Heterocyclic Letters
Vol. 12| No.2|305-309|February -April|2022
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

WILLGERODT KINDLER REARRANGEMENT – A CONVERGENT METHOD TO MANAGE SULFUR HETEROCYCLE

D. Shiamala Devi[a], S. Ilayaraja[a], P. Pitchai[a*] and R. M. Gengan[b]

[a]PG & Research Department of Chemistry, Government Arts College (Autonomous), Kumbakonam, 612 002, Tamilnadu, India.
[b]Department of Chemistry, Steve Biko Campus, Durban University of Technology, Durban, 4001, KwaZulu-Natal, South Africa.
**Corresponding author: pitchaipandian@gmail.com*

ABSTRACT: A one-pot synthesis of 2-morpholinothieno[2,3-*b*]quinolin-4-ol is reported. Benchtop reagents of general organic chemical laboratories are used to produce the target molecules. However the synthetic approach is unusual; the Willgerodt Kindler rearrangement and a subsequent dehydration reaction is utilized to generate a new heterocyclic ring. FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra are used to identify the structure of 2-morpholinothieno[2,3-*b*]quinolin-4-ol.

KEYWORDS: Willgerodt Kindler rearrangement, dictamnine, octasulphur, 3-acyl-2,4-dihydroxyquinoline, 2-morpholinothieno[2,3-*b*]quinolin-4-ol.

INTRODUCTION

Quinoline is a special heterocycle with extensive application in synthetic organic chemistry; the 3rd position is available for quick electrophilic attack while the 2nd and 4th position is activated for nucleophilic attack at any circumstances. Hence, the biochemical pathways of plants favour the production of several derivatives existing as alkaloids. Although quinine was one of the first natural alkaloid used as an antimalarial drug,[i] new synthetic drug like chloroquine, mefloquine and primaquine have been used for better efficacy. The quinoline derivatives were also applied as drug for several ailments such as lupus erythematosus, rheumatoid arthritis, trypanocide, and cancer.[ii-viii] Cryptosanguinolentine, Cryptolepine, and cryptotakiene are other quinoline antimalarials with potential activity and minimal side effects.[ix] The quinolone derivatives were also reported as good HIV-integrase inhibitors due to their explicit amide linkage.[10] Hydroxychloroquine was the first drug approved by the World Health Orgaisation(WHO) for treating infected Covid-19 patients in the first outbreak of the pandemic.[x-xv]

Thioamides are one of the carboxylic acid derivatives with comprehensive reactivity in organic synthesis and drug discovery.[xvi] In comparison with carboxylic acid amides, the NH group of thioamides are efficient hydrogen donor while sulphur is a weak hydrogen acceptor. They also

possess different bond length and unique bond rotating ability, thereby they have proven essential as building blocks for the manufacture of biologically active heterocyclic skeleton.[xvi] Thionation of carboxylic amides using phosphorus pentasulfide,[xvii] thiolysis of nitriles or iminium salts,[xviii] Friedel Crafts type reaction of thiocyanates[xix] and thioacylation of amines[xx] are the accepted procedures to synthesis thioamides. In recent years, the Willgerodt Kindler reaction has been spotlighted in the synthesis of thioamides; in this reaction, an alkenyl ketone is converted into a primary thioamide through oxidation or rearrangement as reported by Willgerodt on 1887.[xxi] However, in 1923 Karl Kindler modified the reaction by using elemental sulphur and a secondary amine such as morpholine **2** under thermal condition to form the thioamide derivatives.[xxii]

EXPERIMENTAL:

GENERAL PROCEDURE:

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer as potassium bromide discs unless otherwise indicated. ^{1}H-NMR spectra were obtained on a Bruker (400 MHz) instrument in $CDCl_3$ solution using tetramethylsilane as an internal standard. *J* values are given in Hz. Column chromatography utilised Merck silica gel 60 and hexane and ethyl acetate as eluants. All the basic chemicals were purchased from *sd fine* chemicals (India).

