Synthesis of Aminopyridazines from Azidopyridazines and Tetrazolo[1,5-*b*]pyridazines[1,2]

Th. Kappe,* A. Pfaffenschlager, W. Stadlbauer

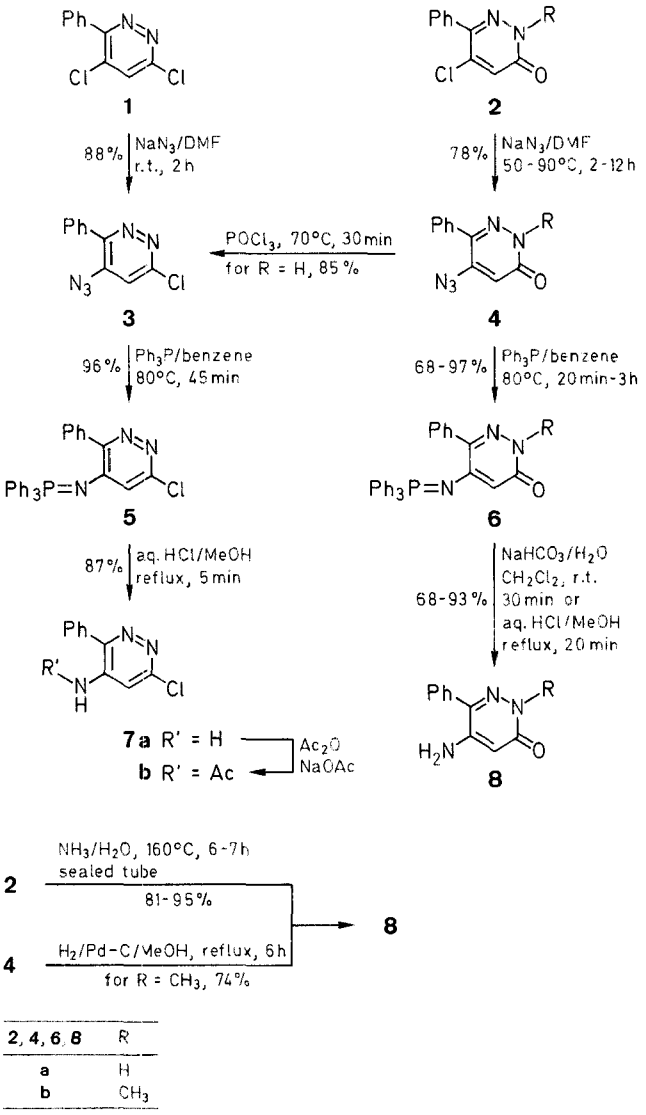
Laboratory of Organic Synthesis, Institute of Organic Chemistry, Karl-Franzens-University Graz, Heinrichstraße 28, A-8010 Graz, Austria

This work is dedicated to Prof. Dr. Hans Junek on the occasion of his 60th birthday.

Azidopyridazines **3, 4, 24** and tetrazolo[1,5-*b*]pyridazines **10, 13, 28** can be converted to the corresponding aminopyridazines, by reaction with triphenylphosphine via phosphazenes and subsequent hydrolysis (Staudinger reaction).

There are many methods available for the reduction of organic azides to the corresponding amines. The most common are: hydrogenolysis with metal catalysts,[3] electrolysis,[4] or other reducing agents.[5] These methods have the disadvantages that either sensitive substituents are attacked or the reduction fails when the azido group exists in the isomeric ring closed tetrazolo form. We have utilized the 70 year old Staudinger reaction[6,7] for the conversion of azides to amines. The azides are reacted with tertiary phosphines to yield phosphazenes, intermediary phosphazides have been isolated in some cases,[7,8] which can be hydrolyzed with aqueous acids or bases to triphenylphosphine oxide and amines.[6] Due to the mild reaction conditions and good yields for both steps, the Staudinger reaction has been used mostly to reduce sensitive systems eg. sugars, β-lactams, epoxides, etc.[9] We have applied this reaction to azidopyridazines and found, that in some cases, containing either sensitive halogen, alkylthio substituents or unreactive tetrazolo forms, only the use of the Staudinger reaction led to the desired products.

The conversion of 5-chloro pyridazines to 5-aminopyridazines via 5-azidopyridazines was initially examined. The 5-azido-3-chloro-6-phenylpyridazine **(3)** is prepared either by a regioselective substitution reaction of the 3,5-dichloro-6-phenylpyridazine **1** with sodium azide or, by chlorination of the 5-azido-3-hydroxy-6-phenylpyridazinone **4a** with phosphoryl chloride. Reaction of **3** with triphenylphosphine led to the formation of the phosphazene **5**, hydrolysis of which with aqueous hydrochloric acid led to the amine **7a** in good yield. Acetylation of **7a** with acetic anhydride affords the acetylamino derivative **7b** (Scheme **A**).



