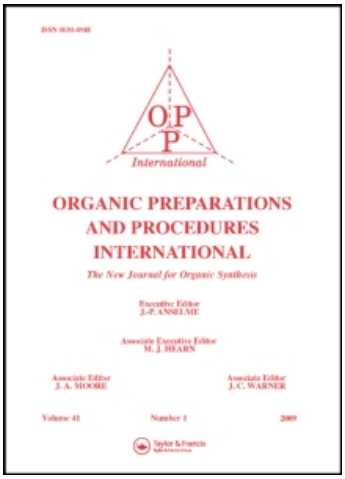

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REACTION OF NITRILIUM SALTS WITH 6-AMINOURACIL

Submitted by (02/29/96)

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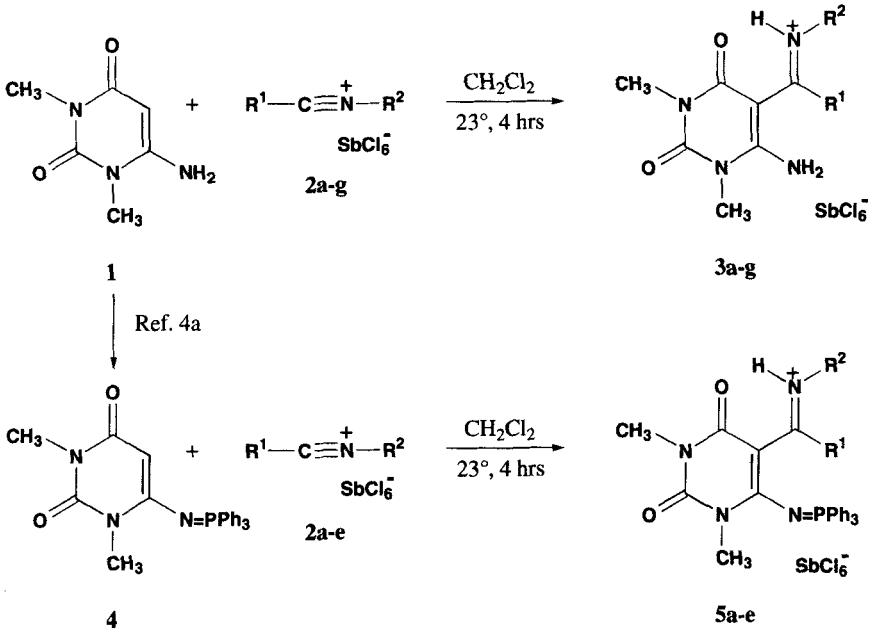
Nitrilium salts **2** show considerable reactivity towards many types of nucleophiles.[1] We now describe the reaction of nitrilium salts with iminophosphorane **4**, whose nucleophilic properties have been explored by Wamhoff and Molina.[2]

The annulation of uracils has recently attracted interest due to the biological activities of the products.[3] The Staudinger reaction of iminophosphoranes (*e.g.* **4**) has been used for the preparation of various types of nitrogen containing heterocycles.[4] The chemistry of iminophosphoranes as useful building blocks for the preparation of heterocycles has been reviewed.[5] The aminouracil (**1**) reacts as a C-nucleophile with nitrilium salts **2** to give the uracils **3** in high yield; no reaction of **2** was observed with the amino group of **1**. However, conversion of **3** into **5** upon reflux with triphenylphos-



