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SYNTHESIS OF BRIDGEHEAD-NITROGEN HETEROCYCLES FROM PYRYLIUM SALTS: PREPARATION OF THE NOVEL TRICYCLIC THIAZOLO[2,3-c]PYRIDO[2,1-f][1,2,4]TRIAZINE RING SYSTEM

Pedro Molina*, Alberto Tárraga, Mercedes Lorenzo-Peña,
and Arturo Espinosa

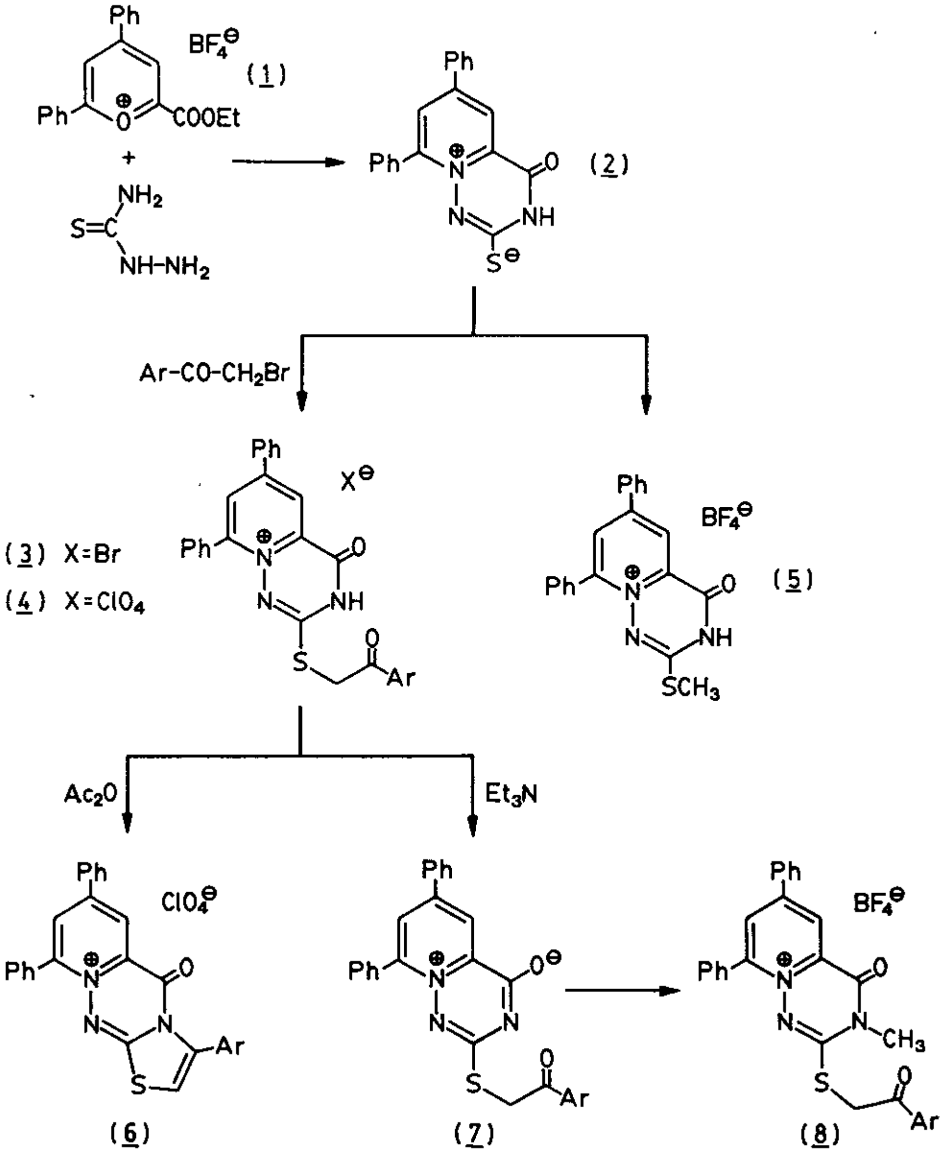
Departamento de Química Orgánica, Facultad de Ciencias,
Universidad de Murcia, 30001 Murcia, Spain

Abstract- A number of thiazolo[2,3-c]pyrido[2,1-f][1,2,4]triazine derivatives have been prepared by reaction of the 4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate, available from 2-ethoxycarbonyl-4,6-diphenylpyrylium cation and thiosemicarbazide, with phenacyl bromides and subsequent cyclization by the action of acetic anhydride.