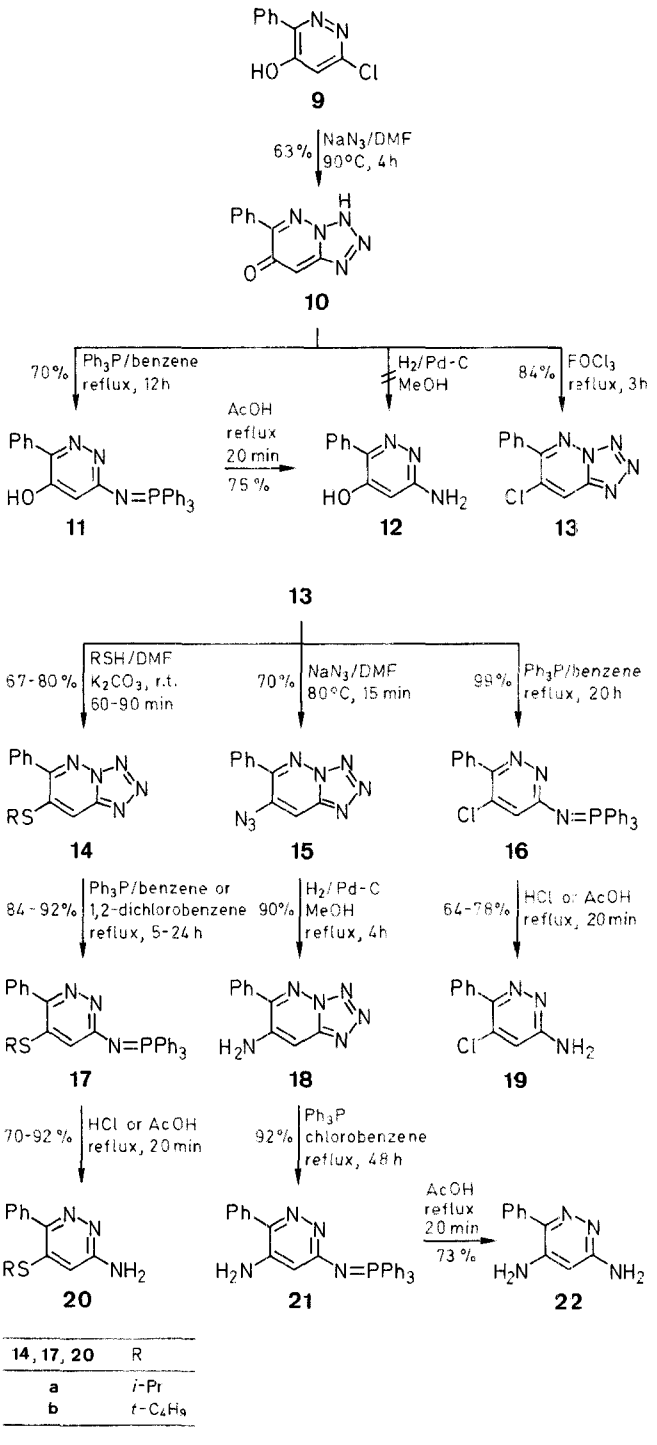
2, 4, 6, 8	R
a	H
b	CH_3

Scheme A

An examination of other possible routes to the 5-aminopyridazine **7a** shows that the three step sequence via the phosphazene **5** is a superior method. 5-Aminopyridazine **7a** cannot be prepared by direct amination due to numerous competing side reactions. Catalytic hydrogenation of the azide group is also unsuccessful as it leads to catalytic dehalogenation.

In a similar manner the 5-chloro-3-hydroxy-6-phenylpyridazinones **2** are converted to the corresponding 5-aminopyridazinones **8** via the azide derivatives **4** and the phosphazenes **6** in excellent yield. The hydrolysis step is performed using an aqueous bicarbonate solution at room temperature or by refluxing in dilute aqueous hydrochloric acid. The aminopyridazinones **8** are also obtained by direct amination of the chloropyridazinones **2** by heating with ammonia in a sealed tube. If this method is used the exact conditions described in the experimental part must be observed, otherwise a competitive hydrolysis to a stable 5-hydroxypyridazinone takes place. Finally **8** can also be obtained by the hydrogenation of the azide **4** with a catalytic amount of palladium.

Next we examined the conversion of 3-chloropyridazines to 3-aminopyridazines via tetrazolo[1,5-*b*]pyridazines. 3-Chloro-5-hydroxy-6-phenyl-pyridazine (**9**), the structural isomer of the pyridazine **2a** does not react with sodium azide to give the corresponding azidopyridazinone, but instead yields the tautomeric ring closed 7-hydroxy-6-phenyltetrazolo[1,5-*b*]pyridazine **10** (Scheme **B**). In the infra red spectrum of **10**, no azide band is present, and the equilibrium is assumed to lie totally on the tetrazolo side.[10,11] Attemped reduction of the tetrazolo moiety of **10** by catalytic hydrogenation, analogous to the azide compound **4**, failed to yield the corresponding amino compound **12**. The influence of solvent on the hydrogenation was studied, different protic and aprotic solvents were tried, also acidic solvents such as trifluoroacetic acid, but no reduction occurred. Other reducing reagents such as sodium dithionite or zinc dust, were also used but the reduction of **10** to the amine **12** was still unsuccessful.