PREPARATION OF 2-MORPHOLINOTHIENO[2,3-*B*]QUINOLIN-4-OL 5:

A mixture of 0.01 mole of 3-acyl-2,4-dihydroxy quinoline **1**, 0.01 mole of morpholine **2**, 0.015 mole of sulfur and catalytic amount of *p*-toluene sulfonic acid were subjected to heat at 120°-130°C for 8 hr. Then the reaction mixture was cooled and poured in to 1000 mL of ice cold water, filtered, dried and purified by column chromatography in petroleum ether and ethyl acetate (75:25).

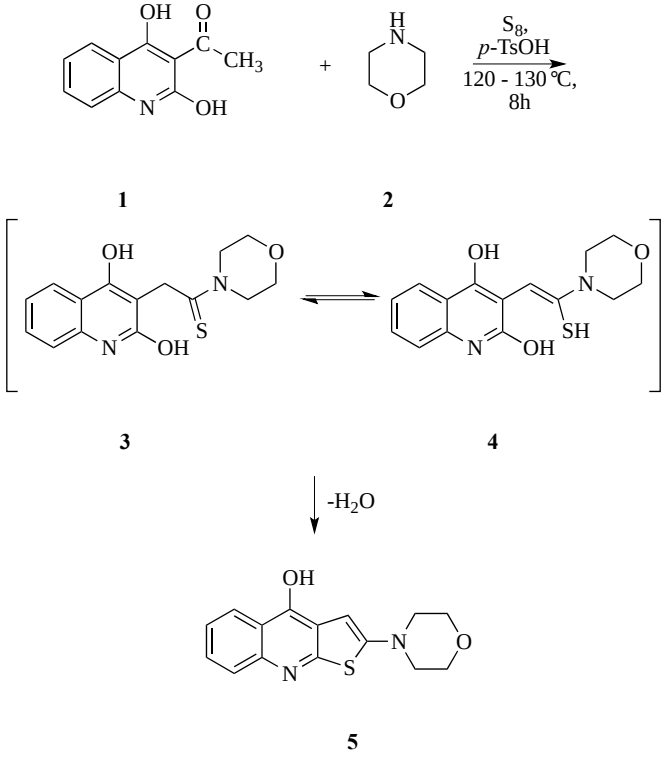
ANALAYTICAL DATA:

3-Acyl-2,4-dihydroxyquinoline **1**: 1.15 g (0.01 mol); morpholine **2**: 3 mL; Yield: 0.847 g (55%); m.p: 270°C; FT-IR (KBr, υ_{max}, cm^{-1}): 3238, 1634, 1562 ; ^{1}H-NMR(400 MHz, $CDCl_3$) : δ 8.50 (bs, 1H, Quinolino-C_4-O-H), δ 8.05 (d, 1H, *J* = 8.44 Hz, Quinolino-C_5-H), δ 7.91 (d, 1H, *J* = 8.44 Hz, Quinolino-C_8-H), δ 7.70 (t, 1H, *J* = 8.24 Hz Quinolino-C_7-H), δ 7.57 (t, 1H, *J* = 7.84 Hz, Quinolino-C_6-H), δ 5.58 (s, 1H, thieno-C_3-H), δ 4.20 (m, 8H, 2 x C**H**$_2$-C**H**$_2$); ^{13}C-NMR(100 MHz, $CDCl_3$): δ 156.14, 151.72, 147.87, 134.75, 130.83, 129.67, 128.53, 127.77, 126.62, 125.52, 112.14, 107.87, 63.84, 61.72.

RESULTS AND DISCUSSION:

In this work, our aim is focused to create a functional group with a nitrogen atom to afford the indole or quinoline ring. The Willgerodt Kindler reaction is a modern reaction with the mechanism indicating thio-substituted iminium-aziridinium rearrangements by the migration of carbonyl group to the end of the chain. 3-Acyl-2,4-dihydroxyquinoline **1** was chosen as a major substrate; it was synthesized by using our earlier reported procedure.[xxiii-xxiv] An equivalent mole of 3-acyl-2,4-dihydroxyquinoline **1**, morpholine **2**, 0.015 mole of octasulphur and catalytic amount of *p*-toluene sulfonic acid were mixed in a round bottom flask. The reaction mixture was heated at 120-130°C in an oil bath with stirring. The reaction was monitored by using TLC. After 8 h, the dark brown pasty material was cooled and poured into ice cold water. The creamy white precipitate was filtered and washed well with water. It was dried and purified through column chromatography with 25% ethyl acetate in petroleum ether. According to Willgerodt Kindler rearrangement, the expected product in this reaction condition is 2-(2,4-dihydroxyquinolin-3-yl)-1-morpholinoethanethione **3**. FT-IR data indicated the ketonic C=O stretching at approximately 1700 cm^{-1} is absent. The expected amide C=O

