Words: Synthesis, 2-Amino biphenyl, N-substituted (biphenylyl) amides, Spectral studies.

INTRODUCTION

Biphenyl and its derivatives have been reported to possess interesting applications in various fields. Biphenyl has been employed in the manufacture of fire-proofing agents[1] and carbon fibres with high strength[2]. It has also been found an effective eliminator for *Aspergillus niger* infection in some types of grapes[3]. Mixed ligand metal complexes of Cu(II) ions with diphenic acid have been reported to exhibit antibacterial and antifungal activities[4]. Some derivatives of dimethyl ester of diphenic acid have shown anti-HIV activity[5].

A recent review on flurbiprofen, a biphenyl analogue with its chemotherapeutic values, has been published by Kumar and his co-workers[6]. Some substituted biphenyl dicarboxylic acid amides have been reported to possess antimicrobial[7] and anticoagulant[8] properties and have also been used as vulcanizing agents[9]. The esters of biphenyl acetic acid have shown analgesic, antipyretic and antiinflammatory activities in humans[10]. Biphenyl-4-acetamide hydroxamates have been reported to show antiinflammatory activity[11].

As the amino group has been very reactive, a large number of amino biphenyl derived compounds have been synthesized. Amino derivatives have been found useful in the commercial preparation of crystal violet lactone[12]. Amino biphenyl-fluorescent analogues have been employed in the detection of protein and nucleic acids[13]. Chemiluminescent labels can also be prepared from 2-amino biphenyl molecule[14]. The compounds have also exhibited antifungal, anti-HIV, insecticidal, antibiotic, plant protectants and microbicidal activities.

Amino biphenyl analogues are useful in the treatment of urinary tract diseases[15], as HIV inhibitors and as insecticidal agents[16]. 3-Amino biphenyl derivatives have been used in the synthesis of HIV inhibitors[17], in the preparation of dyes as a new class of fluorescent for cell membrane probes[18] and for the synthesis of naphthopyridinones as testerone 5α-reductase inhibitors[19].

2-Amino biphenyl derived compounds have also been reported as the starting material for the preparation of HIV inhibitors[17] and in the synthesis of many insecticidal agents[16]. The synthesis of new azo Schiff bases as potential bacteriostats has been described in literature[20]. (Trifluoromethyl) pyrrolecarboxamide derivatives of 2-amino biphenyl have been used as plant protectants[21]. Other thiazolecarboxamide analogues have been reported to show agrochemical fungicidal activity[22]. In view of these observations and in continuation of our research work on biologically active biphenyl analogues, it was proposed to synthesize N-substituted (biphenyl) amides derived from the condensation of 2-amino biphenyl precursor and different acid chlorides.

EXPERIMENTAL

All the melting points were taken in concentrated sulphuric acid bath and are uncorrected. Thin layer chromatography on silica gel-G was used to check the purity of the compounds. ^{1}H NMR spectra were recorded on Bruker DRX-300 spectrometer using TMS as an internal standard. IR spectra were recorded on Shimadzu 8201 PC spectrometer and mass spectra were recorded on Jeol SX-102 (FAB) spectrometer.

Acetyl chloride (2a)

A mixture of acetic acid (**1a**, 4 mL) and freshly distilled $SOCl_2$ (5 mL) was heated on a water bath for 1.5 h. The fractional distillation of the reaction mixture at 52–53°C afforded acetyl chloride (**2a**, 4.4 g) as an oil, a part of which was used for the next step.

Propionyl chloride (2b)

A mixture of propionic acid (**1b**, 0.9 mL) and distilled $SOCl_2$ (1 mL) was heated on a water bath for 1.5 h. The crude reaction mixture containing propionyl chloride (**2b**, 1.06 g) was then used for the next step without concentrating or purifying.

Benzoyl chloride (2c)

To a stirred solution of benzoic acid (**1c**, 1 g) in dry $CHCl_3$ (15 mL), PCl_5 (1.5 g) was added portionwise and the mixture stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to give benzoyl chloride (**2c**, 1.1 g) as crude oil which was used without further purification.