In the last few years we were involved in a program aiming to develop synthetic approaches for nitrogen-bridgehead heterocycles utilizing readily available 2-functionalized pyrylium cations as starting materials. In this context, we have reported the reaction of 2-ethoxycarbonyl-4,6-diphenylpyrylium tetrafluoroborate (1) with unsubstituted and N^3-arylamidrazones to give 4-oxidopyrido[2,1-f][1,2,4]triazinium betaines and 4-oxo-3,4-dihydropyrido[2,1-f][1,2,4]triazinium salts respectively[1]. Similarly, we have found that compound (1) reacts with thiocarbonohydrazide and carbonohydrazide to give the cross-conjugated betaines 3-amino-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate[2] and 3-amino-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-olate[3] repectively. On the other hand, compound (1), reacts with hydrazides to give the corresponding N-amido pyridinium salts which by the action of hydrazine undergo cyclization to give 2-substituted 3-amino-4-oxo-6,8-diphenyl-3,4-dihydropyrido-[2,1-f][1,2,4]triazin-9-ium salts[4].

We now describe a general method for the preparation of some derivatives of the unknown thiazolo[2,3-c]pyrido[2,1-f][1,2,4]triazine ring system from 2-ethoxycarbonyl-4,6-diphenylpyrylium cation (1) by sequential treatment with thiosemicarbazide, phenacyl bromides and cyclodehydration by the action of acetic anhydride.

The pyrylium salt (1), readily available from ethyl pyruvate, benzylidenacetophenone and boron trifluoride diethyl ether[5], reacts with thiosemicarbazide in methanol at reflux temperature for 8 h to give 4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate (2) as a crystalline solid in 43% yield. Compound (2) undergoes S-alkylation by the action of phenacyl bromides to give the corresponding 4-oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium bromides (3), which by treatment with perchloric acid in ethanol at reflux temperature are converted into the corresponding perchlorates (4) in almost quantitative yields (Table 1). Similarly, compound (2) reacts with trimethyloxonium tetrafluoroborate to give the S-methyl derivative (5) in high yield. Compounds (4) undergo cyclization by the action of acetic anhydride to give the corresponding 3-aryl-5-oxo-7,9-diphenylthiazolo[2,3-c]pyrido[2,1-f][1,2,4]triazin-10-ium perchlorates (6) as crystalline solids in high yields (Table 2).



On the other hand, when ethanolic solutions of compounds (4) are treated with equimolecular amount of triethylamine, betaines (7) are isolated as crystalline solids in high yields. Methylation of compounds (7) with trimethyloxonium tetrafluoroborate leads exclusively to 3-methyl-4-oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium tetrafluoroborates (8) in high yields, because of the availability of the lone pair at N-1 position is strongly decreased by influence of the positive charge on the neighbouring bridgehead nitrogen atom [6].

Structural elucidation of (2)-(8) is accomplished on the basis of spectral and microanalytical data. The ir spectra of (2), (3), (4), (5), (6) and (8) show a strong absorption band in the region 1690-1738 cm^{-1}, attributable to the carbonyl group in the triazinone moiety, while the presence of another different carbonyl group in compounds (3), (4), (7) and (8) is confirmed by the absorption band in the region 1664-1693 cm^{-1}. In the ^1H-nmr spectra of (3), (4), (7) and (8) the chemical shift of the methylene group (S-$\underline{CH_2}$-COAr) is characteristic at δ 4.6 ppm, while in the ^1H-nmr spectra of compounds (6) this signal is absent, although a new signal correspspnding to the proton at 2 position appears at δ 7.1 ppm as a singlet.

