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Synthesis of Sulfonamide, Sulfanilamide and Carbamate Derivatives of 4-Pyrones†

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Sulfonamide, carbamate and sulfanilamide derivatives of 4-pyrones **6–10** were synthesized by treatment of 3,5-bis(2-aminophenyl)-4*H*-pyran-4-one and 2,6-bis(4-aminophenyl)-3,-5-dimethyltetrahydro-4*H*-pyran-4-one with tosyl chloride, ethyl chloroformate and 4-(4-acetylaminobenzene)sulfonyl chloride in 40–88% yields. Hydrolysis of compound **10** in hydrochloric acid-ethanol produced **11** in 39% yield.

Key Words: Synthesis, 4*H*-Pyran-4-one, Tetrahydro-4*H*-pyran-4-one, Sulfonamide, Sulfanilamide, Carbamate.

INTRODUCTION

The pyran-4-one and benzopyran-4-one groups of naturally occurring compounds have aroused considerable interest due to their biological activities[1]. Phenoxan and aureothin are isolated natural products that have been shown to have anti-HIV activity[2]. Allixin is one of phytoalexins, first isolated from garlic, *Allium sativum* L. and its anti-tumor promoter activity *in vivo* and radical scavenging effect were reported later[3]. A number of 4-pyrone derivatives have a beneficial application in agriculture as plant growth regulators, active against fungi[4]. Heterocyclic sulfonamides, sulfanilamides and carbamates are biologically active and synthetically useful compounds[5].

The antibacterial sulfonamides continue to play an important role in chemotherapy, alone or in combination with other drugs[6]. Carbamates are useful as protecting group in organic synthesis particularly in peptide synthesis[7]. For these reasons, the chemistry of these compounds has been the subject of many investigations. Although the chemistry of 4-pyrones has been investigated[8], but the chemistry of sulfonamide, sulfanilamide and carbamate derivatives of 4-pyrones has received less attention. Thus, in this paper, the synthesis of the title compounds **6–11** is reported.

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EXPERIMENTAL

^{1}H NMR and ^{13}C NMR were recorded with an FT-NMR-Bruker (400 MHz) spectrometer in $CDCl_3$, DMSO-d_6, CD_3CN using tetramethylsilane as internal standard and chemical shifts were reported in ppm units. The IR spectra were obtained using KBr pellets on a 4300-Shimadzu, tensor 27-Bruker. Mass spectra were recorded on Finnigan-Mat model 8400, 70 eV mass spectrometer and elemental analyses on Heareus-CHN-Rapid. Melting points were recorded on Electrothermal 9100 and are uncorreted.

3,5-Bis[2-(4-tolylsulfonamido)phenyl]-4*H*-pyran-4-one (6): 3,5-Bis-(2-aminophenyl)-4*H*-pyran-4-one (**3**) (0.1 g, 0.36 mmol) was dissolved in dry acetone (20 mL) with stirring. Pyridine (0.18 mL) was added to the flask. Then *p*-toluenesulfonyl chloride (0.14 g, 0.72 mmol) was dissolved in dry acetone (7 mL) and was added dropwise to the flask at room temperature. The resulting mixture was stirred at room temperature for 18 h and the solvent was removed under reduced pressure. The crude product was dried and recrystallized from ethanol, yielding the title compound, white solid, 70% yield, m.p. 228–229°C. (Found: C 63.1, H 4.5, N 5.0%; $C_{31}H_{26}N_2O_6S_2$ requires C 63.4, H 4.4, N 4.7%). ν_{max} (KBr, cm^{-1}) 3343, 3067, 1625, 1552, 1332, 1166, 1092, 813. δ_H 7.56 (s, 2H, N—H), 7.05–7.50 (m, 16H, aromatic-H), 7.37 (s, 2H, C_2 and C_6-H), 2.39 (s, 6H, —CH_3). δ_C 176.56, 154.31, 143.46, 137.40, 135.89, 130.59, 129.30, 129.16, 128.63, 127.42, 127.32, 126.91, 21.49.

