Nitrogen-Bridgehead Heterocycles from 2-Ethoxycarbonyl-4,6-diphenylpyrylium Cation[1]

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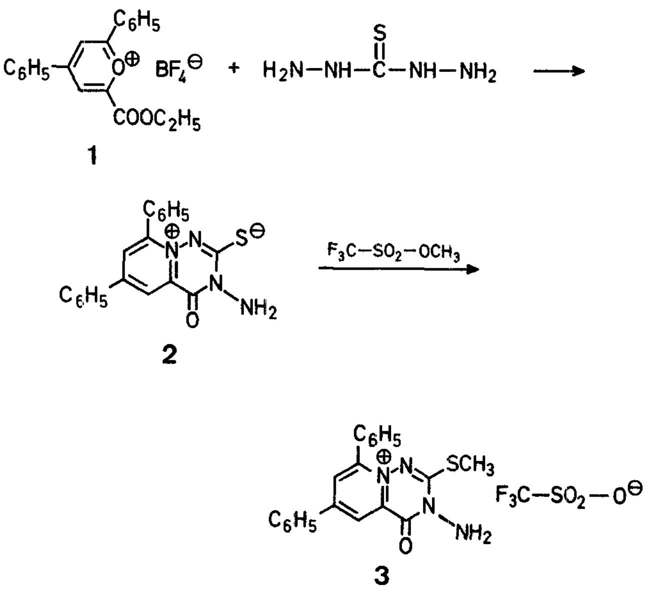
In spite of much work on the reaction of pyrylium cations with nitrogen nucleophiles[2], only few studies have been devoted to the reaction of 2-functionalised pyrylium cations, in particular, 2-ethoxycarbonyl pyrylium salts, with ambident nitrogen nucleophiles. The reaction of 2-ethoxycarbonyl-4,6-diphenylpyrylium tetrafluoroborate (**1**) with primary amines has been shown to give the corresponding pyridinium salts which undergo deethoxycarbonylation on treatment with *t*-butylamine[3,4]. Similarly, compound **1** reacts with aldehyde and ketone hydrazones to yield the corresponding alkylidenaminopyridinium salts; the ketone derivatives cyclise under basic conditions to give oxidopyrido[1,2-*b*]pyridazinium betaines[5]. The reaction of **1** with phenylhydrazine and semicarbazide leads to dihydropyrazoloquinoline and 4-oxopyrido[2,1-*f*][1,2,4]triazinium-2-oxide derivatives, respectively[5]. Recently, we have reported the reaction of compound **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[6].

The present paper records work which is part of our attempts to prepare bridgehead-nitrogen heterocycles from pyrylium (**1**) and amino compounds.

The pyrylium salt **1**, readily available from ethyl pyruvate, benzylideneacetophenone, and boron trifluoride-diethyl ether[3], reacts with thiocarbohydrazide at room temperature in methanol to give 3-amino-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 84% yield. Compound **2** undergoes *S*-methylation on reaction with methyl triflate at room temperature in dry dichloromethane to give 3-amino-2-methylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium triflate (**3**) as a crystalline solid in 82% yield.



Structures **2** and **3** are based on microanalytical data and spectral evidence. Compound **2** displays a clear I.R. absorption at ν = 1660 cm^{-1} which is assigned to the carbonyl stretching vibration; the presence of a primary amino group is confirmed by the presence of two absorption bands at ν = 3270 and 3160 cm^{-1}, respectively. The ^{1}H-N.M.R. spectrum shows two doublets for the pyridinium ring protons at δ = 9.25 and 8.7 ppm (J = 2 Hz), and a singlet at δ = 1.97 ppm for the amino group. The ^{1}H-N.M.R. spectrum of compound **3** shows a singlet at δ = 2.15 ppm attributable to the *S*-methyl group.

Compound **2** reacts with phenacyl bromides at reflux temperature in methanol (12 h) to give 3-aryl-6-oxo-8,10-diphenyl-2 *H*, 6 *H*-pyrido[2,1-*f*][1,3,4]thiadiazino[2,3-*c*][1,2,4]triazin-11-ium bromides (**4**) as yellow crystalline solids in high yields.