3-Nitrobenzoyl chloride (2d)

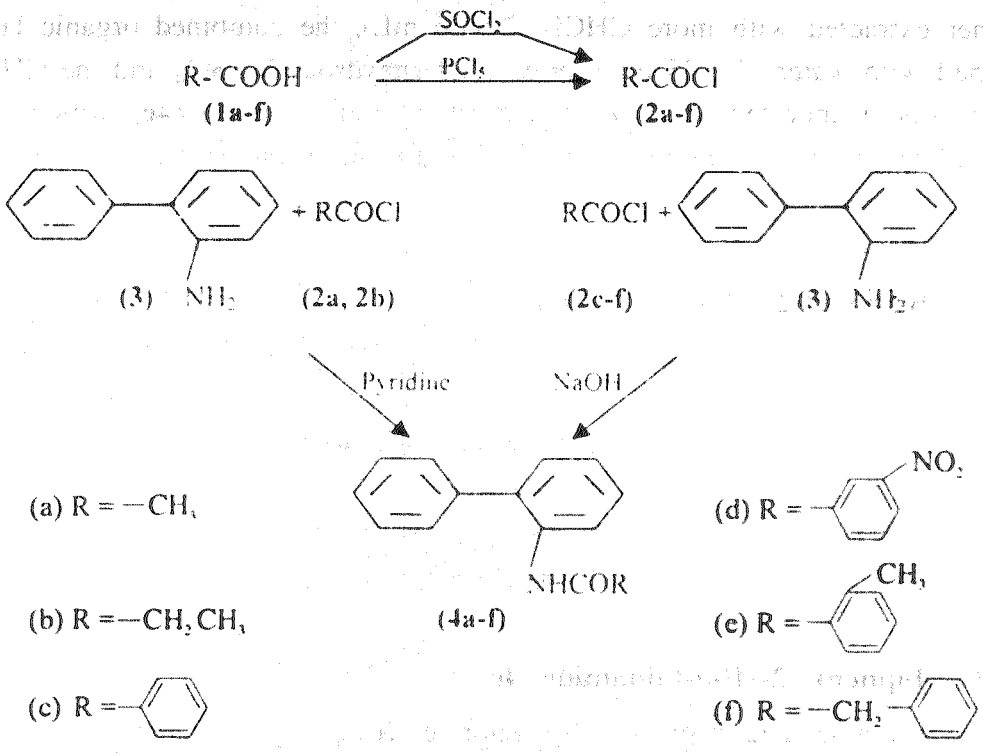
It was prepared from 3-nitrobenzoic acid (**1d**, 1 g) and PCl_5 (1.5 g) according to the procedure as described for **2c** as crude oil (**2d**, 1.1 g) and was used without further purification.

***o*-Toluoyl chloride (2e)**

It was prepared from *o*-toluic acid (**1e**, 1 g) and PCl_5 (1.5 g) by the method as mentioned for **2c** as crude oil (**2e**, 1.13 g) and was used as such with no purification.

Phenylacetyl chloride (2f)

It was prepared from phenyl acetic acid (**1f**, 1 g) and PCl_5 (1.5 g) according to the method as described for **2c** as crude oil (**2f**, 1.12 g) and was used without further purification.



Scheme-1

N-[1,1′-biphenyl-2-yl]-acetamide (4a)

A mixture of acetyl chloride (**2a**, 0.55 g), dry benzene (10 mL), dry pyridine (4 mL) and 2-amino biphenyl (**3**, 0.5 g) was stirred at room temperature for 24 h. Water was then added to the reaction mixture and the benzene layer was separated. The aqueous layer was further extracted with more benzene (3 × 15 mL) and the combined organic layer was washed with water (3 × 15 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to give a crude product (**4a**) which was crystallized from benzene-hexane (1 : 9) as light brown amorphous powder, m.p. 91–92°C, yield 0.46 g (74%); IR (ν_{max}, cm^{-1}): 3289 ν(NH), 1660 ν(C=O); ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H, $—CH_3$), 7.15–7.51 (m, 9H, Ar—H); MS: m/z 212 ($M^+ + 1$), 211 (M^+).

N-[1,1′-biphenyl-2-yl]-propionamide (4b)

It was prepared from a mixture of propionyl chloride (**2b**, 1.06 g), dry benzene (10 mL), dry pyridine (4 mL) and 2-amino biphenyl (**3**, 0.5 g) by the procedure as described for **4a** and crystallized from hexane to afford **4b** as light brown amorphous powder, m.p. 58–59°C, yield 0.4 g (60%); IR (ν_{max}, cm^{-1}): 3241 ν(NH), 1655 ν(C=O); ^1H NMR ($CDCl_3$): δ 1.09 (t, 3H, $—CH_3$), 2.22 (q, 2H, $—CH_2$), 7.13–7.49 (m, 9H, Ar—H); MS: m/z 226 ($M^+ + 1$), 225 (M^+).

