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PREPARATION OF [1,2,4]TRIAZOLO[5,1-c][1,2,4]TRIAZINE DERIVATIVES FROM 3,4-DIAMINO[1,2,4]TRIAZINE

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Abstract - *3,4-Diamino[1,2,4]triazine 1 reacts with diarylcarbodiimides to give the 7-arylamino-3-methyl-8H-4-oxo[1,2,4]triazolo[5,1-c][1,2,4]triazines 2 in good yields. The reaction of the iminophosphorane 4 with thioureas leads directly to 2 in moderate yields.*

As a part of an investigation on fused heterocycles, we have been engaged in the preparation of bridgehead nitrogen heterocycles which contain the [1,2,4]triazolo moiety. In this context we have previously reported that the reaction of functionalized N-aminoheterocycles with carbodiimides leads to fused [1,2,4]triazoles[1].

We now describe two general methods for the preparation of some derivatives of the [1,2,4]triazolo[5,1-c][1,2,4]triazine ring system. The methods described so far for the preparation of [1,2,4]triazolo[5,1-c][1,2,4]triazines can be classified in three groups: a) from 5-hydrazino[1,2,4]triazines and carbon-inserting reagents[2,3,4]; b) from 3-hydrazino[1,2,4]triazoles and α-dicarbonyl compounds[5,6,7]; and c) from [1,2,4]triazole-5-diazonium salts and active-methylene compounds[8,9,10]. Our approach is based on the reaction of 3,4-diamino[1,2,4]triazine with diarylcarbodiimides to give N-heteroaromatic guanidines as highly reactive intermediates which undergo cyclization under the reaction conditions to give fused [1,2,4]triazoles.

Thus, the N-aminoheterocycle, 3,4-diamino-6-methyl-5-oxo-4,5-dihydro[1,2,4]triazine 1, readily available from diaminoguanidine hydrobromide and pyruvic acid[11], reacts with diarylcarbodiimides in dry toluene at reflux temperature for 24 h to give the corresponding 7-arylamino-3-methyl-8H-4-oxo[1,2,4]triazolo[5,1-c][1,2,4]-triazines 2a-c as crystalline solids in good yields (70-97%) (Method A).

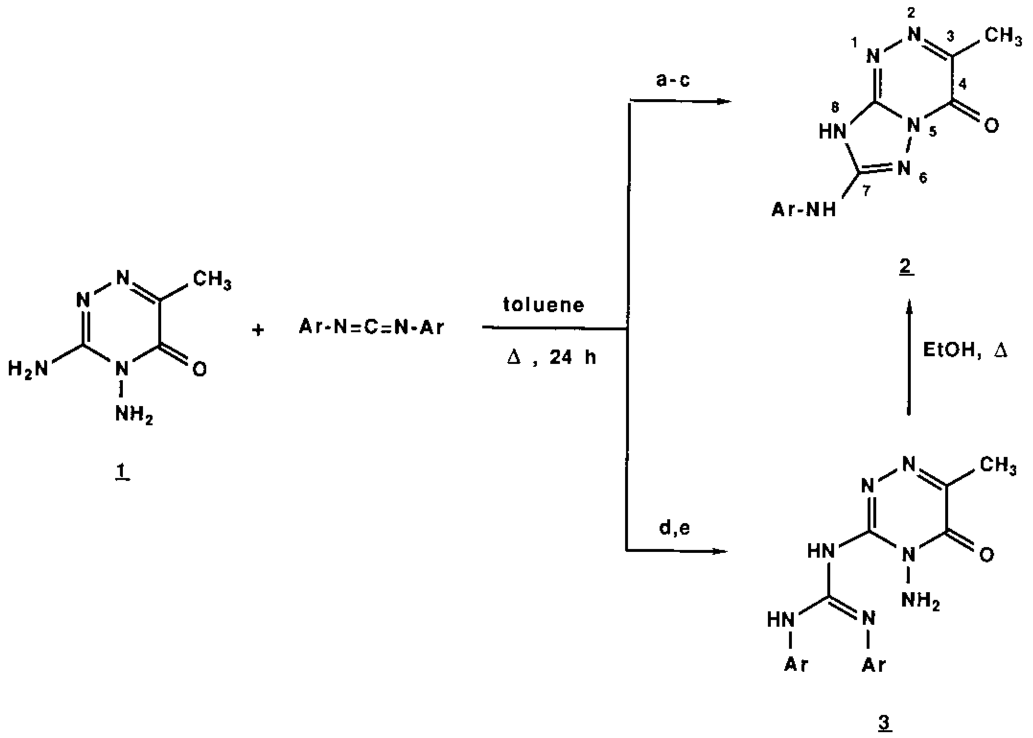
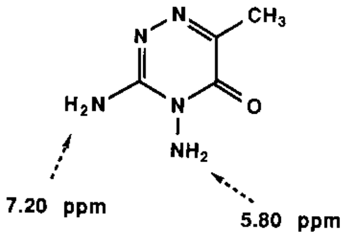