EXPERIMENTAL

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were run using NaCl plates on a Nicolet FT-5DX spectrophotometer in Nujol emulsions. ^1H-nmr spectra were obtained on a Varian EM-360 A spectrometer at 60 MHz. Mass spectra were recorded on a Hewlett-Packard 5993 C spectrometer. Elemental analyses were performed with a Perkin Elmer 240 instrument.

Preparation of 4-Oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate 2. To a solution of 2-ethoxycarbonyl-4,6-diphenylpyrylium tetrafluoroborate **1** (0.39 g, 1 mmol) in methanol (20 ml), thiosemicarbazide (0.092 g, 1 mmol) was added. The reaction mixture was stirred at reflux temperature for 8 h. After cooling, the precipitated solid was separated by filtration and recrystallised from chloroform to give **2** (0.14 g, 43%) as orange prisms; mp 186-187°C (Found: C, 68.72; H, 4.08; N, 12.55. $C_{19}H_{13}N_3OS$ requires C, 68.86; H, 3.95; N, 12.68 %); ν_{max} (Nujol) 1690, 1625, 1490, 1400, 1330, 1260, 1210, 1150, 1030, 1000, 985, 910, 885, 770, 700; δ ($DMSO-d_6$) 8.90 (1H,d,J=2Hz), 8.70 (1H,d,J=2Hz), 8.65-7.15 (11H,m); m/z (%) 331 (M^+, 14), 299 (29), 270 (7), 258 (13), 230 (91), 191 (44), 64 (100).

TABLE 1. Preparation of 4-Oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium Perchlorates 4.

Entry	Ar	Mp(°C)	Yield	Found			Molecular	Required		
			(%)	C	H	N	Formula	C	H	N
a	C_6H_5	266-267	69	58.81	3.72	7.59	$C_{27}H_{20}ClN_3O_6S$	58.96	3.67	7.64
b	4-$H_3CO.C_6H_4$	243-244	75	57.90	3.75	7.13	$C_{28}H_{22}ClN_3O_7S$	57.98	3.82	7.25
c	4-$Cl.C_6H_4$	261-262	81	55.61	3.30	6.93	$C_{27}H_{19}Cl_2N_3O_6S$	55.49	3.28	7.19
d	4-$C_6H_5.C_6H_4$	260-261	77	63.28	3.95	6.57	$C_{33}H_{24}ClN_3O_6S$	63.31	3.86	6.71
e	4-$Br.C_6H_4$	212-213	71	51.43	2.93	6.71	$C_{27}H_{19}BrClN_3O_6S$	51.57	3.05	6.68
f	4-$O_2N.C_6H_4$	257-258	98	54.38	3.31	9.61	$C_{27}H_{19}ClN_4O_8S$	54.51	3.22	9.42

TABLE 2. Preparation of 3-Aryl-5-oxo-7,9-diphenylthiazolo[2,3-c]pyrido[2,1-f][1,2,4]triazin-10-ium Perchlorates 6.

Entry	Ar	Mp(°C)	Yield	Found			Molecular	Required		
			(%)	C	H	N	Formula	C	H	N
a	C_6H_5	222-223	90	61.13	3.35	7.84	$C_{27}H_{18}ClN_3O_5S$	60.96	3.41	7.90
b	4-$H_3CO.C_6H_4$	185-186	92	59.72	3.66	7.35	$C_{28}H_{20}ClN_3O_6S$	59.84	3.59	7.48
c	4-$Cl.C_6H_4$	232-233	93	57.38	2.92	7.45	$C_{27}H_{17}Cl_2N_3O_5S$	57.25	3.03	7.42
d	4-$C_6H_5.C_6H_4$	301-303	99	65.31	3.52	7.13	$C_{33}H_{22}ClN_3O_5S$	65.18	3.65	6.91
e	4-$Br.C_6H_4$	236-237	95	52.84	2.93	7.01	$C_{27}H_{17}BrClN_3O_5S$	53.09	2.80	6.89
f	4-$O_2N.C_6H_4$	197-199	98	56.32	3.09	9.54	$C_{27}H_{17}ClN_4O_7S$	56.21	2.97	9.71