N-[1,1′-biphenyl-2-yl]-benzamide (4c)

To the stirred mixture of 2-amino biphenyl (**3**, 0.7 g) in $CHCl_3$ (15 mL) and 20% aq. NaOH (15 mL), a solution of benzoyl chloride (**2c**, 1.1 g) in dry $CHCl_3$ (20 mL) was slowly added and the reaction mixture stirred at room temperature for 24 h. The chloroform layer was separated. The aqueous layer was further extracted with more $CHCl_3$ (3 × 20 mL), the combined organic layer washed with water (3 × 25 mL), dried over anhydrous Na_2SO_4 and the $CHCl_3$ layer was evaporated *in vacuo* to afford a crude product (**4c**) which was crystallized from benzehe-hexane (1 : 9) as light purple amporphous powder, m.p. 91–92°C, yield 0.45 g (40%); IR (ν_{max}, cm^{-1}): 3266 ν(NH), 1645 ν(C=O); ^1H NMR ($CDCl_3$): δ 7.19–7.61 (m, 14H, Ar—H); MS: m/z 274 ($M^+ + 1$), 273 (M^+).

N-[1,1′-biphenyl-2-yl]-3-nitrobenzamide (4d)

It was prepared from 3-nitrobenzoyl chloride (**2d**, 1.1 g and 2-amino biphenyl (**3**, 0.7 g) by the procedure as described for **4c** and crystallized from benzene-hexane (1 : 9) as light brown amorphous powder (**4d**), m.p. 130–31°C, yield 1 g (76%); IR (ν_{max}, cm^{-1}): 3251 ν(NH), 1650 ν(C=O), 1529, 1349 $\nu(NO_2)$; ^1H NMR ($CDCl_3$): δ 7.20–7.58 (m, 9H, Ar—H), 8.38 (m, 2H, Ar—H, *ortho* to NO_2 group), 8.27 (m, 1H, Ar—H, *ortho* to C=O group); MS: m/z 319 ($M^+ + 1$), 318 (M^+).

N-[1-1′-biphenyl-2-yl]-*o*-toluamide (4e)

It was synthesized from *o*-toluoyl chloride (**2e**, 1.13 g) and 2-amino biphenyl (**3**, 0.7 g) according to the method as mentioned for **4c** and crystallized from benzene-hexane (1 : 9) to afford light purple amide (**4e**), m.p. 90–91°C, yield 0.85 g (72%); IR (ν_{max}, cm^{-1}): 3414 ν(NH), 1675 ν(C=O); ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H, $—CH_3$), 7.12–7.65 (m, 13H, Ar—H); MS: m/z 288 ($M^+ + 1$), 287 (M^+).

N-[1,1′-biphenyl-2-yl]-phenyl acetamide (4f)

It was prepared from phenylacetyl chloride (**2f**, 1.12 g) and 2-amino biphenyl (**3**, 0.7 g) by the method as described for **4c** and crystallized from benzene-hexane (1 : 9) to give fluffy white product (**4f**), m.p. 95–97°C, yield 0.9 g (76%); IR (ν_{max}, cm^{-1}): 3269 ν(NH), 1653 ν(C=O); ^1H NMR ($CDCl_3$): δ 3.58 (s, 2H, $—CH_2—$), 7.03–7.36 (m, 14H, Ar—H); MS: m/z 288 ($M^+ + 1$), 287 (M^+).

RESULTS AND DISCUSSION

Commercially available acetyl chloride **(2a)** was used for the preparation of amide, 4a, Though it was also prepared in our laboratory from the reaction of acetic acid and thionyl chloride. The pure acetyl chloride (b.p. 52°C) was then obtained by fractional distillation of the reaction mixture. Similarly, the synthesis of propionyl chloride **(2b)** was accomplished from propionic acid and thionyl chloride. However, the propionyl chloride was not isolated by fractional distillation of the reaction mixture because both the product and $SOCl_2$ had about the same boiling point (79°C). Therefore, the reaction mixture containing propionyl chloride was used as such for the next step.

The aromatic acid chlorides were successfully prepared by using PCl_5 as chlorinating agent. Thus, when the benzoic acid and other substituted acids like 3-nitrobenzoic acid, *o*-toluic acid and phenylacetic acid were treated with PCl_5 in dry $CHCl_3$ at room temperature, the acid chlorides were formed. All aliphatic and aromatic acid chlorides were used immediately without further purification to avoid any hydrolysis back to acids.

