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Short communication

SHORT COMMUNICATION

Synthesis of quinolone substituted 2-azetidinone derivatives

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Abstract: Acetanilide was converted into 2-chloro-3-formylquinoline by reaction with DMF–$POCl_3$ at 80–90 °C and then condensed with aromatic primary amines to give Schiff bases **3a**–**c**. These Schiff bases were then reacted with acid chlorides in toluene in the presence of a base to give 1,3,4-trisubstituted-2-azetidinones.

Keywords: acetanilide; 2-chloro-3-formylquinoline; aromatic amine; acid chloride; tributylamine; 2-azetidinone.

INTRODUCTION

Malaria is one of the most widespread diseases in the world besides tuberculosis and AIDS. The World Health Organization estimates that about 40 % of the world's population presently lives under malarial threat and approximately 300–500 million cases of malaria occur annually, leading to 1–3 million deaths. Mortality is particularly high in children under the age of five, accounting for about 25 % of childhood deaths in Africa.[1,2] Malaria is caused by different species of *Plasmodium*, of which *Plasmodium falciparum* is the most virulent human malarial parasite and the others include *P. vivax*, *P. malariae* and *P. ovale*. A major reason for the continued severity of the worldwide malarial problem is the increasing resistance of malarial parasites to the available antimalarial drugs, such as chloroquine. Although continued attempts to develop a vaccine for malaria are ongoing, drugs remain the only available treatment option.

Quinoline-containing compounds have long been used for the treatment of malaria, beginning with quinine. The systematic modification of quinine led to the potent and inexpensive 4-aminoquinoline drug, chloroquine, and other related drugs. After worldwide development of drug resistance to chloroquine, the ratio-

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nal approach in chemistry and screening efforts produced mefloquine, another quinoline-containing compound that was highly active against the chloroquine resistant strains of *P. falciparum*.

Since the development of mefloquine, there have been several reports of new potent quinoline compounds. Most of these contain the 7-chloroquinoline nucleus of chloroquine and vary in the length and nature of their basic amine side chain. Currently, compounds such as amodiaquine are promising leads for the development of new drugs.

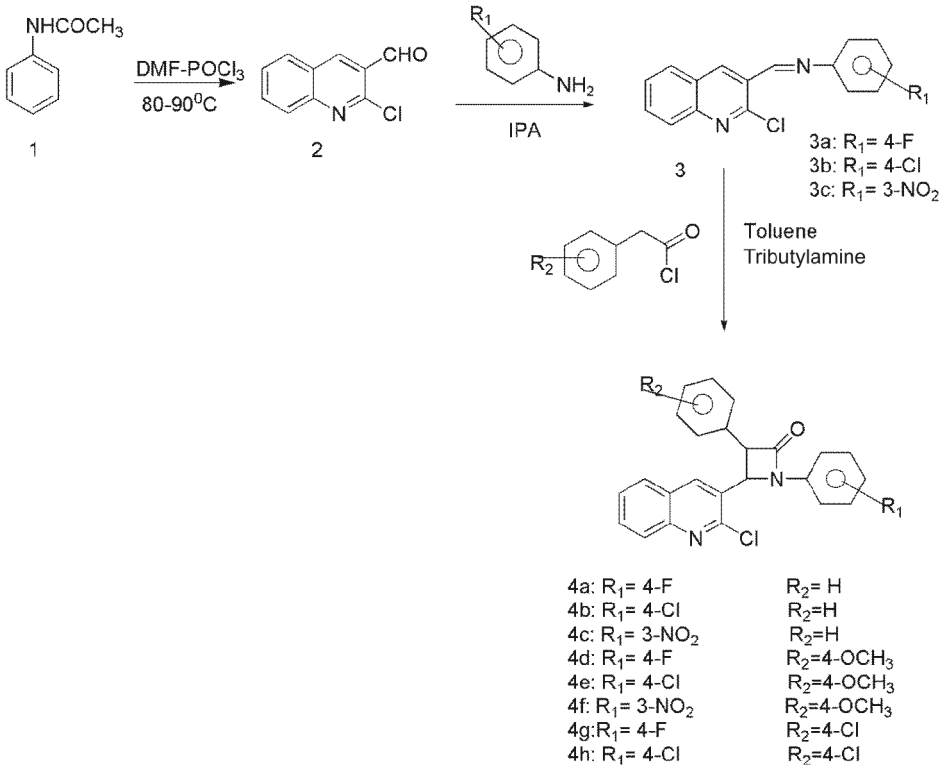
The *β*-lactam class of compounds has served an important and highly successful role in the pharmaceutical industry. Miracle drugs such as penicillins and cephalosporins have significantly improved human health and life expectancy. Although most penicillin- and cephalosporin-like compounds have been obtained by biosynthesis, chemical modification of intermediates for bioassay of antibacterial activity has become important because of the growing resistance of bacteria to penicillin and cephalosporin-like compounds and the need for medicines with more specific antibacterial activity.[3,4] Developments in the field of *β*-lactams[5–8] during the last decades indicate that the only essential feature for the antibacterial activity in these compounds is the presence of the *β*-lactam (2-azetidinone) ring. Azetidinone derivatives have also been recognized as TNF-alpha converting enzyme (TACE) inhibitors[9] and agents with new biological activities, such as anticancer,[10] anticoccidial,[11] cardiovascular,[12] antiviral,[13] mutagenic,[14] anticonvulsant and anti-inflammatory.[15,16]

Bearing this in mind, it was decided to synthesize 2-azetidinones that have the quinoline moiety at position 3.