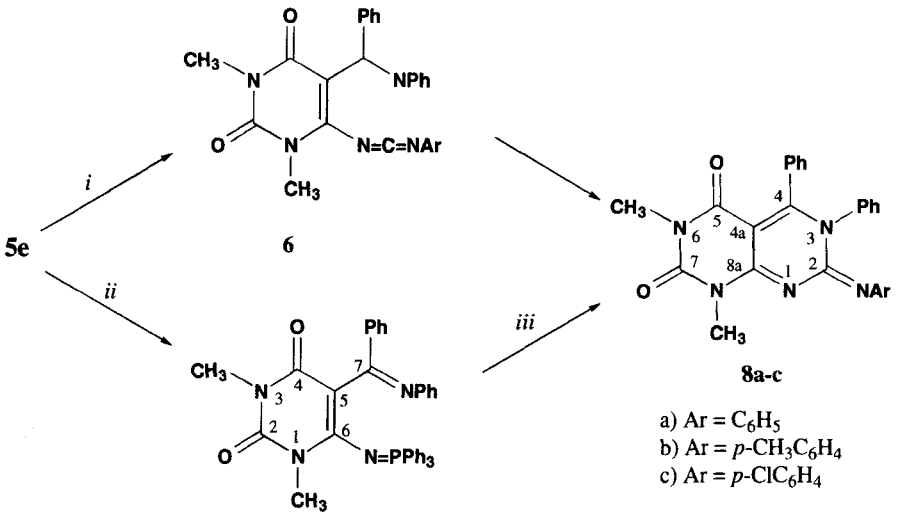
a) $R^1 = R^2 = CH_3$ b) $R^1 = CH_3$, $R^2 = CH(CH_3)_2$ c) $R^1 = CH_3$, $R^2 = C_6H_5$

d) $R^1 = C_6H_5$, $R^2 = CH_3$ e) $R^1 = R^2 = C_6H_5$ f) $R^1 = C_6H_5$, $R^2 = CH(CH_3)_2$

g) $R^1 = CH_2C_6H_4CH_3$, $R^2 = CH(CH_3)_2$

Scheme 1

phine/hexachloroethane gave only poor yields of **5**. The nitrilium salts (**2**) reacted with the phosphoranylidene aminouracil (**4**) to afford iminophosphoranes **5a-e**, which are stable crystalline salts. Except for **5e**, no change was observed when the iminophosphoranes were heated at reflux with arylisocyanates in toluene for several hours; only partial decomposition of the salts occurred. When **5e** was refluxed with arylisocyanates in chlorobenzene for 4 hrs, a slow reaction took place to give the desired products (**8**, NMR evidence). However, with longer reflux time decomposition increased. Iminophosphorane **5e** reacts with arylisocyanates (Staudinger reaction) to give presumably the unstable carbodiimide intermediates **6**, which underwent rapid intramolecular heterocylization on the carbodiimide moiety affording pyrimidines **8a-c**. Attempts to extend this reaction to aliphatic isocyanates were unsuccessful. Only black tars and starting materials were obtained. Refluxing **5e** with triethylamine in toluene for 2 hrs gave the iminophosphorane **7** (78%), which reacted with *p*-tolylisocyanate to afford **8b** (60%). Compounds **3**, **5**, **7** and **8** were characterized by ^{1}H, ^{13}C-nmr, ir and elemental analysis.



i) ArNCO, Et_3N, $PhCH_3$ *ii*) Et_3N, $PhCH_3$ *iii*) *p*-$CH_3C_6H_4NCO$, $PhCH_3$

Scheme 2

EXPERIMENTAL SECTION

The melting points are uncorrected. IR spectra were obtained with samples prepared as KBr pellets on a Perkin-Elmer FTIR 1600 spectrometer. ^{1}H and ^{13}C-nmr spectra were determined on Brucker WM-250 and AC-250 spectrometers using TMS as an internal standard. Elemental analysis were determined by CHN-microanalysis Lab. Fakultät Chemie, Universität Konstanz, Germany. The preparation of the nitrilium salts and of compounds **3** and **5** was carried out with exclusion of moisture in solvents dried by standard methods.[6]

Table 1. Yields, mps, Form and Elemental Analyses of Compounds **3**, **5**, **7** and **8**