3,5-Bis(2-ethylcarbamatophenyl)-4*H*-pyran-4-one (7): 3,5-Bis-(2-aminophenyl)-4*H*-pyran-4-one (**3**) (0.1 g, 0.36 mmol) was dissolved in dry acetone (20 mL) with stirring. Pyridine (0.18 mL) was added to the flask. A solution of ethyl chloroformate (0.078 g, 0.72 mmol) in dry acetone (7 mL) was added dropwise to the flask in an ice-water bath. The resulting mixture was stirred in an ice-water for 2 h and the solvent was removed under reduced pressure. The isolated product was dried and purified by preparative layer chromatography (R_f, 0.33) on silica gel using petroleum ether (40–60) as eluent to give the title compound, 40% yield, m.p. 98°C. ν_{max} (KBr, cm^{-1}) 3307, 1724, 1639, 1518, 1223, 1055, 761. δ_H 8.03 (s, 2H, C_2 and C_6 -H), 7.8 (2H, N—H), 7.21–7.48 (m, 8H, aromatic-H), 4.12 (q, J = 7.1 Hz, 4H, —CH_2), 1.22 (t, J = 7.1 Hz, 6H, —CH_3). δ_C 177.1, 155.3, 154.59, 130.70, 130.11, 129.88, 124.92, 124.75, 124.44, 61.12, 14.54. m/z 423 (M^+).

2,6-Bis[4-(4-tolylsulfonamido)phenyl]-3,5-dimethyltetrahydro-4*H*-pyran-4-one (8): 2,6-Bis(4-aminophenyl)-3,5-dimethyltetrahydro-4*H*-pyran-4-one (**5**) (0.155 g, 0.5 mmol) and pyridine (0.12 mL) were dissolved in dry acetone (5 mL) with stirring. Then *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) was dissloved in dry acetone (5 mL) and added dropwise to the flask at room temperature. The resulting mixture was stirred at room temperature for 18 h. The reaction mixture was poured into water (50 mL), cooled for 12 h and precipitate filtered off, washed with water and purified by preparative layer chromatography on silica gel using ethyl acetate/petroleum ether (40–60) 1 : 1 as eluent. White solid, 80% yield, m.p. 230–231°C. (Found: C 63.5, H 5.7, N 4.5%; $C_{33}H_{34}N_2O_6S_2$ requires C 64.0, H 5.5, N4.5%). ν_{max} (KBr, cm^{-1}) 3260, 1705, 1512, 1328, 1153, 1090, 910; 810. δ_H 9.28 (br, 2H, N—H), 7.64 (d, J = 8.57 Hz, 4H, Ph—H), 7.25 (d, 8H,

aromatic-H), 7.11 (d, J = 8.57 Hz, 4H, aromatic-H), 4.20 (d, J = 9.45 Hz, 2H, pyran-C_2 and C_6-H), 2.80 (m, 2H, pyran-C_3 and C_5-H), 2.31 (s, 6H, ph-CH_3), 0.65 (d, 6H, J = 6.5 Hz, —CH_3). δ_C 209.5, 144.8, 138.8, 137.6, 137.3, 130.5, 129.1, 128.0, 121.3, 118.4, 86.1, 51.7, 21.5, 10.1.

2,6-Bis(4-ethylcarbamatophenyl)-3,5-dimethyltetrahydro-4*H*-pyran-4-one (9): A solution of 2,6-bis(4-aminophenyl)-3,5-dimethyltetrahydro-4*H*-pyran-4-one (**5**) (0.155 g, 0.5 mmol) and pyridine (0.12 mL) were dissolved in dry acetone (5 mL) with stirring. A solution of ethyl chloroformate (0.1 mL, 1 mmol) in dry acetone (5 mL) was added dropwise to the flask in an ice-water bath. The resulting mixture was stirred for 2 h. The reaction mixture was poured into water (50 mL), cooled for 3 h and precipitate was filtered off, washed with water and purified by preparative layer chromatography on silica gel using ethyl acetate-petroleum ether (40–60) 2 : 1 as eluent, to give the title compound, 88% yield, m.p. 215°C. (Found: C 65.7, H 6.8, N 5.8%; $C_{25}H_{30}N_2O_6$ requires C 66.0, H 6.6, N 6.1%). ν_{max} (KBr, cm^{-1}) 3344, 2983, 1729, 1702, 1532, 1226, 1066, 838. δ_H 7.76 (br, 2H, N—H), 7.44 (d, J = 8.76 Hz, 4H, aromatic-H), 7.36 (d, J = 8.76 Hz, 4H, aromatic-H), 4.29 (d, J = 11 Hz, 2H, pyran-C_2 and C_6-H), 4.14 (q, J = 7 Hz, 4H, —OCH_2—), 2.92 (m, 2H, pyran-C_3 and C_5-H), 1.24 (t, J = 7.40 Hz, 6H, CH_3), 0.75 (d, J = 6.66 Hz, 6H, CH_3). δ_C 208.9, 153.5, 139.0, 134.0, 127.8, 117.8, 84.6, 60.1, 50.2, 14.5, 9.8.

