A Facile Iminophosphorane-Mediated Synthesis of 1,2,4-Triazolo[5,1-*c*][1,2,4]triazine Derivatives

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As a part of an investigation on fused heterocycles we have reported the preparation of bridgehead nitrogen heterocycles which contain the *s*-triazole moiety e.g. 1,2,4-triazolo[1,5-*a*]pyridine[1,2], 1,2,4-triazolo[3,4-*b*][1,3,4]thia-di azole[3], 1,3,4-triazolo[3,2-*a*]pyridine[4], and 1,2,4-triazolo[4,3-*b*][1,2,4]triazole[5,6]. On the other hand we have recently reported[7] the preparation of derivatives of 1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazines. We now describe a new general method for the synthesis of otherwise not readily accesible 1,2,4-triazolo[5,1-*c*][1,2,4]triazine derivatives which contain the 1,2,4-triazole and 1,2,4-triazine moieties.

The methods described for the preparation of the 1,2,4-triazolo[5,1-*c*][1,2,4]triazine ring system can be classified in three groups. The first is based on cyclisative condensation reactions of 3-hydrazino-[8,9,10] or 3,4-diamino-1,2,4-

Tabelle 1. Compounds **3** and **4** prepared

Compound No	Ar^1	Yield[a] [%]	m.p.[b] [°C]	Molecular Formula[c] or Lit. m.p. [°C]	I.R. (Nujol)[d] ν (cm^{-1})	^1H-N.M.R.[e] δ [ppm]	M.S. (70 eV)[f] m/e (rel. int. %)
3a	C_6H_5	80	236–237°	235–236°[11]	3296, 3182, 1682, 1636, 1596, 1551, 1511, 1450, 1308, 1160, 1115, 996, 764, 706, 670	9.10 (s, 1H, $N\underline{H}$); 7.0–8.2 (m, $5H_{arom}$); 5.80 (s, 2H, $N\underline{H}_2$); 2.30 (s, 3H, $C\underline{H}_3$)	217 (M^+,82), 216 (71), 188 (6), 158 (14), 133 (16), 127 (28), 119 (47), 118 (60), 117 (35), 110 (20), 104 (13), 92 (47), 91 (56), 77 (100), 65 (45), 51 (45), 42 (47)
3b	$4-H_3CO-C_6H_4$	94	217–219°	$C_{11}H_{13}N_5O_2$ (247.3)	3340, 3305, 3270, 3210, 1690, 1610, 1560, 1505, 1240, 1160, 1100, 1025, 980, 915, 830, 720, 700	9.00 (s, 1H, $N\underline{H}$); 6.8–7.9 (m, $4H_{arom}$, A_2B_2); 5.80 (s, 2H, $N\underline{H}_2$); 3.80 (s, 3H, OCH_3); 2.30 (s, 3H, $CC\underline{H}_3$)	247 (M^+,22), 232 (4), 188 (4), 149 (22), 148 (21), 133 (40), 122 (29), 121 (100), 106 (14), 105 (18), 92 (10), 80 (14), 78 (13), 64 (10), 42 (23)
3c	$4-Cl-C_6H_4$	80	251–253°	$C_{10}H_{10}ClN_5O$ (251.7)	3325, 3280, 3190, 1685, 1630, 1590, 1550, 1495, 1415, 1165, 1090, 1000, 930, 825, 765, 700	9.30 (s, 1H, $N\underline{H}$); 7.3–8.1 (m, $4H_{arom}$, A_2B_2); 5.85 (s, 2H, $N\underline{H}_2$); 2.30 (s, 3H, $C\underline{H}_3$)	253 (M^+2,26), 252 (26), 251 (M^+,78), 250 (49), 236 (4), 192 (10), 154 (21), 153 (34), 152 (55), 151 (27), 147 (14), 128 (26), 127 (100), 113 (16), 111 (48), 99 (43), 90 (36), 75 (49), 63 (28), 42 (60)
4a	C_6H_5	70	136–138°	$C_{28}H_{24}N_5OP$ (477.5)	3295, 1636, 1591, 1557, 1540, 1494, 1450, 1435, 1311, 1278, 1221, 1163, 1115, 1053, 1028, 997, 889, 852, 748, 725, 711, 694, 673	9.10 (s, 1H, $N\underline{H}$); 6.9–8.1 (m, $20H_{arom}$); 2.20 (s, 3H)	477 (M^+,14), 432 (5), 277 (32), 276 (100), 262 (15), 228 (3), 198 (10), 183 (65), 152 (12), 122 (20), 119 (5), 108 (45), 91 (15), 77 (40), 51 (20)
4b	$4-H_3CO-C_6H_4$	54	150–152°	$C_{29}H_{26}N_5O_2P$ (507.5)	3310, 1630, 1597, 1557, 1545, 1510, 1460, 1245, 1166, 1110, 1030, 888, 826, 747, 721, 689	9.00 (s, 1H, $N\underline{H}$); 6.9–8.1 (m, $19H_{arom}$); 3.85 (s, 3H); 2.20 (s, 3H)	507 (M^+,11), 277 (27), 276 (100), 262 (10), 200 (5), 198 (6), 185 (10), 183 (42), 152 (8), 148 (7), 147 (6), 133 (18), 122 (15), 108 (24), 107 (10), 105 (7), 77 (12)
4c	$4-Cl-C_6H_4$	91	205–207°	$C_{28}H_{23}ClN_5OP$ (511.9)	3310, 1635, 1585, 1560, 1535, 1490, 1440, 1410, 1280, 1235, 1160, 1115, 1055, 890, 855, 835, 800, 750, 720, 710, 695	9.20 (s, 1H, $N\underline{H}$); 7.2–8.1 (m, $19H_{arom}$); 2.20 (s, 3H)	513 (M + 2,2), 511 (M^+,6), 278 (5), 277 (28), 276 (100), 262 (11), 198 (6), 185 (9), 184 (8), 183 (41), 152 (16), 125 (5), 122 (12), 108 (19), 107 (9), 77 (10)

