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An Efficient Synthesis of Derivatives of 1*H*-pyrazolo[3,4-b]-quinolines

Rajkumar U. Pokalwar

Department of Chemistry, Degloor College Degloor, S. R.T. M. University, Nanded- 431717 (Maharashtra), INDIA

* *Correspondence: E-mail: rajupokalwar@rediffmail.com*

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ABSTRACT: A simple and high yielding method was developed for the synthesis of derivatives of 1*H*-pyrazolo[3,4-b]-quinolines was obtained from 2-chloroquinolin-3-carbaldehydes, by using hydrazine hydrate at room temperature and at reflux temperature in ethanol as the solvent. This method developed for the synthesis of 1*H*-pyrazolo[3,4-b]-quinolines gave excellent yields.

Keywords: 2-chloroquinoline-3-carbaldehyde; hydrazine hydrate; 1*H*-pyrazolo[3,4-b]-quinolines; ethanol.

INTRODUCTION: Quinolines[1] are an important class of heterocyclic compounds and have been screened for biological activities such as bactericidal,[2] antitumor,[3] anti-inflammatory,[4] antimalarial[5] activities. Quinolines such as 2-chloroquinoline-3-carbaldehyde occupy a prominent position as they are key intermediates for further annelation and for various functional group interconversions.[6]

Literature Review: Investigation of biologically active compounds possessing the indazole heterocyclic core has resulted in the discovery of potent HIV protease inhibitors, serotonin receptor, antagonist, aldol reductase inhibitors and acetylcholinesterase inhibitors.[7,8] Recently another indazole derivative, ABT-102 has been identified as a potent vanilloid receptor antagonist.[9] The pyrazole nucleus is found in a number of anti-inflammatory-analgetic drug such as phenylbutazone,[10] benzydamine,[10] and tetrydamine.[11] Recently the anti-inflammatory activity of the pyrazolopyridone[12], cyclopentapyrazole[13] and thienopyrazole[14] was reported. Ruechardt et al.[15] reported that the indazoles substituted on the six membered ring were generally prepared via diazotization of the corresponding toluidines. Tono-oka et al.[16] reported the indazoles substituted on the six membered ring via nitrozation of their N-acetyl derivatives (Jacobsen modification). Meyer et al.[17] reported the condensation of ortho substituted benzaldehydes with hydrazines looked particularly straightforward and attractive for the synthesis of indazoles. Cui et al.[18] reported the condensation of the corresponding esters of fluoro benzoic acid, fluorobenzophenones, and fluoro benzonitriles with hydrazine. Lukin et al.[19] reported the reaction of ortho-fluorobenzaldehyde and their ortho methyl oximes with hydrazine has been developed as a new practical synthesis of indazoles. Bhaduri et al.[20] reported the formation of 3-substituted 1*H*-pyrazolo[3,4-b]quinoline derivatives.

MATERIALS AND METHODS:

General Procedure:

6-methyl-1*H*-pyrazolo[3,4-b]quinoline (2a): To the stirred solution of 2-chloro-6-methylquinoline-3-carbaldehyde (0.5 gm, 2.4 mmol) and ethanol 10 ml was added hydrazine hydrate (1.5 gm, 30 mmol). The reaction mixture was stirred at room temperature for 3 hr then refluxed for 3 hr. The progress of the reaction was monitored by the TLC using Hexane: Ethyl acetate (8:2) as the solvent system. After the completion of the reaction, the reaction mixture was cooled to room temperature. The solid obtained was filtered, washed with water. The solid was purified in ethanol. The solid was dried in vacuum oven at 40 ^{0}C for 6.0 hr (dry wt. = 0.30 gm).

Experimental Section: 2-chloroquinoline-3-carbaldehydes were prepared in the laboratory by the reported method. Ethanol was procured from S. D. Fine-chem. All melting points were determined in open capillaries on Kumar's melting point apparatus. The products were characterized by their spectral data. ^{1}H NMR spectra were recorded on Varian Gemini in $CDCl_3$ at 400 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quatrro-II

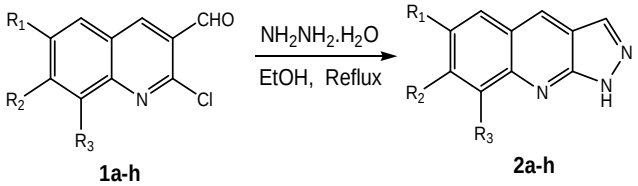
using electrospray Ionization technique, showing (m+1) peak as a molecular ion peak. The test for the purity of products and the progress of the reactions were accomplished by TLC on Merck silica gel plates.

RESULTS AND DISCUSSION: The formation of 1*H*-pyrazolo[3,4-b]-quinolines was observed during the course of our studies on various quinoline derivatives, the findings are therefore reported in this section. This synthesis of pyrazoloquinolines involves a completely novel strategy of synthesis from the ones reported earlier.

Herein we wish to report an efficient, environmentally benign method for the formation of 1*H*-pyrazolo[3,4-b]quinolines (2a-h) (Scheme 1, Table I) of various 2-chloroquinoline-3-carbaldehyde (1a-h) (Scheme 1) with hydrazine hydrate at room temperature and at reflux temperature in ethanol as the solvent. After completion of the reaction, the reaction mixture was cooled and the desired product isolated. Eight compounds were synthesized using this methodology in high yields. All the compounds synthesized were unequivocally characterized on the basis of analytical data.

Table 1: Characterization data of 1*H*-pyrazolo[3,4-b]quinolone.

Entry	R_1	R_2	R_3	Melting Point (^{0}C)	Yield (%)	Reac. 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_2H_5	H	H	160-162	62	6
2h	H	H	C_2H_5	112-114	65	6



1a-h 2a-h

Scheme 1: synthesis of 1*H*-pyrazolo[3,4-b]-quinolines.

Spectral Data:

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

^{1}H NMR ($CDCl_3$), δ ppm: 2.1 (s, 3H, Ar-C<u>H</u>$_3$); 5.88 (s, 1H, -N<u>H</u>); 7.51 (d, 1H, Ar-<u>H</u>, C_7); 7.58 (s, 1H, Ar-<u>H</u>, C_5); 7.85 (d,1H, Ar-<u>H</u>, C_8); 8.16 (s, 1H, Ar-<u>H</u>, C_3); 8.52 (s, 1H, Ar-<u>H</u>, C_4).
ES-MS: m/z 183.9 (m+1)

CONCLUSION: In conclusion, a new methodology was developed for the synthesis of 1*H*-pyrazolo[3,4-b]-quinolines (2a-h) from 2-chloroquinolin-3-carbaldehyde (1a-h) under reflux in ethanol in high yields. All the reactions were performed under mild reaction conditions, shorter reaction time and in quantitative yields. The methodology developed will be of much use to combinatorial chemist.

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