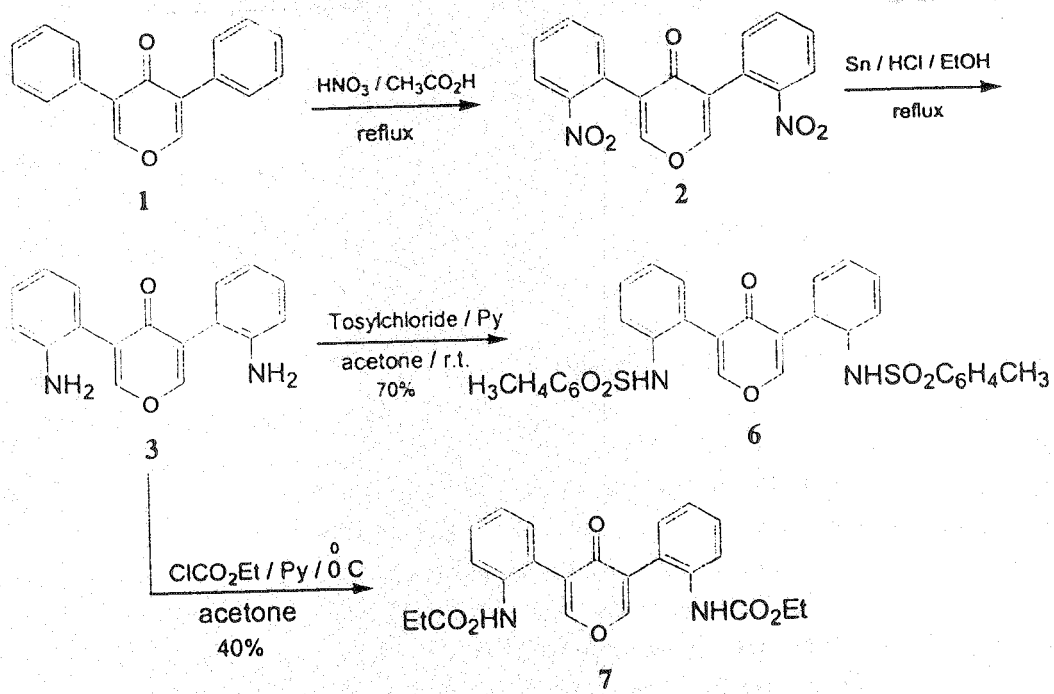
2,6-Bis[4-(4-acetamidobenzene sulfonamido)phenyl]-3,5-dimethyltetrahydro-4*H*-pyran-4-one (10): 2,6-Bis(4-aminophenyl)-3,5-dimethyltetrahydro-4*H*-pyran-4-one (**5**) (0.31 g, 1 mmol) and pyridine (0.24 mL) were dissolved in dry acetone (15 mL) with stirring. *p*-acetamidobenzenesulfonyl chloride (0.466 g, 2 mmol) was dissolved in dry acetone (15 mL) and was added dropwise to the flask at room temperature. The resulting mixture was stirred for 24 h at room temperature. The reaction mixture was poured into water (100 mL), cooled for 12 h and precipitate was filtered, washed with water and purified by preparative layer chromatography on silica gel using chloroform-ethanol 9 : 1 as eluent to give the title compound, 76% yield. (Found: C 59.8, H 5.3, N 7.8%.; $C_{35}H_{36}N_4O_8S_2$ requires C 59.6, H 5.1, N 7.9%). ν_{max} (KBr, cm^{-1}) 3261, 2977, 1702, 1592, 1513, 1323, 1157, 837. δ_H 10.27 (s, 2H, N—H), 10.18 (s, 2H, N—H), 7.66 (8H, aromatic-H), 7.27 (d, J = 7.33 Hz, 4H, aromatic-H), 7.04 (d, J = 7.33 Hz, 4H, aromatic-H), 4.22 (d, J = 12 Hz, 2H, pyran-C_2 and C_6-H), 2.85 (m, 2H, pyran-C_3 and C_5-H), 2.05 (s, 6H, —CO—CH_3), 0.58 (d, J = 8 Hz, 6H, CH_3). δ_C 208.5, 169.1, 143.1, 137.5, 135.7, 132.9, 128.1, 127.9, 119.9, 118.5, 84.3, 50.2, 24.1, 9.7.