Cmpd	Yield (%)	mp.[a] (°C)	Form	Elemental Analyses, Calcd (Found) C	H	N
3a	74	178-179	pale yellow needles	19.81(19.75)	2.77(2.86)	10.27(10.15)
3b	79	187-190	yellow needles	22.67(22.91)	3.34(3.56)	9.76(9.66)
3c	89	190-192	yellow fine crystals	27.67(27.63)	2.82(2.86)	9.22(9.03)
3d	73	148-150	yellow powder	27.67(27.89)	2.82(2.99)	9.22(9.42)
3e	91	195-198	yellow powder	34.07(33.81)	2.86(2.89)	8.36(8.57)
3f	83	237-240	yellow needles	30.22(30.17)	3.33(3.38)	8.81(8.73)
3g	85	219-222	yellow plates	32.57(32.35)	3.80(3.87)	8.44(8.20)
5a	77	212-215	yellow powder	40.24(40.17)	3.50(3.55)	6.95(6.95)
5b	94	174-176	orange crystals	40.42(40.20)	3.79(3.84)	6.39(6.38)
5c	97	184-186	orange crystals	44.28(44.13)	3.48(3.46)	6.45(6.37)
5d	67	213-216	yellow powder	44.28(44.33)	3.48(3.55)	6.45(6.44)
5e	79	205-208	yellow powder	47.78(47.53)	3.47(3.46)	6.02(6.14)
7	78	184-186	yellow powder	74.73(74.90)	5.26(5.35)	9.42(9.15)
8a	81	218-220	pale yellow powder	71.71(71.55)	4.86(4.72)	16.08(16.01)
8b	60	249-252	orange crystals	72.14(72.38)	5.16(5.06)	15.58(15.61)
8c	72	235-237	yellow powder	66.45(66.29)	4.29(4.43)	14.90(14.77)

a) All compounds except **7** and **8c** melt with decomposition.

General Procedure for the Preparation of (6-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo pyrimidyl-5)alkylideneammonium Hexachloroantimonate (3a-g).-A solution of 0.74 g (5.0 mmol) of **1** in 25 mL of methylene chloride was added at 23° to a suspension of 5.0 mmol of **2** in 25 mL of methylene chloride. After stirring at 23° for 4 hours, 30 mL of dry ether was added and the crystalline precipitate was collected.

General Procedure for the Preparation of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-[(triphenyl-phosphoranylideneamino) pyrimidyl-5)]alkylideneammonium Hexachloroantimonate (5a-e).- A solution of 2.07 g (5.0 mmol) of **4**[4a] in 25 mL of methylene chloride was added at 23° to a suspension of 5.0 mmol of **2** in 25 mL of methylene chloride. After stirring the reaction mixture at 23° for 3 hours, 30 mL of ether was added. The precipitate was collected by filtration. Recrystallization from $CHCl_3/Et_2O$ (1:1), gave **5** as fine yellow crystals.

1,3-Dimethyl-5-[phenyl(N-phenylimino)methyl]-6-(triphenylphosphoranylideneamino)uracil (7).- A solution of Et_3N (0.71 g, 7 mmol) in toluene (5 mL) was added to a solution of **5e** (5.65 g, 5.0 mmol) in toluene (20 mL). The reaction mixture was boiled under reflux for 2 hours. Evaporation of solvent and repeated extraction of residue with $CHCl_3/H_2O$ (1:2) afforded a product which was crystallized from $CHCl_3/Et_2O$ (2:1) to give **7** as yellow powder (78%).

General Procedure for the Preparation of 2,3,5,6,7,8-Hexahydro-2-imino-6,8-dimethyl-3,4-diphenyl pyrimidino(4,5-d)pyrimidine-5,7-diones (8a-c).- The appropriate isocyanate (6 mmol) and

Et_3N (0.61 g, 6.0 mmol) were added to a solution of **5e** (5.65 g, 5.0 mmol) in dry toluene (25 mL). After refluxing for 30 hours, the solvent was evaporated and the residue was repeatedly extracted with $CHCl_3/H_2O$ (1:2). Workup afforded a product, which was crystallized from $CHCl_3/Et_2O$ (2:1) to give crystalline powders (**8a-c**).

