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ETHYL CYANOACETATE AS 1,3-BIFUNCTIONAL REAGENT IN THE PYRIMIDINE TO PYRIDINE RING TRANSFORMATIONS

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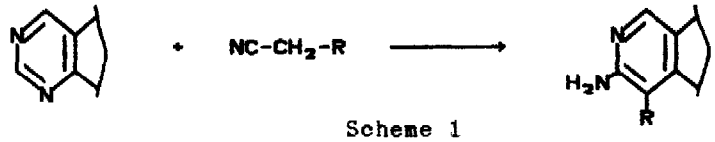
Abstract: By using of the double-labelled $C^*N^*-CH_2-COOEt$ compound it has been proved that transformation of 6-nitro-1,2,4-triazolo[1,5-a]pyrimidine into 2-triazolylamino-3-carbethoxy-5-nitropyridine proceeds with incorporation of the C-C-N fragment of ethyl cyanoacetate into the pyridine ring.

It is known that pyrimidines activated for a nucleophilic attack either by the quaternary nitrogen atom or by introducing the nitro group in the ring are easily transformed by action of CH-active acetonitriles into 2-aminopyridines.[1,2] Similar pyrimidine to pyridine ring transformations have been observed to take place in reactions of pteridines,[3] purines and 8-azapurines[4] with acetonitrile derivatives. (Scheme 1). It is remarkable that in all these reactions the $N_{(1)}-C_{(2)}$ part of the pyrimidine ring is substituted by the C-C fragment of acetonitrile employed.

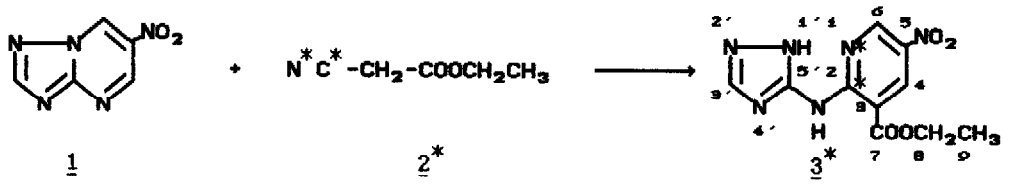


Scheme 1

We have discovered that ethyl cyanoacetate can act as 1,3-bifunctional nucleophile donating its C-C-N fragment into the forming pyridine ring in the course of the transformation of 6-nitro-1,2,4-triazolo[1,5-a]pyrimidine 1 into 2-triazolylamino-5-nitropyridine 3 (Scheme 2).[5,6] Indeed, the reaction of triazolopyrimidine 1 with the double-labelled ethyl cyanoacetate 2* containing approximately 70% excess of both ^{13}C and ^{15}N isotopes in the cyano group resulted in the compound 3* in which the N-1 and C-2 atoms of the pyridine ring proved to have the same percentage of excess of ^{15}N and ^{13}C respectively (Scheme 2).

Evidence for the structure 3 has been obtained by X-ray crystallography analysis.[6] Convincing arguments that all excess of ^{15}N and ^{13}C isotopes is present in the pyridine ring is provided by the ^{13}C NMR spectra[7] of the compound 3*. The enhanced intensity of the C-2 signal as well as a

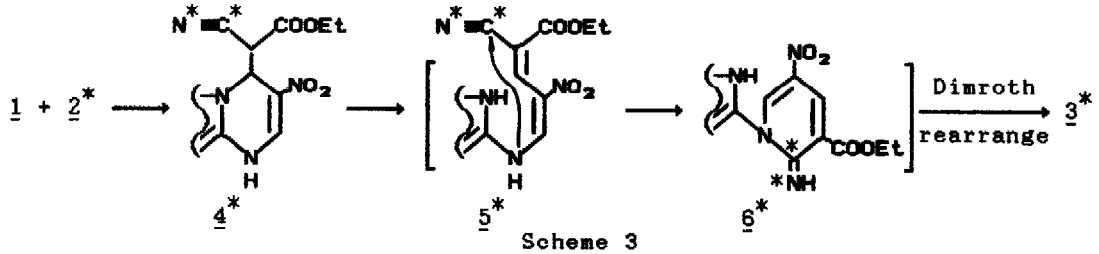
number of characterictic J(^{13}C, ^{13}C) and J(^{13}C, ^{15}N) coupling constants ^{1}J(C-2, C-3), ^{1}J(C-2, N-1), ^{1}J(C-6, N-1) are very indicative. Alternative position of the ^{15}N isotope label in the exocyclic amino group must be excluded since no coupling constant between C-5 of the triazole ring and nitrogen-15 has been observed.



Scheme 2

Thus, the reaction discovered is a novel type of the pyrimidine to pyridine ring transformation (Scheme 3) and, as far as we know, it is the first example when ethyl cyanoacetate reacts as the 1,3-C,N-bifunctional nucleophilic reagent.

The data obtained allow us to suggest that the reaction is initiated by the formation of σ-adduct 4* registered by ^{1}H NMR followed by the conversion into 3* through intermediates 5* and 6* (Scheme 3).



Scheme 3

References and Notes

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6. V.L. Rusinov, T.L. Pilicheva, A.A. Tumashov, G.G. Alexandrov, E.O.Sidorov, I.V. Karpin, O.N. Chupakhin, ibid., in press.
7. The ^{13}C NMR spectral data for 3* in DMSO-d_6: C-2 156.21 (d, ^{1}J(C/N)= =3.7 Hz), C-3 108.29 (dd, ^{1}J(C/C)=65.3 Hz, ^{2}J(C/N)=1.8 Hz), C-4 135.74 (s), C-5 137.92 (m), C-6 149.31 (d, ^{1}J(C/N)=3.7 Hz), C-7 166,06 (d, ^{2}J(C/C)=3 1 Hz), C-8 63.34 (s), C-9 14.18 (s), C-3' 148.52 (s), C-5' 150.67 (s).

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