14, 17, 20	R
a	*i*-Pr
b	*t*-C_4H_9

Scheme B

However, reaction of the tetrazole **10** with triphenylphosphine in boiling benzene affords in 70% yield the open chain phosphazene **11**, which can easily by hydrolyzed to the aminopyridazine **12**. A problem exists in the isolation of the 3-amino-5-hydroxy-6-phenyl-pyridazine **(12)** when using the standard hydrolysis method with aqueous hydrochloric acid (procedure D. 1 in the experimental part), as described in the Staudinger method[6,7] and used in various publications.[9] The amine **12** is soluble in basic or acidic solution and the isolated precipitate is polluted with triphenylphosphine oxide; hence yields are low. Better results are obtained using acetic acid instead of hydrochloric acid and extracting the formed triphenylphosphine oxide from the reaction mixture with ethyl acetate. This modification increases the yield to 75%.

The Staudinger method was also applied to the formation of aminopyridazines with sensitive substituents. Chlorination of 7-hydroxy-6-phenyltetrazolo[1,5-*b*]pyridazine **(10)** with phosphoryl chloride yields the chloro-substituted tetrazolo[1,5-*b*]pyridazine **13**. Substitution of the chlorine with mercaptanes leads to the alkyl sulfide **14**, which can now be reduced to the alkyl-3-amino-6-phenyl-5-pyridazine sulfide **(20)** via the phosphazene route. This reaction is impossible to perform by conventional catalytic hydrogenation. Applying the general route to the phosphazene **17** followed by hydrolysis with hydrochloric acid yielded **20**, as its hydrochloride salt (81–92%). The hydrolysis of **17** with acetic acid followed by extraction with ethyl acetate (see experimental) yielded the the free amines **20**, 70% yield.

The chloro substituted tetrazolo[1,5-*b*]pyridazine **13** is similarly reduced to the amine **19** under mild conditions. The intermediate phosphazene **16** can also be hydrolysed to **19**, the amine is present as its hydrochloride salt or as the free amine depending upon the hydrolysis conditions (Scheme **B**).

Substitution reaction of the chlorine of **13** with sodium azide leads to the 7-azido-6-phenyltetrazolo[1,5-*b*]pyridazine **(15)**. In this compound, where the two azide groups are present in two different tautomeric forms, the open chain azide moiety can easily be hydrogenated by using palladium as catalyst to yield the 7-amino-6-phenyltetrazolo[1,5-*b*]pyridazine **18**, while the tetrazolo moiety (the "masked azide") is not attacked by this reaction. To obtain the 3,5-diamino-6-phenylpyridazine **(22)**, again the reaction sequence via the phosphazene **21** is necessary. Best results were obtained using the acetic acid/ethyl acetate method for hydrolysis.

