Solvent free and High yielding Synthesis of new dimethyl 1-(2-chloroquinolin-3-yl)-2,2-dicyanoethylphosphonate from 2-chloroquinoline-3-carbaldehyde

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Abstract : A simple solvent free and high yielding method was developed for the synthesis of new derivatives of dimethyl 1-(2-chloroquinolin-3-yl)-2,2-dicyanoethylphosphonate from 2-((2-chloroquinolin-3-yl)methylene)malononitrile, obtained from 2-chloroquinolin-3-carbaldehydes by using dimethylphosphite in the presence of DBU as catalyst at room temperature. All the synthesized compounds were characterized by IR, ^{1}HNMR, Mass spectroscopy.

Keywords 2-chloroquinoline-3-carbaldehyde, Knoevenagel condensation, Michael addition, dimethylphosphite, DBU.

I. INTRODUCTION

Quinoline ring system represents a very important and major class of heterocyclic compounds and is used as a key intermediate for many pharmacologically important compounds.[1-3] The derivatives of quinoline exhibits physiological and biological activities as antimalarial,[4-7]anti-inflammatory,[8-11] antitumor,[12-14] DNA binding capacity,[15]antibacterial,[16]antimicrobial,[17-21] anticancer[22]and antiparasiticproperties.[23]Also quinoline is used in the study of bioorganic and bioorganometallic processes.[24]
Organophosphorous compounds are important substrates in the study of biochemical processes[25] and are widely used as biologically active compounds. Phosphonates are versatile intermediates in organic synthesis due to their application in the Wadsworth-Emmons and related reactions.[26 -27] In the last few years, phosphonates have been the focus of intensive studies due to their interest as stable transition state analogue enzyme inhibitors. In fact, the phosphonates and phosphonic acid moieties may be accepted by enzymes as false substrates and interfere with biological processes.[28-31] Owing to their synthetic and biological values, the chemistry of phosphonates has stimulated increasing interest and the development of new organophosphorous compounds and new methodologies for their preparation still remains of great interest.[32-34] Simoni et al[35] reported the tetramethylguanidine catalyzed addition of dialkylphosphates to a variety of α,β- unsaturated compounds including carboxylic acid esters, ketones, and nitriles as well as, saturated aldehydes, ketones and imines. Wasielewski and coworkers[36] described the addition of sodium diethylphosphite to ethyl acrylate to give 3-phosphonopropionates. Chambers et al[37] reported the addition of dimethyl phosphonate to methyl N-acetyl-2- aminoacrylate, which was prepared by trimethylphosphite mediated esterification of the corresponding acid. Synthesis of the GABA-B antagonist, Phaclofen, which features a Michael addition of a phosphonates to β-nitrostyrene was reported by Hal.l[38] Addition of H-P bond to olefins promoted by AIBN or base described by Zhao.[39] Tan and co-workers[40] showed TBD catalyzed P-C bond formation via the conjugateaddition.

Knoevenagel condensation reactions have been extensively studied as an important carbon-carbon bond forming reaction. Generally, this reaction is catalyzed by a Lewis acid or base.[41-45]
Literature survey revealed that condensation of 2-((2-chloroquinolin-3-yl)methylene)malononitrile with dimethyl phosphite have not been reported. Herein we wish to report an efficient, environmentally benign method for the preparation of dimethyl 1-(2-chloroquinolin-3-yl)-2,2-dicyanoethylphosphonate.

II. MATERIAL AND METHODS

In laboratory 2-chloroquinoline-carbaldehyde[1] was prepared using reported method. Required solvents and reagents are purchased from spectrochem, Avra chemicals and S.D. fine chem. otherwise stated. Physical constants (melting point) were carried out in open capillaries at atmospheric pressure. Proton NMR were recorded on AVANCE in $CDCl_3$+DMSO and $CDCl_3$ at 300 MHz, 400 MHz using standard as TMS. Perkin- Elmer and Shimadzu FTIR were used for recording of IR spectra. Thermo exactive orbitrap methods (FTMS) used for mass spectra analysis, showing a molecular ion peak.