2,6-Bis[4-(4-aminobenzene sulfonamido)phenyl]-3,5-dimethyltetrahydro-4*H*-pyran-4-one (11): A mixture of 2,6-bis[4-(4-acetamidobenzene sulfonamido)phenyl]-3,5-dimethyltetrahydro-4*H*-pyran-4-one (0.176 g, 0.25 mmol), ethanol (3 mL) and HCl (37%) (0.3) mL were refluxed for 20 min. Then the reaction mixture was cooled, water (20 mL) was added to the mixture and made just alkaline with concentrated ammonia solution (d, 0.880), then precipitate filtered and washed with water and purified by preparative layer chromatography in two steps ethyl acetate and chloroform/ethanol (19 : 1) using as eluent, to give title compound, 39% yield. (Found: C 59.7, H 5.4, N 9.3%; $C_{31}H_{32}N_4O_6S_2$

requires C 59.9, H 5.2, N 9.0%). ν_{max} (KBr, cm^{-1}) 3473, 3378, 3243, 2974, 1706, 1595, 1319, 1152, 832. δ_H 7.85 (br, 2H, N—H), 7.41 (d, J = 8.76 Hz, 4H, aromatic-H), 7.27 (d, J = 8.76 Hz, 4H, aromatic-H), 7.07 (d, J = 8.76 Hz, 4H, aromatic-H), 6.55 (d, J = 8.76 Hz, 4H, ph-H), 4.81 (br, 4H, NH_2), 4.22 (d, J = 10.9 Hz, 2H, pyran-C_2 and C_6-H), 2.83 (m, 2H, pyran-C_3 and C_5-H), 0.67 (d, J = 6.51 Hz, 6H, —CH_3). δ_C 209.1, 138.3, 136.7, 129.5, 128.5, 125.8, 120.8, 120.7, 113.4, 85.5, 51.1, 9.4.

RESULTS AND DISCUSSION

As shown in **Scheme-1,** 3,5-bis(2-nitrophenyl)pyrone (**2**) and corresponding amine (**3**) were prepared[9, 10]. Treatment of **3** with *p*-toluenesulfonyl chloride and ethyl chloroformate in the presence of pyridine in acetone gave 3,5-bis[2-(4-tolylsulfonamido)phenyl]-4*H*-pyran-4-one (**6**) and 3,5-bis(2-ethylcarbamato-phenyl)-4*H*-pyran-4-one (**7**) in 70, 40% yields, respectively **(Scheme-1).**