[a] Yield of isolated pure product.

[b] Uncorrected.

[c] The microanalyses were in good agreement with the calculated values (C ± 0.07, H ± 0.12, N ± 0.13).

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

[e] Recorded at 60 MHz on a Varian EM-360A spectrometer, with TMS as internal standard; for compounds **3** DMSO-d_6 was used as solvent while for compounds **4** $CDCl_3$ was used.

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

Product No.	Ar^1	Ar^2	Yield[a] [%]	m.p.[b] [°C]	Molecular Formula[c]	I.R. (Nujol)[d] ν(cm^{-1})	^{1}H-N.M.R. (DMSO-d$_6$/TMS)[e] δ[ppm]	M.S. (70 eV)[f] m/e (rel. int. %)
7a	4-Cl—C_6H_4	4-Cl—C_6H_4	83	183–185°	$C_{17}H_{12}Cl_2N_6O$ (387.2)	3285, 1685, 1625, 1575, 1495, 1400, 1335, 1265, 1235, 1160, 1090, 1055, 830, 750, 715	9.60 (s, 1H, N$\underline{H}$); 7.4–8.0 (m, 8H$_{arom}$); 2.40 (s, 3H)	388 (M + 2,21), 386 (M$^+$,100), 360 (23), 358 (36), 288 (15), 277 (13), 248 (30), 163 (60), 152 (93), 138 (56), 125 (18), 111 (44), 99 (26), 75 (36), 63 (12)
7b	4-H_3CO—C_6H_4	4-H_3CO—C_6H_4	86	282–284°	$C_{19}H_{18}N_6O_3$ (378.4)	3275, 1685, 1625, 1575, 1515, 1465, 1370, 1300, 1250, 1180, 1060, 1030, 830, 750, 720	9.10 (s, 1H, N$\underline{H}$) 6.8–7.8 (m, 8H$_{arom}$); 3.90 (s, 3H) 3.80 (s, 3H) 2.40 (s, 3H)	378 (M$^+$,100), 350 (23), 322 (10), 240 (32), 159 (30), 148 (66), 134 (35), 133 (42), 122 (18), 105 (10), 77 (17), 64 (9)
7c	C_6H_5	C_6H_5	82	335–337°	$C_{17}H_{14}N_6O$ (318.3)	3300, 1675, 1625, 1575, 1495, 1420, 1260, 1155, 1100, 1080, 1060, 1030, 770, 765, 735, 690	9.40 (s, 1H, N$\underline{H}$) 7.2–8.2 (m, 10H$_{arom}$); 2.40 (s, 3H)	318 (M$^+$,100), 290 (23), 220 (28), 194 (5), 180 (10), 129 (25), 118 (46), 117 (7), 104 (36), 103 (10), 93 (16), 91 (10), 77 (56), 65 (18)
7d	C_6H_5	4-Cl—C_6H_4	76	318–320°	$C_{17}H_{13}ClN_6O$ (352.8)	3295, 1670, 1615, 1570, 1545, 1495, 1430, 1235, 1100, 1060, 1010, 835, 775, 740, 720	9.70 (s, 1H, N$\underline{H}$) 7.5–8.1 (m, 9H$_{arom}$); 2.40 (s, 3H)	354 (M + 2,12), 352 (M$^+$,34), 324 (13), 254 (11), 214 (14), 154 (12), 152 (36), 140 (19), 138 (60), 130 (11), 129 (100), 127 (37), 126 (16), 118 (95), 113 (10), 111 (30), 104 (34), 103 (27), 91 (24), 77 (97)
