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An efficient, highspeed synthesis of pyrazolo[4,5-c] quinolines

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ABSTRACT

4-Chloro-3-cyanoquinolin-2-ones cyclised with substituted hydrazines in a facile manner to give 3-amino(1H)pyrazolo[4,5-c]quinolin-4(5H)ones in very good yields.

KEYWORDS

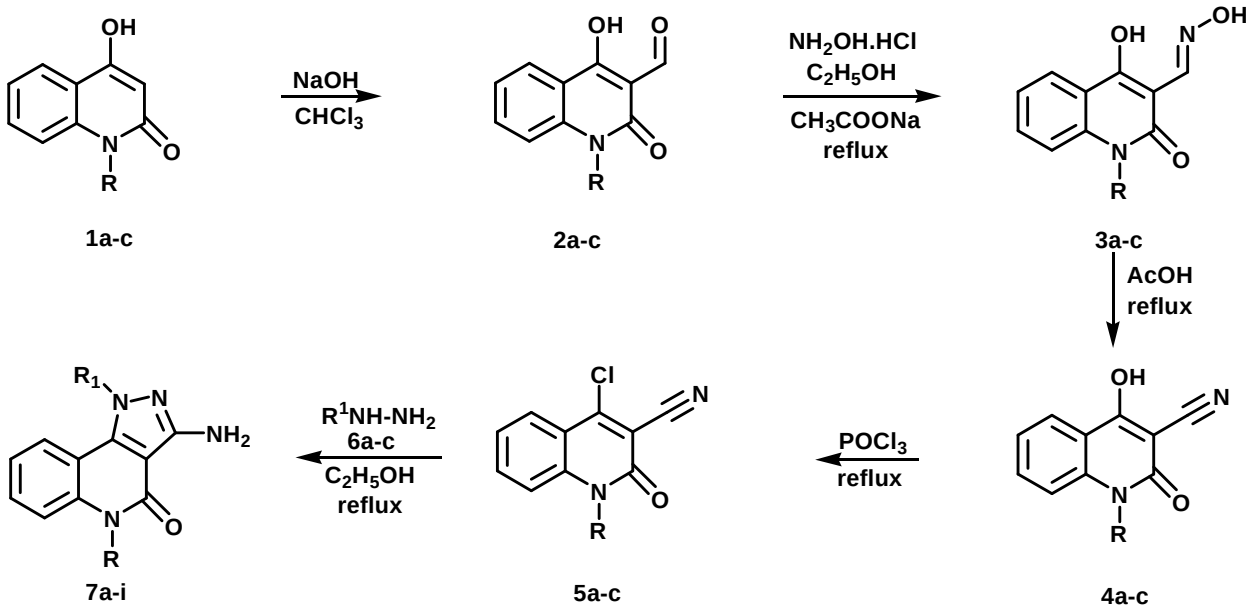
4-Chloro-3-cyanoquinolin-2-ones;
3amino(1H)pyrazolo[4,5-c]quinolin-4(5H)ones;
Substituted hydrazines.

INTRODUCTION

Recently the quinolines have emerged as an area of intense interest because of their varied physiological activities. Several quinolines like Ciprofloxacin and Norfloxacin are already in clinical use for more than two decades, with high chemotherapeutic relevance. The recent development of new fluoroquinolones effective against *Streptococcus pneumoniae* is a potentially important advance in the management of pneumococcal infections. Several of these agents are more active than ciprofloxacin and have been either approved or are in the final stages of clinical trials, including levofloxacin, sparfloxacin, and clinafloxacin. All these compounds are considered to act by blocking DNA synthesis. Hence they are effective against both penicillin-sensitive and penicillin-resistant organisms[1-5]. Pyrazoles also exhibit interesting anti inflammatory activity[6,7] and are already in clinical use for their efficient medicinal properties. Many pharmaceutical compositions containing pyrazoloquinolones were prepared for use as tranquilizers, anti-tumor, anti-cancer, anti-depressants, anti-inflammatories, anti-psoriatics, anti-convulsants and anxiolytic drugs[6-14]. This observation prompted us to work in this area[15-20] and to report the high-speed synthesis of pyrazolo quinolinones.