General Procedure for the Formation of 4-Oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium Perchlorates 4. To a solution of 4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate 2 (0.5 g, 1.5 mmol) in absolute ethanol (20 ml), an equimolecular amount of the appropriate phenacyl bromide was added. The reaction mixture was stirred at reflux temperature for 8 h. After cooling, the precipitated solid was separated by filtration, dried and recrystallised from ethanol to give 3. To a suspension of 3 (1 mmol) in ethanol (15 ml), 70% perchloric acid (2 ml) was added. The mixture was kept under reflux temperature for 2 h, and the resulting precipitated solid was filtered off and recrystallised from ethanol to give 4 (see Table 1).

Preparation of 2-Methylthio-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium Tetrafluoroborate 5. 4-Oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate 2 (0.331 g, 1 mmol), trimethyloxonium tetrafluoroborate (0.148 g, 1 mmol) and dry dichloromethane (10 ml) were stirred under reflux temperature for 4 h. After cooling, the white precipitated solid was separated by filtration, dried and recrystallised from ethanol to give 5 (0.38 g, 88%) as colourless prisms; mp 236-237°C (Found: C, 55.31; H, 3.89; N, 9.92. $C_{20}H_{16}BF_4N_3OS$ requires C, 55.45; H, 3.72; N, 9.70 %); ν_{max} (Nujol) 3165, 1738, 1630, 1596, 1557, 1404, 1376, 1359, 1280, 1265, 1213, 1060, 904, 769, 717, 698 cm^{-1}; δ ($CDCl_3$/TFA) 9.05 (1H,d,J=2Hz), 8.40 (1H,d,J=2Hz), 8.1-7.5 (10H,m), 2.3 (3H,s); m/z (%) 346 ($M^+-BF_4^-$,13), 345 (M^+-HBF_4,54), 299 (23), 298 (100), 258 (3), 231 (23), 230 (65), 77 (32).

General Procedure for the Formation of 3-Aryl-5-oxo-7,9-diphenylthiazolo[2,3-c]pyrido[2,1-f][1,2,4]triazin-10-ium Perchlorates 6. A solution of the appropriate 4-oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium perchlorate 4 (2 mmol) in acetic anhydride (15 ml) was heated under reflux temperature for 1 h. After cooling, diethyl ether (30 ml) was added and the separated solid was collected by filtration, washed with diethyl ether (2x5 ml), dried and recrystallised from ethanol to give 6 (see Table 2 and 3).

General Procedure for the Formation of 2-Phenacylthio-6,8-diphenylpyrido[2,1-f][1,2,4]triazin-9-ium-4-olate 7. To a suspension of the appropriate 4-oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium perchlorate 4 (2 mmol) in ethanol (30 ml), an equimolecular amount of triethylamine was added. The resulting mixture was stirred at room temperature for 4 h. The solid was filtered off, dried and recrystallised from ethanol to give 7.

7a, Ar=C_6H_5 (0.74 g, 86%) as white prisms; mp 197-200°C (Found: C, 72.28; H, 4.13; N, 9.51. $C_{27}H_{19}N_3O_2S$ requires C, 72.14; H, 4.26; N, 9.35 %); ν_{max} (Nujol) 1676, 1639, 1608, 1577, 1473, 1437, 1364, 1322, 1291, 1218, 1192, 1161, 1146, 1000, 979, 902, 792, 762, 755, 722, 697, 686, 642; δ ($CDCl_3$/TFA) 9.05 (1H,d, J=2Hz), 8.5 (1H,d,J=2Hz), 8.05-7.30 (15H,m), 4.60 (2H,s).

