

Potassium carbonate catalysed synthesis of 1*H*-pyrazolo[3,4-*b*]-quinolines from 2-chloroquinolin-3-carbaldehyde

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Abstract

An efficient, environmentally benign, and operationally simple method was developed for the synthesis of a series of 1*H*-pyrazolo[3,4-*b*]quinoline derivatives (2a-h), as illustrated in (Scheme 7 and Table-1). The desired compounds were obtained through the reaction of various 2-chloroquinoline-3-carbaldehyde derivatives (1a-h) with hydrazine hydrate. The reactions were investigated under reflux temperature, using ethanol as a relatively green and environmentally friendly solvent and potassium carbonate as the catalyst. The synthetic transformation proceeded through the condensation of the aldehyde functionality with hydrazine hydrate, followed by intramolecular cyclization to afford the corresponding fused 1*H*-pyrazolo[3,4-*b*]quinoline framework. The use of ethanol as the reaction medium, and potassium carbonate as catalyst provides a convenient and environmentally benign approach to these heterocyclic compounds. The method was applicable to a range of substituted 2-chloroquinoline-3-carbaldehydes, allowing the preparation of compounds 2a-h in a straightforward manner. All synthesized compounds were unequivocally characterized using appropriate analytical and spectroscopic data, confirming their structures and purity. The results demonstrate that this methodology provides a simple and efficient route for the preparation of structurally diverse 1*H*-pyrazolo[3,4-*b*]quinoline derivatives

Introduction

Quinolines¹⁻³ constitute an important class of heterocyclic compounds with diverse biological properties. Several quinoline derivatives have been investigated for their potential biological activities, including bactericidal,⁴ antitumor,⁵ anti-inflammatory,⁶ and antimalarial⁷ effects. Among these derivatives, 2-chloroquinoline-3-carbaldehydes occupy a prominent position because they serve as versatile key intermediates for the annelation of a wide range of ring systems and for various functional group transformations.⁸⁻⁹

Investigations into biologically active compounds containing the indazole heterocyclic core (Fig. 1) have led to the discovery of potent HIV protease inhibitors, serotonin receptor antagonists, aldose reductase inhibitors, and acetylcholinesterase inhibitors.¹⁰⁻¹¹ More recently, another indazole derivative, ABT-102 (Fig. 2), has been identified as a potent antagonist of the vanilloid receptor.¹²

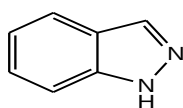


Fig 1

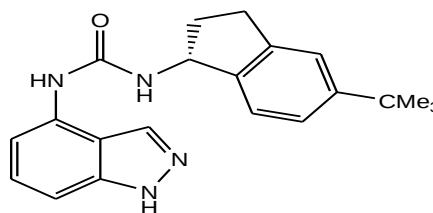


Fig 2

The pyrazole nucleus is present in several anti-inflammatory and analgesic drugs, including phenylbutazone,¹³ benzydamine,¹³ and tetrydamine.¹⁴ More recently, anti-inflammatory activity has also been reported for pyrazolopyridone derivatives¹⁵ (Fig. 3), cyclopentapyrazoles¹⁶ (Fig. 4), and thienopyrazole¹⁷ (Fig. 5).

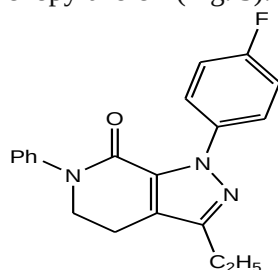


Fig 3

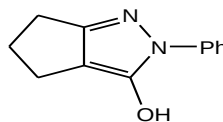


Fig 4

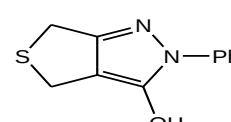
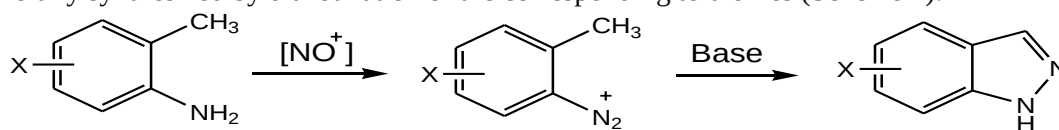


