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ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS OF 4-AZOLOYL-2-AMINOQUINOLINES

Fathy M. ABDEL-GALIL, Bahia Y. RIAD, Sherif M. SHERIF and Mohamed H. ELNAGDI*

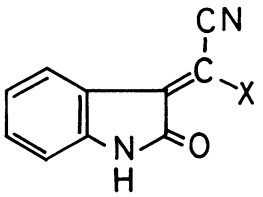
Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R. Egypt

A novel synthesis of 4-azoloyl-2-aminoquinolines via the reaction of the 3-cyanomethylene derivatives of isatin with the 2-pyrazolin-5-one derivatives and 2-ethoxycarbonylmethyl-2-thiazolin-4-one is reported.

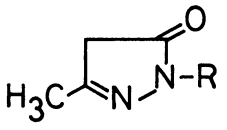
The considerable biological and medicinal activities of quinoline derivatives in the past times have stimulated considerable research in this field.[1,2] As a part of a programme directed for exploring the synthetic potentiality, scope, and limitation of activated nitriles in heterocyclic synthesis[3,4] we report here a novel synthesis of 4-azoloyl-2-aminoquinolines via the reaction of 3-cyanomethylene derivatives of isatin (Ia,b) with the 2-pyrazolin-5-one derivatives (IIa,b). The compounds obtained possess latent functional substituents and appear promising for further chemical transformations.[5] Moreover, they are of interest for biological studies.

Thus, in a typical procedure, equimolar amounts (20 mmoles) of Ia and the 3-methyl-2-pyrazolin-5-one derivatives (IIa,b) are refluxed in ethanol (30 ml) in the presence of catalytic amounts of triethylamine for 2-3 hrs. Removal of ethanol and trituration with water affords products of molecular formulas corresponding to addition of IIa,b to Ia.

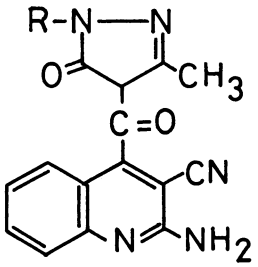
We took six alternate theoretically possible structures into consideration (cf. structures III - VIII and Table 1). Structure III was readily established for the reaction products based on the IR and ^{1}H-NMR data which revealed quinoline H-5 at a much lower field (δ 8.5 ppm) than that anticipatable for structures IV - VIII. Moreover, the IR spectra revealed absorptions corresponding to NH_2, CN, and two CO



