

SYNTHESIS OF ORIGINAL PYRROLONAPHTHYRIDINES BY 1,3-DIPOLAR CYCLOADDITION REACTIONS OF NAPHTHYRIDINIUM DICYANOMETHYLIDES WITH DIMETHYL ACETYLENE-DICARBOXYLATE

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Abstract- The pyrrolo[2,1-*f*][1,6]naphthyridine, pyrrolo[1,2-*a*][1,8]- and [1,5]naphthyridines along with their corresponding 2,3- and 1,2-dihydrocompounds are synthesized from naphthyridinium dicyanomethylides and dimethyl acetylenedicarboxylate.

The 1,3-dipolar cycloadditions¹ are of great interest in organic chemistry for their ability to provide in good yield a variety of 5-membered heterocyclic compounds. Thus, ylide of tertiary nitrogen base may react as 1,3-dipole and cyclise with dipolarophiles.² In continuation of our studies on nitrogen bridgehead heterocycles,³ we report here the application of such reaction to [1,5],[1,6] and [1,8]naphthyridines to obtain original heterocyclic systems.⁴

The naphthyridines (**1a,b**)⁵ react with tetracyanoethylene oxide (TCNEO) in THF to give the corresponding dicyanomethylides (**2a,b**). The ir spectrum of these compounds exhibit a characteristic strong doublet nitrile absorption at 2135, 2165 cm⁻¹ for **2a**, consistent with a dicyanomethylide structure.²

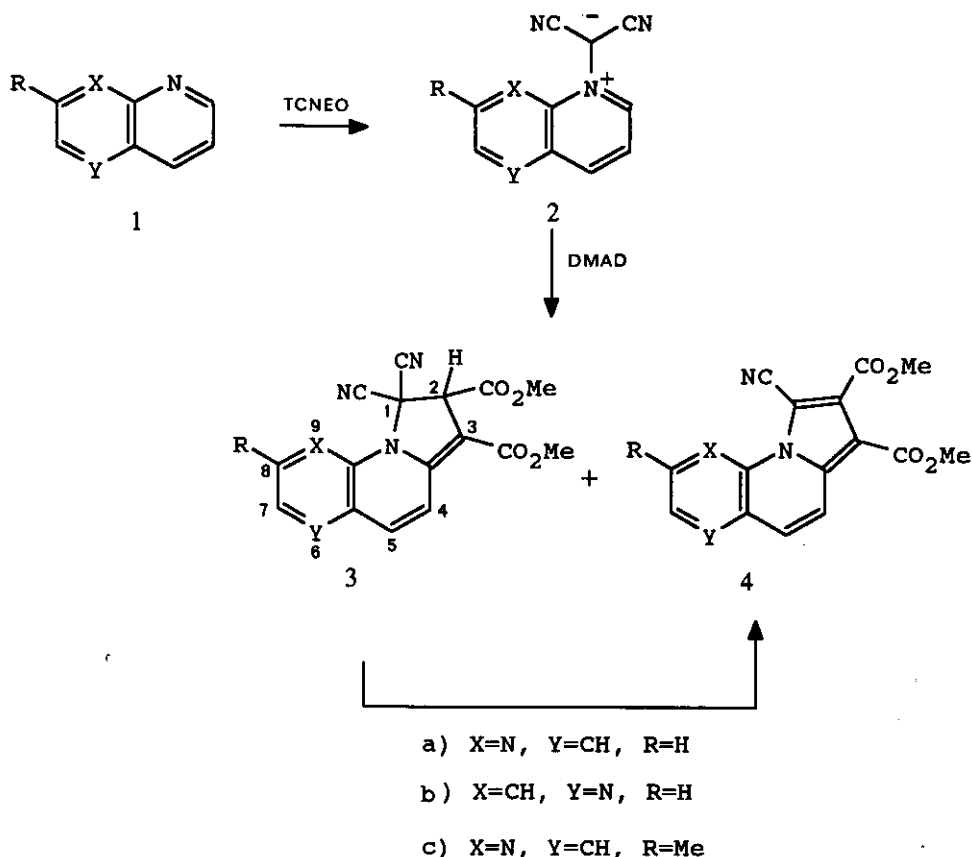
Reaction of dimethyl acetylenedicarboxylate (DMAD) with naphthyridinium methylide (**2a**) in acetonitrile afforded the dihydrocycloadduct (**3a**) and the aromatic derivative (**4a**). The compound (**3a**) was aromatized by elimination of HCN with alumina in methylene chloride to give **4a**. Reaction of the dicyanomethylide (**2b**) with DMAD lead only to **4b**.

