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HETEROCYCLIC SYNTHESIS VIA A TANDEM AZA-WITTIG REACTION/ HETEROCUMULENE-MEDIATED ANNULATION REACTION.NEW METHODOLOGY FOR THE PREPARATION OF QUINAZOLINE DERIVATIVES.

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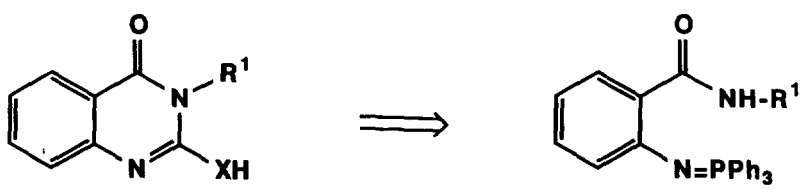
Summary: *The aza-Wittig reaction of iminophosphoranes derived from N-substituted o-azidobenzamides or 2-(o-azido)phenyl benzimidazole with isocyanates, carbon dioxide or carbon disulphide, lead to functionalized 4(3H)-quinazolinones and benzimidazo[1,2-c] quinazolines respectively.*

The quinazoline skeleton, when selectively functionalized, is a building blok for the preparation of numberous alkaloids and substances with pronounced biological activities. However, no general and simple approach to 2-amino-4(3H)-quinazolinones, which are of considerable interest as starting material for pharmaceuticals and other biologically active compounds, has been so far reported. On the other hand, the aza-Wittig reaction of iminophosphoranes with heterocumulenes is a very useful reaction in preparative heterocyclic chemistry. Consequently the discovery of novel functionalized iminophosphoranes is important in this respect.

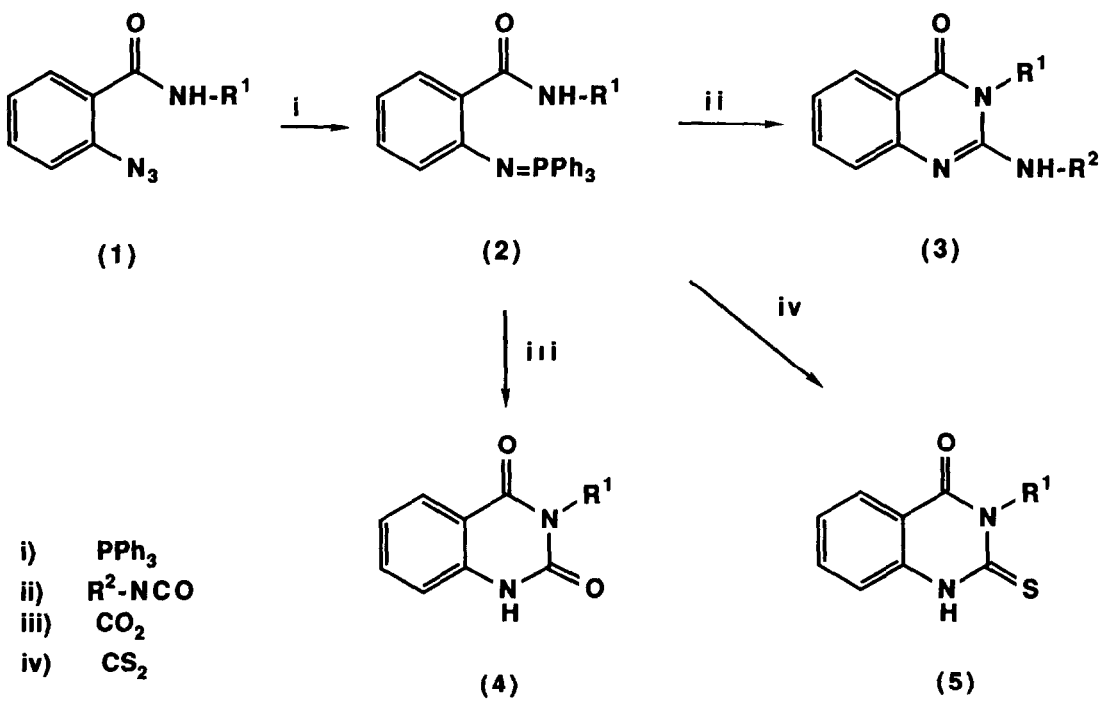
Continuing our interest in the iminophosphorane-mediated synthesis of heterocycles[1], we wish to describe an useful method for the preparation of quinazoline derivatives by an aza-Wittig reaction of iminophosphoranes (2) with heterocumulenes: e.g. isocyanates, carbon dioxide and carbon disulphide.



X= O, S, NR^2

The preparation of the desired 2-aminosubstituted-4(3H)-quinazolinones (3) was accomplished very easily through the classical Staudinger reaction of N-substituted o-azidobenzamidas (1) with triphenylphosphine in ether at room temperature to give the iminophosphoranes (2), aza-Wittig reaction of iminophosphorane (2) with isocyanates leads to quinazolinones (3), the yield of the isolated product being higher than 93-98%. Similarly, compounds (2) react with carbon dioxide and carbon disulphide to give the quinazoline derivatives (4) and (5) respectively in good yields. The results are summarised in the Table. Compounds (3), (4) and (5) were characterised on the basis of their spectroscopic data and mass spectrometry.

