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Water-mediated one-pot synthetic route for pyrazolo[3,4-*b*]quinolines

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ABSTRACT

First time one-pot water-mediated synthetic route has been developed by carrying condensation of 2-chloro-3-formyl quinolines and hydrazine hydrate/phenyl hydrazine using thermal/microwave energy resources. The route is convenient, eco-friendly, and scalable.

Pyrazole and its derivatives are gaining importance in medicinal and organic chemistry. They have displayed broad spectrum of pharmacological and biological activities such as *anti*-bacterial, *anti*-depressant, and *anti*-hyperglycemic.[1] Quinoline derivatives are found to process *anti*-malarial, *anti*-inflammatory, *anti*-tuberculosis, and *anti*-breast cancer activities.[2]

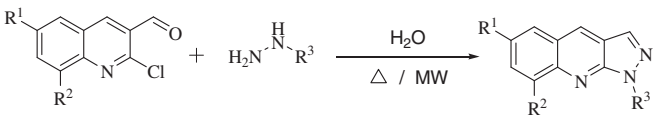
Keeping in view the potential biological activities of the pyrazoles and quinolines, the chemists have tried to synthesize and evaluate bioactivities of molecules having these ring systems in a molecular frame work as in fused or bonded forms. One of the such forms, pyrazolo[3,4-*b*]quinolines have displayed bioactivities, such as *anti*-viral, *anti*-microbial, and *anti*-malarials.[3]

Considering the applicability of pyrazolo[3,4-*b*]quinolines, several attempts are made to provide convenient synthetic routes. The literature reveals that the widely used methods for obtaining the pyrazolo[3,4-*b*]quinolines are using 2-chloro-3-formyl quinolines as precursors/starting materials. In one of the routes, the 2-chloro-3-formyl quinolines have been condensed with hydrazine hydrate/phenyl hydrazine in refluxed ethanol and obtained moderate yields of the pyrazolo[3,4-*b*]quinolines.[4] The neat one-pot condensation of the 2-chloro-3-formyl quinolines and hydrazine hydrate/phenyl hydrazine using organic catalyst, *P*-TSA under microwave has also been reported.[5]

It has been recorded that in these routes the products, pyrazolo[3,4-*b*]quinolines, obtained were not found to be pure and always accompanying with intermediate Schiff bases, 1-[(2-chloroquinolin-3-yl)methylene]hydrazines/1-[(2-chloroquinolin-3-yl)methylene]-2 phenylhydrazines. To avoid this difficulty the attempts are found to be directed to get the target products in pure form with unambiguous structures by following multistep synthetic route. The reported multistep route covers (i) the protection of 2-chloro-3-formyl quinolines; (ii) then the nucleophilic displacement of chloro by hydrazine hydrate to 1-[3-(1,3-dioxolan-2-yl)quinolin-2-yl]hydrazines; and (iii) the deprotection and cyclization of intermediates, 1-[3-(1,3-dioxolan-2-yl)quinolin-2-yl]hydrazines to pyrazolo[3,4-*b*]quinolines.[6]

The above literature routes are found to have one or other kinds of difficulties and therefore not convenient. Keeping the above scope in mind and in continuation of our earlier efforts toward the syntheses of biodynamic heterocycles,[7] here we thought to develop a simple, eco-friendly, and economic synthetic one-pot route for pyrazolo[3,4-*b*]quinolines (Scheme 1).

The literature reveals that recently water and polyethylene glycol have been gaining important as clean, safe, and recyclable media for various organic transformations.[8] Polyethylene glycol is being relatively expensive than water, the attempts are therefore directed to carry the organic transformation using thermal or



1a 2a-h

2a: R^1 = H, R^2 = H, R^3= H
2b: R^1 = OMe, R^2 = H, R^3 = H
2c: R^1 = Me, R^2 = H, R^3 = H
2d: R^1 = H, R^2 = Et, R^3 = H
2e: R^1 = H, R^2 = H, R^3= Ph
2f: R^1 = OMe, R^2 = H, R^3 = Ph
2g: R^1 = Me, R^2 = H, R^3 =Ph
2h: R^1 = H, R^2 = Et, R^3 =Ph

Scheme 1. Synthesis of pyrazolo[3,4-*b*]quinolines.