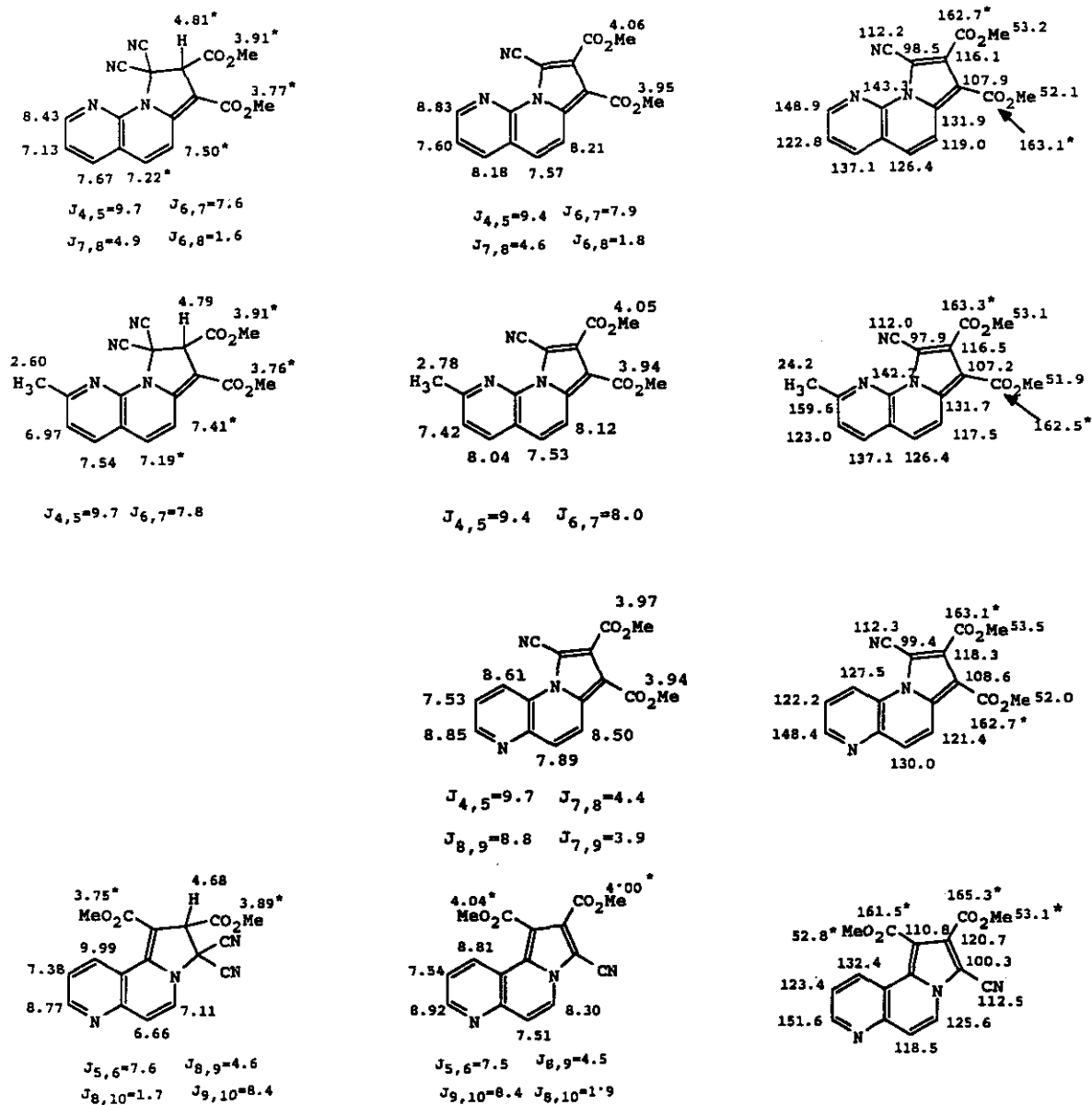
Diez-Barra *et al.*⁶ have showed that two main factors determine the reactivity of heterocycles toward

TCNEO: the nucleophilicity of the nitrogen atom and the steric hindrance around it. For six membered and benzocondensed systems the second factor is preponderant.