stretching is also not found in the FT-IR spectrum. However, a clean plot of ^{1}H-NMR spectrum showed eight proton multiplet from δ 4.1 to 4.3 for morpholino hydrogens, a broad singlet with a one proton count at δ 8.5 is presented for the C_4-OH of quinoline ring. The disappearance of a broad singlet at 11.0 for the respective C_2-OH of quinoline ring and appearance of one proton singlet at δ 5.85 for C_3-H of thieno ring supported that the expected product **3** underwent further dehydration and evolved 2-morpholinothieno[2,3-*b*]quinolin-4-ol **5** as a product. ^{13}C-NMR spectrum supported the structure of **5** with the appearance of morpholino carbons at δ 51.72 and 63.84 while the respective δ value for ketonyl or amide carbonyl carbon were not found.



CONCLUSION:

In conclusion, we used the Willgerodt Kindler rearrangement to create a fused quinoline-thiophene heterocycle. The one pot synthesis of 2-morpholinothieno[2,3-*b*]quinolin-4-ol is achieved through the frequent dehydration and cyclization due to the catalytic activity of *p*-toluene sulphonic acid. Compound **5** resembles the structure of dictamnine, a furo quinoline alkaloid therefore it is expected to gather momentum in the future in biological applications.

ACKNOWLEDGEMENT:

The authors thank Directorate of Collegiate Education for endorsing the research activities at Government Arts and Science colleges of Tamilnadu, India.

REFERENCES:

i. Flannery E.L.; Chatterjee A.K. and Winzeler E.A.; Antimalarial drug discovery - approaches and progress towards new medicines; Nat. Rev. Microbiol.; 2013;**11**, 803.