Table. New Pyridazines **3–8, 10–22, 24–26, 28–30** Prepared

Starting Material	Reaction Conditions Temp. (°C)/Time (h)	Method	Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6) δ, J (Hz)
1[12]	r.t./2	A	**3**	88	115–117	$C_{10}H_6ClN_5$	2300 (w), 2180 (w),	7.3–7.55 (m, 3 H_{arom});
4a	70/0.5	B		85	(MeOH/H_2O)	(231.7)	2130 (s), 1585 (w),	7.6–7.8 (m, 2 H_{arom});
							1560 (m), 1540 (m)	7.9 (s, 1 H, H-4)
2a[15]	90/3	A	**4a**	78	160 (dec)	$C_{10}H_7N_5O$	2250 (w), 2115 (s);	6.8 (s, 1 H, H-4); 7.1–
					(EtOH)	(213.2)	1710 (s); 1645 (s)	7.5 (m, 5 H_{arom})
2b[13]	50/12	A	**4b**	78	90 (dec)	$C_{11}H_9N_5O$	2140 (s), 1670 (s);	–
					(EtOH/H_2O)	(227.2)	1590 (s), 1570 (w)	
3	80/0.75	C	**5**	96	165–168	$C_{28}H_{21}ClN_3P$	1590 (w), 1580 (w),	–
					(benzene)	(465.9)	1529 (s)	
4a	80/3	C	**6a**	98	192	$C_{28}H_{22}N_3OP$	1635 (s), 1590 (w),	5.1 (s, 1 H, H-4);
					(benzene)	(447.5)	1570 (m), 1530 (m)	7.1–8.0 (m, 20 H_{arom});
								11.8 (s, 1 H, NH)
4b	80/24	C	**6b**	68	76	$C_{29}H_{24}N_3OP$	3000 (m), 2850 (m),	–
					(cyclohexane)	(461.5)	1665 (s), 1615 (s)	
							1575 (s)	
5	reflux/5 min	D-1	**7a**	87	133–135	$C_{10}H_{18}ClN_3$	3350 (m), 3330 (m),	6.45 (s, 2 H, NH_2);
					(EtOH)	(205.7)	3180 (m), 1660 (s)	6.85 (s, 1 H, H-4);
								7.55 (s, 5 H_{arom})
6	r.t./0.5	D-3	**8a**	93	280–284	$C_{10}H_9N_3O$	3430 (s), 3190 (s),	6.7 (s, 1 H, H-4);
					(MeOH)	(187.2)	1645 (s), 1615 (s)	7.3–7.7 (m, 5 H_{arom})[b]
2a[15]	160/6	F		81				
4b	reflux/6	E	**8b**	74	274 (dec)	$C_{11}H_{11}N_3O$	3480 (s), 3300 (m),	3.65 (s, 3 H, CH_3);
2b[13]	150/7	F		95	(EtOH)	(201.2)	1640 (s), 1610 (sh),	6.0 (s, 2 H, NH_2);
6b	reflux/0.33	D-1		68			1600 (m), 1590 (sh)	6.8 (s, 1 H, H-4);
								7.3–7.5 (m, 5 H_{arom})
9[12]	80–90/4	A	**10**[c]	63	205 (dec)	$C_{10}N_7N_5O$	3060 (w), 1625 (s),	7.3–7.6 (m, 4 H_{arom});
					((1,2-dichloro-	(213.2)	1605 (s), 1580 (m),	7.7–8.0 (m, 2 H_{arom})
					benzene)		1550 (sh)	
10	80/12	C	**11**	70	126	$C_{28}H_{22}N_3OP$	3030 (w), 1600 (s),	–
					(MeOH/H_2O)	(447.5)	1590 (sh)	
11	reflux/0.33	D-2	**12**[d]	75	247–248	$C_{10}H_9N_3O$	3300 (b), 1660 (m),	5.7 (s, 1 H, H-4);
					(EtOAc)	(187.2)	1635 (s), 1590 (m)	6.4 (s, 2 H, NH_2);
								7.3–8.1 (m, 5 H_{arom})
10	reflux/18 + 0.33	C + D-2		67				
10	105/3	B	**13**	84	126–127	$C_{10}H_6ClN_5$	3090 (w), 1620 (m),	7.4–7.7 (m, 5 H_{arom});
					(EtOH)	(231.7)	1525 (m), 1500 (m)	
13	r.t./1.5	G	**14a**	67	132–134	$C_{13}H_{13}N_5S$	1620 (s), 1605 (s),	1.2 (d, 6 H, J = 7,
					(EtOH)	(271.3)	1585 (sh), 1545 (m)	2 × CH_3); 3.7 (m, 1 H,
								CHS); 7.3–7.7
								(m, 5 H_{arom}); 8.4
								(s, 1 H, H-8)

Table. (continued)

