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PYRAZOLOPYRIDAZINONES BY 1,3-DIPOLAR CYCLOADDITION OF DIAZOMETHANE TO PYRIDAZIN-3(2H)-ONES

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Abstract - N-methylpyridazin-3(2H)-ones 1-3 react slowly with diazomethane to give, as main products, the N,N'-dimethylpyrazolo [3,4-d] pyridazin-4(5H)-ones 10a and 10b in a 1 : 2 ratio. The reaction of diazomethane with the N-methyl-4-bromopyridazin-3(2H)-one (4) leads to N^1,N^6-dimethylpyrazolo [3,4-d] pyridazin-7(6H)-one (9a). In the first case, the regioselectivity of the primary 1,3-dipolar cycloaddition is the reverse of that observed in enone systems.

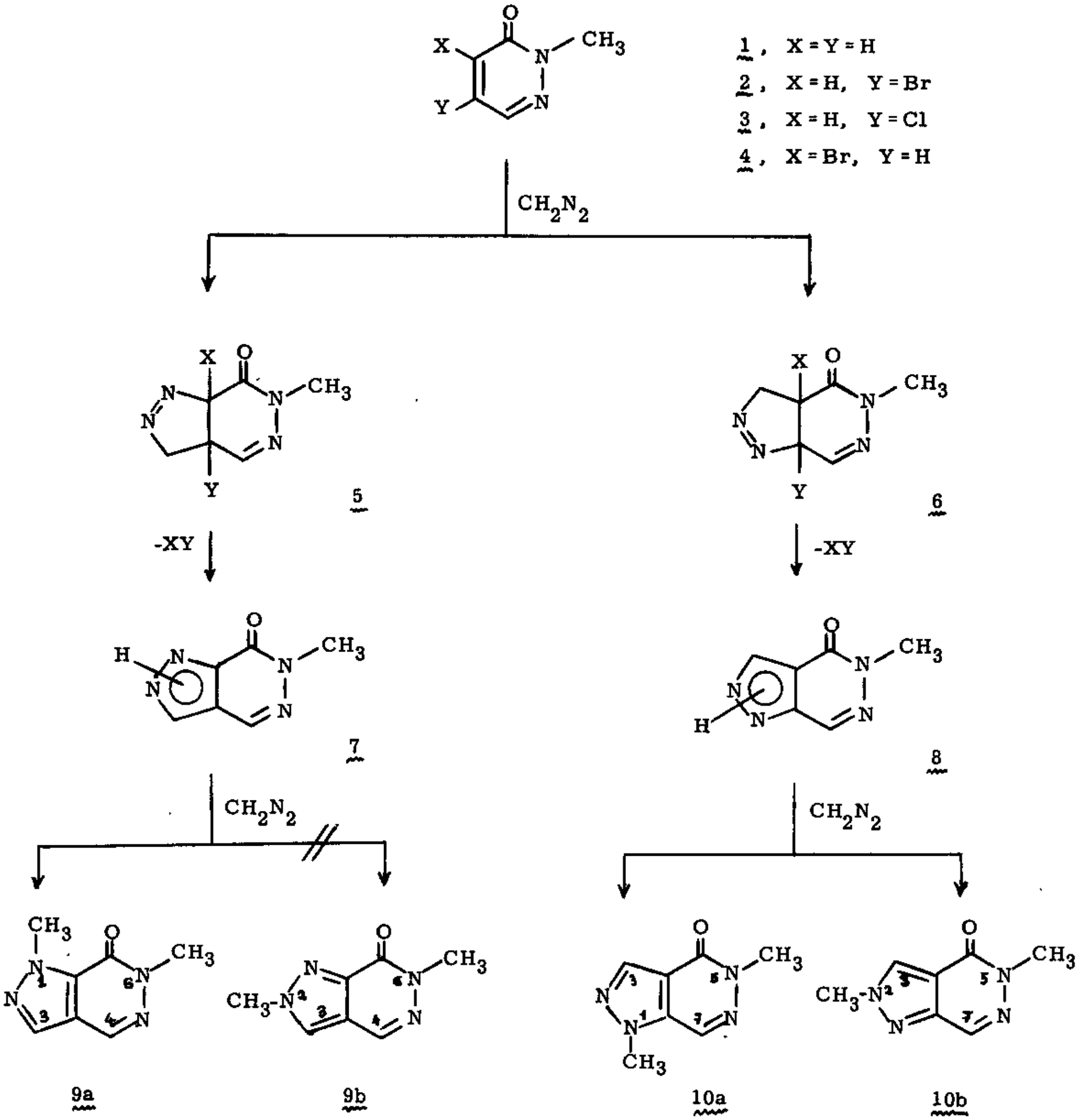
While 1,3-dipolar cycloaddition of diazoalkanes to substituted alkenes and alkynes has been extensively investigated[1,2,3], very little is known about the reaction with heterocyclic dipolarophiles. However, examples are described in which the cycloaddition to a pyridone[4] and a pyridazinone[5] are claimed as the first step in a C-alkylation or ring-expansion procedure, respectively.