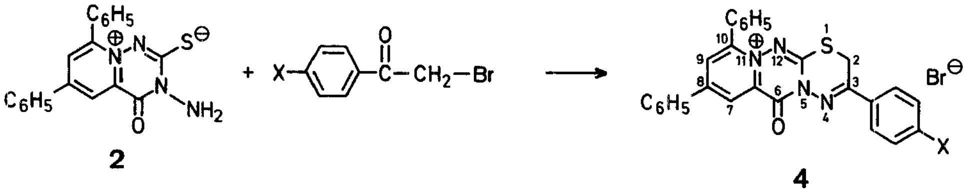


Table 1. 3-Aryl-6-oxo-8,10-diphenyl-2*H*,6*H*-pyrido[2,1-*f*][1,3,4]thiadiazino[2,3-*c*][1,2,4]triazin-11-ium Bromides (**4**) prepared

4	X	Yield[a] [%]	m.p.[b] [°C] (solvent), appearance	Molecular Formula[c]	M.S.[d] *m/e*	I.R. (Nujol)[e] ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$)[f] δ [ppm]
a	H	76	200–202° (ethanol), yellow prisms	$C_{27}H_{19}BrN_4OS$ (527.2)	447 (4), 415 (30), 388 (17), 298 (49), 230 (100), 203 (12), 202 (10), 135 (4), 116 (4), 115 (10), 105 (38), 82 (30), 81 (22), 80 (30), 79 (23), 77 (32)	1720, 1620, 1600, 1530, 1410, 1290, 1280, 1230, 1010, 910, 780, 770, 725, 720, 705	4.45 (s, 2H); 7.2–8.41 (m, 15H); 8.7 (d, 1H, *J* = 2 Hz); 9 (d, 1H, *J* = 2 Hz)
b	Br	66	230–232° (ethanol), yellow prisms	$C_{27}H_{18}Br_2N_4OS$ (606.1)	526 (2), 494 (19), 298 (39), 230 (68), 215 (2), 213 (2), 203 (32), 202 (33), 196 (2), 194 (3), 185 (96), 183 (100), 156 (36), 155 (36), 115 (8), 82 (42), 81 (24), 80 (42), 79 (22), 77 (23)	1730, 1620, 1590, 1530, 1410, 1295, 1230, 1210, 1080, 1025, 915, 910, 850, 785, 780, 720, 710	4.5 (s, 2H); 7.1–8 (m, 14H); 8.6 (d, 1H, *J* = 2 Hz); 8.9 (d, 1H, *J* = 2 Hz)
c	Cl	70	233–235° (ethanol), yellow prisms	$C_{27}H_{18}BrClN_4OS$ (561.7)	481 (3), 449 (22), 298 (51), 230 (100), 203 (20), 202 (21), 171 (4), 169 (4), 152 (4), 150 (4), 140 (45), 139 (45), 115 (5), 113 (12), 111 (13), 82 (96), 81 (28), 80 (97), 79 (28), 77 (8)	1720, 1620, 1590, 1530, 1490, 1400, 1350, 1290, 1230, 1090, 1070, 1000, 910, 905, 845, 820, 780, 730, 720, 705	4.45 (s, 2H); 7.4–8.5 (m, 14H); 8.8 (d, 1H, *J* = 2 Hz); 9 (d, 1H, *J* = 2 Hz)
d	NO_2	87	249–251° (ethanol/ether), orange prisms	$C_{27}H_{18}BrN_5O_3S$ (572.2)	492 (4), 460 (17), 298 (15), 230 (14), 203 (13), 202 (14), 180 (11), 161 (13), 150 (14), 122 (11), 115 (12), 82 (97), 81 (45), 80 (100), 79 (45), 77 (14)	1730, 1620, 1570, 1520, 1400, 1350, 1290, 1270, 1200, 1070, 1025, 860, 820, 770, 750, 720, 690	4.45 (s, 2H); 7.2–8.5 (m, 14H); 8.75 (d, 1H, *J* = 2 Hz); 9 (d, 1H, *J* = 2 Hz)
e	C_6H_5	75	218–219° (ethanol/ether), green plates	$C_{33}H_{23}BrN_4OS$ (603.3)	523 (5), 491 (21), 298 (15), 230 (37), 211 (11), 203 (13), 202 (14), 192 (13), 181 (100), 153 (32), 115 (5), 82 (67), 81 (30), 80 (65), 79 (30), 77 (9)	1710, 1620, 1590, 1520, 1435, 1400, 1290, 1270, 1230, 1215, 1070, 1030, 1005, 900, 840, 830, 785, 780, 770, 730, 715, 710, 645	4.45 (s, 2H); 7.2–8.4 (m, 19H); 8.75 (d, 1H, *J* = 2 Hz); 9 (d, 1H, *J* = 2 Hz)
f	OCH_3	75	211–213° (ethanol/ether), yellow plates	$C_{28}H_{21}BrN_4O_2S$ (557.2)	477 (4), 445 (15), 298 (15), 230 (35), 203 (15), 202 (16), 165 (12), 146 (13), 135 (10), 115 (17), 107 (7), 82 (75), 81 (29), 80 (75), 79 (29), 77 (10)	1710, 1620, 1590, 1560, 1520, 1430, 1400, 1250, 1220, 1200, 1140, 1110, 1080, 1030, 1010, 1000, 955, 895, 845, 820, 775, 770, 755, 720, 685, 640	3.85 (s, 3H); 4.45 (s, 2H); 6.95–8.45 (m, 14H); 8.75 (d, 1H, *J* = 2 Hz); 9 (d, 1H, *J* = 2 Hz)