Starting Material	Reaction Conditions Temp. (°C)/Time (h)	Method	Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6) δ, J (Hz)
13	r.t./1	G	**14b**	80	134–136 (EtOH)	$C_{14}H_{15}N_5S$ (285.4)	2980 (m), 1600 (w), 1455 (s), 1430 (s)	1.3 (s, 9H, 3 × CH_3); 7.4–7.7 (m, 5H_{arom}); 6.6 (s, 1H, H-8)
13	80/0.25	A	**15**	70	190 (dec) (DMF/H_2O)	$C_{10}H_6N_8$ (238.2)	2140 (s), 2110 (s), 1620 (m), 1600 (m)	7.4–7.8 (m, 5H_{arom}); 8.7 (s, 1H, H-8)
13	80/20	C	**16**	99	160–162 (EtOH/H_2O)	$C_{28}H_{21}ClN_3P$ (465.9)	3050 (w), 1560 (s), 1500 (m), 1480 (s)	7.3 (s, 1H, H-4); 7.4–8.2 (m, 20H_{arom})
14a	80/24	C	**17a**	84	158–161 (cyclohexane)	$C_{31}H_{28}N_3PS$ (505.6)	3050 (w), 2980 (w), 1540 (s), 1470 (m)	–
14b	132/5	C[e]	**17b**	92	194–196 (EtOH/H_2O)	$C_{32}H_{30}N_3PS$ (519.7)	2980 (w), 1590 (w), 1570 (w), 1550 (s)	–
15	reflux/4	E	**18**	90	230–231 (MeOH)	$C_{10}H_8N_6$ (212.2)	3480 (m), 3200 (br), 1635 (s), 1610 (m)	6.4 (s, 2H, NH_2); 7.2 (s, 1H, H-8); 7.5–7.7 (m, 5H_{arom})
16	reflux/0.33	D-1	**19** ·HCl	64	182–186 (H_2O)	$C_{10}H_9Cl_2N_3$ (242.1)	3070 (b), 1660 (s), 1585 (m), 1570 (m)	7.4–7.6 (m, 5H_{arom}); 7.9 (s, 1H, H-4)
16	reflux/0.33	D-2	**19**	78	156–157 (toluene)	$C_{10}H_8ClN_3$ (205.7)	3300 (m), 3150 (m), 1630 (s), 1590 (s)	6.7 (br s, 2H, NH_2); 7.0 (s, 1H, H-4); 7.3–7.7 (m, 5H_{arom})
17a	reflux/0.33	D-1	**20a** ·HCl	81	172 (dec) (H_2O)	$C_{13}H_{16}N_3ClS$ (281.8)	3150–2800 (br), 1600 (m), 1550 (s)	–
17a	reflux/0.33	D-2	**20a**	70	217–219 (EtOH/H_2O)	$C_{13}H_{15}N_3S$ (245.3)	3300 (m), 3170 (m), 1630 (s), 1580 (s)	1.2 (d, 6H, J = 7, 2 × CH_3); 3.4 (m, 1H, CHS); 6.2 (s, 2H, NH_2); 6.7 (s, 1H, H-4); 7.1–7.6 (s, 5H_{arom})
17b	reflux/0.33	D-1	**20b** ·HCl	92	198 (dec) (H_2O)	$C_{14}H_{18}ClN_3S$ (295.8)	3200–2700 (mb), 1625 (sh), 1600 (m)	1.5 (s, 9H, 3 × CH_3); 7.3–7.4 (m, 5H_{arom}); 7.8 (s, 1H, H-4); 8.6 (s, 3H, NH_3^+)
17b	reflux/0.33	D-2	**20b**	70	229–230 (EtOH/H_2O)	$C_{14}H_{17}N_3S$ (259.4)	3300 (m), 3150 (m), 1640 (sh), 1615 (s)	1.2 (s, 9H, 3 × CH_3); 6.3 (s, 2H, NH_2); 7.0 (s, 1H, H-4); 7.3–7.4 (m, 5H_{arom})
18	reflux/48	C[e]	**21**	92	266–267 (EtOH/H_2O)	$C_{28}H_{23}N_4P$ (446.5)	1650 (m), 1590 (s), 1575 (m), 1520 (m)	5.3 (s, 2H, NH_2); 6.2 (s, 1H, H-8); 7.2–7.9 (m, 20H_{arom})
21	reflux/0.33	D-1	**22**[f]	73	176–178 (toluene)	$C_{10}H_{10}N_4$ (186.2)	3500 (s), 1685 (m), 1650 (s), 1610 (s)	6.0 (s, 2H, NH_2); 7.2–7.6 (m, 6H, 5H_{arom} + H-4)
23[13]	20/24	A	**24**	91	160 (dec) (DMF/H_2O)	$C_{11}H_9N_5O$ (227.2)	2160 (s), 1620 (s), 1610 (sh), 1490 (m)	3.7 (s, 3H, CH_3); 6.5 (s, 1H, H-4); 7.1–7.5 (m, 3H_{arom}); 7.8–8.1 (m, 2H_{arom})
24	reflux/6	E	**25**	72	274 (dec) (EtOH)	$C_{11}H_{11}N_3O$ (201.2)	3320 (s), 3130 (s), 3000 (sh), 2750 (m), 1665 (s), 1600 (s)	3.95 (s, 3H, CH_3); 6.85 (s, 1H, H-4); 7.3–7.9 (m, 5H_{arom})[b]
23[13]	150/6	F		79				
26	reflux/0.25	D-1		70				
24	reflux/24	C	**26**	67	67 (cyclohexane)	$C_{29}H_{24}N_3OP$ (461.5)	3010 (w), 1660 (s), 1610 (s), 1580 (s)	–
27[14]	80/4	A	**28**	97	210–212 (DMF/H_2O)	$C_{10}H_7N_5$ (197.2)	3350 (m), 1600 (w), 1555 (s), 1470 (s)	7.4–8.3 (m, 5H_{arom}); 8.7 (dd, 2H, J = 9, 16, H-4 + H-5)
28	reflux/48	C[e]	**29**	77	153 (cyclohexane)	$C_{28}H_{22}N_3P$ (431.5)	3060 (w), 1600 (s), 1585 (w), 1495 (sh)	–
29	reflux/0.33	D-1	**30**	77	156–157 (toluene)	$C_{10}H_9N_3$ (171.2)	3420 (s), 1650 (s), 1600 (w), 1550 (w)	6.3 (br, 2H, NH_2); 6.8 (d, 1H, J = 9, H-4); 7.2–7.9 (m, 6H, 5H_{arom} + H-5)

[a] Satisfactory microanalyses obtained: C ± 0.33, H ± 0.32, N ± 0.36.

[b] Solvent: CF_3CO_2H.