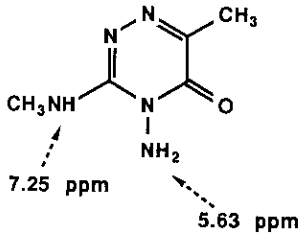
TABLE 1. Preparation of 7-Arylamino-3-methyl-8*H*-4-oxo[1,2,4]triazolo[5,1-*c*][1,2,4]triazines 2.

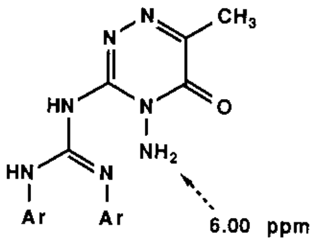
Entry	Ar	Mp(°C)	Yield(%)		Found / Required			Molecular
			A	B	C	H	N	Formula
2a	C_6H_5	298-300	70	30	54.57	4.21	34.51	$C_{11}H_{10}N_6O$
					54.54	4.16	34.69	
2b	p-H_3C-C_6H_4	337-339	75	36	56.31	4.53	32.68	$C_{12}H_{12}N_6O$
					56.24	4.72	32.79	
2c	p-H_3CO-C_6H_4	334-335	97	41	53.12	4.30	30.68	$C_{12}H_{12}N_6O_2$
					52.94	4.44	30.87	
2d	p-Cl-C_6H_4	335-337	55	33	47.61	3.39	30.42	$C_{11}H_9ClN_6O$
					47.75	3.28	30.37	
2e	p-Br-C_6H_4	328-330	57	45	41.22	2.71	26.09	$C_{11}H_9BrN_6O$
					41.14	2.82	26.17	

The ir spectra of compounds 2 show a strong absorption band in the region 3336-3296 cm^{-1} due to the NH group, and other one at 1699-1687 cm^{-1} attributable to the C=O bond. In the ^{1}H-nmr spectra the chemical shift of the C$_3$-methyl group is characteristic at δ 2.00 ppm. The mass spectra show the expected molecular ion peaks, and other significative is due to the fragment [Ar-NH-CN]$^{+\cdot}$.

Compound 1 reacts with bis(p-chlorophenyl)- and bis(p-bromophenyl)carbodiimide to give guanidines 3d,e as crystalline solids in good yields (78-80%). The structure of compounds 3 has been tentatively assigned on the basis of the chemical shift of the amino group at position 4 by comparison with the chemical shift of the same group in the ^{1}H-nmr spectra of 1 and 4-amino-6-methyl-3-methylamino-5-oxo-4,5-dihydro[1,2,4]triazine, recorded in DMSO-d^{6} solutions.

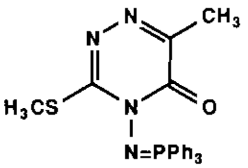




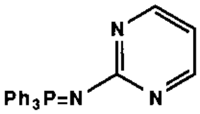


By heating in ethanolic solution, compounds 3 are converted into 2d,e in high yields.