Table 2. Spectroscopic Data of Compounds **3,5,7** and **8**

Cmpd	IR (cm^{-1})	^{1}H-NMR[a] δ, *J* (Hz)	^{13}C-NMR[a] δ
3a	3444, 3366 1704, 1644 1520	2.56 (s, CH_3), 3.24 (s, NCH_3) 2.26 (d, *J* = 5, CH_3), 3.43 (s, NCH_3) 6.88 (b, NH_2), 12.01 (b, NH)	19.7, 28.9, 31.5, 32.9 (CH_3) 88.5 (C5), 150.0, 159.1, 163.7 174.7 (C2, C4, C6, C7)
3b	3433, 3344 1698, 1644 1522	1.37 (d, *J* = 8, CH_3), 2.59 (s, CH_3) 3.24, 3.43 (s, NCH_3), 4.22 (m,CH) 6.86 (b, NH_2), 12.08 (b, NH)	19.3, 22.4, 28.9, 31.5 (CH_3), 48.8 (CH), 88.2 (C5), 149.9, 159.1 164.0, 172.0 (C2, C4, C6, C7)
3c	3488, 3391 1709, 1620	2.18 (s, CH_3), 3.30, 3.39 (s, NCH_3)	
3d	3453, 3364 1724, 1643 1605	1.24 (d, *J* = 6.4, CH_3), 2.34 (s, CH_3) 3.28, 3.36 (s, NCH_3), 4.08 (m, CH) 4.14 (s, CH_2), 6.70 (bs, NH_2) 7.12-8.28 (Ph), 12.71 (b, NH)	21.1, 22.7, 31.5, 36.2 (CH_3) 49.7 (CH), 88.4 (C5), 128.8, 131.0, 131.4, 139.9 (Ph), 149.9, 158.8, 164.2, 172.3, (C2, C4, C6, C7)
3e	3457, 3365 1731, 1633 1597	2.97 (d, *J* = 5, CH_3), 3.31, 3.32 (s, NCH_3), 5.96 (b, NH_2) 7.55-7.78 (Ph), 12.76 (NH)	28.7, 29.0, 31.0 (CH_3), 86.8 (C5), 128.6, 130.3, 131.9, 133.6 (Ph), 149.6, 159.2, 173.1 (C2, C4, C6, C7)
3f	3450, 1729 1636, 1589	1.25 (d, *J* = 6.4, CH_3), 3.30, 3.32 (s, NCH_3), 5.84 (b, NH_2) 7.58-7.82 (Ph), 12.90 (NH)	23.1, 29.1, 31.6 (CH_3), 50.2 (CH), 86.6 (C5), 128.4, 130.5 131.9, 133.6 (Ph), 149.6, 159.3 164.3, 170.9 (C2, C4, C6, C7)
3g	3839, 1734 1632, 1564	3.36, 3.37 (s, NCH_3) 6.16 (b, NH_2), 6.97-7.59 (Ph) 14.02 (NH)	29.2, 31.8 (CH_3), 88.2 (C5) 127.0, 129.3, 130.0, 130.4, 131.2 136.9 (Ph), 149.6, 159.9, 164.8 171.4 (C2, C4, C6, C7)
5a	1714, 1630 1522, 1484	2.01 (s, CH_3), 2.62 (d, *J* = 5.2, CH_3) 3.17, 3.49 (s, NCH_3), 7.60-7.86 (Ph), 10.77 (q, *J* = 5.2, NH)[b]	19.9, 27.7, 31.5, 32.0 (CH_3) 95.8 (C5), 150.5, 161.3 (C2, C4) 162.0 (d, *J* = 9, C6), 173.7 (C7)[b]
5b	3447, 1707 1633, 1616	1.03 (d, *J* = 6.4, CH_3), 2.10 (s, CH_3) 3.23, 3.43 (s, NCH_3), 3.51 (m, CH) 7.57-7.82 (Ph), 11.53 (bs, NH)	19.6, 22.6, 28.7, 33.3 (CH_3), 48.2 (CH), 97.2 (C5), 126.1, 127.7 130.3, 130.7, 133.9, 134.1, 134.8 134.9 (Ph), 151.2, 164.1, 164.7 172.4 (C2, C4, C6, C7)[c]
5c	1717, 1644 1607, 1583[d]	2.18 (s, CH_3), 3.30, 3.39 (s, NCH_3) 6.81-7.77 (Ph), 13.95 (bs, NH)[c]	22.0, 28.8, 33.7 (CH_3), 97.5 (C5) 149.9 (C2), 162.1 (d, *J* = 6, C6), 164.3, 173.3 (C4, C7)[c]
5d	1707, 1649 1605, 1530[d]	2.71 (d, *J* = 5.4, CH_3), 3.05, 3.23 (s, NCH_3), 7.07-7.76 (Ph) 11.66 (q, *J* = 4.5, NH)[b]	22.9, 28.1, 31.9 (CH_3), 92.1 (C5) 151.3 (C2), 158.1 (d, *J* = 8, C6) 158.3, 175.5 (C4, C7)[b]

