Heterocyclization Reactions of 2-Arylideneamino-4,5-Diphenylfuran-3-Carbonitriles

M. Abdel-Megid, A.M. Elkazak, M. Seada and O. Farouk

Chemistry Department, Faculty of Education, Roxy, Cairo, A.R.Egypt

Abstract: Condensation of 2-amino-4,5-diphenylfuran-3-carbonitrile (1) with both 3-formyl-6-methylchromone (2) and p-chlorobenzaldehyde afforded the respective 2-arylideneamino furans 3 and 4. The effect of hydrazines, hydroxylamine, urea and thiourea on compound 3 was studied. Also, the reaction of compound 4 with hydrazine hydrate yielded the additional product 10, which reacted with aromatic aldehyde, acid chloride, carbon disulphide and TEOC to afford the furyltriazoles while its reaction with diethyl oxalate yielded furyltriazine 19.

Key words: Furancarbonitrile, chromone, triazoles and triazine.

INTRODUCTION

Polysubstituted furans are important heterocyclic molecules as well as having practical utility as recurring unit in many natural and medicinal molecules. Many of the naturally occurring furans have shown interesting biological activities, such as cytotoxic and antitumor properties[1,2] as well as antispasmodic[3], antimicrobial[4,5] and several other potentially useful activities[6].

Motivated by these facts, and as a part of our program directed to synthesize new bioactive heterocycles[7-10], the present investigation deals with the use of 2-arylideneamino-4,5-diphenylfuran-3-carbonitrile in the synthesis of some new interesting heterocyclic compounds of expected biological activities.

RESULTS AND DISCUSSION

Condensation of 2-amino-4,5-diphenylfuran-3-carbonitrile (1)[11] with 3-formyl-6-methylchromone (2)[12] and p-chlorobenzaldehyde in absolute ethanol containing few drops of hydrochloric acid afforded the respective 2-arylideneamino derivatives 3 and 4, respectively. (Scheme 1)

Structure of compounds 3 and 4 was established via their correct elemental analyses and spectroscopic data. IR spectrum of them showed the absence of NH2 function at 3400-3100 cm⁻¹. Also compound 3 showed the presence of C=O function at 1640 and C-O at 1069 cm⁻¹ which confirmed the presence of pyranone ring. Compounds 3 and 4 were used as suitable intermediates for the synthesis of some new heterocycles bearing furan nucleus in their structures. Thus, when compound 3 was allowed to react with hydrazines such as hydrazine hydrate and phenylhydrazine, the obtainable product did not show absorption band attributed to C=N function near 2200 cm⁻¹ and it also showed violet coloration with iron III chloride which confirmed the presence of phenolic OH group in their structures. The product could be explained via cycloaddition of the hydrazine at C=N forming intermediate 5 which underwent further two nucleophilic addition one at C=N and the other at C2 of γ-pyronone ring causing ring opening of it giving the furyropyrazolopyrimidines 6a,b. (Scheme 2)

Scheme (1)

Similar behavior was observed when compound 3 reacted with hydroxylamine hydrochloride in pyridine-water mixture and afforded furyroisoxazolopyrimidine 7. While furyropyrimidopyrimidinone 8 and furyropyrimidopyrimidinethione 9 were obtained on treatment of 3 with urea and thiourea in boiling sodium ethoxide, respectively. (Scheme 3)
On the other hand, addition of hydrazine hydrate to compound 4 gave 2-\([\alpha-(4\text{-chlorophenyl})\-\alpha\text{-hydrazino}]\)methylamino-4,5-diphenylfuran-3-carbonitrile (10), where IR of which displayed absorption band at 2212 cm\(^{-1}\) due to C=N function in addition to bands at 3400-3190 attributed to NH, NH\(_2\) groups. Compound 10 was used as convenient intermediate for the preparation of some new furotriazolopyrimidines. Thus, on the condensation of 10 with triethylorthoformate under fusion condition not give the target furyl1,2,4-triazole 11 was obtained based on elemental and spectroscopic data. IR spectrum of 12 showed the absence of C=N function near 2200 cm\(^{-1}\). The structure of 12 can be explained by the sequence shown in Scheme 4.