7e	4-Cl—C_6H_4	C_6H_5	80	288–290°	$C_{17}H_{13}ClN_6O$ (352.8)	3250, 1685, 1630, 1590, 1570, 1495, 1420, 1265, 1235, 1095, 1055, 1020, 840, 760, 750, 695	9.50 (s, 1H, N$\underline{H}$) 7.1–8.0 (m, 9H$_{arom}$); 2.40 (s, 3H)	354 (M + 2,18), 352 (M$^+$,54), 324 (18), 254 (28), 214 (24), 165 (20), 163 (63), 154 (16), 153 (10), 152 (55), 151 (17), 140 (13), 138 (42), 125 (18), 118 (100), 111 (43), 104 (62), 99 (27), 93 (21), 92 (22), 77 (95)
7f	C_6H_5	4-H_3CO—C_6H_4	70	308–310°	$C_{18}H_{16}N_6O_2$ (348.4)	3300, 1670, 1620, 1560, 1545, 1510, 1495, 1245, 1100, 1060, 1030, 830, 765, 725, 695	9.20 (s, 1H, N$\underline{H}$) 6.9–7.9 (m, 9H$_{arom}$); 3.80 (s, 3H), 2.40 (s, 3H)	348 (M$^+$,47), 320 (12), 307 (5), 292 (6), 224 (11), 210 (11), 160 (7), 148 (15), 134 (100), 133 (30), 129 (14), 122 (22), 119 (13), 118 (67), 103 (15), 91 (13), 77 (44)
7g	4-H_3CO—C_6H_4	C_6H_5	84	223–225°	$C_{18}H_{16}N_6O_2$ (348.4)	3250, 1685, 1625, 1580, 1510, 1455, 1340, 1305, 1255, 1170, 1100, 1055, 1030, 840, 755, 690	9.40 (s, 1H, N$\underline{H}$) 7.2–8.1 (m, 9H$_{arom}$); 3.95 (s; 3H) 2.40 (s, 3H)	348 (M$^+$,35), 320 (10), 250 (15), 210 (15), 160 (17), 159 (100), 148 (25), 147 (14), 134 (41), 133 (51), 119 (10), 118 (42), 105 (11), 104 (14), 93 (8), 92 (22), 90 (10), 77 (50)
7h	4-Cl—C_6H_4	4-H_3CO—C_6H_4	81	298–300°	$C_{18}H_{15}ClN_6O_2$ (382.8)	3260, 1670, 1625, 1590, 1570, 1550, 1515, 1495, 1440, 1335, 1270, 1250, 1090, 1060, 1020, 845, 830, 755	9.40 (s, 1H, N$\underline{H}$) 7.0–8.1 (m, 8H$_{arom}$); 3.85 (s, 3H), 2.40 (s, 3H)	384 (M + 2,13), 382 (M$^+$,40), 354 (13), 258 (10), 244 (13), 163 (9), 154 (15), 152 (48), 148 (23), 147 (11), 138 (7), 135 (10), 134 (100), 133 (32), 125 (7), 122 (25), 111 (18), 105 (11), 90 (12), 77 (14)
7i	4-H_3CO—C_6H_4	4-Cl—C_6H_4	90	320–322°	$C_{18}H_{15}ClN_6O_2$ (382.8)	3250, 1685, 1625, 1590, 1570, 1560, 1510, 1495, 1260, 1180, 1090, 1055, 1010, 835, 810, 750, 680	9.40 (s, 1H, N$\underline{H}$) 7.1–8.0 (m, 8H$_{arom}$); 3.90 (s, 3H), 2.40 (s, 3H)	384 (M + 2,10), 382 (M$^+$,31), 354 (11), 244 (11), 160 (12), 159 (100), 154 (7), 152 (19), 148 (22), 147 (13), 138 (7), 134 (29), 133 (41), 126 (10), 111 (13), 92 (10), 77 (16)

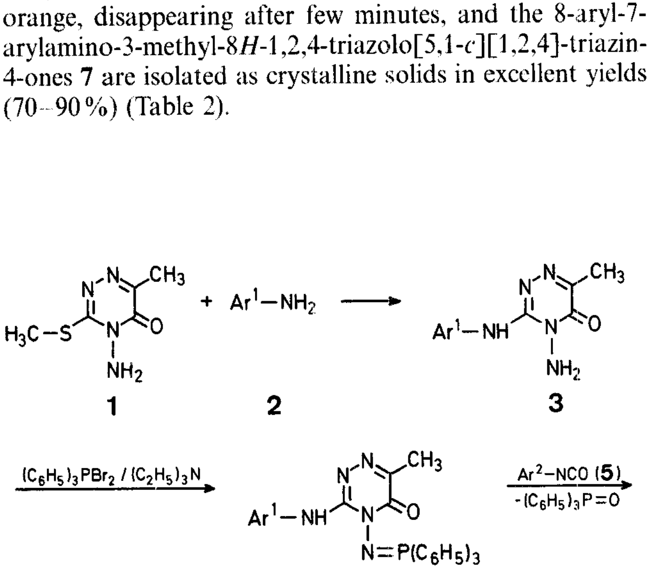
[a,b,d,f] As in the Table 1.