We believe that the conversion (2) ⟶ (3) involves initial aza-Wittig reaction between iminophosphorane (2) and the isocyanate to yield a



carbodiimide as highly reactive intermediate which undergoes cyclization by intramolecular attack of the carboxamide group on the sp-hybridised carbon atom of the carbodiimide moiety to give (3)[2]. This assumption is supported by two facts: a) when iminophosphoranes derived from N,N-disubstituted o-azidobenzamides were used, the reaction with aryl isocyanates led to the corresponding (o-carboxamido)phenyl-aryl carbodiimides and b) the iminophosphorane derived from o-azidobenzamide was converted into the corresponding o-ureido benzonitrile. Although reaction of carbodiimides with carbono-

hydrazide[3] and thiocarbonohydrazide[4] have been reported, to our knowledge this is the first example reported of heterocyclization based on the reaction of carbodiimides with carboxamides.

This approach has also shown to be useful for the preparation of the otherwise not readily available benzimidazo[1,2-c]quinazoline ring system. Thus, iminophosphorane (6) readily available from o-azidobenzoic acid by sequential treatment with o-phenylendiamine and triphenylphosphine, reacts with aromatic isocyanates in dry dichloromethane at room temmperature to give 6-arylamino benzimidazo[1,2-c]quinazolines (8) in good yields. Similarly, compoud (7) reacts with carbon dioxide and carbon disulphide to give (9) and (10) respectively in high yields.

The above method has the advantage of the easy accesibility of starting materials, mild reaction conditions, good yields in the iminophophorane preparation as well as in the cyclization step, and versatility for the introduction of different substituents (arylamino, carbonyl and thiocarbonyl) at position 2 of the pyrimidine ring. Application of this annulation approach to a number of other quinazoline derivatives can be anticipated.

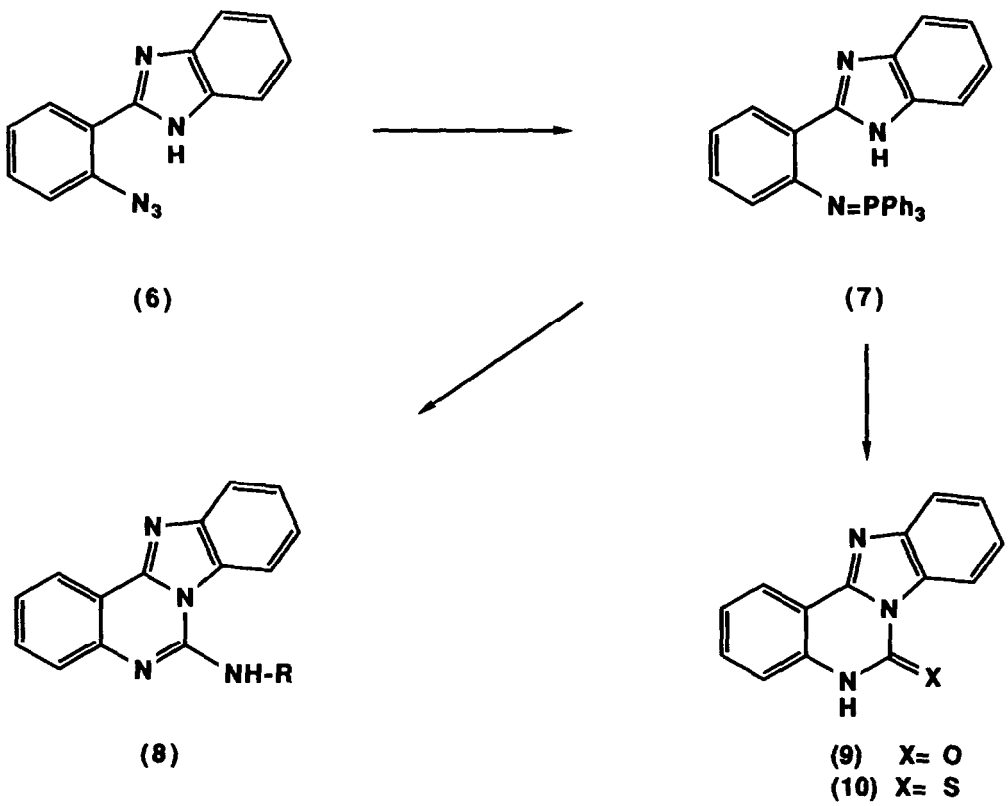


Table. Quinazolines [(3)-(5)] and Benzimidazo[1,2-c] quinazolines [(8)-(10)].

Compound[a]	R^1	R^2	Yield (%)	m.p. (°C)
3a	CH_3	4-CH_3O-C_6H_4	96	233-234
3b	CH_3	4-Cl-C_6H_4	98	186-187
3c	4-CH_3-C_6H_4	CH_3	93	158-160
3d	4-CH_3-C_6H_4	4-CH_3O-C_6H_4	98	156-158
4a	CH_3		96	248-250
4b	4-CH_3-C_6H_4		84	267-268
5a	CH_3		93	274-275
8a	C_6H_5		84	322-323
8b	4-CH_3O-C_6H_4		74	250-251
8c	3-CH_3-C_6H_4		86	254-255
9			76	334-335
10			71	308-310

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

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REFERENCES.

1. P. Molina, A. Arques, V. Vinader, J. Becher, and K. Brondum, Tetrahedron Lett., 1987, 4451;
P. Molina, P.M. Fresneda, and P. Alarcon, Tetrahedron Lett., 1988, 379.
2. M.P. Groziak, J.W. Chern, and L.B. Townseud, J. Org. Chem., 1986, 51, 1065.
3. F. Kurzer, and M. Wilkinson, J. Chem. Soc. (C), 1970, 19.
4. F. Kurzer, and M. Wilkinson, J. Chem. Soc. (C), 1986, 2099.

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