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TANDEM AZA-WITTIG REACTION/ELECTROCYCLIC RING-CLOSURE A FACILE ENTRY TO THE SYNTHESIS OF FUSED PYRIMIDINES: PREPARATION OF PYRAZOLO[3,4-d] AND 1,2,3-TRIAZOLO[4,5-d]PYRIMIDINE DERIVATIVES.

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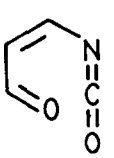
Summary: The aza-Wittig reaction of iminophosphoranes derived from 5-azido-4-formyl azoles, with isocyanates or carbon disulfide, leads to functionalized fused pyrimidines.

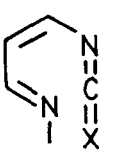
The structural diversity and biological importance of fused pyrimidines have made them attractive targets for synthesis over many years. Recent development of physiologically highly potent purines analogues with interesting (antiviral, antiallergic, radioprotective, and especially anticancer) activities have promted a great current interest in facile and general routes to these molecules in synthetically useful yields[1].

On the other hand, the aza-Wittig reaction of iminophosphoranes with heterocumulenes e.g. carbon dioxide, carbon disulfide and isocyanates or isothiocyanates is a very useful reaction in synthetic heterocyclic chemistry. Consecuently, improvements which increase the efficiency or enlarge its applicability are always desirable and the discovery of novel functionalized iminophosphoranes bearing a moiety able to react with the aza-Wittig product is important in this respect[2].

In the course of our studies directed towards the synthesis of fused heterocycles we had occasion to explore heterocyclization reactions of carbodiimides and isothiocyanates[3]. We now reported a fundamentally, new approach to the synthesis of pyrazolo[3,4-d]pyrimidines and 1,2,3-triazolo[4,3-d]pyrimidines (8-azapurines). Our approach is centred on the aza-Wittig reaction of iminophosphoranes with heterocumulenes to give a 1,3,5-hexatriene moiety containing a nitrogen atom at one end and cumulated double bond at the other, which undergoes electrocyclic ring-closure to give the cyclic valence tautomer



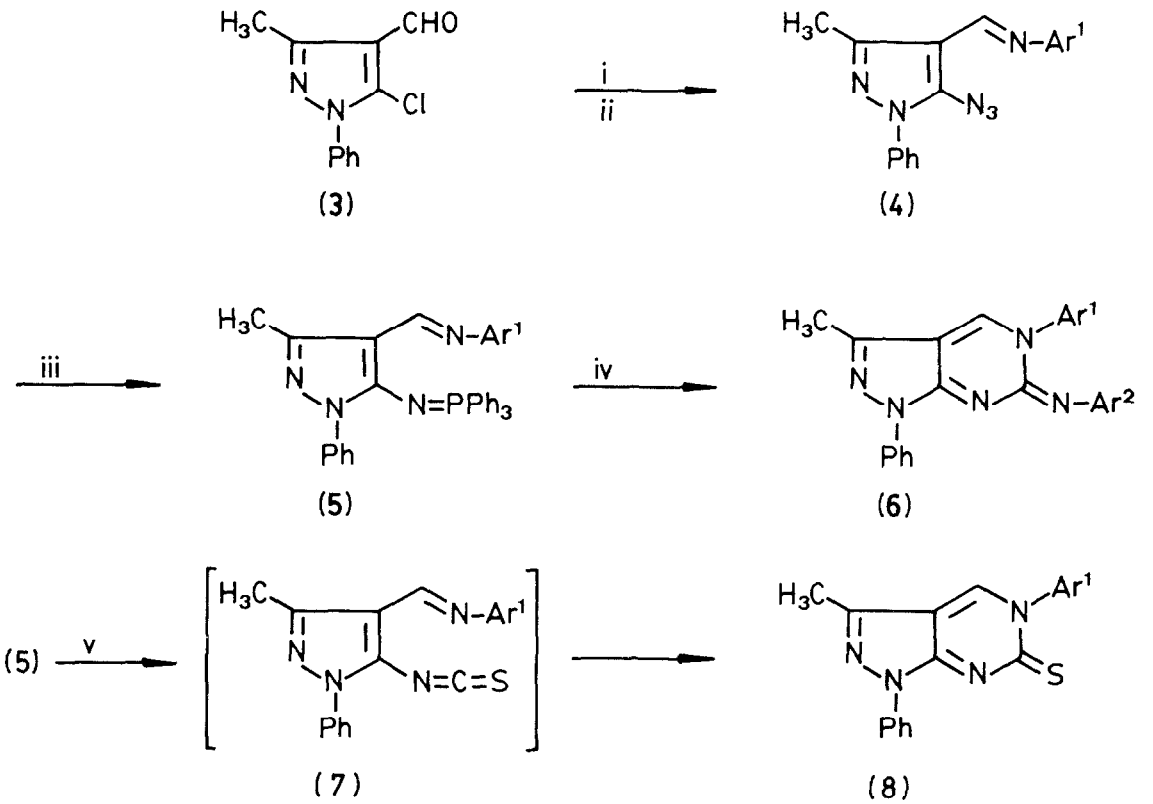
(1)



(2)