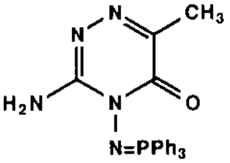
On the other hand the N-aminoheterocycle 1 reacts with triphenylphosphine dibromide in the presence of triethylamine to give the iminophosphorane 4 in excellent yield (94%). The ir spectrum of compound 4 shows two bands at 3318 and 3239 cm^{-1} due to the amino group, and a strong band at 1659 cm^{-1} attributable to the carbonyl group. In the ^{1}H-nmr spectrum recorded in CDCl$_3$ the methyl and the amino groups appear as singlets at δ 2.40 and δ 6.10 ppm respectively. The mass spectrum shows the expected molecular ion peak, and other significative appears at m/z 318 due to the fragment [Ph$_3$P=N-NCO]$^{+\cdot}$. The ^{31}P-nmr study confirms that the triphenylphosphoranylideneamino group is attached at position 4 of the [1,2,4]triazine ring: the value found for the compound 4 is similar to the iminophosphorane derived from 4-amino-6-methyl-3-methylthio-5-oxo-4,5-dihydro-[1,2,4]triazine and higher than iminophosphoranes derived from anilines[12] and C-aminoheterocycles.



δ_P 20.58 ppm

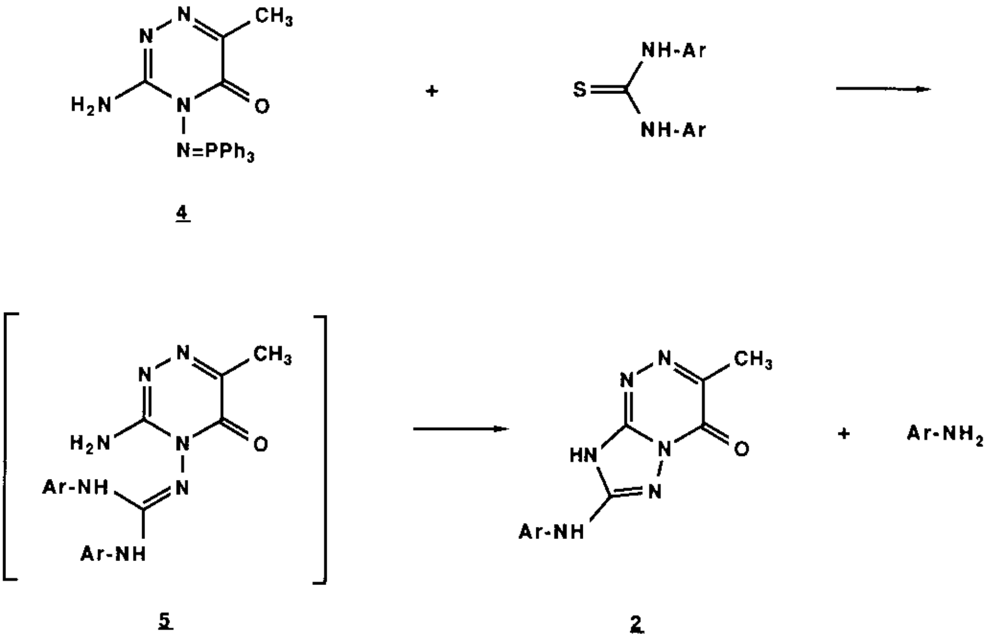


δ_P 15.42 ppm



4 δ_P 20.37 ppm

Iminophosphorane 4 reacts with arylthioureas in dry toluene at reflux temperature for 24 h to afford the corresponding triazolotriazines 2 in moderate yields (30-45%) (Method B). We believe that the conversion 4 → 2 involves initial aza-Wittig reaction between the iminophosphorane 4 and the thiourea to give a non-isolated intermediate guanidine[13] which undergoes cyclization and elimination of amine to give 2.



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. ^{1}H and ^{31}P-nmr spectra were obtained on a Varian FT-80 spectrometer using tetramethylsilane as external reference for ^{1}H and 85% H_3PO_4 as external reference for ^{31}P-nmr. The EI-mass spectra were obtained with a Hewlett-Packard 5993 C spectrometer. Elemental analyses were performed with a Perkin-Elmer 240 C instrument.