[a] Yield of isolated pure product.

[b] Uncorrected.

[c] The microanalyses were in good agreement with the calculated values: C, ±0.16; H, ±0.21; N, ±0.15.

[d] Recorded at 70 eV. on a Hewlett-Packard 5993 C instrument.

[e] Recorded on a Nicolet FT 5DX spectrometer.

[f] Recorded at 60 MHz on a Varian EM-360A spectrometer.

Table 2. 1-Substituted 5-Oxo-7,9-diphenyl-1,5-dihydro[1,2,4]triazolo[5,1-*c*]pyrido[2,1-*f*][1,2,4]triazin-10-ium-2-thiolates (**5**) prepared

5	R	Yield[a] [%]	m.p.[b] [°C] (solvent), appearance	Molecular Formula[c]	M.S.[d] *m/e*	I.R. (Nujol)[e] ν [cm⁻¹]	¹H-N.M.R. (CDCl₃/TFA/(TMS$_{int}$)[f] δ [ppm]
a	C_6H_5	58	274–275° (AcOH), orange prisms	$C_{26}H_{17}N_5OS$ (447.3)	415 (19), 414 (37), 389 (27), 298 (19), 258 (7), 230 (91), 203 (66), 202 (66), 91 (16), 77 (66), 64 (100), 58 (26)	1710, 1620, 1540, 1500, 1435, 1200, 1185, 890, 805, 770, 750, 725, 695	7.15–8.2 (m, 15H); 8.5 (d, 1H, *J* = 2 Hz); 9.2 (d, 1H, *J* = 2 Hz)
b	4-Br—C_6H_4	88	296–298° (AcOH), brown prisms	$C_{26}H_{16}BrN_5OS$ (526.2)	494 (2), 467 (16), 298 (3), 258 (4), 230 (9), 203 (4), 202 (5), 77 (4), 64, 100, 58 (4)	1710, 1630, 1500, 1200, 1180, 1140, 990, 920, 830, 770, 755, 750, 710, 700	7.25–8.3 (m, 14H); 8.55 (d, 1H, *J* = 2 Hz); 9.25 (d, 1H, *J* = 2 Hz)
c	4-Cl—C_6H_4	60	286–287° (AcOH), orange prisms	$C_{26}H_{16}ClN_5OS$ (481.8)	450 (13), 424 (19), 298 (15), 258 (12), 230 (63), 203 (28), 77 (45), 64 (100), 58 (8)	1710, 1630, 1550, 1500, 1440, 1180, 1140, 1100, 920, 900, 830, 770, 750, 745, 710, 700	7.2–8.1 (m, 1H); 8.3 (d, 1H, *J* = 2 Hz); 9.05 (d, 1H, *J* = 2 Hz)
d	4-H_3C—C_6H_4	60	300–302° (AcOH), orange prisms	$C_{27}H_{19}N_5OS$ (461.3)	429 (10), 403 (7), 298 (5), 258 (5), 230 (20), 203 (13), 115 (8), 105 (10), 91 (16), 77 (40), 64 (100), 58 (21)	1720, 1630, 1520, 1480, 1440, 1340, 1190, 1150, 920, 890, 820, 770, 760, 750, 720, 700	2.45 (s, 3H); 7.2–8.2 (m, 14H); 8.55 (d, 1H, *J* = 2 Hz); 9.3 (d, 1H, *J* = 2 Hz)
e	*c*-C_6H_{11}	50	256–258° (AcOH), brown prisms	$C_{26}H_{23}N_5OS$ (453.3)	497 (11), 471 (23), 298 (9), 258 (12), 230 (71), 203 (13), 202 (13), 77 (15), 64 (100), 58 (11)	1690, 1620, 1530, 1440, 1400, 1280, 1200, 1030, 1000, 925, 885, 840, 810, 770, 740, 695	1.4–2.3 (m, 11H); 7.2–8.1 (m, 10H); 8.3 (d, 1H, *J* = 2 Hz); 9.1 (d, 1H, *J* = 2 Hz)