Similar behavior was observed and furo-1,2,4-triazolopyrimidines 14, 16 and 18 were obtained when compound 10 reacted with benzoyl chloride, \(p\)-chlorobenzaldehyde and carbon disulphide respectively. While 3-(4-chlorophenyl)-6-hydroxy-4-(4,5-diphenyl-3-cyano-2-furyl)-2,3-dihydro-1,2,4-triazin-5-one (19) was obtained on treatment of 10 with diethyl oxalate in boiling sodium ethoxide solution. (Scheme 5)
Furthermore, reaction of compound 4 with benzhydrazide afforded the benzyolhydrazino 20 while treatment of 4 with thioglycollic acid in dry dioxan not gave furylthiazolidinone 21 but compound 22 was produced. As, Hnmr which showed signals at 9.18 (OH) and 8.10ppm (nh). (Scheme 6).

Experimental: All the reported melting points were uncorrected. The IR spectra were recorded on FTIR Jasco 4100 spectrophotometer using KBr wafer technique. Hnmr spectra were measured on Varian Gemini spectrophotometer 200 MHz using TMS (δ ppm) as an internal standard and. Mass spectra were obtained using GCMS-Scheimadzu Qp-2010, GAS-chromatograph (GC-14A) and JEOL-JMS-AX500 Mass spectrometer.
2-Amino-4,5-diphenylfuran-3-carbonitrile (1): This compound was prepared according to the reported method[11].

2-(6-Methyl-4-oxochromen-3-yl)methylideneamino-4,5-diphenyl-furan-3-carbonitrile (3): A mixture of 1 (0.01 mole) and 3-formyl-6-methylchromone (0.01 mole) in absolute ethanol (20 ml) containing few drops of concentrated hydrochloric acid was heated under reflux for 2h. After cooling, the solid obtained was filtered off and recrystallized from dioxan to give 3 as golden yellow crystals, yield 90%, m.p. 243-4ºC. IR spectrum, υ, cm⁻¹: 3056 (CH aromatic); 2923 (CH aliphatic); 2225 (C/N); 1574-1545 (C=N and C=C); 1068 (C-O-). 1Hnmr spectrum, δ, ppm (J, Hz): 2.40 (3H, s, CH₃); 7.23-8.88 (13H, m, Ar-H); 9.14 (1H, s, C₂-H, pyrone); 10.12 (1H, s, N=CH). Mass spectrum, m/z (I, %): 431 [M+1] (2.0), 429 (1.23), 403 (1.13), 218 (21.4), 216 (21.4), 192 (20.2), 89 (100), 77 (89.1). Found, %: C 78.10; H 4.30; N 6.60. C₂₈H₁₈N₂O₃. Calculated, %: C 78.13; H 4.22; N 6.51.

2-(4-Chlorobenzylideneamino)-4,5-diphenylfuran-3-carbonitrile (4): A mixture of 1 (0.01 mole) and p-chlorobenzaldehyde (0.01 mole) in absolute ethanol (20 ml) containing few drops of concentrated hydrochloric acid was heated under reflux for 2h. After cooling, the solid product so formed, was collected and recrystallized from ethanol to give 4 as golden yellow crystals, yield 89%, m.p. 243-4ºC. IR spectrum, υ, cm⁻¹: 3056 (CH aromatic); 2225 (C=O); 1586-1546 (C=N and C=C); 1068 (C-O-). 1Hnmr spectrum, δ, ppm (J, Hz): 2.30 (3H, s, CH₃); 7.23-7.44 (15H, m, Ar-H, C₂-H and bridged-H); 7.48 (1H, s, NH); 7.71 (2H, br.s, NH₂); 8.68 (1H, s, OH). Mass spectrum, m/z (I, %): 463 [M+1] (0.23), 400 (0.33), 368 (0.34), 260 (20.32), 231 (6.18), 188 (10.23), 148 (16.87), 100 (36.27), 96 (86.8), 68 (81.52%), 54 (100). Found, %: C 75.29; H 3.95; N 7.32; Cl 9.26. C₂₄H₁₅N₂OCl. Calculated, %: C 75.30; H 3.90; N 7.40; Cl 9.20. C₂₃H₁₈N₂O₃Cl. Calculated, %: C 73.50; H 3.90; N 7.40; Cl 9.20. C₂₃H₁₈N₂O₃Cl. Calculated, %: C 75.29; H 3.95; N 7.32; Cl 9.26.