[c] The microanalyses were in good agreement with the calculated values (C ± 0.14, H ± 0.15, N ± 0.16).

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

triazines[11] with carbon-inserting reagents; the second involves condensations of 3-hydrazino-1,2,4-triazoles with α-dicarbonyl compounds[12,13,14]. However, the generality of these methods are impaired by a degree of ambiguity in the mode of the ultimate ring closure. The third method involves coupling of 1,2,4-triazole-5-diazonium salts with active methylene compounds[15,16,17].

The *N*-aminoheterocycle, 4-amino-6-methyl-3-methylthio-5-oxo-4,5-dihydro-1,2,4-triazine (**1**), readily available from 4-amino-6-methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine and methyl iodide[11], reacts with arylamines **2** (170 °C for 5 h) to give the 4-amino-3-arylamino-6-methyl-5-oxo-4,5-dihydro-1,2,4-triazines **3** as crystalline solids in excellent yields (80–95 %). Compounds **3** react with triphenylphosphine dibromide in the presence of triethylamine in dry benzene under nitrogen to give the iminophosphoranes **4** in moderate to good yields (Table 1). When solutions of **4** in dry benzene are treated with aryl isocyanates **5** at room temperature, the colour of the reaction mixture quickly turns deep orange, disappearing after few minutes, and the 8-aryl-7-arylamino-3-methyl-8*H*-1,2,4-triazolo[5,1-*c*][1,2,4]-triazin-4-ones **7** are isolated as crystalline solids in excellent yields (70–90 %) (Table 2).



1 2 3

4

6 7

Structural elucidation of **7** was accomplished on the basis of spectral data and microanalyses. Thus, the stretching vibration of the C=O group is found characteristically in the region 1670–1685 cm^{-1}; bands are also found due to the secondary amino group. Salient features of the ^{1}H-N.M.R.-spectra are given in the Table 2. Mass spectra of **7** show the expected molecular ion peaks and the fragmentation pattern is according with the proposed structures.

We believe that the mechanism of the conversion **4** → **7** involves initial condensation of the iminophosphorane **4** with the aryl isocyanate to give a carbodiimide **6** as intermediate, which cyclizes to form **7**. This mechanism is similar to that suggested for the preparation of mesoionic compounds from iminophosphoranes derived from *N*-aminoheterocycles and heterocumulenes[18].

Advantages of the present simple route to triazolotriazines **7** are:

- unambigous position of the aryl substituents;
- good yields;
- mild and convenient reaction conditions;
- general availability of starting materials.

4-Amino-3-arylamino-6-methyl-5-oxo-4,5-dihydro-1,2,4-triazines 3:
The unreported triazines **3b** and **3c** are prepared according to the procedure used for **3a**[11] (Table 1).

3-Arylamino-6-methyl-4-triphenylphosphoranylidenamino-5-oxo-4,5-dihydro-1,2,4-triazines 4; General Procedure:
Bromine (0.8 g, 5 mmol) in dry benzene (10 ml) is added dropwise to a stirred solution of triphenylphosphine (1.31 g, 5 mmol) in dry benzene (10 ml) at 0–5 °C under nitrogen. The mixture is stirred for 1 h and then allowed to warm to room temperature. A solution of the appropriate 4-amino-3-arylamino-6-methyl-5-oxo-4,5-dihydro-1,2,4-triazine **3** (5 mmol) and triethylamine (1 g, 10 mmol) in benzene is added; after 5 h heating under reflux triethylammonium bromide is deposited. The salt is separated by filtration and the filtrate concentrated to dryness to afford a crude product which is recrystallized from benzene to give **4** as colourless prisms (Table 1).

8-Aryl-7-arylamino-3-methyl-8*H*-1,2,4-triazolo[5,1-*c*][1,2,4]-triazin-4-ones 7; General Procedure:
To a solution of iminophosphorane **4** (2 mmol) in dry benzene (40 ml) the appropriate aryl isocyanate **5** (2 mmol) is added. The colour of the reaction mixture turns deep orange, disappearing after few minutes. The colourless solution is stirred at room temperature for 6 h. The white precipitated solid is collected by filtration and recrystallized from ethanol to give **7** as crystalline solids (Table 2). By addition of diethyl ether to the benzene liquors, triphenyl phosphine oxide is separated.

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