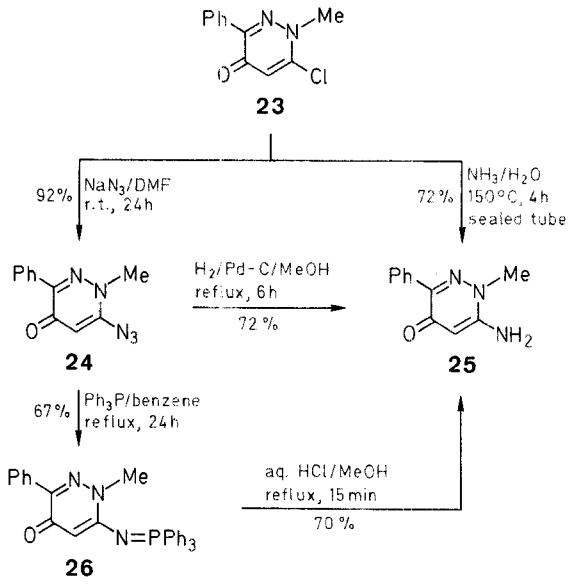
[c] MS: m/z (%) = 213 (6, M^+), 158 (4), 130 (6), 129 (20), 128 (12), 103 (10), 102 (100).

[d] ^{13}C-NMR (DMSO-d_6/TMS): δ = 97 (C-4), 125–135 (C_{arom}), 150 (C-6), 155 (C-3), 168 (C-5).
MS: m/z (%) = 187 (100, M^+), 159 (42), 130 (73), 118 (13), 104 (33).

[e] Chlorobenzene was used as the solvent

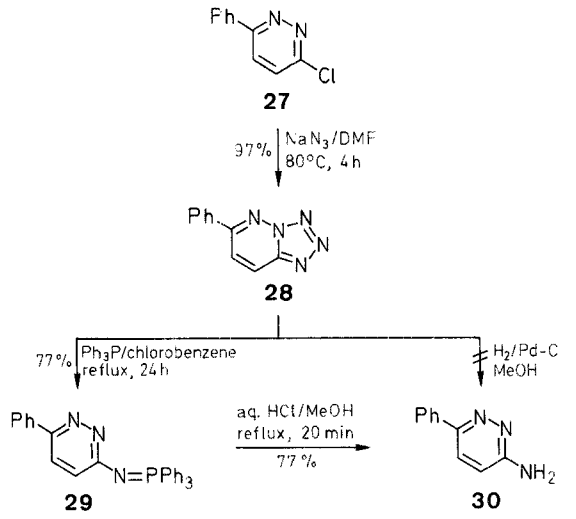
[f] Product purified by extraction with hot toluene. Contains $\frac{1}{4}CH_3CO_2H$ as solvent of crystallization as evidenced by elemental analyses and ^{1}H-NMR data (δ = 1.7 (s, $\frac{1}{4}CH_3CO$).
MS: m/z (%) = 186 (100, M^+); 168 (5), 158 (18), 157 (16), 130 (52), 116 (79), 103 (39), 90 (57), 77 (42).

The 3-azido-2-methyl-6-phenyl-5-pyridazinone **(24)** cannot exist in a tautomeric tetrazole form and can be transformed either via the phosphazene **26** or directly by catalytic hydrogenation to the corresponding 3-aminopyridazine **25** (Scheme **C**). A third possibility is the reaction of the chloropyridazine **23** with aqueous ammonia in a sealed tube, but only exact use of the reaction conditions leads to the amino compound; deviation leads to the hydrolysis product, the 3-hydroxy-2-methyl-6-phenyl-5-pyridazinone.



Scheme **C**

Another pyridazine system, the 3-chloro-6-phenyl-pyridazine **(27)** leads to the 6-phenyl-tetrazolo[1,5-*b*]pyridazine **(28)**, which again cannot be reduced with the standard methods to yield the 2-amino-6-phenyl-pyridazine **(30)**. Only ring opening of the tetrazole ring system by reaction with triphenylphosphine to the phosphazene **29** and subsequent hydrolysis with hydrochloric acid leads to the 2-amino-6-phenyl-pyridazine **(30)** in 77% yield (Scheme **D**).



Scheme **D**

The present work demonstrates that azide groups can be reduced successfully to the amino function using the Staudinger reaction, in the presence of chloride groups sensitive to normal reduction conditions, or containing sulfur substituents which usually prohibit catalytic reduction methods. Moreover, tetrazolo[1,5-*b*]pyridines ("masked" α-azidoazines) can also be converted to amines by this strategy. To our knowledge, this two step reaction sequence has not been hitherto reported in the literature.[16] Sasaki[11] has examined, in great detail, the kinetics of the ring opening of tetrazoloazines with triphenylphosphine in various solvents. This study explains the mechanism as nucleophilic attack of triphenylphosphine on the tetrazole ring and not as reaction with a tautomeric azide form. Furthermore, for most of the compounds studied by Sasaki[11] no azide tautomer was observed also at elevated temperatures. Only in cases where there is an observed equilibrium between the tetrazole and α-azidoazine tautomers, it is concluded that they react competitively with triphenylphosphine.

The analytical and spectral data of all the compounds prepared are given in the Table along with the reaction conditions.

Melting points are uncorrected and were obtained on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 (open capillary tubes). ^{1}H-NMR spectra were recorded on a Varian EM 360 instrument (TMS as internal standard). ^{13}C-NMR spectra were performed on a Varian XL 200 instrument. Mass spectra were obtained on a Finnigan 4021 (EI: 70 eV, CI: 120 eV, methane). Microanalyses were performed on a C,H,N-Automat Carlo Erba 1106. IR spectra were recorded on a Perkin-Elmer 298 (KBr pellets).

