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Glycerol mediated safer synthetic route for pyrazolines bearing quinolino and benzene sulfonamido pharmacophores

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ABSTRACT

*Organic transformations need organic solvents. Most of the organic solvents which are in use while performing the transformations for obtaining products of societal use are volatile organics responsible for environmental pollution. These solvents are from exhaustible petrochemical source. Herein pyrazolines, 3-(4'-tosylaminophenyl)-5-(2'-chloro-substituted quinolin-3-yl)-4,5-dihydropyrazolines (**2a-f**) were synthesized from cyclocondensation of chalcones, 3-(2-Chloro-substitutedquinolin-3-yl)-1-(4-(tosylamino)phenyl)prop-2-en-1-ones(**1**) with hydrazine using greener medium, glycerol at 90 ^{o}C.*

Keywords: Sulfonamide, 2-chloro-3formylquinolin, pyrazoline glycerol, green synthesis.

INTRODUCTION

Pyrazoles are found as core structural component of numerous agrochemicals and pharmaceutical agents. They possess a broad spectrum of biological activities such as antibacterial[1], antifungal[2], antitubrcular[3], antitumor[4], antidepressant[5], anticonv ulsant[6] insecticidial[7] antidiabetic[8] and molluscicidal[9]. Among various pyrazoline derivatives, 2-pyrazolines seem to be most frequently studied pyrazoline type compounds. Sulfonamides constitute is a useful structural element in medicinal chemistry and has broad application in drug development. Sulfonamides have been found to possess a large number of biological activities, include anticancer[10], antifungal[11], antitumor[12] and antimicrobial[13] activities. Quinolines and their derivatives are important constituents of several pharmacologically active synthetic compounds. Quinoline based fused heterocyclic systems are found as potential anticancer agents[14] and have antimalarial activity[15].

Pyrazolines are usually synthesized by condensing the chalcons with hydrazine[16], aryl hydrazines[17] and acid hydrazids[18] in ethanolic and acetic acid medium. Cyclocondensation of chalcones with hydrazine hydrate, carried in acetic acid has been accelerated by microwave irradiation[19]. K_2CO_3 mediated microwave irradiation has been shown to be an efficient method for the synthesis of pyrazolines[20].

It is observed that the reported methods, used for this cyclocondensation are having one or other kind of drawback such as longer reaction times, high temperature, low yield, and media used are found to be carcinogenic and hazardous. Therefore, the search for a better reaction system for the synthesis of pyazolines in term of mild reaction conditions, economic viability, selectivity and environmental concerns continues to attract the interest of synthetic organic chemists. In this context, more attention is found to be directed on use of nonvolatile organic solvents as an alternative like PEGs, water and ionic liquids. However all these are having own limitations.

In organic synthesis, the choice of the solvent is crucial step in a chemical reaction. The development of green methodologies from renewable resources has gained much interest recently because of the extensive use of solvent in almost all of the chemical industries and of the predicted disappearance of fossil oil[21]. Glycerol (1,2,3-proanetriol) is a well known substance that can be naturally found under the form of fatty acid esters. Traditionally, glycerol is obtained as a byproduct in four different processes: soap manufacture, fatty acid production, fatty ester production[22] and microbial production[23]. It can also be synthesized from propylene oxide[22]. In recent years, the increase in the production of fatty acid methyl esters from vegetaloils to be used as biofuels (biodiesel) has leaded to a surplus in the production of glycerol and subsequent dramatic decrease in its price.

Glycerol is non toxic, biodegradable, renewable, recyclable and easily available liquid. It has higher boiling point and lower vapor pressure. The unique physico-chemical nature of glycerol makes it an ideal reaction medium for organic syntheses. Glycerol itself has been recently proposed as a green solvent[24]. It is widely used in many organic reaction for conversion that include pd-catalyzed Heck[25,26], base[26] and acid[27] promoted condensation, catalytic hydrogenation[28] and asymmetrical reduction. Recently C. S. Radatz *et. al.* reported glycerol as recyclable solvent for synthesis of benzodiazepines and benzimidazoles[29].

Considering the biological significance of these heteryl nuclei, in continuation of our work on bioactive heterocycles[30] and need to develop greener alternative route for the pyazolines herein, we report environmentally bengin safer synthetic route for. 3-(4'-tosylaminophenyl)-5-(2'-chloro-substitutedquinolin-3-yl)-4,5-dihydro pyrazolines using glycerol as greener medium.

MATERIALS AND METHODS

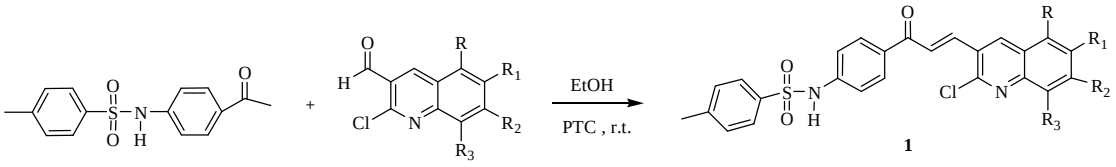
General procedures. All chemicals were obtained from commercial sources and used without any further purification. The melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a FT-IR (JASCO FT- IR) Japan. The ^{1}H NMR was measured on Bruker DRX-300, 300 MHZ FT NMR with low and high temperature in DMSO using TMS as internal reference. Mass spectra were recorded on an Ieo SX 102/DA-600 mass spectrometer.