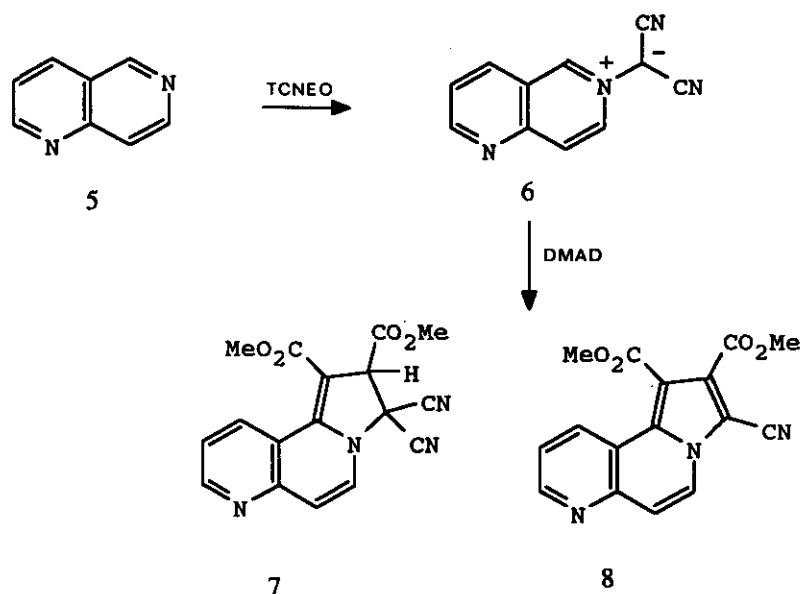
In an other way, it was reported that the reaction of dicyanomethylide of 3,6-dimethylpyridazine was cyclized with DMAD with loss of a methyl group.⁷ So it is interesting to study the reactivity of 2-methyl[1,8]naphthyridine. The 1,3-dipolar cycloaddition of the dicyanomethylide (2c) with DMAD gave methyl heterocycles (3c) and (4c). These results showed that ylide was formed at N-8 according the precedent results.

The ¹H and ¹³C nmr data of compounds (3,4,7 and 8) are given in Figure 1:⁸ Thus, on the base of the pyrrolic proton and its chemical shift, compounds (3) are identified to proton migration products of the primary adducts.⁹ The assignments for compounds (4,7, and 8) were made from ¹H-¹H COSY and XH HETCOR. Finally, the methyl protons and carbons are discriminated from a NOE DIFF experiment.



Figure 1: ¹H and ¹³C-nmr data for compounds (3,4,7 and 8).

In order to study orientation in 1,3-dipolar cycloaddition on asymmetric naphthyridine, we applied the previous synthetic method to [1,6]naphthyridine. The addition of DMAD with the N-6 dicyanomethylide of [1,6]naphthyridinium prepared as previously reported¹⁰ can occur at C-5 or C-7. This reaction afforded after flash chromatography on silica gel two compounds (7) and (8) in 23 and 44% yield, respectively. The mass spectrum of 8 indicates an aromatized structure with a parent peak at $m/z = 309$. In ^1H nmr spectrum two doublets at δ 8.30 and 7.51 with a J value of 7.6 Hz established a C-5 cyclization. Examination of the mass spectral fragmentation pattern of 7 gave its molecular weight (M^+) at 336 with an easy loss of HCN ($M^+ - 27$) showed a dihydroadduct structure identified by nmr to dimethyl 3,3-dicyano-2,3-dihydropyrrolo[2,1-*f*]-[1,6]naphthyridine-1,2-dicarboxylate.



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