[a, b] see Table 1.

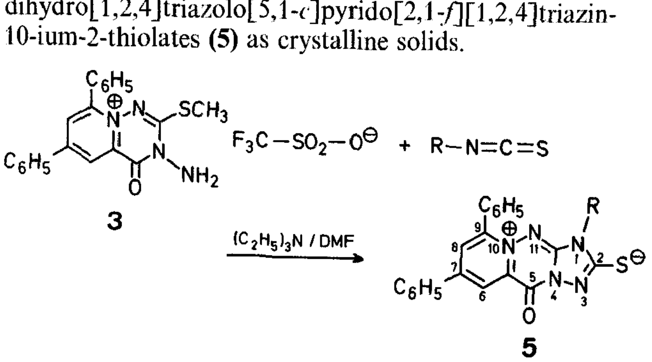
[c] The microanalyses were in good agreement with the calculated values: C, ±0.22; H, ±0.22; N, ±0.17.

[d, e, f] see Table 1.

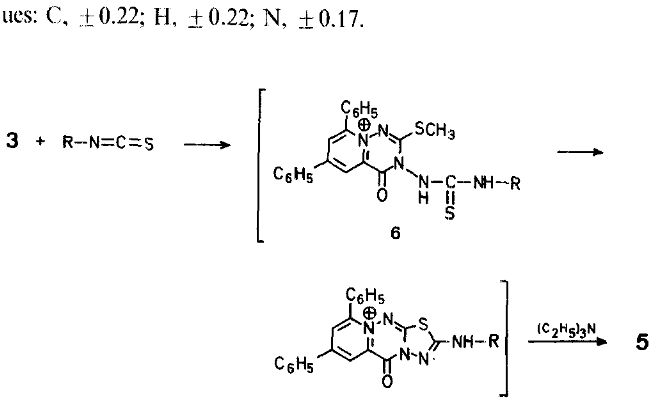
Compounds **4** display a clear I.R. absorption at ν = 1730–1710 cm⁻¹ which is assigned to the carbonyl stretching vibration. The ¹H-N.M.R. spectra of **4**, show among others, signals for —CH_2— at δ = 4.5–4.4 ppm. Compounds **4** are converted into the corresponding tetrafluoroborates by treatment with tetrafluoroboric acid.

Attempts to promote the sulfur extrusion from compounds **4** by treatment with triethylamine were unsuccessful.

Compound **3** reacts with isothiocyanates in dimethylformamide in the presence of triethylamine at room temperature (24h) to give 3-substituted 5-oxo-7,9-diphenyl-1,5-dihydro[1,2,4]triazolo[5,1-*c*]pyrido[2,1-*f*][1,2,4]triazin-10-ium-2-thiolates (**5**) as crystalline solids.



We assume that this reaction involves initial addition of the amino group to the isothiocyanate to give the thiourea derivative **6** the S-atom of which induces the intramolecular nucleophilic displacement of the methylthio group to form the 1,3,4-thiadiazole ring which, under the reaction conditions, undergoes rearrangement to the zwitterionic compound **5**. This mechanism is similar to that suggested[7] for the reaction of 1-amino-2-methylthio-4,6-diphenyl-pyridinium iodides with isothiocyanates under the same conditions.