ii. Rodolfo T.; Stefanie C.; Pinto L.; Fabio T.; Maranhão C. and Liana V.; Chloroquine: modes of action of an undervalued drug; Immunol. Lett.; 2013, **153** (1), 50.
iii. Al-Bari, M.A.A.; Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases; Pharmacol. Res. Perspect.; 2017, **5** (1), e00293.
iv. Yuan Z.; Zhi L.; L-Juan Z. and Hang-Tao X.; The utility of chloroquine in cancer therapy; Curr. Med. Res. Opin.; 2015, **31** (5), 1009.
v. Anna C.C.A.; Erika M.; Wilian A.C.; Andre S.P.; Maria M.F.S.A.; Daniele C.S.B.; Jessica. S.G.; Mario R. M. and Antoniana U.K.; Chloroquine analogs as antimalarial candidates with potent in vitro and in vivo activity; Int. J. Parasitol. Drugs Drug Resist.; 2018, **8** (3), 459.
vi. Titus, E.O.; Recent developments in the understanding of the pharmacokinetics and mechanism of action of chloroquine; Ther. Drug Monit.; 1989, **11** (4), 369.
vii. Pussard E. and Verdier F.; Antimalarial 4-aminoquinolines: mode of action and pharmacokinetics; Fundam. Clin. Pharmacol.; 1994, **8** (1), 1.
viii. Ciska V.; Hannelore M.; Macro B.S.; Vikas P.S.; Pan P.; Vidula S.; Patrizia A. and Gauthier B.; Repurposing Drugs in Oncology (ReDO)-chloroquine and hydroxychloroquine as anti-cancer agents; E-cancer Med. Sci.; 2017, **11**, 781.
ix. Lavrado J.; Moreira R. and Paulo A.; Indoloquinolines as Scaffolds for Drug Discovery; Current Medicinal Chemistry; 2010, **17**, 2348 (and the references cited therein).
x. Motohide S.; Takahisa M.; Hisateru A.; Takashi M.; Masaki Y.; Yoshiharu I.; Hiroshi K.; Yuji M.; Wataru W.; Kazunobu Y.; Satoru I.; Eiichi K.; Masao M. and Hisashi S.; Novel HIV-1 Integrase Inhibitors Derived from Quinolone Antibiotics; J. Med. Chem.; 2006**, 49**, 1506.
xi. Beura S. and Prabhakar C.; In-silico strategies for probing chloroquine based inhibitors against SARS-CoV-2; J. Biomol. Struct. Dyn.; 2020, 1.
xii. Adeoye A.O.; Oso B.J.; Olaoye I.F.; Tijjani H. and Adebayo A.I.; Repurposing of chloroquine and some clinically approved antiviral drugs as effective therapeutics to prevent cellular entry and repli- cation of coronavirus; J. Biomol. Struct. Dyn.; 2020, 1-11.
xiii. Devaux C.A.; Rolain J.M.; Colson P. and Raoult D.; New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?; Int. J. Antimicrob. Agents; 2020, **55**, 19–20.
xiv. Sahraei Z.; Shabani M.; Shokouhi S. and Saffaei A.; Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine; Int. J. Antimicrob. Agents; 2020, **55**,1.
xv. Gevers S.; Kwa M.S.G.; Wijnans E. and van Nieuwkoop C.; Safety considerations for chloroquine and hydroxychloroquine in the treat- ment of COVID-19; Clin. Microbiol. Infect.; 2020, 4539.
xvi. (a) Murai T.; Chalcogeno- carboxylic Acid Derivatives, ed. S. Kato, Springer-Verlag Berlin, Berlin; 2005, **251**, 247.; (b) Hurd R. N. and Delamater G.; Chem. Rev.; 1961, **61**, 45; (c) Jagodzinski T. S.; Chem. Rev.; 2003, **103**, 197.
xvii. Cava M. P. and Levinson M. I.; Thionation Reactions of Lawesson's Reagent; Tetrahedron; 1985, **41**, 5061.
xviii. (a) Charette A. B. and Grenon M.; Mild Method for the Conversion of Amides to Thioamides; J. Org. Chem., 2003, 68, 5792; (b) Charette A. B. and Chua P.;

Thiolysis and hydrolysis of imino and iminium triflates: Synthesis of secondary and tertiary thioamides and ^{18}O-labeled amides; Tetrahedron Lett., 1998, **39**, 245.

xix. (a) Aki S.; Fujioka T.; Ishigami, M. and Minamikawa J.; A practical synthesis of 3,4-diethoxybenzthioamide based on Friedel-Crafts reaction with potassium thiocyanate in methanesulfonic acid; Bioorg. Med. Chem. Lett., 2002, **12**, 2317; (b) Jagodzinski T.; Jagodzinska E. and Jablonski Z.; A Friedel-Crafts synthesis of N-substituted thiophenecarbothioamides; Tetrahedron, 1986, **42**, 3683.

xx. Messeri T.; Sternbach D.D. and Tomkinson N.C.O.; A novel deprotection/ functionalisation sequence using 2,4-dinitrobenzenesulfonamide: Part 2; Tetrahedron Lett., 1998, **39**, 1673.

xxi. Willgerodt C.; Ber. Dtsch. Chem. Ges.; 1987, **20**, 2467.

xxii. Kindler K.; Liebigs Ann. Chem.; 1923, **413**, 187.

xxiii. Pitchai P.; Uvarani C.; Gengan R. M. and Mohan P. S.; A one pot microwave assisted synthesis of 3-acyl-2,4-dihydroxyquinoline followed by synthesis of 7-methyldibenzo[*c*,*f*][2,7]naphthyridin-6(5*H*)-ones *via* three routes; Indian Journal of Chemistry; 2013, **52B**(06),776.

xxiv. Pitchai P.; Nepolraj A.; Sathiyaseelan M. and Gengan R. M.; 2,4-dihydroxy-3-(indol-2-)-yl-quinoline via a substantial methodology – Fisher indole synthesis; Heterocyclic Letters; 2016, **6** (1), 11.

Received on March 15, 2022.