For this purpose 4-chloro-3-cyanoquinolin-2(1H)ones (5) and N-substituted hydrazines have been selected as suitable starting materials. The readily displaceable chlorine and the reactive cyano group in the adjacent position in 4-chloro-3-cyanoquinolin-2(1H)ones can be utilized for building up the pyrazolo[4,5-c]quinoline system. For the synthesis of 4-chloro-3-cyanoquinolin-2(1H)ones (5), 4-hydroxyquinolin-2(1H)ones (1) are formylated to the respective 3-formyl-4-hydroxyquinolin-2(1H)-ones (2), by Reimer- Tiemann reaction[21] which are then converted to corresponding aldoximes (3). 3-Aldoximino-4-hydroxyquinolin-2(1H)ones (3) are converted to 3-cyano-4-hydroxyquinolin-2(1H)ones (4) which are finally treated with $POCl_3$ to give 3-cyano-4-chloroquinolin-2(1H)ones(5). Scheme 1.

A one pot synthesis of 3-amino-pyrazolo[4,5-c]quinolin-4(5H)ones(7) was designed and developed by condensing 4-chloro-3cyanoquinolin-2(1H)ones(5) with hydrazines(6). Scheme 1.



a b c

(1-5) R = CH_3 C_2H_5 C_6H_5

7	a	b	c	d	e	f	g	h	i
R	CH_3	C_2H_5	C_6H_5	CH_3	C_2H_5	C_6H_5	CH_3	C_2H_5	C_6H_5
R^1	H	H	H	CH_3	CH_3	CH_3	C_6H_5	C_6H_5	C_6H_5

Scheme 1

EXPERIMENTAL

The infrared spectra were obtained in KBr on Shimadzu 435 instrument. Positions of absorptions are quoted to ± 2.5cm^{-1}. The proton magnetic resonance spectra were recorded on JOEL (200 MHz), Bruker (300 MHz) spectrophotometers and ^{13}C NMR spectra were recorded on Bruker(100.40 MHz) and JOEL(50 MHz) spectrophotometers with TMS as internal standard. The chemical shift values are given in ppm (δ) and coupling constants in Hertz. The mass spectra were recorded on Perkin-Elmer Hitachi RMU-6L and VG-Micro Mass 7070H instrument of direct inlet probe.

As a representative case, an equimolar mixture of 3-formyl-4-hydroxy-1-methylquinolin-2(1H)-one (2a) and hydroxylamine hydrochloride is refluxed in absolute ethanol, in the presence of anhydrous sodium acetate for 30 minutes. The resulting compound (m.p.196-7^{0}c) has been identified as 4-hydroxy-1-methyl-3-aldoximinoquinolin-2(1H)one (3a) from its spectral characteristics viz., molecular ion at m/z 218 in the mass spectrum and the presence of oxime-OH and 4-OH (around 3200 cm^{-1})>N-C =O (1630 cm^{-1}) and >C=N (1600 cm^{-1}) groups in the IR spectrum.

3-Aldoximino-4-hydroxy-1-methylquinolin-2(1H)-one (3a) on refluxing in acetic acid for 3 hours offered a crystalline compound (TLC single spot) m.p. 290-2^{0}c. Mass spectrum of the compound showed the molecular ion peak at m/z 200. IR spectrum (KBr) displayed absorptions at 1640cm^{-1} due to >N-C=O, 2200 cm^{-1}due to –CN and 3100 cm^{-1} due to –OH groups. With the aid of above spectral data, the structure of the compound is assigned as 3-cyano-4-hydroxy-1-methylquinolin-2(1H)-one (4a), which is also been prepared directly by refluxing an equimolar mixture of 3-formyl-4-hydroxy-1-methylquinolin–2(1H)one (2a), hydroxylamine hydrochloride and anhydrous sodium acetate in acetic acid. In this procedure the yield is considerably low (40%) when compared with the earlier method (80%).

Treatment of 3-cyano-4-hydroxy-1-methylquinolin-

2(1H)one (4a) with excess $POCl_3$ for 10 hours resulted in the formation of a crude product, which was purified by column chromatography (yield 60%), m.p. 220-222^{0}c. Analysis of Mass, IR, and ^{1}H NMR spectra of the compound helped in identifying it as 4-chloro-3-cyano-1-methylquinolin-2(1H)one (5a). Mass spectrum displayed the molecular ion at m/z 218 (100%), along with a (M+2) peak at m/z 220 (30%). IR spectrum (KBr) showed signals at 2250 (CN), 1640(N-C=O) and 760 cm^{-1} (C-Cl); ^{1}H NMR spectrum ($CDCl_3$) revealed resonances at δ3.80 (s, 3H, N-CH_3), δ7.20-7.90 (m, 3H, arom.H), and δ8.10 (dd, 1H, H-5).