Reaction of Chloropyridazines to Azidopyridazines or Tetrazolo Compounds; General Procedure A (see Table):

NaN_3 (3.9 g, 0.06 mol) is added to a solution of the appropriate chloropyridazine (0.02 mol) in DMF (20 mL). The suspension is stirred for the stated time and temperature. Then the mixture is diluted with water (100 mL). The resulting precipitate is filtered and recrystallized from the appropriate solvent.

Chlorination of Hydroxypyridazines or Tautomeric Pyridazinones by Reaction with Phosphoryl Chloride; General Procedure B (see Table):

A solution of the appropriate pyridazinone or hydroxypyridazine (0.01 mol) in $POCl_3$ (15 mL) is heated for the specified time and temperature. The excess of $POCl_3$ is then removed *in vacuo* and the residue is poured onto ice (10 g) and brought to pH 5.5 with 0.2 N NaOH. The crude product is filtered and recrystallized from the appropriate solvent.

Reaction of Azidopyridazines or Tetrazolopyridazines with Triphenylphosphine to Triphenylphosphoranylideneaminopyridazines; General Procedure C (see Table):

A solution of the appropriate azidopyridazine or tetrazolopyridazine (0.02 mol) and Ph_3P (5.7 g, 0.025 mol) is heated for the specified time and temperature in benzene (100 mL) or chlorobenzene derivatives. The solvent is removed *in vacuo*, the residue is triturated with cyclohexane (100 mL) to remove excess of Ph_3P, filtered by suction and recrystallized from the appropriate solvent.

Hydrolysis of Triphenylphosphoranylidene Aminopyridazines; General Procedure D (see Table):

Method 1: A mixture of the appropriate triphenylphosphoranylideneaminopyridazine (0.05 mol) in 0.5 N HCl (500 mL) and MeOH (30 mL) is heated under reflux for the specified time. After cooling to room temperature the precipitated Ph_3PO is removed by filtration, and the filtrate is brought to pH 10 with 2 N NaOH solution. The resulting precipitate is filtered by suction and recrystallized from the appropriate solvent.

Method 2: A solution of the appropriate triphenylphosphoranylideneaminopyridazine (0.01 mol) in AcOH (80%, 30 mL) is heated under reflux for 20 min. After cooling to room temperature, water (20 mL) is added and the solution is extracted with EtOAc (2 × 25 mL). The aqueous layer, which contains now the aminopyridazine, is evaporated to dryness *in vacuo*. The resulting oily residue is triturated with ether (100 mL), and the precipitate is filtered and recrystallized.

Method 3: A solution of the appropriate triphenylphosphoranylideneaminopyridazine (0.01 mol) is dissolved in CH_2Cl_2 (50 mL) (or $CHCl_3$) and then treated with an aqueous 5% $NaHCO_3$ solution (50 mL) at room temperature. After stirring for 30 min the mixture is

filtered through a phase-separating filter, the solvent of the organic layer is removed *in vacuo*, and the residue is recrystallized from the appropriate solvent.

Reduction of Azidopyridazines to Aminopyridazines by Catalytic Hydrogenolysis on Pd/C; General Procedure E (see Table):
The azidopyridazine (0.02 mol) is dissolved in MeOH (300 mL). After the addition of 10% Pd/C (400 mg) H_2 is bubbled through the stirred and refluxed mixture, till no starting material is detected by TLC ($CHCl_3$/acetone, 3:1; about 4–6 h). The mixture is filtered hot, the filtrate is evaporated to dryness *in vacuo*, and the residue is recrystallized from the appropriate solvent.

Direct Amination of Chloropyridazines by Reaction with Ammonia; General Procedure F (see Table):
The appropriate chloropyridazine (0.05 mol) is heated in conc. aq. ammonia (50 mL) in a sealed tube. After cooling, the mixture is triturated with EtOH, and the residue filtered and recrystallized.

Alkylthiolation of Tetrazolo[1,5-*b*]pyridazines; General Procedure G (see Table):
The appropriate tetrazolopyridazine (0.01 mol) and the corresponding thiol (0.01 mol) are dissolved in dry DMF (30 mL). Anhydrous K_2CO_3 (4.15 g, 0.03 mol) is added, and the mixture is stirred at room temperature for 90 min. Then the mixture is poured into ice water (100 mL) and stirred till the crude product begins to crystallize. The product is collected by suction filtration and purified by recrystallization from the appropriate solvent.

5-Acetylamino-3-chloro-6-phenylpyridazine (7b):
5-Amino-3-chloro-6-phenylpyridazine (**7a**; 5.0 g, 0.024 mol) is heated together with NaOAc (0.2 g) in Ac_2O (40 mL). The solvent is removed *in vacuo*, and the residue is triturated with EtOH (200 mL) and filtered to give **7b** as colorless crystals; yield: 3.2 g (54%); mp 174–175°C (MeOH).