The amides **(4a–f)** were synthesized by the condensation of corresponding acid chlorides **(2a–f)** and commercially available biphenyl compound containing amino group at position no. 2 (2-amino biphenyl). The aliphatic acid chlorides (**2a** and **2b**) were condensed with 2-amino biphenyl in a mixture of dry benzene and dry pyridine at room temperature for 24 h to afford the amides (**4a** and **4b**). The pyridine which is basic in nature was used in these experiments to trap the HCl evolved. The acetyl chloride and propionyl chloride were used in excess of the required quantity. Since both had low boiling points (52° and 79°C respectively) so these were removed easily by distillation. The other amides **(4c–f)** were prepared by the condensation of corresponding acid chlorides **(2c–f)** with 2-amino biphenyl in chloroform using 20% aq. NaOH solution as HCl trapping agent. The aromatic acid chlorides were also used in excess of the calculated quantity. Since they are soluble in hexane so these were easily removed during washing the amides repeatedly. All the amides were recrystallized from benzene-hexane solvent mixture (1 : 9) in the pure form.

Biological Activity

All (biphenyl-2-yl) amides have been studied for their antimicrobial activity against *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus.* The culture of each species was incubated at 37°C and the zone of inhibition was measured after 24 h. Most of these compounds were found active against these cultures.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. K.P. Madhusudanan, Head, RSIC, CDRI, Lucknow for providing spectral data. The library facilities of CDRI are also gratefully acknowledged. Thanks are also due to Dr. M.C. Yadav, Principal, Narain (P.G.) College, Shikohabad for providing Laboratory facilities.

REFERENCES

1. G.I. Murzaev, *Chem. Abstr.*, **125**, 331074m (1996).
2. M. Higuchi and I. Nakayama, *Chem. Abstr.*, **135**, 228140n (2001).
3. J.P. Singh, S. Sharma and R. Yamadagni, *Indian Phytopathol.*, **38**, 531 (1985).
4. F. Darain, L.A. Banu, S. Ahmad and M.S. Islam, *Oriental J. Chem.*, **15**, 269 (1999).
5. K.H. Lee, Y. Kashiwada, L. Xie, L.M. Cosentino, M. Manak, J.-X. Xie, Y.-C. Cheng and R.E. Kilkuskie, *Chem. Abstr.*, **126**, 135627a (1997).
6. P. Kumar, P.K. Pathak, V.K. Gupta, B.K. Srivastava and B.S. Kushwaha, *Asian J. Chem.*, **16**, 558 (2004).
7. T. Yoshihara and H. Suzuki, *Chem. Abstr.*, **123**, 49798p (1995).
8. W.P. Dankulich, D.G. McGarry, C. Burns, T.F. Gallagher and F.A. Volz, *Chem. Abstr.*, **133**, 89545s (2000).
9. T. Ko and N. Miyahara, *Chem. Abstr.*, **90**, 122834d (1979).
10. S. Aoyanagi and J. Nagase, *Chem. Abstr.*, **105**, 60421j (1986).
11. M.F. Haslanger and D.S. Karnewsky, *Chem. Abstr.*, **105**, 208613w (1986).
12. N. Yang and L. Yang, *Chem. Abstr.*, **135**, 108613x (2001).
13. S. Fujita, M. Momyama, N. Kagyama, Y. Kondo and H. Hori, *Chem. Abstr.*, **119**, 265985g (1993).
14. F. McCapra and I. Beheshti, *Chem. Abstr.*, **121**, 157542t (1994).
15. G.W. Bantle, T.R. Elworthy, A. Guzman, S. Jaime-Figueroa, T. Lopez, J. Francisco, D.J. Morgans (Jr.), A. Perez-Medrano, E.B. Sjogren and F.X. Talamas, *Chem. Abstr.*, **130**, 125098x (1999).
16. K. Kodaka, K. Kinoshita, M. Nakaya, K. Ebihara, S. Shiraishi, E. Yamada and S. Numata, *Chem. Abstr.*, **117**, 90295m (1992).
17. S.K. Singh, R.J. Patch, A. Gopalsamy and P.V. Pillai, *Chem. Abstr.*, **121**, 157320u (1994).
18. W.-Y. Leung, F. Mao, R.P. Haugland and D.H. Klaubert, *Bioorg. Med. Chem. Lett.*, **6**, 1479 (1996).
19. L.D. Von, D.W. Graham and S.D. Aster, *Chem. Abstr.*, **132**, 151690v (2000).
20. A. Halve and A. Goyal, *Oriental J. Chem.*, **12**, 87 (1996).
21. M. Eberle and H. Walter, *Chem. Abstr.*, **132**, 166122k (2000).
22. Y. Yoshikawa, H. Kawashima, K. Tomitani, J. Yanase and J. Kishi, *Chem. Abstr.*, **123**, 198788n (1995).

(*Received*: 12 April 2005; *Accepted*: 12 December 2005) AJC-4531