Experimental Procedure

Synthesis of 2-((2-chloroquinolin-3-yl)methylene)malononitrile(2a)

To the stirred solution of 2-chloroquinoline-3-carbaldehyde (0.96 gm, 5 mmol) and malonanitrile(0.45 gm, 7.5 mmol) was added DBU (2 to 3 drops) at room temperature. The progress of reaction was monitored by the TLC (solvent system- hexane: ethyl acetate). After the completion of the reaction (10 min), reaction mixture was dissolved in 10 mL of ethanol and was added 30 mL of cold water. The obtained solid was filtered and washed with water, dried under vacuum (1.15 gm, 95%).

Synthesisofdimethyl 1-(2-chloroquinolin-3-yl)-2,2-dicyanoethylphosphonate(3a)

Toa mixture of 2-((2-chloroquinolin-3-yl)methylene)malononitrile(1.0 gm, 4.1 mmol) and dimethylphosphite (1.65 gm, 15 mmol) was added DBUin catalytic amount and was stirred at room temperature for 45-60 min. 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 dissolved in methanol and was concentrated. The concentrated mass was dissolved in methylene chloride (10 ml)and precipitated by slowly addition of 30 mL hexane to afford the pure compound (1.25 gm, 85%).

Spectral Data

2-((2-chloroquinolin-3-yl)methylene)malononitrile(2a)

IR (KBr, cm^{-1}): 2221 (-C≡N);

FT-MS: m/z 240.2 (m+1) and 242.2 (m+3).

dimethyl (1-(2-chloroquinolin-3-yl)-2,2-dicyanoethyl)phosphonate(3a)

IR (KBr, cm^{-1}): 2252 (-C≡N); 1235 (-P=O); 1032 (-P-O-C).

^{1}H NMR ($CDCl_3$, δ ppm):2.6 (d, 1H,(-CH-CH); 2.85(d, 1H, -CH-CH); 3.5 (s, 3H, $-OCH_3$); 3.6 (s, 3H, $-OCH_3$), 7.62 (t, 1H, Ar-H); 7.8 (t, 1H, Ar-H); 7.92 (d,1H, Ar-H); 8.04 (d, 1H, Ar-H); 8.35 (s, 1H, Ar-H)

FT-MS: m/z 350.1 (m+1) and 352.1 (m+3).

dimethyl (1-(2-chloro-6-methylquinolin-3-yl)-2,2-dicyanoethyl)phosphonate(3b)

IR (KBr, cm^{-1}): 2254 (-C≡N); 1238 (-P=O); 1030 (-P-O-C).

^{1}H NMR ($CDCl_3$, δ ppm):2.32 (s, 3H, Ar-CH_3); 2.54 (d, 1H, -CH-CH); 2.90 (d, 1H, -CH-CH); 3.54 (s, 3H, $-OCH_3$); 3.62 (s, 3H, $-OCH_3$), 7.60 (d, 1H, Ar-H); 7.70(d, 1H, Ar-H); 7.95 (d,1H, Ar-H); 8.30 (s, 1H, Ar-H)

FT-MS: m/z 364.2 (m+1) and 364.2 (m+3).

dimethyl (1-(2-chloro-7-methylquinolin-3-yl)-2,2-dicyanoethyl)phosphonate(3c)

IR (KBr, cm^{-1}): 2255 (-C≡N); 1240 (-P=O); 1025 (-P-O-C).

^{1}H NMR ($CDCl_3$, δ ppm):2.35 (s, 3H, Ar-CH_3) 2.50 (d, 1H, -CH-CH); 2.96 (d, 1H, -CH-CH); 3.60 (s, 3H, $-OCH_3$); 3.65 (s, 3H, $-OCH_3$), 7.52 (d, 1H, Ar-H); 7.72 (d, 1H, Ar-H); 7.95 (d,1H, Ar-H); 8.30 (s, 1H, Ar-H)

FT-MS: m/z 364.1 (m+1) and 366.1 (m+3).

dimethyl (1-(2-chloro-8-methylquinolin-3-yl)-2,2-dicyanoethyl)phosphonate (3d)

IR (KBr, cm^{-1}): 2257 (-C≡N); 1241 (-P=O); 1028 (-P-O-C).