Fig 5

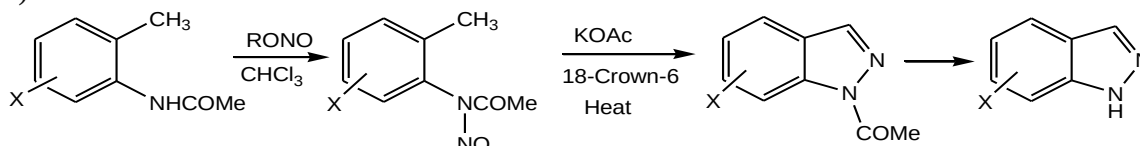
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Some of the reported methods are given below,
Ruechardt et al.¹⁸ reported that indazoles bearing substituents on the six-membered ring were generally synthesized by diazotization of the corresponding toluidines (Scheme 1).



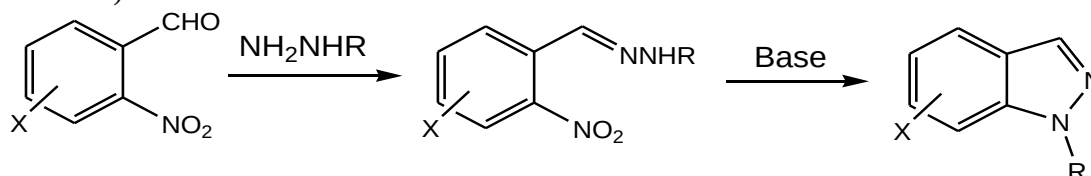
Scheme 1

Tono-oka et al.¹⁹ reported the synthesis of six-membered-ring-substituted indazoles through the nitrosation of their corresponding N-acetyl derivatives using the Jacobsen modification (Scheme 2).



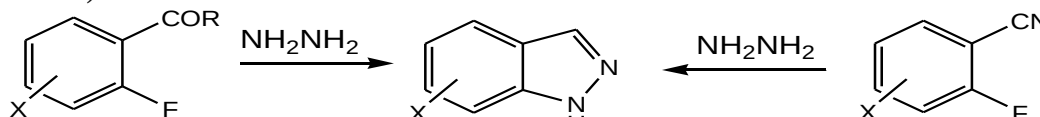
Scheme 2

Meyer et al.²⁰ reported that the condensation of ortho-substituted benzaldehydes with hydrazines offers a particularly straightforward and attractive approach to the synthesis of indazoles (Scheme 3).



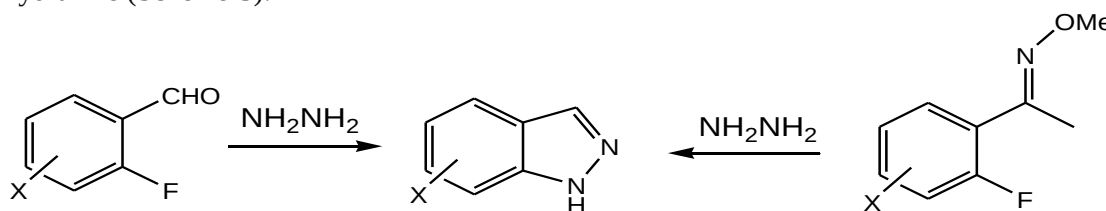
Scheme 3

Cui et al.²¹ reported the synthesis of indazoles through the condensation of hydrazine with the corresponding esters of fluorobenzoic acids, fluorobenzophenones, and fluorobenzonitriles (Scheme 4).