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Table 1
Physical parameters of pyrazolo[3,4-*b*]quinolines

Entry	Products	Time (h)		Yields[a] (%)		Mp (°C)	
		A	B	A	B	Found	Reported (Lit.)[4]
1	**2a**[b]	7	1.5	91	93	202–204	203–204
2	**2b**[b]	8	1.5	91	93	217–219	217–218
3	**2c**[b]	7	1.5	91	93	176 (d)	175 (d)
4	**2d**[c]	9	1.7	90	92	164–166	–
5	**2e**[b]	7	1.7	91	93	171–172	172 (d)
6	**2f**[b]	8	2	90	90	149–151	150 (d)
7	**2g**[b]	9	2	89	89	179–181	176–178
8	**2h**[c]	10	2.5	85	87	175–176	—

d: Decomposed. A: Conventional heating; B: Microwave heating.
[a] Isolated yields
[b] Elemental analyses of the products **2a**, **2b**, **2c**, **2e**, **2f**, and **2g** have not been done as these products are reported in the literature and the isolated products were pure and their melting points are in good agreement with those reported.[4]
[c] C, H, and N analyses of products **2d** and **2h** have been carried out and the results are in agreement with the corresponding calculated values.

microwave resources in water. It is also reported that boiling water under microwave irradiation behaves as hydrophobic medium and helps to form homogenous mass with organic substrates/reagents present with it and hence accelerates the rate of reaction.[9]

The above-referred utility of water as medium has prompted to attempt one-pot cyclocondensation of 2-chloro-3-formyl quinolines and hydrazine hydrate/phenyl hydrazine using thermal and microwave energy resources. It was noticed that the cyclocondensation leading to the titled compounds has occurred under these conditions. To optimize the condition required for this one-pot route, the following attempts were made by carrying reference reaction using 2-chloro-3-formyl quinoline and hydrazine hydrate/phenyl hydrazine. It was observed that pyrazolo[3,4-*b*]quinoline was obtained with better to excellent yield (91%), when one-pot condensation of 2-chloro-3-formyl quinoline and molar excess of hydrazine hydrate/phenyl hydrazine was carried under reflux for 7 h using thermal energy.

The same condensation when carried using identical mole proportions as above in refluxed water under microwave irradiation found to give 93% of pyrazolo[3,4-*b*]quinoline within 1.5 h. Using these optimized conditions the other pyrazolo[3,4-*b*]quinolines have been synthesized and their characteristic details are recorded in Table 1.

Thus developed route is one-pot and would be going under completion via intermediate hydrazone (Schiff base) formation and subsequent to that cyclization. The products obtained are free from impurities and the medium used is readily available, cheaper, and safe.

In conclusion, first time the cyclocondensation of substituted 2-chloro-3-formyl quinolines and hydrazine hydrate/phenyl hydrazine has been carried out using water as a reaction medium and obtained better yields of pyrazolo[3,4-*b*]quinolines. Thus, here we have provided safe, economic, and convenient synthetic route for biodynamic pyrazolo[3,4-*b*]quinolines.

Experimental procedure of the synthesized compounds and their characterization data are incorporated in the reference part.[10,11]