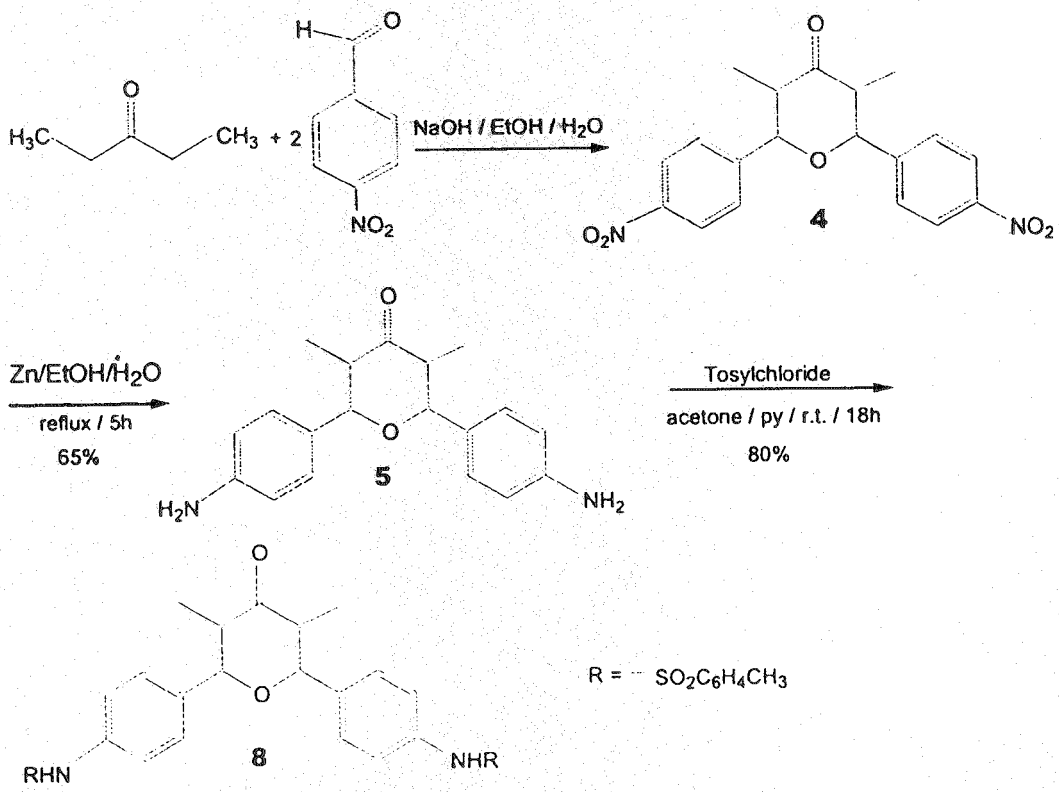
Scheme-1

^{1}H NMR spectrum of **6** displayed a signal at 7.56 ppm that is attributed to the amide proton. The signals due to aromatic and vinyl protons appeared at 7.37–7.50 ppm. The singlet at 2.39 ppm is assigned to the methyl protons. The ^{13}C NMR spectrum showed fourteen signals, one for the carbonyl and twelve for the aromatic carbons and one for the two methyl carbons.

^{1}H NMR spectrum of **7** showed a signal at 7.8 ppm that is attributed to the N—H proton. The signals due to aromatic protons appeared at 7.21–7.48 ppm. The singlet at 8.03 ppm is assigned to the vinyl protons. The triplet at 1.23 ppm is assigned to the methyl protons. The doublet at 4.12 ppm is assigned to the methylene protons.

2,6-Bis-(4-nitrophenyl)tetrahydropyrone (**4**) was prepared according to literature[11]. Reduction of **4** with zinc dust in 78% ethanol-water under reflux condition

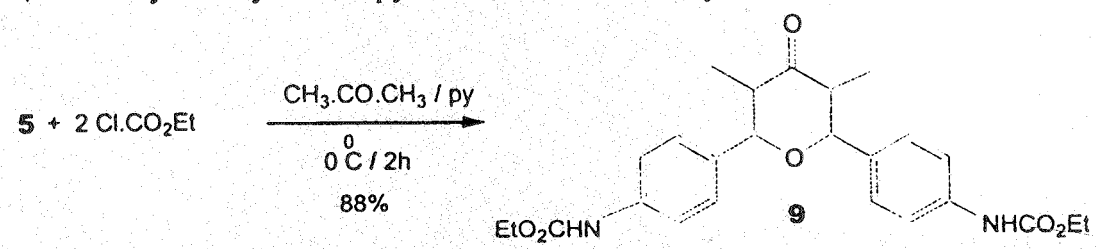
gave 2,6-bis(4-aminophenyl)-3,5-dimethyltetrahydro-4*H*-pyran-4-one (DAPP) (5) in 65% yield. The reaction of 5 with 2 equivalents *p*-toluenesulfonyl chloride in acetone and in the presence of pyridine afforded 2,6-bis[4-(4-tolylsulfonamido)phenyl]-3,5-dimethyltetrahydro-4*H*-pyran-4-one (8) in 80% yield **(Scheme-2).**



Scheme-2

IR spectrum of 8 showed a sharp band at 3260 cm^{-1} assignable to ν(N—H) stretching and two bands at 1327, 1152 cm^{-1}, that is characteristic of SO_2 groups. ^1H NMR spectrum (CD_3CN, DMSO-d_6) exhibited a broad peak at 9.28 ppm due to N—H proton. ^{13}C NMR spectrum (CD_3CN, DMSO-d_6) of the compound showed only the expected thirteen signals: one for the carbonyl carbon, four for the aliphatic carbons and eight others for the aromatic carbons.