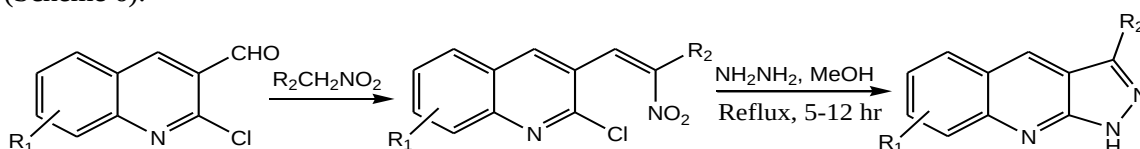
Scheme 4

Lukin et al.²² reported a new practical method for the synthesis of indazoles involving the reaction of ortho-fluorobenzaldehydes and their corresponding ortho-methyl oximes with hydrazine (Scheme-5).



Scheme 5

Bhaduri et al.²³ reported the formation of 3-substituted 1H-pyrazolo[3,4-b]quinoline derivatives (Scheme 6).



Scheme 6

Present Work:

The literature survey reveals that indazoles have been synthesized through several approaches, including the diazotization of o-aminotoluenes,¹⁸ nitrosation of o-N-acetyltoenues,¹⁹

condensation of *o*-nitrobenzaldehydes with hydrazines,²⁰ condensation of esters of *o*-fluorobenzoic acids, *o*-fluorobenzophenones, and *o*-fluorobenzonitriles with hydrazine,²¹ condensation of fluorobenzaldehydes and their corresponding *o*-methyl oximes with hydrazine,²² and ring-closure reactions of nitrovinylquinolines with hydrazine.²³

During our studies on various quinoline derivatives, we observed the formation of 1*H*-pyrazolo[3,4-*b*]quinolines. The findings are therefore presented in this section. The synthesis of these pyrazoloquinolines proceeds through a novel synthetic strategy that differs from the methods reported previously.

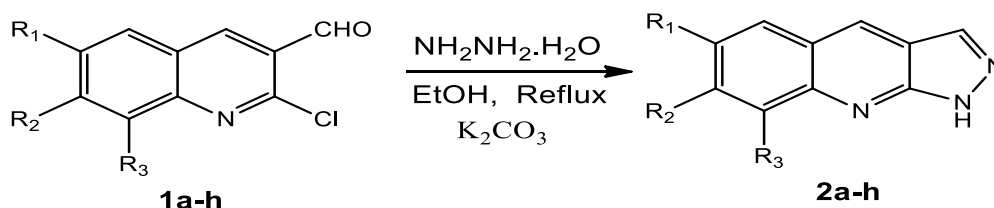
Result and Discussion:

Herein, we report an efficient and environmentally benign method for the synthesis of 1*H*-pyrazolo[3,4-*b*]quinoline derivatives (2a–h) from the corresponding 2-chloroquinoline-3-carbaldehydes (1a–h) (Scheme 7, Table I). The reaction was carried out using hydrazine hydrate as the key reagent and potassium carbonate as the catalyst in ethanol solvent. The transformation was investigated under reflux conditions.

The reaction proceeded through the interaction of the 2-chloroquinoline-3-carbaldehyde derivatives with hydrazine hydrate, leading to the formation of the corresponding fused pyrazole ring and consequently affording the desired 1*H*-pyrazolo[3,4-*b*]quinoline derivatives. Upon completion of the reaction, as indicated by the disappearance of the starting material, the reaction mixture was allowed to cool to room temperature. The desired products were then isolated using an appropriate work-up procedure and purified to obtain the corresponding pyrazoloquinoline derivatives.

Using this methodology, a series of eight 1*H*-pyrazolo[3,4-*b*]quinoline derivatives (2a–h) bearing different substituents on the quinoline framework were successfully synthesized. The products were obtained in high yields, demonstrating the efficiency and broad applicability of the developed synthetic protocol. The use of ethanol and potassium carbonate catalyst as the reaction medium, together with hydrazine hydrate and relatively simple reaction conditions, makes this approach attractive from the perspective of operational simplicity and environmental considerations.