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10. *Experimental:* All chemicals and solvents were purchased from Spectrochem and S. D. Fine-chem. (India). All the melting points were recorded by open capillary method and are uncorrected. The reactions were carried out in a Milstone MicroSYNTH Labstation for Synthesis, MW oven having a maximum power output of 1200 W. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz using DMSO-d_6 solvent and tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on Single-Quadrupole Mass Detector 3100, Waters. The observed molecular ions are having 1 amu higher m/z in the spectra than the expected. Elemental analyses were performed on CHNS auto analyzer, Thermo Finnigan.
General procedures (A and B) for the synthesis of pyrazolo[3,4b]quinolines (**2a–h**)
(A) *Conventional (thermal) method:*
A mixture of 2-chloro-3-formyl quinolines **1** (5 mmol), hydrazine hydrate 98% (15 mmol), and phenyl hydrazine (7.5 mmol) was refluxed with stirring in water (25 mL). The progress of the reaction was monitored by TLC using hexane–ethyl acetate (7:3). On completion of the reaction, the reaction mass was cooled and thus the obtained solid was filtrated, washed with water, and dried. The crude products were crystallized from ethanol. The other details of the products are recorded in Table 1.
(B) *Non-conventional (microwave irradiation) method:*
A mixture of 2-chloro-3-formyl quinolines **1** (5 mmol), hydrazine hydrate 98% (15 mmol) and phenyl hydrazine (7.5 mmol) was refluxed with stirring in water (25 mL) under microwave irradiation at 1000 W for 1.5–2.5 h. The progress of the reaction was monitored by TLC using hexane–ethyl acetate (7:3). After completion of the reaction, the reaction mass was cooled and thus the obtained solid was filtrated, washed with water, and dried. The crude products were crystallized from ethanol. The other details of the products are recorded in Table 1.
11. *Spectral data of compounds*: 1*H*-Pyrazolo[3,4-*b*]quinoline (**2a**): Yellow solid; mp: 202–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.50 (t, 1H, J = 8 Hz), 7.80 (t, 1H, J = 8 Hz), 8.00 (d, 1H, J = 8 Hz), 8.15 (d, 1H, J = 8 Hz), 8.44 (s, 1H), 8.95 (s, 1H), 13.56 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 115.87, 123.37, 123.95, 127.77, 129.66, 130.43, 130.54, 134.15, 147.72, 151.59. Mass: m/z 170 (M^+). 6-Methoxy-1*H*-pyrazolo[3,4-*b*]quinoline (**2b**): Yellow solid; mp: 217–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 3.90 (s, 3H), 7.44–7.48 (m, 2H), 7.91 (d, 1H, J = 8 Hz), 8.36 (s, 1H), 8.78 (s, 1H), 13.47 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 55.40, 105.68, 115.82, 124.33, 124.67, 128.30, 129.13, 133.36, 144.17, 150.80, 154.86. Mass: m/z 200 (M^+). 6-Methyl-1*H*-pyrazolo[3,4-*b*]quinoline (**2c**): Yellow solid; mp: 176 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 2.74 (s, 3H); 7.39 (t, 1H, J = 1.2 Hz and J = 8 Hz); 7.66 (d, 1H, J = 6.4 Hz); 7.99 (d, 1H, J = 8 Hz); 8.42 (s, 1H); 8.92 (s, 1H). 13.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 18.45, 115.51 123.00, 123.77, 127.64, 130.01, 130.76, 133.91, 134.84, 146.94, 151.14. Mass: m/z 184 (M^+). 8-Ethyl-1*H*-pyrazolo[3,4-*b*]quinoline (**2d**): Yellow solid; mp: 164–166 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 1.35 (t, 3H), 3.27 (q, 2H), 7.41 (t, 1H, J = 8 Hz), 7.63 (d, 1H, J = 8 Hz), 7.95 (d, 1H, J = 8 Hz), 8.41 (s, 1H), 8.91 (s, 1H), 13.63 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 14.97, 24.48, 115.51, 123.11, 123.91, 127.65, 128.47, 130.85, 133.89, 140.55, 146.25, 151.17. Mass: m/z 198 (M^+). Elemental Anal. Calcd: $C_{12}H_{11}N_3$ C, 73.09; H, 5.58; N, 21.30.

Found: C, 73.03; H, 5.50; N, 21.23. 8-Ethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**2h**): Yellow solid; 175–176 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 1.29 (t, 3H), 3.10 (q, 2H), 6.82–7.45 (m, 5H, Ar-H), 7.60 (t, 1H, J = 8 Hz), 7.65 (d, 1H, J = 8 Hz), 7.97 (d, 1H, J = 8 Hz), 8.23 (s, 1H), 8.86 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 15.05, 23.69, 119.71, 125.51, 126.36, 127.48, 127.55, 128.08, 129.03, 129.12, 129.26, 130.68, 133.61, 137.62, 141.10, 144.54, 144.59, 146.95. Mass: m/z 274 (M^+). Elemental Anal. Calcd: $C_{18}H_{15}N_3$: C, 79.12; H, 5.49; N, 15.38. Found: C, 79.05; H, 5.44; N, 15.32.