RESULTS AND DISCUSSION

2-Chloro-3-formylquinoline (**2**) was prepared according to a procedure reported[17] in literature by reacting acetanilide (**1**) with DMF–$POCl_3$ at 80–90 °C and characterized by its physical and spectral data, which were in accordance with the literature. The IR spectrum of compound **2** showed a band for one carbonyl group at 1726 cm^{-1} and the ^{1}H-NMR spectrum indicated the presence of an aldehyde proton at δ 10.60 ppm. 2-Chloro-3-formylquinoline (**2**) was condensed with various aromatic amines to yield Schiff bases **3a**–**c**. The reactions were monitored by TLC. After completion of the reactions, the products were filtered and dried to afford the Schiff bases **3a**–**c**, which were characterized by their physical and spectral data. In general their IR spectra showed the absence of a carbonyl band and the appearance of a band for –CH=N– at 1612 cm^{-1}. Other bands were present at 1501 & 1593 cm^{-1}. The ^{1}H-NMR spectra showed the absence of an aldehyde proton and presence of a –CH=N– (azomethine) proton at δ 9.0 ppm.

These Schiff bases **3a**–**c** were then reacted with acid chlorides in the presence of a base to yield the 1,3,4-trisubstituted-2-azetidinones **4a**–**h**. The IR spectra of compounds **4a**–**h** showed the absorption for one carbonyl. In the ^{1}H-NMR spectra, two doublets for C_3-H and C_4-H were present. The envisaged reaction sequence is depicted in Scheme 1.



Scheme 1. The reaction sequence.

The structures of compounds **4a**–**h** were established based on their IR and ^{1}H-NMR spectra. As reported in the literature, *cis*-isomer shows higher values of the coupling constant than the *trans*-isomer.[18] The majority of the isolated compounds showed lower values of the coupling constant, confirming the *trans*-azetidinone. However, a few of them showed a mixture of both, in which the *trans*-azetidinones contained small amounts of *cis*-azetidinone (Table I).

EXPERIMENTAL

All the compounds were identified by examination of their spectral data and physical properties. The reported yields refer to the isolated yields of the desired products. Melting points were determined on Buchi-545 melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC. The IR spectra were recorded on a Perkin

Elmer Spectrum-1 (FTIR) instrument using KBr discs, The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ using an Avance 400 MHz Bruker spectrometer with TMS as the internal standard. The mass spectra were recorded on a Thermo Finigan Ion Trap GCMS Polaris Q instrument. The dry reactions were performed under nitrogen with magnetic/mechanical stirring. The analytical and spectral data of the synthesized compounds are given in the Supplementary material to this paper.

TABLE I. Stereochemistry of compounds **4a**–**h**

Compound	R1	R2	Isolated isomer
4a	4-F	H	*Trans*
4b	4-Cl	H	*Trans:cis* (86:14)
4c	3-NO_2	H	*Trans*
4d	4-F	4-OCH_3	*Trans:cis* (78: 22)
4e	4-Cl	4-OCH_3	*Trans*
4f	3-NO_2	4-OCH_3	*Trans*
4g	4-F	4-Cl	*Trans*
4h	4-Cl	4-Cl	*Trans*

*Synthesis of 2-chloro-3-formylquinoline (**2**)*

To a stirred solution of acetanilide (6.75 g, 50.0 mmol) in dry DMF (10.95 g, 150.0 mmol) at 0–5 °C, $POCl_3$ (92.1 g, 600 mmol) was added dropwise and the mixture was stirred at 80–90 °C for a time ranging between 4–16 h. The mixture was then poured onto crushed ice, stirred for 5 min and the resulting solid was filtered, washed well with water and dried. The compounds were purified by recrystallisation from either ethyl acetate or acetonitrile.

General procedure for the synthesis of N-*[(2-chloroquinolin-3-yl)methylene]benzenamine derivatives (**3a**–**c**)*

An intimate mixture of 2-chloro-3-formylquinoline (**2**) (10 mmol) and the corresponding aromatic primary amine (11 mmol) was refluxed in 2-propanol (25 mL) for 6–7 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled to 10 °C and the product was filtered and washed with cold 2-propanol to obtain the solid products.

*General procedure for the synthesis of 1,3,4-trisubstituted-2-azetidinones (**4a**–**h**)*

A mixture of an *N*-((2-chloroquinolin-3-yl)methylene)benzenamine derivative (10 mmol) (**3a**–**c**), acid chlorides (20 mmol) and tri-*n*-butylamine (30 mmol) in toluene (50 mL) was refluxed for 3–4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was then cooled to room temperature and 1:1 HCl (40–50 mL) was added. The organic layer was separated and washed with water, followed by $NaHCO_3$ solution and finally with water and dried over anhydrous sodium sulfate before the solvent was removed under reduced pressure. The required compound was isolated using column chromatography (*n*-hexane:ethyl acetate = 90:10) and thereafter it was crystallized from ethanol.

CONCLUSION

In conclusion, novel 4-(2-chloroquinolin-3-yl)-1,3-diphenylazetidin-2-ones were synthesized under mild condition starting from acetanilide.

SUPPLEMENTARY MATERIAL

Analytical and spectral data for the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

СИНТЕЗА ХИНОЛИЛ-СУПСТИТУИСАНИХ 2-АЗЕТИДИНОНА

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Ацетанилид је преведен у 2-хлор-3-формилхинолин помоћу DMF–$POCl_3$ загревањем на 80–90 °C, а кондензацијом са примарним аминима производ је преведен у Шифове базе **3a–c**. Шифове базе реакцијом са хлоридима карбоксилних киселина у присуству базе, у толуену, као производ дају 1,3,4-трисупституисане 2-азетидине.

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