The 1,3-dipolar cycloaddition of diazoalkanes to pyridazinones may be of theoretical and practical interest. In principle, pyridazinones could act as dipolarophiles through the α,β-unsaturated carbonyl system, although the presence of heteroatoms and the partial aromatic character of the heterocycle could substantially modify the reactivity and the expected regioselectivity. From a synthetic point of view a direct cycloaddition of diazoalkanes to the pyridazinones would lead to pyrazolopyridazinone derivatives of recent interest owing to their potential pharmacological activity[6].

In this paper we present results which provide information regarding the behaviour of simple N-methylpyridazin-3(2H)-ones (1-4)[7] as dipolarophiles in 1,3-dipolar cycloaddition to diazomethane[8].

In a typical procedure, the N-methylpyridazin-3(2H)-one (5 mmol), dissolved in methanol (20 ml), and 30 ml of ethereal diazomethane (20 mmol) were allowed to react at 0°C for 15-90 days. Further additions of diazomethane solution were made, if necessary, in order to maintain an excess of this reagent. The progress of the reaction was monitored by t.l.c. and ^{1}H-n.m.r.

The reaction of the parent N-methylpyridazin-3(2H)-one (1) with diazomethane proceeds



slowly and after 15 days the starting material disappears and three new compounds are formed in 90 % yield. The analytical and spectral data of the mixture indicate that the three compounds are isomeric *N*,*N*'-dimethylpyrazolopyridazinones. The products can be accounted for satisfactorily in terms of initial formation of the cycloadducts 5 and/or 6, which undergo aromatisation to 7 and/or 8, followed by methylation to the *N*,*N*'-dimethylated derivatives.

The main components of the mixture, which appear in an approximate ratio of 1 : 2 (by ^{1}H-n.m.r.), are obtained in pure form by recrystallization from ethanol and identified as 10a and 10b by comparison of the melting points, i.r. and ^{1}H-n.m.r. spectra with those previously described by Marquet et al.[9] Further confirmation was provided by the fact that the physical and spectral data of the compounds differ significantly from those of the isomers 9a and 9b prepared by the procedure described by us[6]. The minor component (~10%) was not isolated, but the ^{1}H-n.m.r. spectrum from the crude mixture includes signals identical to those of an authentic sample of 9a[6].

The physical and spectral data for compounds 9a,b and 10a,b are summarized in the Table. The ^{1}H-n.m.r. spectral data for compounds 10a and 10b are in accord with those previously reported[9]. We have made, however, unambiguous assignments by comparison of the spectra of both compounds with those of the adducts obtained by reaction with deuterated diazomethane. Further evidence of the structure and assignments in compounds 9b and 10b is provided by the fact that the H-3 pyrazole proton is long-range coupled (J ~ 0.5 Hz) with the NMe-2 protons.

Table : Physical and spectral data for *N*,*N*'-dimethylpyrazolo [3,4-*d*] pyridazinones

Compound nº	m.p. °C	IR[a] CO	UV[b]	^{1}H-n.m.r.[c] H-3	H-4 (H-7)	NMe-1 (NMe-2)	NMe-5 (NMe-6).
9a	157	1655	266	8.12[d]	8.35	4.29[d]	(3.71)
9b[e]	215	1650	267	8.30	8.46	(4.28)	(3.74)
10a	229	1650	281	8.26[d]	(8.65)	4.10[d]	3.71
10b	178	1660	278	8.75[d]	8.42	(4.13)[d]	3.65

[a] In nujol mulls. [b] In ethanol solution. [c] In DMSO-d_6 solution, using TMS as internal standard. [d] Disappears in the deuterated compound. [e] Data from reference[6].

The formation of 10a and 10b as main components demonstrate that the 1,3-dipolar cycloaddition of diazomethane to pyridazinone 1 is regioselective, yielding preferentially the adduct 6. The orientation is, however, the opposite of that commonly observed in the reaction with α,β-unsaturated carbonyl compounds.

A similar result is found in the cycloaddition of diazomethane to the 5-halogenated pyridazinones. In this case, however, the reactivity of 2 and 3 is somewhat lower and after 15 days only a 40-50% of the dipolarophile is transformed. After 30 days, the reaction is complete and leads to a mixture of 10a and 10b (in ca. 1 : 2 ratio)[10], which arise by dehydrohalogenation of the primary adducts 6 (X = H, Y = Br, Cl) followed by *N*-methylation.

In contrast, 1,3-dipolar cycloaddition of diazomethane to *N*-methyl-4-bromopyridazin-3(2*H*)-one (4) proceeds extremely slowly and affords N^1,N^6-dimethylpyrazolopyridazin-7(6*H*)-one 9a as the sole product, identified by comparison with an authentic sample[6].

This result indicates that the halogen in the 4-position reverses the regiochemistry observed in pyridazinones 1 - 3 and tends to make the reaction less favorable.

In summary, the regiochemistry of the 1,3-dipolar cycloaddition of diazomethane to pyridazinones 1-3 is the reverse of that observed using enones as dipolarophiles. Similar results have been reported for tropone[11] and the opposite orientation is interpreted in terms of the reverse absolute values of LUMO coefficients at the α,β positions of tropone and unsaturated ketones. Furthermore, the fact that in our case a bromo substituent in 4-position reverses the orientation found in pyridazinones 1 - 3, parallels the results described in the respective halotropones[12].

Further work in this area is in progress.

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