$C_{12}H_{10}ClN_3O$	calc.	C 58.19	H 4.07	N 16.97
(247.6)	found	57.69	4.03	16.65

IR: ν = 3320 (w), 3280 (w), 3070 (w), 1715 (s), 1595 (m) cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 2.1 (s, CH_3), 7.4–7.7 (m, 5 H_{arom}), 8.35 (s, H-4), 9.7 (br, NH).

Received: 1 December 1988; revised: 10 April 1989

(1) Organic Azides in Heterocyclic Synthesis, Part 8; for Part 7, see: Lapachev, V.V., Stadlbauer, W., Kappe, T. *Monatsh. Chem.* **1988**, *119*, 97.

(2) Pyridazines with Heteroatom Substituents in Position 3 and 5, Part 4. For Part 3, see: Schober, B.D., Megyeri, G., Kappe, T. *J. Heterocycl. Chem.*, **1989**, *26*, 169.

(3) Egki, M., Dreiding, A.S. *Helv. Chim. Acta* **1986**, *69*, 1442.
Gaoni, Y. *Tetrahedron Lett.* **1988**, *29*, 1591.
Hamman, S., Beguin, C.G. *J. Fluorine Chem.* **1987**, *37*, 191.
Nagasaka, T., Tamano, H., Maekawa, T., Hamaguchi, F. *Heterocycles* **1987**, *26*, 617.
Nagawa, Y., Honda, K., Nakanishi, H. *Synthesis* **1987**, 905.

(4) Knittel, D. *Monatsh. Chem.* **1984**, *115*, 523.

(5) Bartra, M., Urpi, F., Vilarrasa, J. *Tetrahedron Lett.* **1987**, *28*, 941.
Campbell, J.M., Abbas, N., Sainsbury, M. *Tetrahedron* **1985**, *41*, 5637.
Effenberger, F., Beisswenger, T., Az, R. *Chem. Ber.* **1985**, *118*, 4865.
Knotz, H., Zbiral, E. *Liebigs Ann. Chem.* **1986**, 1736.
Rolla, F. *J. Org. Chem.* **1982**, *47*, 4372.
Rosen, T. Lico, I.M., Chu, D.T.W. *J. Org. Chem.* **1988**, *53*, 1580.
Sarma, J.C., Sarma, R.P. *Chem. Ind. (London)* **1987**, *21*, 764.
Soai, K., Yokoyama, S., Ookawa, A. *Synthesis* **1987**, 49.

(6) Staudinger, H., Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.

(7) For a review see:
Gololobov, Yu.G., Zhmurova, I.N., Kasukhin, L.F. *Tetrahedron* **1981**, *37*, 437.
Heydt, H., Regitz, M., in: *Houben-Weyl*, 4th ed., Vol. E2, Georg Thieme Verlag, Stuttgart, 1982, p. 96.
Scriven, E.F.V. *Chem. Rev.* **1988**, *88*, 351.

(8) Onys'ko, P.P., Proklina, N.V., Prokopenko, V.P., Gololobov, Yu.G. *Zh. Org. Khim.* **1984**, *54*, 325.

(9) Bachi, M.D., Klein, J. *J. Chem. Soc. Perkin Trans. I* **1983**, 1925.
Bachi, M.D., Vaya, J. *J. Org. Chem.* **1979**, *44*, 4393.
Knouzi, N., Vaultier, M., Carrie, R. *Bull. Soc. Chim. Fr.* **1985**, 815.
Altenbach, H.J., Stegelmeier, H., Wilhelm, M., Voss, B., Lex, J., Vogel, E. *Angew. Chem.* **1979**, *91*, 1028; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 962.
Garcia, J., Vilarrasa, J., Bordas, X., Banaszek, A. *Tetrahedron Lett.* **1986**, *27*, 639.

(10) Tisler, M. *Synthesis* **1973**, 123

(11) Sasaki, T., Kanematsu, K., Murata, M. *Tetrahedron* **1972**, *28*, 2383.

(12) Schönbeck, R., Diskus, A., Kloimstein, E., Mayr, H. *Austrian Patent* 310765 (1973), Österr. Stickstoffwerke A.G.; *C.A.* **1974**, *80*, 95999.

(13) Kos, C. *Dissertation*, University of Graz, 1985, p. 28.

(14) Gabriel, S., Colman, J. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 395.

(15) Drury, K., Reicheneder, F. *Belgian Patent* 630379 (1963), BASF; *French Patent* 1352099 (1964), BASF; *C.A.* **1964**, *60*, 13256, 15888.

(16) There exists only one example in the recent literature regarding the Staudinger reaction of tetrazolo[1,5-*b*]pyridazine-8-carbonitrile,[17] but this reaction was also carried out in our laboratory by A. Pfaffenschlager (see references 26 and 27 and the acknowledgement quoted in Ref. 17).

(17) Haider, N., Heinisch, G., Laßnigg, D. *J. Heterocycl. Chem.* **1988**, *25*, 119.