Table 2. Continued

Cmpd	IR (cm^{-1})	^{1}H-NMR[a] δ, *J* (Hz)	^{13}C-NMR[a] δ
5e	1717, 1636 1605, 1530[d]	3.32, 3.38 (s, NCH_3), 6.46-7.78 (Ph), 11.94 (b, NH)	28.9, 33.3 (CH_3), 98.3 (C5), 151.9 164.5, 166.1, 170.3 (C2, C4, C6, C7)
7	1687, 1623 1564[d]	2.78, 3.30 (s, NCH_3), 6.72-7.86 (Ph)[f]	28.0, 31.9 (CH_3), 151.4, 151.7 152.9, 162.1 (C2, C4, C6, C7)[f]
8a	1721, 1671 1631, 1606 1582[d]	3.20, 3.43 (s, NCH_3), 7.02-7.23 (Ar)[f]	28.1, 29.9 (CH_3), 94.0 (C4a) 116.5, 122.9, 127.5, 127.9, 128.2 128.6, 128.8, 129.0, 129.2, 132.6 138.3 (Ar), 149.1, 151.4, 158.7 165.7 (C2, C4, C5, C7, C8a)[f]
8b	1719, 1670 1628, 1582[d]	2.20 (s, CH_3), 3.20, 3.41 (s, NCH_3), 6.93-7.25 (Ar)[f]	21.1, 28.1, 29.3 (CH_3), 94.1 (C4a) 122.4, 122.9, 127.5, 127.9, 128.1 128.7, 128.8, 129.0, 129.4, 131.9 132.7, 137.9 (Ar), 149.4, 151.4, 155.1 158.7, 165.8 (C2, C4, C5, C7, C8a)[f]
8c	1721, 1671 1625, 1602[d]	3.20, 3.43 (s, NCH_3), 6.96-7.26 (Ar)[f]	28.1, 29.5 (CH_3), 94.4 (C4a) 124.4, 127.4, 127.5, 128.0, 128.2 128.8, 129.1, 132.5, 138.2, 146.8 149.3 (Ar), 151.3, 155.4, 158.6 165.7 (C2, C4, C5, C7, C8a)[f]

a) In CD_3CN, TMS, 22°. b) In DMSO-d_6, TMS, 22°. c) At 40°. d) In CH_2Cl_2. e) In $CDCl_3$, TMS, 50°. f) In $CDCl_3$, TMS, 22°.

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CONSTRUCTION OF THE PYRAZOLO[1,5-*a*][6,1]BENZODIAZONINE AND PYRAZOLO[1,5-*a*][7,1]BENZODIAZECINE SKELETONS

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Intramolecular 1,3-dipolar cycloadditions offer a synthetic entry to a large variety of heterocyclic systems containing a five-membered ring fused to another ring of variable size.[1] The latter parameter, however, markedly affects the entropy aspect and thus the effectiveness of the intramolecular process.[2] We now report the successful use of intramolecular nitrilimine cycloaddition to construct the hitherto unreported pyrazolo[1,5-*a*][6,1]benzodiazonine and pyrazolo[1,5-*a*][7,1]benzodiazecine systems.

The synthetic sequence involves the following stages: (*i*) site-selective alkynylation of the *o*-aminobenzanilide (**1**);[4] (*ii*) diazotisation of **2** and subsequent coupling with methyl α-chloroacetoacetate to give the hydrazonyl chlorides **3**; (*iii*) treatment of the latter with silver carbonate in order to generate the transient nitrilimines **4**, whose intramolecular cycloadditionled to the target system **5**. In view of the well-known factors working against the formation of large rings,[3] the cyclization yields of **4** are highly satisfactory thus making the present synthesis worthy of attention.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi apparatus and are not corrected. IR spectra were recorded on a FT IR Perkin Elmer 1725 X spectrophotometer. Mass spectra were taken with a WG-70EQ apparatus. ^{1}H NMR spectra were obtained on a Bruker 300 MHz apparatus, chemical shifts are given as ppm from TMS. Compound **1** was prepared according to the literature.[4]