Synthesis of 3-(4'-tosylaminophenyl)-5-(2'-chloro-substitutedquinolin-3-yl)-4,5-dihydro pyrazolines (2a-2f).
3-(2-Chloro-substitutedquinolin-3-yl)-1-(4-(tosylamino)phenyl)prop-2-en-1-one (0.005 mol), and hydrazine hydrate (0.01 mol) were dissolved in glycerol (20 mL) and the reaction mixture was allowed to stir at 90 ^{o}C for 4 h. The progress of the reaction was monitored on TLC plate using hexane: ethyl acetate. After completion, the reaction mixture was poured into ice-cold water and was extracted with EtOAc. The solvent was removed and crude product was subjected to column chromatography to obtained pure pyrazolines.

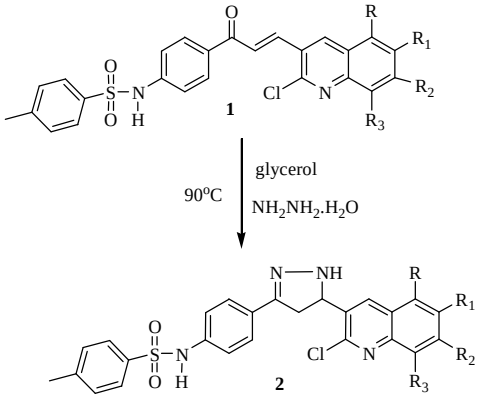
Characteristic absorption of (**2f**) as one of the representative products (**2a-f**) has been presented bellow MS (scanning mode ES$^+$) (m/z): 522 (M^+), 524 (M^+ + 2). IR (KBr) cm^{-1} 3263 (N-H, str.), 3168 (C-H, str. aromatic), 1601 (C=C, str. aromatic), 1579 (C=N, str. pyrazoline), 1376 and 1164 (SO_2, asymmetric and symmetric stretching, respectively) ^{1}H NMR (DMSO-d_6) δ: 1.32 (t, 3H, C$\underline{H}_3$CH$_2$O-), 2.33 (s, 3H, CH$_3$), 2.71, 2.79 (dd, 2H, methylene protons of pyrazoline), 3.94 (q, 2H, –OC$\underline{H}_2$CH$_3$) 4.83 (m, 1H, methine proton of pyrazoline), 5.49 (s, 1H, NH pyrazoline poton exchange with D_2O), 6.98 to 8.48 (m, 11H, aromatic protons), 8.83 (s, 1H, quinoline) and 10.32 (s, 1H, SO_2NH exchange with D_2O).

RESULTS AND DISCUSSION

The key intermediates, 3-(2-chloro-substitutedquinolin-3-yl)-1-(4-(tosylamino)phenyl)prop-2-en-1-ones (**1**) were synthesized by following literature[30b] procedure. We have synthesized 3-(4'-tosylaminophenyl)-5-(2'-chloro-substitutedquinolin-3-yl)-4,5-dihydro pyrazolines (**2**) in good yield by condensing compounds (**1**) with hydrazine hydrate in glycerol at 90 ^{o}C . The reaction sequence outlined in **Scheme 1 & 2**



Scheme 1. Synthesis of chalcones.



Scheme 2. **Synthesis of pyrazolines**.

Table 1. **Physical data of pyrazolines** (**2a-f**).

Products	R	R_1	R_2	R_3	Yield[a] (%)	Mp (°C)
2a	H	H	H	H	92	166-168*
2b	H	H	CH_3	H	91	163-165*
2c	H	H	Cl	H	90	138-140*
2d	H	OCH_3	H	H	89	158-160*
2e	H	H	H	CH_3	91	162-163*
2f	H	OCH_2CH_3	H	H	90	160-161N

[a] yields of the isolated product.

[*] Mps. and structure were confirmed by comparison of the IR, [1] NMR and mass analyses with those authentic materials. MPs. of the compound are in good agreements [31].

[N] New compound was characterized by IR. [1] NMR and mass analyses.

Overall, Water is the first solvent of choice, regarding the greener reaction media yet the negligible solubility of many organic compounds in water limits its application and ionic liquids have been reported as recyclable environmentally bengin reaction media. However ionic liquids are non-biodegradable and their production is also associated with use of high amounts of hazardous and volatile organic solvents. Polyethylene glycol (PEGs) which has been well established as a green solvent due to number of advantages. Recently we have reported PEG-400 is alternative greener media for synthesis of pyrazolines[31], but there is a disadvantage due to longer reaction time. However the polarity of glycerol and the intermolecular forces that arise from its structure can make a reaction more selective and accelerate the rate of an organic reaction. Glycerol has three hydroxyl groups that are responsible for its solubility in water and has a higher boiling point, lower vapor pressure as compared with water, make it easy to isolate the reaction product by simple extraction.

CONCLUSION

In conclusion, we develop environmental benign condensation, protocol for obtaining the pyazolines using glycerol, biodegradable and renewable viscous solvent as medium under catalyst free condition. The clean and eco-friendly nature of the conversion, shorter reaction times, non tedious workup and yields are excellent.

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