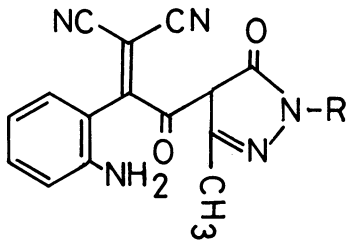
Ia, X = CN
b, X = CO_2Et



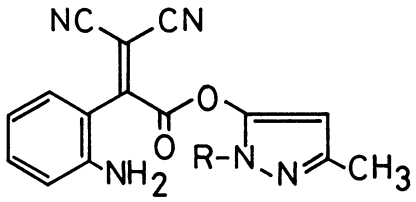
IIa, R = H
b, R = Ph



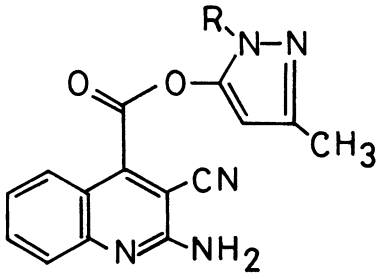
IIIa, R = H
b, R = Ph



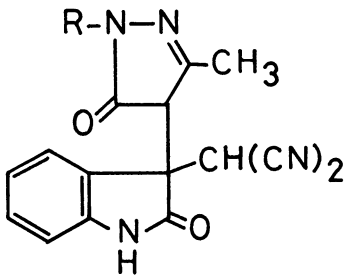
IV



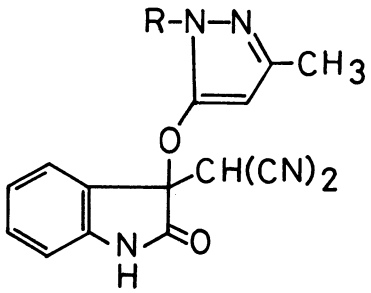
V



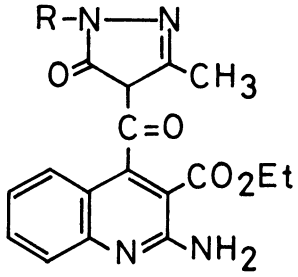
VI



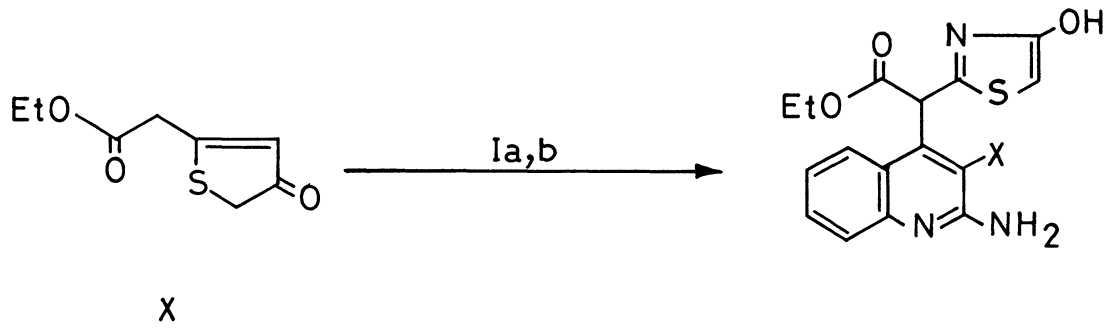
VII



VIII



IXa, R = H
b, R = Ph



XIa, X=CN
b, X=CO_2Et

Table 1. 4-Azoloyl-2-aminoquinoline derivatives IIIa,b, IXa,b and XIa,b

Compound*	Cryst. Solvent	M.p. [°C]	Yield [%]	Mol. Formula
IIIa	Ethanol	285-286	69	$C_{15}H_{11}N_5O_2$
IIIb	Ethanol/H_2O	219	70	$C_{21}H_{15}N_5O_2$
IXa	Ethanol	281-283	74	$C_{17}H_{16}N_4O_4$
IXb	Ethanol	235	65	$C_{23}H_{20}N_4O_4$
XIa	Ethanol	260-261	82	$C_{18}H_{14}N_4O_4S$
XIb	Acetic acid	276-277	71	$C_{20}H_{19}N_3O_6S$

*) Satisfactory elemental analyses for all the newly synthesised compounds were obtained.

groups (1680 and 1640 cm^{-1}) as required by structure III. The formation of IIIa,b from the reaction of IIa,b with Ia is assumed to proceed via the reaction of the active methylene in IIa,b with Ia to yield the acyclic intermediate IV which is then readily cyclised into the final isolable product III. The rearrangement of isatin into quinolines via the reaction with ketones is a well known reaction.[6]

Also rearrangement of Ia into quinolines via reaction with diazo compounds has been reported.[7] However, to our knowledge this is the first reported conversion of indoles into quinolines via similar route.

In a fashion similar to the behaviour of Ia towards IIa,b, compound Ib reacted with IIa,b to yield the quinoline derivatives IXa,b.

Compounds Ia,b also reacted with 2-ethoxycarbonylmethyl-2-thiazolin-4-one (X) to yield 1:1 adducts. Several theoretically isomeric structures were considered; however, structure XI could only be intelligibly interpreted for this structure.

Now the behaviour of Ia,b towards a variety of other active methylene reagents is under investigation. Results will be included in another communication.[5]

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