^{1}H NMR ($CDCl_3$, δ ppm):2.56 (s, 3H, Ar-CH_3) 2.64 (d, 1H, -CH-CH); 2.95 (d, 1H, -CH-CH); 3.66 (s, 3H, $-OCH_3$); 3.72 (s, 3H, $-OCH_3$), 7.65 (t, 1H, Ar-H); 7.71 (d, 1H, Ar-H); 7.89 (d,1H, Ar-H); 8.35 (s, 1H, Ar-H)

FT-MS: m/z 350.1 (m+1) and 352.1 (m+3).

dimethyl (1-(2-chloro-6-methoxyquinolin-3-yl)-2,2-dicyanoethyl)phosphonate(3e)

IR (KBr, cm^{-1}): 2254 (-C≡N); 1236 (-P=O); 1026 (-P-O-C).

^{1}H NMR ($CDCl_3$, δ ppm): 2.72 (d, 1H, -CH-CH); 2.92 (d, 1H, -CH-CH); 3.5 (s, 3H, $-OCH_3$); 3.6 (s, 3H, $-OCH_3$),3.99 (s, 3H, Ar-OCH_3); 7.22 (d, 1H, Ar-H); 7.35 (d, 1H, Ar-H); 7.85 (d,1H, Ar-H); 8.30 (s, 1H, Ar-H)

FT-MS: m/z 380.1 (m+1) and 382.1 (m+3).

dimethyl (1-(2-chloro-7-methoxyquinolin-3-yl)-2,2-dicyanoethyl)phosphonate (3f)

IR (KBr, cm^{-1}): 2250 (-C≡N); 1232 (-P=O); 1024 (-P-O-C).

^{1}H NMR ($CDCl_3$, δ ppm): 2.71 (d, 1H, -CH-CH); 2.95 (d, 1H, -CH-CH); 3.55 (s, 3H, $-OCH_3$); 3.62 (s, 3H, $-OCH_3$),3.97 (s, 3H, Ar-OCH_3) 7.32 (d, 1H, Ar-H); 7.38 (d, 1H, Ar-H); 7.96 (d,1H, Ar-H); 8.31 (s, 1H, Ar-H)

FT-MS: m/z 380.1 (m+1) and 382.1 (m+3).

Table I data of2-((2-chloroquinolin-3-yl)methylene)malononitrile

Entry	R_1	R_2	R_3	Time (min)	Yield (%)	Melting Point (°C)
2a	H	H	H	10	95	150-152
2b	CH_3	H	H	15	93	164-166
2c	H	CH_3	H	10	91	140-142
2d	H	H	CH_3	10	94	172-174
2e	OCH_3	H	H	15	92	148-150
2f	H	OCH_3	H	15	91	165-167