X= S, NR

pyrimidine ring. It has previously been reported that open-chain system type (1) undergo ring-closure to give the corresponding 1,3-oxazin-2-one[4], however the heterocumulene was an intermediate in a complex reaction sequence and was not isolated. We report here the first preparation, isolation and cyclization of systems of type (2), in which the central C-C double bond belongs to an heteroaromatic ring. Thus, the 5-chloro-4-formylpyrazole (3) reacts with sodium azide in dimethylsulfoxide at 60°C for 1 h to give the 5-azido-4-formylpyrazole which by treatment with aromatic amines in ethanol at room temperature for 6 h leads to the corresponding 5-azidopyrazoles (4). Compounds (4) react with triphenylphosphine in dry dichloromethane at room temperature for 15 h to give the corresponding iminophosphorane (5). The reaction of (5) with isocyanates in dry dichloromethane at room temperature for 4 h gave triphenylphosphine oxide and the fused pyrimidines (6), the yield of the isolated product being higher than 60%. When compounds (5) were treated with carbon disulfide in dry dichloromethane at room temperature for 6 h, pyrimidines (8)



Reagents: i) NaN_3/DMSO; ii) Ar^1-NH_2; iii) Ph_3P; iv) Ar^2NCO; v) S_2C

were formed in high yields. The results are summarized in the Table. Compounds (6) and (8) were characterized on the basis of their spectroscopic data and mass spectrometry[5].

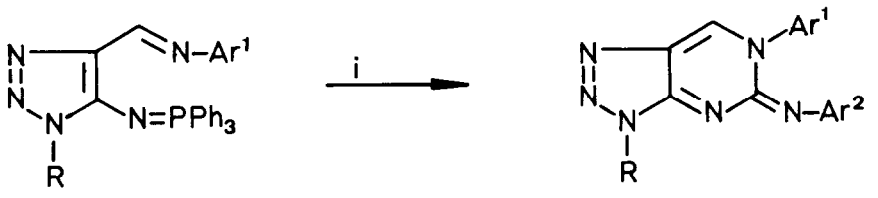
The mechanism of the conversion (5)⟶(8) is supported by the isolation in some cases of the intermediate (7) and the demostration that is was converted to the corresponding fused pyrimidine in nearly quantitative yield.

Table. Pyrazolo[3,4-d]pyrimidines (6) and (8) from Iminophosphoranes (5)

Compound[a]	Ar^1	Ar^2 / S	Yield %	M.P./°C
6a	C_6H_5	4-Cl-C_6H_4	65	166-167
6b	C_6H_5	4-H_3CO-C_6H_4	67	119-120
6c	C_6H_5	C_2H_5	63	178-179
6d	4-H_3C-C_6H_4	4-H_3CO-C_6H_4	70	132-134
6e	4-H_3C-C_6H_4	C_2H_5	61	120-121
8a	C_6H_5	S	97	141-142
8b	4-H_3C-C_6H_4	S	75	152-153

[a] All new compounds reported here gave satistactory elemental analyses.

This approach has also shown to be useful for the preparation of 1,2,3-triazolo[4,5-d]pyrimidines. Thus, iminophosphoranes (9), themselves readily available from the corresponding 5-chloro-4-formyl-1,2,3-triazole by sequenti-



(9) (10)

Reagent: i) Ar^2-NCO

al treatment with sodium azide (dimethylsulfoxide, 60° C, 1 h), aromatic amines (ethanol, room temperature, 2 h) and triphenylphosphine (dichloromethane, room temperature, 10 h), react with aromatic isocyanates in dry dichloromethane at room temperature to give 1,2,3-triazolo 4,5-d pyrimidines (10) in good yields[6].

The above method has the advantage of the easy accesibility of starting materials[7], mild reaction conditions, the good yields in the iminophosphorane preparation as well as in the cyclization step, and the high substitution in the pyrimidine moiety.

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3. P. Molina, P.M. Fresneda and F.Hurtado, Synthesis, 1987, 45.
4. A.E. Baydar and G.V. Boyd, J.C.S. Chem. Comm., 1976, 718.
5. For example: (6c), ^{1}Hnmr (80 MHz, $CDCl_3$) δ 1.3(t,3H), 2.75(s,3H), 3.8(q,2H), 7.6-8.1(m,10H) and 8.95(s,1H); i.r. ν_{max}(Nujol) 1659 s, 1500 vs; m/z (%) 329 (M^+, 36), 328(100); (8b), ^{1}Hnmr (80 MHz, $CDCl_3$) δ 2.56 (s,3H), 2.78(s,3H), 7.5-7.8(m,7H), 8.1-8.3(m,2H) and 9.45(s,1H); i.r. ν_{max} (Nujol) 1642 vs, 1545 vs and 1058 s; m/z (%) 332(M^+, 64), 331(100).
6. For example: (10a), R=4-H_3CO-C_6H_4-CH_2, Ar^1=4-H_3C-C_6H_4, Ar^2=4-Cl-C_6H_5; m.p. 131°C, yield: 71%; ^{1}Hnmr (80 MHz, $CDCl_3$) δ 2.40(s,3H), 4.00(s,3H), 5.82 (s,2H), 7.1-8.0(m,12H), 9.93(s,1H); i.r. ν_{max}(Nujol) 1540 vs, 1511 vs, 1251 s; m/z (%) 456(M^+, 10), 121(100). (10b), R=4-H_3CO-C_6H_4-CH_2, Ar^1=4-H_3C-C_6H_4, Ar^2=4-H_3CO-C_6H_4; m.p. 124°C; yield: 61%; ^{1}Hnmr (80 MHz, $CDCl_3$) δ 2.42(s,3H), 3.9(s,6H), 5.80(2,2H), 7.1-8.1(m,12H), 9.91(s,1H); i.r. ν_{max}(Nujol) 1540 s, 1511 vs, 1245 s, 1036 s; m/z (%) 453(M^+, 3), 186(5), 121(100).
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