3-Amino-6-methyl-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro[1,2,4]triazine 4. Bromine (1.44 g, 9 mmol) in dry benzene (15 ml) was added dropwise to a stirred solution of triphenylphosphine (2.36 g, 9 mmol) in dry benzene (20 ml) at 0-5°C under nitrogen. The mixture was stirred for 1 h and then allowed to warm to room temperature. A solution of triethylamine (1.82 g, 18 mmol) in dry benzene (20 ml) and 3,4-diamino-6-methyl-5-oxo-4,5-dihydro[1,2,4]triazine 1 (1.27 g, 9 mmol) were added to the above mixture; after heating under reflux for 24 h, the deposited triethylammonium bromide was separated by filtration and the filtrate was concentrated to dryness to afford a crude product which was recrystallized from chloroform/cyclohexane (1:1, v/v) to give the iminophosphorane 4 (3.39 g, 94%) as colourless prisms, mp 214-216°C (Found: C, 65.71; H, 4.96; N, 17.67. $C_{22}H_{20}N_5OP$ requires C, 65.83; H, 5.02; N, 17.45); ir ν max (Nujol) 3318, 3239, 1659, 1545, 1500, 1404, 1206, 1109, 1087, 1008, 959, 923, 753, 725 cm^{-1}; ^{1}H-nmr δ ($CDCl_3$) 8.3-7.4 (15H,m), 6.12 (2H,s), 2.35 (3H,s); m/z(%) 401(M$^+$, 35), 400(67), 318(15), 304(18), 303(27), 301(38), 288(26), 276(12), 262(23), 261(16), 240(10), 200(15), 185(21), 183(100), 108(10).

General Procedure for the Formation of 7-Arylamino-3-methyl-8H-4-oxo[1,2,4]-triazolo[5,1-c][1,2,4]triazines 2. Method A. To a solution of 3,4-diamino-6-methyl-5-oxo-4,5-dihydro[1,2,4]triazine 1 (1 g, 7 mmol) in dry toluene (25 ml) the appropriate diarylcarbodiimide (7 mmol) was added. The reaction mixture was stirred at reflux temperature for 24 h; after cooling the precipitated solid was collected by filtration, dried and recrystallized from ethanol to give 2 as colourless prisms.

In the cases of bis(p-chlorophenyl)- and bis(p-bromophenyl)carbodiimide the reaction products were found to be the corresponding heteroaryl guanidines 3.

(3a) Ar= p-Cl-C_6H_4 (78%), as colourless prisms,mp 203-205°C, from dichloromethane (Found: C, 50.63; H, 3.60; N, 24.27. $C_{17}H_{15}Cl_2N_7O$ requires C, 50.51; H, 3.74; N, 24.25); ir ν max (Nujol) 3341, 1682, 1614, 1591, 1557, 1166, 1093, 1013, 832, 736, 728 cm^{-1}; ^{1}H-nmr δ (DMSO-d^6) 9.78 (1H,s), 8.0-7.1 (8H,m), 5.97 (2H,s), 5.45 (1H,s), 2.05 (3H,s); m/z(%) 407(M$^+$ + 4, 1), 405(M$^+$ + 2, 5), 403(M$^+$, 10), 280(2), 278(11), 276(23), 129(33), 127(100), 113(4), 111(10), 75(13), 65(19).

TABLE 2. Spectral Data of Compounds 2.

Compound No.	Ir ν (cm^{-1})	^{1}H-nmr[a] δ (ppm)	Ms[b] m/z (%)
2a	3336,1699,1619,1580,1359,742,691.	10.00(1H,s); 8.0-7.0(6H,m); 2.00(3H,s).	242(M$^+$,96),144(18),119(18),118(100),104(12),91(19),77(40),68(11),65(16),51(29).
2b	3330,1687,1648,1614,1574,1557,1518,826,747,719.	10.05(1H,s); 8.1-7.0(5H,m); 2.00(6H,s).	256(M$^+$,66),158(24),133(21),132(100),131(34),118(24),117(15),106(14),92(21),91(89),77(29),65(35).
2c	3296,3183,1687,1631,1585,1512,1246,1223,1178,1030,798,742.	10.00(1H,s); 8.0-7.0(5H,m); 4.13(3H,s); 2.10(3H,s).	272(M$^+$,100),257(43),159(20),148(28),133(89),122(26),105(27),92(21),77(22),65(21).
2d	3336,1687,1625,1609,1563,1042,1008,826,804.	10.05(1H,s); 8.1-7.1(5H,m); 2.05(3H,s).	278(M$^+$+2,31),276(M$^+$,100),154(31),152(99),140(6),138(16),128(4),126(12),113(11),111(36),83(21).
2e	3336,1687,1636,1614,1585,1552,1087,1008,838,799,744.	10.10(1H,s); 8.1-7.5(5H,m); 2.05(3H,s).	323(M$^+$+2,14),321(M$^+$,19),198(77),196(87),184(15),182(15),172(11),170(10),157(37),155(35),143(30),117(51),91(67),90(99),83(37),76(48),75(57).