7b, Ar=4-$H_3COC_6H_4$ (0.8 g, 83%), as white prisms; mp 213-214°C (Found: C, 69.02; H, 4.31; N, 8.86. $C_{28}H_{21}N_3O_3S$ requires C, 70.13; H, 4.41; N, 8.76 %). ν_{max} (Nujol) 1693, 1636, 1612, 1599, 1510, 1473, 1456, 1435, 1400, 1359, 1323, 1263, 1207, 1168, 1032, 979, 827, 767, 723, 702, 690 cm^{-1}; δ ($CDCl_3$) 9.05 (1H,d,J=2Hz), 8.50 (1H,d,J=2Hz), 8.10-6.90 (14H,m), 4.50 (2H,s), 4.10 (3H,s).

7c, Ar=4-ClC_6H_4 (0.92 g, 96%), as white prisms; mp 229-230°C (Found: C, 66.91; H, 3.62; N, 8.75. $C_{27}H_{18}ClN_3O_2S$ requires C, 67.01; H, 3.75; N, 8.68 %); ν_{max} (Nujol) 1698, 1642, 1613, 1591, 1473, 1446, 1435, 1402, 1356, 1317, 1290, 1199, 1165, 1091, 979, 855, 790, 769, 725, 704, 694 cm^{-1}; δ($CDCl_3$/TFA) 9.15 (1H,d,J=2Hz), 8.50 (1H,d,J=2Hz), 8.20-7.30 (14H,m), 4.60 (2H,s).

TABLE 3. Spectral Data of Compounds 4 and 6.

Compound	IR(cm^{-1})	^{1}H-NMR^a(ppm)
4a	3098,1733,1682,1630,1552,1323,1292, 1213,1195,1118,1053,999,902,765,758, 717,692,636,623.	9.10(1H,d,J=2Hz),8.40(1H,d,J=2Hz) 8.10-7.20(15H,m), 4.60(2H,s).
4b	3160,1721,1647,1625,1596,1570,1510, 1313,1261,1203,1174,1095,1022,985, 896,841,785,769,700,688,623.	9.05(1H,d,J=2Hz),8.40(1H,d,J=2Hz) 8.1-6.9(14H,m), 4.60(2H,s), 4.0(3H,s).
4c	3098,1738,1687,1625,1585,1552,1462, 1196,1123,1089,1055,995,983,930,899, 851,812,766,700,681,627.	9.27(1H,d,J=2Hz),8.60(1H,d,J=2Hz) 8.3-7.3(14H,m), 4.81(2H,s).
4d	3166,1726,1664,1626,1601,1553,1483, 1466,1383,1309,1211,1194,1156,1099, 999,988,901,843,767,720,696,690,624.	9.23(1H,d,J=2Hz),8.51(1H,d,J=2Hz) 8.3-7.3(19H,m), 4.76(2H,s).
4e	3075,1738,1687,1625,1585,1551,1291, 1217,1194,1121,990,983,929,896,850, 810,765,700.	9.10(1H,d,J=2Hz),8.50(1H,d,J=2Hz) 8.2-7.3(14H,m), 4.60(2H,s).
4f	3105,1741,1717,1627,1587,1548,1520, 1465,1349,1289,1216,1193,1125,1099, 1061,982,900,859,845,771,745,704,689.	9.10(1H,d,J=2Hz),8.30(1H,d,J=2Hz) 8.2-7.3(14H,m), 4.65(2H,s).
6a	1738,1619,1585,1545,1432,1331,1197, 1172,1100,1010,991,958,763,713,698.	9.10(1H,d,J=2Hz),8.45(1H,d,J=2Hz) 8.1-7.4(15H,m), 7.10(1H,s).