2-(4-Chlorobenzylideneamino)-4,5-diphenylfuran-3-carbonitrile (3): A mixture of 1 (0.01 mole) and phenylhydrazine (0.01 mole) in sodium ethoxide [finely divided sodium metal (0.01 mole) in absolute ethanol (20 ml)] was heated under reflux for 3h. After cooling, the solid obtained was collected and recrystallized from ethanol to give 6b as white crystals, yield 88%, m.p. above 300ºC. IR spectrum, υ, cm⁻¹: 3437 (phenolic-OH); 3311, 3251 (NH₂, NH); 3055 (CH aliphatic); 1650 (C=O); 1613-1532 (C=N and C=C); 1069 (C-O-). 1Hnmr spectrum, δ, ppm (J, Hz): 2.30 (3H, s, CH₃); 7.23-7.44 (15H, m, Ar-H, C₂-H and bridged-H); 7.48 (1H, s, NH); 7.71 (2H, br.s, NH₂); 8.68 (1H, s, OH). Mass spectrum, m/z (I, %): 538 [M] (1.22), 518 (1.13), 429 (1.19), 368 (2.17), 260 (4.82), 213 (3.35), 140 (4.23), 77 (6.22), 46 (100). Found, %: C 75.90; H 4.70; N 10.50. C₃₄H₂₆N₄O₃. Calculated, %: C 75.82; H, 4.87; N, 10.40.

8-Amino-3-(2-hydroxy-5-methylbenzoyl)-6,7-diphenylfuro[2',3';4,5]pyrimido-[1,2-b]pyrazole (6a): A mixture of 3 (0.01 mole) and hydrazine hydrate (0.01mole) in sodium ethoxide [finely divided sodium metal (0.01 mole) in absolute ethanol (20 ml)] was heated under reflux for 3h. After cooling, the solid obtained was collected and recrystallized from ethanol to give 6a as yellow crystals, yield 85%, m.p. above 300ºC. IR spectrum, υ, cm⁻¹: 3438 (phenolic-OH); 3313-3190 (NH₂, NH); 3059 (CH aromatic); 2927 (CH aliphatic); 1650 (C=O); 1591-1543 (C=N and C=C); 1069 (C-O-). 1Hnmr spectrum, δ, ppm (J, Hz): 3.33 (3H, s, CH₃); 7.21-7.44 (13H, m, Ar-H); 9.14 (1H, s, C₂-H, pyrone); 10.12 (1H, s, N=CH). Mass spectrum, m/z (I, %): 463 [M+1] (0.23), 400 (0.33), 368 (0.34), 260 (20.32), 231 (6.18), 188 (10.23), 148 (16.87), 104 (36.27), 96 (86.8), 68 (81.2%), 54 (100). Found, %: C 72.80; H 4.70; N 12.20. C₂₈H₂₂N₄O₃. Calculated, %: C 72.71; H 4.79; N 12.11.

8-Amino-3-(2-hydroxy-5-methylbenzoyl)-1,6,7-triphenylfuro[2',3';4,5]pyrimido-[1,2-b]pyrazole (6b): A mixture of 3 (0.01 mole) and phenylhydrazine (0.01 mole) in sodium ethoxide [finely divided sodium metal (0.01 mole) in absolute ethanol (20 ml)] was heated under reflux for 3h. After cooling, the solid obtained was collected and recrystallized from ethanol to give 6b as white crystals, yield 88%, m.p. above 300ºC. IR spectrum, υ, cm⁻¹: 3437 (phenolic-OH); 3311, 3251 (NH₂, NH); 3055 (CH aromatic); 1650 (C=O); 1613-1532 (C=N and C=C); 1069 (C-O-). 1Hnmr spectrum, δ, ppm (J, Hz): 2.48 (2H, br.s, NH₂); 7.21-7.87 (20H, m, Ar-H, C₂-H and bridged-H); 7.48 (1H, s, OH). Mass spectrum, m/z (I, %): 538 [M] (1.22), 518 (1.13), 429 (1.19), 368 (2.17), 260 (4.82), 213 (3.35), 140 (4.23), 77 (6.22), 46 (100). Found, %: C 75.90; H 4.70; N 10.50. C₃₄H₂₆N₄O₃. Calculated, %: C 75.82; H, 4.87; N, 10.40.
hydrochloride (0.01 mole) in pyridine-water mixture (20 ml) was heated under reflux for 3h. After cooling, the solid obtained was collected and recrystallized from ethanol to give 7 as brown crystals, yield 81%, m.p. above 300ºC. IR spectrum, v cm⁻¹: 3450-3120 (OH and NH₂); 3045 (CH aromatic); 2922 (CH aliphatic); 1641 (C=O); 1561-1504 (C=N and C=C); 1079 (C-O-). Mass spectrum, m/z (I, %): 463 [M] (0.12), 461 (0.11), 386 (0.4), 356 (0.15), 309 (0.11), 77 (53.07), 54 (100). Found, %: C, 72.60; H, 4.60; N, 9.10. C₉H₇N₂O₄. Calculated, %: C 74.32; H 4.23; N 11.18; Cl 7.08.