The structural elucidation of compounds **5** was accomplished on the basis of spectral and microanalytical data. The mass spectra show the characteristic fragment ions (M⁺ − NCS) and M⁺ − 32, and thus are in good agreement with the presence of an exocyclic S-atom. On the other hand, compound **5a** undergoes methylation with methyl iodide to give the *S*-methyl derivative the ¹H-N.M.R. spectrum of which shows a singlet at δ = 3.6 ppm due to the S—CH_3 group.

3-Amino-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**; 3.7 g, 9.4 mmol) in methanol (25 ml), thiocarbohydrazide (1.3 g, 9.4 mmol) is added. A deep red coloration immediately develops and after 4 h at room temperature, the precipitated solid is separated by filtration and recrystallised from acetic acid to give **2**; yield: 2.72 g (84%); yellow needles, m.p. 225–226 °C.

		C	H	N
$C_{19}H_{14}N_4OS$ (346.2)	calc.	65.90	4.04	16.17
	found	65.70	4.09	16.29

M.S.: *m/e* = 314 (M⁺—S, 8%), 298 (9), 284 (5), 258 (5), 230 (100), 115 (6), 77 (10).

I.R. (Nujol): ν = 3270, 3160, 1660, 1625, 1485, 1400, 1340, 1255, 1180, 910, 770, 760, 700 cm^{-1}.

^{1}H-N.M.R. (TFA/TMS$_{ext}$): δ = 1.97 (s, 2H); 8.3–7.15 (m, 10H); 8.7 (d, 1H), J = 2Hz); 9.25 ppm (d, 1H, J = 2Hz).

3-Amino-2-methylthio-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium Trifluoromethanesulfonate (3):
Methyl triflate (0.40 g, 2.4 mmol) is added to a stirred mixture of 3-amino-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium-2-thiolate (**2**; 0.69 g, 2 mmol) and dry dichloromethane (25 ml). The resultant solution is stirred at room temperature for 5 h. The precipitated solid is separated by filtration and recrystallised from ethanol/ether (1/4) to give **3**; yield: 0.83 g (82%); colorless needles; m.p. 259–261 °C.

$C_{21}H_{17}F_3N_4O_4S_2$	calc.	C 49.42	H 3.33	N 10.97
(510.3)	found	49.51	3.27	10.87

M.S.: m/e = 314 ($M^+ - F_3C{-}SO_3^{\ominus} - SCH_3$, 18%), 312 (63), 298 (100), 230 (73), 258 (35), 203 (64), 115 (18), 77 (23).

I.R. (Nujol): ν = 3340, 3260, 1720, 1630, 1530, 1270, 1230, 1150, 1040, 900, 770, 755, 700, 640 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$): δ = 2.15 (s, 3H); 6.27 (s, 2H); 7.3–8.45 (m, 10H), 8.75 (d, 1H, J = 2Hz); 8.9 ppm (d, 1H, J = 2Hz).

6-Oxo-3-aryl-8,10-diphenyl-2*H*,6*H*-pyrido[2,1-*f*][1,3,4]thiadiazino[2,3-*c*][1,2,4]triazin-11-ium Bromides (4); General Procedure:
The appropriate phenacyl bromide (1 mmol) is added to a stirred solution of 3-amino-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium-2-thiolate (**2**; 0.346 g, 1 mmol) in methanol (20 ml). The mixture is stirred at reflux temperature for 13 h, and then allowed to cool. The solvent is removed under reduced pressure and the residue is treated with ether (10 ml). The solid formed is separated by filtration and recrystallised from the appropriate solvent.

1-Substituted 5-Oxo-7,9-diphenyl-1,5-dihydro[1,2,4]triazolo[5,1-*c*]pyrido[2,1-*f*][1,2,4]triazin-10-ium-2-thiolates (5); General Procedure:
To a stirred solution of 3-amino-2-methylthio-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium triflate (**3**; 0.51 g, 0.98 mmol) in dry dimethylformamide (30 ml), triethylamine (0.98 mmol) and the appropriate isothiocyanate (0.98 mmol) are added. The resultant solution is stirred at room temperature for 24 h, then poured into ice/water, and the precipitated solid isolated by suction, washed with cold methanol (20 ml), and recrystallised from acetic acid.

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[1] Part IX of the series: Bridgehead Nitrogen Heterocycles; Part VIII: P. Molina, A. Tárraga, E. Romero, M. Lorenzo Peña, *Synthesis* **1984**, 71.

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