TABLE 3 Continued

6b	1732,1622,1575,1506,1296,1273,1251, 1205,1176,1087,1022,896,827,767,742, 715,694.	9.30(1H,d,J=2Hz),8.60(1H,d,J=2Hz) 8.2-7.3(14H,m), 7.07(1H,s), 4.10(3H,s).
6c	1736,1622,1587,1545,1464,1435,1333, 1196,1169,1098,1089,960,897,844,762, 715,698,623.	9.15(1H,d,J=2Hz),8.51(1H,d,J=2Hz) 8.1-7.4(14H,m), 7.08(1H,s).
6d	1731,1621,1593,1581,1537,1465,1451, 1436,1274,1199,1099,1078,898,766, 719,695,683,624.	9.20(1H,d,J=2Hz),8.52(1H,d,J=2Hz) 8.2-7.5(19H,m), 7.05(1H,s).
6e	1738,1622,1583,1545,1465,1433,1404, 1331,1174,1097,1087,1011,991,959, 895,845,832,765,714,698,624.	9.22(1H,d,J=2Hz),8.59(1H,d,J=2Hz) 8.1-7.4(14H,m), 7.14(1H,s).
6f	1738,1625,1595,1546,1526,1465,1438, 1352,1279,1248,1197,1094,899,858, 839,768,720,702,623.	9.42(1H,d,J=2Hz),9.23(1H,d,J=2Hz) 8.9-7.7(14H,m), 7.10(1H,s).

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[a] Obtained as solutions in $CDCl_3$+TFA, except for compound 6d which was obtained in DMSO-d_6.

General Procedure for the Formation of 3-Methyl-4-oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium Tetrafluoroborates 8. To a suspension of the appropriate betaine 7 (1 mmol) in dry dichloromethane (15 ml), trimethyloxonium tetrafluoroborate (0.148 g, 1 mmol) was added. The reaction mixture was stirred at reflux temperature for 3 h. On cooling, the resulting precipitated solid was filtered off and recrystallised from ethanol to give 8.

8a, Ar=4-$H_3COC_6H_4$ (0.52 g, 90%) as yellow prisms; mp 207-209°C (Found: C, 59.68; H, 4.25; N, 7.16. $C_{29}H_{24}BF_4N_3O_3S$ requires C, 59.91; H, 4.16; N, 7.23 %). ν_{max} (Nujol) 1721, 1664, 1625, 1596, 1534, 1347, 1262, 1206, 1177, 1060, 900, 832, 764, 721, 707; δ($CDCl_3$/TFA) 9.10 (1H,d,J=2Hz), 8.40 (1H,d,J=2Hz), 8.1-6.99 (14H,m), 4.60 (2H,s), 4.0 (3H,s), 3.80 (3H,s); m/z (%) 494 (M^+-BF_4,1), 493 (1), 313 (7), 299 (23), 298 (90), 231 (24), 230 (32), 152 (8), 151 (4), 135 (100), 107 (19), 77 (42).

8b, Ar=4-ClC$_6$H$_4$ (0.55 g, 93%), as white prisms; mp 211-213°C (Found: C, 57.38; H, 3.73; N, 7.28. $C_{28}H_{21}BClF_4N_3O_2S$ requires C, 57.41; H, 3.61; N, 7.17 %). $_{max}$ (Nujol) 1728, 1685, 1628, 1589, 1552, 1435, 1290, 1215, 1195, 1060, 898, 854, 812 765, 723, 702, 682; (CDCl$_3$/TFA) 9.10 (1H,d,J=2Hz), 8.40 (1H,d,J=2Hz), 8.10-7.20 (14H,m), 4.60 (2H,s), 3.80 (3H,s); m/z (%): 500 (M^+-BF$_4$,1), 498 (3), 313 (5), 299 (4), 298 (84), 231 (25), 230 (38), 156 (3), 155 (4), 154 (8), 153 (6), 141 (29), 139 (100), 113 (6), 111 (15), 77 (20).

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