The synthesized compounds were characterized unequivocally using appropriate analytical and spectroscopic techniques. The structural assignments were supported by the obtained analytical data, which were consistent with the proposed structures of the synthesized 1*H*-pyrazolo[3,4-*b*]quinoline derivatives. The results obtained from this study establish a convenient and efficient route for the synthesis of this class of fused heterocyclic compounds.



Scheme 7

General Procedure:

6-methyl-1*H*-pyrazolo[3,4-*b*]quinoline (2a)

To a stirred solution of 2-chloro-6-methylquinoline-3-carbaldehyde (0.5 g, 2.4 mmol) in ethanol (10 mL), hydrazine hydrate (1.5 g, 30 mmol) was added. The resulting reaction mixture was stirred at room temperature for 3 h and subsequently refluxed for an additional 3 h. The progress of the reaction was monitored by thin-layer chromatography (TLC) using hexane/ethyl acetate (8:2, v/v) as the eluent. Upon completion of the reaction, the mixture was cooled to room temperature, and the resulting solid was collected by filtration and washed thoroughly with water. The crude solid was purified by recrystallization from ethanol and subsequently dried in a vacuum oven at 40 °C for 6 h to afford the desired product as a solid (0.30 g).

Experimental Section:

The 2-chloroquinoline-3-carbaldehydes used in the present study were prepared in the laboratory according to the reported procedure. Ethanol was procured from S. D. Fine-Chem. Melting points were determined in open capillary tubes using a Kumar's melting point apparatus and are uncorrected. The synthesized compounds were characterized by spectroscopic and analytical data. ¹H NMR spectra were recorded on a Varian Gemini spectrometer at 400 MHz in CDCl₃, with tetramethylsilane (TMS) used as the internal standard. Mass spectra were recorded on a Micromass Quattro-II mass spectrometer using the electrospray ionization (ESI) technique, with the observed (M+1) peak corresponding to the molecular ion. The purity of the synthesized compounds and the progress of the reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel plates.

Conclusion:

In conclusion, a new and efficient methodology has been developed for the synthesis of 1H-pyrazolo[3,4-b]quinoline derivatives (2a–h) from the corresponding 2-chloroquinoline-3-carbaldehydes (1a–h) under reflux conditions in ethanol and potassium carbonate as catalyst. The reaction proceeded under mild conditions with relatively short reaction times and afforded the desired products in high to quantitative yields. The simplicity of the reaction procedure, operational convenience, and excellent yields make this methodology a useful approach for the synthesis of 1H-pyrazolo[3,4-b]quinoline derivatives. Furthermore, the developed method may be particularly valuable for the preparation of diverse pyrazoloquinoline libraries in combinatorial chemistry.

Spectral Data:

6-methyl-1H-pyrazolo[3,4-b]quinoline (2b)

¹H NMR (CDCl₃), δ ppm: 2.1 (s, 3H, Ar-CH₃); 5.88 (s, 1H, -NH); 7.51 (d, 1H, Ar-H, C₇); 7.58 (s, 1H, Ar-H, C₅); 7.85 (d, 1H, Ar-H, C₈); 8.16 (s, 1H, Ar-H, C₃); 8.52 (s, 1H, Ar-H, C₄).

ES-MS: m/z 183.9 (m+1).

Table I

Characterization data of 1H-pyrazolo[3,4-b]quinoline

Entry	R ₁	R ₂	R ₃	Melting Point (°C)	Yield (%)	Reaction Time (hr)
2a	H	H	H	194-196	65	6
2b	CH ₃	H	H	119-121	68	6
2c	H	CH ₃	H	162-164	60	6
2d	H	H	CH ₃	113-115	65	6
2e	OCH ₃	H	H	173-175	60	6
2f	H	OCH ₃	H	225-227	67	6
2g	OC ₂ H ₅	H	H	160-162	62	6
2h	H	H	C ₂ H ₅	112-114	65	6

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