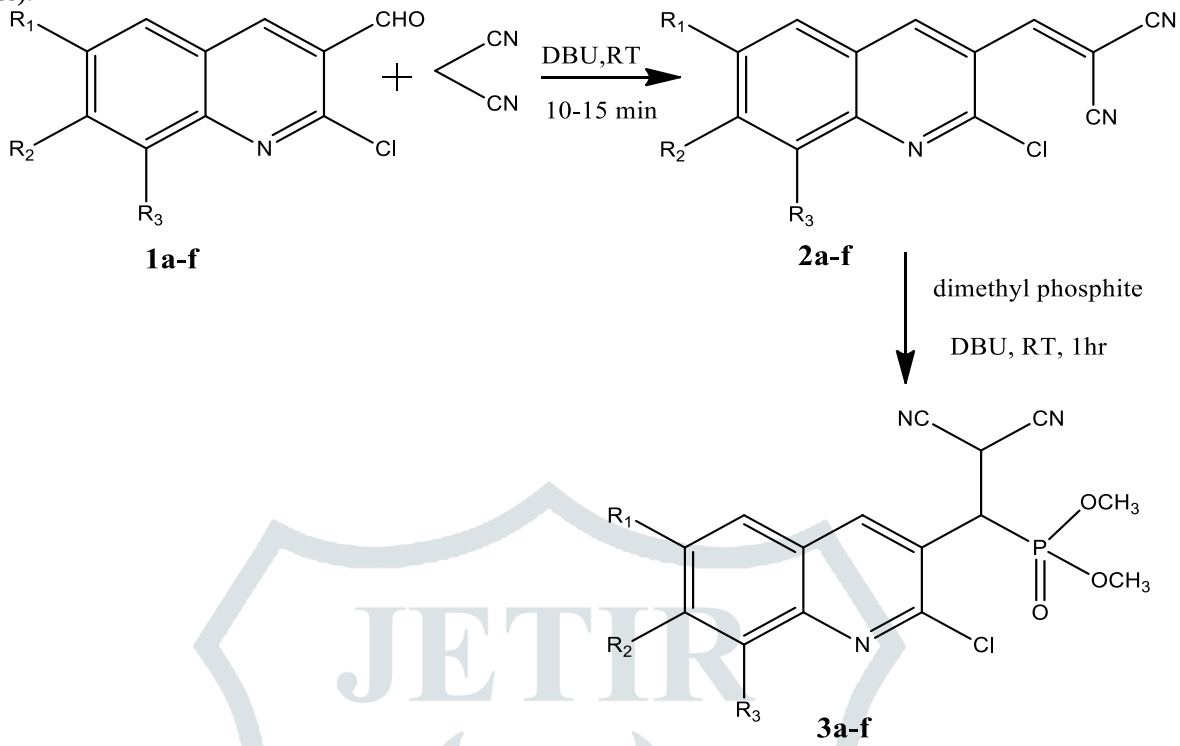
Table II data ofdimethyl (1-(2-chloroquinolin-3-yl)-2,2-dicyanoethyl)phosphonate

Entry	R_1	R_2	R_3	Time (min)	Yield (%)	MP/BP (°C)
3a	H	H	H	50	85	136-138
3b	CH_3	H	H	45	87	128-130
3c	H	CH_3	H	45	84	140-142
3d	H	H	CH_3	50	86	110-112
3e	OCH_3	H	H	60	84	152-154
3f	H	OCH_3	H	50	85	180-182

III. RESULT AND DISCUSSION

2-((2-chloroquinolin-3-yl)methylene)malononitrile**(2a-f) (Scheme 1, Table I)** were synthesized by the Knoevenagel condensation of substituted 2-chloroquinoline-3-carbaldehyde and malonanitrile using catalytic amount of DBU under solvent free condition in excellent yields. The products were characterized by physical and spectroscopic data.

dimethyl 1-(2-chloroquinolin-3-yl)-2,2-dicyanoethylphosphonate**(3a-f)(Scheme 1, Table II)** were then prepared in excellent yields by reacting 2-((2-chloroquinolin-3-yl)methylene)malononitrile**(2a-f)** with dimethylphosphite in the presence of DBU as catalyst without solvent at room temperature. Michael addition product has been confirmed by spectral analysis (IR, NMR and Mass).



Scheme-1: Synthesis of dimethyl 1-(2-chloroquinolin-3-yl)-2,2-dicyanoethylphosphonate

IV. CONCLUSION

In conclusion, a new methodology was developed for the synthesis of novel dimethyl (1-(2-chloroquinolin-3-yl)-2,2-dicyanoethyl)phosphonatederivatives **(3a-f)** from2-((2-chloroquinolin-3-yl)methylene)malononitrile**(2a-f)**, obtained from 2-chloroquinolin-3-carbaldehydes **(1a-f)** by using dimethylphosphite in the presence of DBU as catalyst at room temperature in high yields**.** All the reactions were performed under mild reaction conditions, shorter reaction time and in high yields (Table II).

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