5-(4-Chlorophenyl)-5,6-dihydro-2,8,9-triphenylfuro[2',3':4,5]pyrimido[1,6-b]-1,2,4-triazole (12): A mixture of 10 (0.01 mole) and triethylorthoformate (0.01 mole) was heated under reflux for 1h. The mixture was left to cool at room temperature, the solid obtained was filtered off and recrystallized from ethanol to give 12 as golden yellow crystals, yield 79%, m.p. 216-18ºC. IR spectrum, v, cm⁻¹: 3416 (NH); 3042 (CH aromatic); 1587-1482 (C=N and C=C); 1068 (C-O-). Mass spectrum, m/z (I, %): 424 [M] (9.82), 409 (9.82), 382 (11.66), 364 (61.35), 276 (46.63), 167 (65.03), 105 (100), 77 (28.22). Found, %: C 70.70; H 4.10; N 13.10; Cl 8.40. C₂₅H₁₉N₄OCl. Calculated, %: C 70.67; H 4.03; N 13.19; Cl 8.34.

2-[α-(4-Chlorophenyl)-α-hydrazino]methylamino-4,5-diphenylfuran-3-carbonitrile (10): A mixture of 4 (0.01 mole) and hydrazine hydrate (0.01 mole) in absolute ethanol (20 ml) was heated under reflux for 3h. The solid obtained was filtered off and recrystallized from ethanol to give 10 as white crystals, yield 88%, m.p. 207-9ºC. IR spectrum, v, cm⁻¹: 3441-3196 (NH₂ and 2NH); 3059 (CH aromatic); 2213 (C≡N); 1592-1570 (C=N and C≡C); 1068 (C-O-). ¹Hnmr spectrum, δ (ppm, J, Hz): 3.35 (2H, brs, NH₂); 4.2 (1H, s, HC-N), 7.24-7.44 (14H, m, Ar-H); 7.7 (2H, s, 2NH). Mass spectrum, m/z (I, %): 414 [M] (0.84), 407 (0.60), 376 (0.81), 261 (11.29), 260 (42.40), 214 (12.82), 189 (22.97), 127 (21.31), 105 (12.68), 77 (100), 76 (30.94). Found, %: C 69.50; H 4.70; N 13.40; Cl 8.50. C₂₉H₁₇N₄O₄Cl. Calculated, %: C 69.68; H 4.62; N 13.50; Cl 8.35.

2,5-Bis(4-chlorophenyl)-2,3,5,6-tetrahydro-8,9-diphenylfuro[2',3':4,5]pyrimido-[1,6-b]-1,2,4-triazole (16): A mixture of 10 (0.01 mole) and p-chlorobenzaldehyde (0.01 mole) in absolute ethanol (20 ml) containing few drops of glacial acetic acid was heated under reflux for 2h. After cooling, the solid obtained was filtered off and recrystallized from ethanol to give 16 as golden yellow crystals, yield 85%, m.p. 217-9ºC. IR spectrum, v, cm⁻¹: 3418 (NH); 3042 (CH aromatic); 1618-1587 (C=N and C≡C); 1085 cm⁻¹ (C-O-). Mass spectrum, m/z
(δ, ppm (J, Hz)): 1.57 (1H, s, HC-N); 5.37 (2H, s, SCH2); 7.29-7.71 (14H, m, Ar-H); 8.1 (1H, s, NH); 9.18 (1H, s, OH). Mass spectrum, m/z (I, %): 474 [M] (69.2), 201 (53), 146 (7.7), 145 (61.5), 131 (69.2), 78 (30.8), 61 (46.2), 57 (100). Found, %: C 65.80; H 4.10, N 5.80; S 6.80; Cl 7.50. C26H19N2O3SCl. Calculated, %: C 65.75; H 4.03; N 5.89; S 6.80; Cl 7.50. C26H19N2O3SCl. Calculated, %: C 65.75; H 4.03; N 5.89; S 6.80; Cl 7.50.