[a] Obtained as solutions in DMSO-d^6. [b] Recorded at 70 eV.

(3b) Ar= p-Br-C_6H_4 (80%), as colourless prisms,mp 221-223°C, from dichloromethane (Found: C, 41.30; H, 2.97; N, 19.93. $C_{17}H_{15}Br_2N_7O$ requires C, 41.40; H, 3.06; N, 19.88); ir ν max (Nujol) 3341, 1682, 1614, 1552, 1498, 1297, 1280, 1166, 1008, 838, 824, 784, 757, 733 cm^{-1}; ^{1}H-nmr δ (DMSO-d^6) 9.97 (1H,s), 7.9-6.6 (8H,m), 5.95 (2H,s), 5.55 (1H,s), 2.05 (3H,s); m/z(%) 495(M$^+$ + 4, 4), 493(M$^+$ + 2, 7), 491(M$^+$, 4), 341(10), 339(19), 337(9), 172(99), 170(100), 92(31), 65(40).

When an ethanolic solution of 3a or 3b was heated at reflux temperature for 5 h, the corresponding triazolotriazine 2d or 2e were obtained in 70% or 72% yield respectively.

Method B. To a solution of 3-amino-6-methyl-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro[1,2,4]triazine 4 (2 g, 5 mmol) in dry toluene (50 ml) the appropriate diarylthiourea (5 mmol) was added. The reaction mixture was stirred at reflux temperature for 24 h. Similar work-up to the above method led to pure compounds 2.

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REFERENCES

1. P. Molina, M. Alajarín, A. Ferao, A. Lorenzo, M.J. Vilaplana, E. Aller, and J. Planes, Heterocycles, 1988, 27, 161.
2. J. Daunis, R. Jacquier, and P. Viallefont, Bull. Soc. Chim. Fr., 1969, 2492.
3. J. Daunis and M. Follet, Bull. Soc. Chim. Fr., 1976, 1178.
4. A. Dornow, H. Menzel, and P. Marx, Chem. Ber., 1964, 97, 2185.
5. E.J. Gray, H.N.E. Stevens, and M.F.G. Stevens, J. Chem. Soc., Perkin Trans. I, 1978, 885.
6. E.J. Gray and M.F.G. Stevens, J. Chem. Soc., Perkin Trans. I, 1976, 1492.
7. J. Daunis, H. López, and G. Maury, J. Org. Chem., 1977, 42, 1018.
8. G. Tenant and R.J.S. Vevers, J. Chem. Soc., Perkin Trans. I, 1976, 421.
9. E.J. Gray, M.F.G. Stevens, G. Tenant, and R.J.S. Vevers, J. Chem. Soc., Perkin Trans. I, 1976, 1496.
10. V.L. Rusinov, A.Y. Petrov, and I.Y. Postovskii, Khim. Geterotsikl. Soedin., 1980, 1283 [Chem. Abstr., 1981, 94, 65635].
11. A. Dornow, H. Menzel, and P. Marx, Chem. Ber., 1964, 97, 2173.
12. M. Pomerantz, D.S. Marynick, K. Rajeshwar, W. Chou, L. Throckmorton, E.W. Tsai, P.C.Y. Chen, and T. Cain, J. Org. Chem., 1986, 51, 1223.
13. P. Molina, M. Alajarín, and J. Saez, Synth. Commun., 1983, 13, 67.

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