1-Ethyl and 1- phenyl-4-chloro-3-cyanoquinolin-2(1H)-ones (5b, c) have also been synthesized from the corresponding 4-hydroxyquinolin-2(1H)ones, following the same sequence of reactions described above. The structures of these compounds have been adequately supported by IR, ^{1}H NMR and mass spectra.

4-Chloro-3-cyano-1-methylquinolin-2(1H)one (5a) was treated with N-methyl hydrazine (6b) in refluxing dry ethanol. Colourless crystalline compound that separated from the reaction mixture within few minutes was filtered, dried and purified by recrystallisation from chloroform. TLC of the compound showed a single spot with benzene:ethyl acetate solvent mixture (5:1), m.p.239-40^{0}c. Test for extra elements revealed the presence of only nitrogen and the absence of any halogen (chlorine) in the compound. Mass spectrum recorded the molecular ion at m/z 228 (M^+ 100%). Micro analytical data corresponded to the molecular formula $C_{12}H_{12}N_4O$.

The electronic spectrum revealed the absorption maxima atλ_{max} nm (log E) 250 (4.078), 307 (4.001), 337 (3.618) indicating the presence of benzenoid and quinolone chromophores. IR spectrum (KBr) displayed absorptions due to stretching frequencies of N-C=O at 1630cm^{-1}, an intense stretching at 1600cm^{-1} due to C=N group and a neat doublet due to NH_2 around 3300cm^{-1}. Absence of absorptions due to C-Cl (at 760 cm^{-1}) and CN (at 2250 cm^{-1}) indicate that the two groups have involved in the reaction, thus clearly indicating the formation of the compound having structure **(7d)**.

The fragmentation pattern in mass spectrum supported the assigned structure. The molecular ion (M+ m/z 228) itself was the base peak reflecting the stability of the molecule.

A satisfactory ^{1}H NMR spectrum could not be obtained due to insolubility of the compound in most of the organic solvents. However in the ^{1}H NMR spectrum (C_6D_6) the N-methyl protons were resonating as singlets at δ3.26 (N_1-CH_3) and at δ3.52 (N_5-CH_3) and the aromatic protons of were resonating at δ7.20-7.60 (multiplet).

RESULTS AND DISCUSSIONS

4-Chloro-3-cyanoquinolin-2-ones cyclised with substituted hydrazines to give 3-amino(1H) pyrazolo[4,5-c] quinolin-4(5H)ones in very good yields.

Other substituted 4-chloro-3cyanoquinolin-2(1H)-ones **(5a-c)** have also been condensed with hydrazines **(6a-c)** in refluxing ethanol, resulting in all the cases the corresponding amino(1H)pyrazolo[4,5-c]quinolin-(5H)ones **(7a-i)**, justifying the generality of the synthesis. The yields in these reactions are in the range of 80-90%. The structures of these compounds **(7a-i)** are adequately supported by UV, IR and Mass spectral data.

Nucleophilic attack of hydrazine on the electron deficient carbon (C_4) of 4-chloro-3-cyanoquinolin-2(1H)one(5) and simultaneous expulsion of the chloride ion resulting in the formation of unstable 3-cyano-4-methylhydrazino quinolone intermediate. The second step involves the addition of the amino group to the cyano group forming the unstable cyclic imino intermediate, which finally underwent aromatisation to form the 3-amino(1H)pyrazolo[4,5-c]quinolin-4(5H)one(7).

CONCLUSIONS

4-Chloro-3-cyanaoquinolin-2(1H)-ones are highly reactive towards hydrazines, and readily underwent cyclisation to furnish 3-amino(1H)pyrazolo-[4,5-c]quinolin-4(5H)ones in very good yields (80-90%).

These reactions are quite fast, carried out under simple laboratory conditions and involve nucleophilic substitution, followed by cyclisation accompanying the

nucleophilic addition, furnishing the title compounds in a single step.

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