3-(4-Chlorophenyl)-6-hydroxy-4-(4,5-diphenyl-3-cyano-2-furyl)-2,3-dihydro-1,2,4-triazin-5-one (19): A mixture of 10 (0.01 mole) and diethyl oxalate (0.01 mole) in sodium ethoxide [finely divided sodium metal (0.01 mole) in absolute ethanol (20 ml)] was heated under reflux for 4h. After cooling, the solid obtained was collected and recrystallized from ethanol to give 19 as white crystals, yield 88%, m.p. above 300°C. IR spectrum, ν, cm⁻¹: 3440-3205 (OH and NH); 3057 (CH aromatic); 1470 (C=O); 1555 (C=C); 1076 (C-O-). Hnmr spectrum, δ, ppm (J, Hz): 4.7 (1H, s, HC-N); 7.29-7.49 (14H, m, Ar-H); 7.9 (1H, s, NH); 9.23 (1H, s, OH). Mass spectrum, m/z (I, %): 466 [M-2] (4.50), 129 (17.9), 120 (28.40), 105 (41.8), 103 (10.40), 77 (100). Found, %: C 66.50; H 3.60; N 12.00; Cl 7.60. C26H17N4O3Cl. Calculated, %: C 66.60; H 3.65; N 11.95; Cl 7.56.

2-[α-(4-Chlorophenyl)-α-benzoylethydrazino] methylamino-4,5-diphenylfuran-3-carbonitrile (20): A mixture of 4 (0.01 mole) and phenylhydrazide (0.01 mole) in DMF (20ml) containing few drops of triethylamine was heated under reflux for 3h. After cooling, the solid obtained was collected and recrystallized from benzene to give 20 as yellow crystals, yield 82%, m.p. 152-54°C. IR spectrum, ν, cm⁻¹: 3440-3205 (3NH); 3059 (CH aromatic); 2923 (CH aliphatic); 2212 (C=NC); 1650 (C=O); 1541 (C=C); 1068 (C-O-). Hnmr spectrum, δ, ppm (J, Hz): 1.23 (1H, s, HC-N); 4.1 (1H, s, HN=N); 7.23-7.90 (19H, m, Ar-H); 8.46 (1H, s, HN-C); 11.8 (1H, s, HNCO). Mass spectrum, m/z (I, %): 501 [M] (0.11), 498 (0.12), 411 (0.26), 349 (33), 260 (13.90), 175 (3.35), 164 (7.44), 138 (10.41), 110 (17.24), 104 (100), 76 (67.78). Found, %: C, 71.70; H, 4.30; N, 10.80; Cl, 6.70. C26H17N4O3Cl. Calculated, %: C, 71.74; H, 4.47; N, 10.79; Cl, 6.83.

2-[α-(4-Chlorophenyl)-α-carboxymethylthio] methylamino-4,5-diphenylfuran-3-carbonitrile (22): A mixture of 4 (0.01mole) and thioglycollic acid (0.01mole) in dry benzene (20ml) was heated under reflux for 4h. After cooling, the solid obtained was filtered off and recrystallized from dioxan to give 22 as yellow crystals, yield 79%, m.p. 205-5°C. IR spectrum, ν, cm⁻¹: 3358 (OH); 3194 (NH); 3055 (CH aromatic); 2964 (CH aliphatic); 2210 (C=O); 1658 (C=O); 1497 (C=C); 1076 (C-O-). Hnmr spectrum, δ, ppm (J, Hz): 1.57 (1H, s, HC-N); 3.37 (2H, s, SCH2); 7.24-7.71 (14H, m, Ar-H); 8.1 (1H, s, NH); 9.18 (1H, s, OH). Mass spectrum, m/z (I, %): 474 [M] (69.2), 201 (53), 146 (7.7), 145 (61.5), 131 (69.2), 78 (30.8), 61 (46.2), 57 (100). Found, %: C 65.80; H 4.10, N 5.80; S 6.80; Cl 7.50. C26H17N4O3Cl. Calculated, %: C 65.75; H 4.03; N 5.89; S 6.75; Cl 7.46.

REFERENCES