DAPP (5) was also reacted with 2 equivalents ethyl chloroformate in acetone and in the presence of pyridine at 0°C to give 2,6-bis(4-ethylcarbamatophenyl)-3,5-dimethyltetrahydro-4*H*-pyran-4-one (9) in 88% yield, **(Scheme-3).**

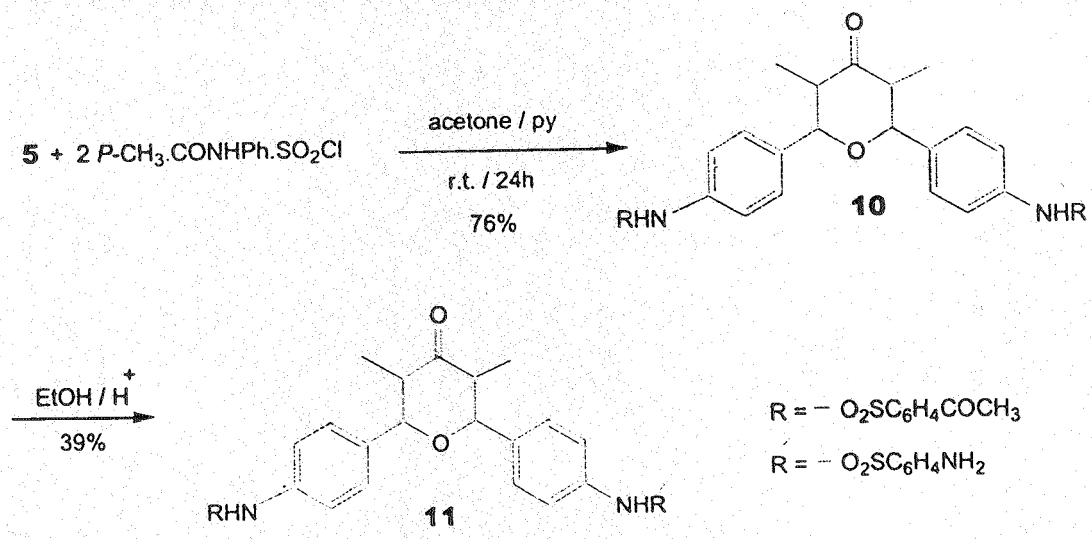


Scheme-3

Its IR spectrum showed N—H band at 3344 cm^{-1}, carbonyl of carbamate at 1729 cm^{-1} and carbonyl of tetrahydropyrone at 1702 cm^{-1}. ^1H NMR spectrum (CD_3CN) exhibited a triplet at 1.24 ppm and a quartet at 4.14 ppm attributable

to ethyl groups of carbamate and a broad peak at 7.76 ppm due to N—H proton. ^{13}C NMR spectrum (CD_3CN) showed ten signals for a variety of carbons of this compound and data of elemental analyses is consistent with structure of molecule.

The reaction of DAPP (**5**) with 2 equivalents *p*-acetamidobenzenesulfonyl chloride in acetone and in the presence of pyridine gave the N-acetyl sulfanilamide (**10**) in 76% yield. Finally, acid catalyzed hydrolysis of **10** furnished sulfonilamide (**11**) in 39% yield **(Scheme-4).**



Scheme-4

IR spectrum of **10** showed a band at 1702 cm^{-1} assignable to carbonyl groups and two bands at 1323, 1157 cm^{-1}, characteristic of SO_2 groups. ^1H NMR spectrum exihibited two broad signals at 10.27, 10.18 ppm due to N—H protons. ^{13}C NMR spectrum showed fourteen signals. Also the IR spectrum of **11** exhibited two bands at 3473 and 3378 cm^{-1} due to NH_2 groups and the ^1H NMR spectrum (CD_3CN) showed a broad peak at 4.81 ppm attributable to NH_2 protons and a broad peak at 7.85 ppm assignable to N—H proton of sulfonamide. The ^{13}C NMR spectrum (CD_3CN) showed twelve signals. One for the carbonyl carbon and three for the aliphatic carbons and eight others for the aromatic carbons.

Conclusion

In this study, sulfonamide and carbamate derivatives of 3,5-bis(2-aminophenyl)-4*H*-pyran-4-one and 2,6-bis(4-aminophenyl)tetrahydro-4*H*-pyran-4-one (DAPP) have been synthesized with quantitative yields by reaction of these compounds with *p*-toluenesulfonyl chloride, *p*-acetamidobenzenesulfonyl chloride and ethyl chloroformate. The sulfanilamide (**11**) has been synthesized by acid catalysed hydrolysis of 2,6-bis[4-(4-acetamidobenzenesulfonamido)-phenyl]-3,5-dimethyltetrahydro-4*H*-pyran-4-one (**10**).

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REFERENCES

1. (a) G.R. Green, J.M. Evans and A.K. Vong, in: Comprehensive Heterocyclic Chemistry-II, Pergamon, Oxford, Vol. 5, pp. 469–500 (1996). (b) M. Miyano, J.R. Deason, A. Nakao, M.A. Stealey, C.I. Villamil, D.D. Shon and R.A. Mueller, *J. Med. Chem.*, **31**, 1052 (1988). (c) T. Kanazawa, Y. Ohkawa, T. Kuda, Y. Minobe, T. Tani and M. Nishizawa, *Chem. Pharm. Bull.*, **45**, 1046 (1997).
2. (a) D. Garey, M.L. Ramirez, S. Gonzales, A. Wertsching, S. Tith, K. Keefe and M.R. Pena, *J. Org. Chem.*, **61**, 4853 (1996). (b) Y. Ishibashi, S. Ohba, S. Nishiyama and S. Yamamura, *Tetrahedron Lett.*, **37**, 2997 (1996).
3. (a) Y. Kodera, H. Matsuura, S. Yoshida, T. Sumida, Y. Itakura, T. Fuwa and H. Nishino, *Chem. Pharm. Bull.*, **37**, 1656 (1989). (b) T. Moriguchi, H. Matsuura, Y. Itakura, H. Katsuki, H. Saito and N. Nishiyama, *Life Sci.*, **61**, 1413 (1997). (c) H. Arimoto, S. Asano and D. Uemura, *Tetrahedron Lett.*, **38**, 7761 (1997).
4. (a) J. Zamocka, E. Misikova and J. Durinda, *Pharmazie*, **46**, 610 (1991), *Chem. Abstr.*, **116**, 106031q (1992). (b) M. Veverka, *Chem. Pap.*, **46**, 206 (1992); *Chem Abstr.*, **118**, 38726j (1992).
5. (a) R.G.G. Leenders, K.A.A. Gerrits, R. Ruijtenbeek, H.W. Scheeren, H.J. Haisma and E. Boven, *Tetrahedron Lett.*, **10**, 1701 (1995). (b) A. Jose, B. Dilbirs, J.D. Glass, M.A. Holahan and M. Renyer, *J. Med. Chem.*, **39**, 480 (1996). (c) J. Alsina, F. Rabanal, C. Chiva, E. Giralt and F. Albericio, *Tetrahedron*, **34**, 10125 (1998). (d) M. Aresta and A. Dibenedetto, *Chem. Eur. J.*, **8**, 685 (2002).
6. (a) C.T. Supuran, A. Scozzafava and A. Casini, *Med. Res. Rev.*, **23**, 146 (2003). (b) B.W. Clare and C.T. Supuran, *Eur. J. Med. Chem.*, **34**, 463 (1999). (c) C.T. Supuran, F. Briganti, S. Tilli, W.R. Chegwidden and A. Scozzafava, *Bioorg. Med. Chem.*, **9**, 703 (2001).
7. (a) S. Massa, R.D. Santo and M. Artico, *J. Heterocycl Chem.*, **27**, 1131 (1990). (b) T.W. Greene and P.G.M. Wuts, in: Protective Groups in Organic Synthesis, Wiley, New York, pp. 403, 327 (1991).
8. J. Staunton, *Comprehen. Org. Chem.*, **4**, 659 (1979).
9. D.D. Perrin and W.L.F. Armerigo, Purification of Laboratory Chemicals, Pergamon Press, p. 360 (1988).
10. A.R. Katritzky and H. Faid-Allah, *J. Heterocycl. Chem.*, **22**, 1333 (1985).
11. J.M. Garcia, F. Garcia, R. Sanz, J.G. De La Campa, A.E. Lozano and J. De Abajo, *J. Polym. Sci., Part A: Polym. Chem.*, **39**, 1825 (2001).

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