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DBU CATALYZED SYNTHESIS OF *O,O*- DIETHYL PHOSPHOROTHIOATES

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Abstract:
A highly effective and simple method was developed for the synthesis of *O,O*- Diethyl Phosphorothioates**(3a-h)** from2-chloroquinolin-3-yl-methanol derivatives **(2a-h)** using *O,O*-diethyl phosphorochloridothioate in the presence of DBU as catalyst at room temperature in quantitative yields. The reactions were performed under mild reaction conditions, shorter reaction time and in quantitative yields. All the synthesized compounds were characterized by IR, ^{1}HNMR and mass spectroscopy.

Keywords:
2-chloroquinolin-3-yl-methanol, DBU, 2-chloroquinoline-3-carbaldehyde, *O,O*-diethyl Phosphorothioates, *O,O*-diethyl phosphorochloridothioate.

Introduction:
Quinoline ring system is a very important and major class of heterocyclic compounds, it represents a key intermediate for many pharmacologically important compounds.[1]
The quinoline derivatives shows physiological and biological activities such as antimalarial,[2], anti-inflammatory,[3] antitumor,[4] DNA binding capacity,[5] antibacterial,[6] antimicrobial,[7] anticancer, [8] anti-tuberculosis,[9] antihistamine,[10] antifungal, [11] anti-HIV, [12] antihypertensive [13] and antiparasitic properties.[14] Quinoline also used in the study of bio-organic and bio-organometallic processes.[15]
Organo-Phosphonates [16] and α-aminophosphonates are important biologically active compounds [17] due to their structural analogy to amino acids. They also act as peptide mimics,[18] enzyme inhibitors,[19] antibiotics and pharmacological agents.[20]
Phosphorothioates have been found a wide range of applications such as industrial, agricultural and medicinal chemistry due to their biological and physical properties, as well as synthetic intermediates.[21] Phosphorothioates also used as pesticides.[22] In the recent, a number of phosphorothioates have been applicable for potential chemotherapeutic agents[23] and inhibitors of some enzymes.[24] Phosphorothioates are synthesized by reactions of dialkyl phosphites with sulfenyl chlorides,[25] sulfenyl cyanides [26], thiosulpohnates,[27] disulphides,[28] and sulfur [29], as well as by condensation of phosphorochloridates with thiols [30]. All these methods suffer from some disadvantages, including drastic reaction conditions and severe side reactions.
DBU have been widely used as a catalyst in many reactions such as Michael addition reaction of ß-ketoesters to acrylates and enones,[31]conjugate addition of acylsilanes to unsaturated esters and ketone,[32] for intramolecular aldehyde ketone Benzoin reactions[33] and in combination with other catalysts for oxidation of aldehydes to methyl esters.[34]
In continuation of our work related to phosphorus chemistry [35], we were interested in the synthesis of *O,O*-diethyl phosphorothioates using DBU as versatile catalyst.

Result and discussion:

In the present article we report on a two-step synthesis of *O,O*-diethyl phosphorothioates containing highly bioactive quinoline moiety. In the first step, 2-chloroquinolin-3-yl methanol derivatives **2a-h** were synthesized by reduction of the corresponding substituted 2-chloroquinoline-3-carbaldehydes **1a–h** with sodium borohydride in methanol at room temperature, and in the second step compounds **2a–h** were converted into *O,O*-diethyl *O*-(2-chloroquinolin-3-yl)- methyl phosphorothioates **3a–h** by treatment with *O,O*-diethyl phosphorochloridothioate in acetone in the presence of DBU as catalyst at room temperature (Scheme-1, Table-1). Phosphorothioates **3a–h** were isolated in almost quantitative yield and were characterized by IR, ^{1}H NMR, and mass spectra.

Materials and methods:

2-Chloroquinoline-3-carbaldehydes **1a–h** were prepared according to the procedure described previously[1] and were purified by column chromatography over silica gel (60–120 mesh). *O,O*-Diethyl phosphorochloridothioate was commercial product (Lancaster). Acetone, sodium borohydride, DBU and methanol were purchased from S.D. Fine Chem. All melting points were determined in open capillaries on Kumar's melting point apparatus. The ^{1}H NMR spectra were recorded on a Varian Mercury Plus spectrometer (400 MHz) in $CDCl_3$ using TMS as internal standard. The IR spectra were measured in KBr on a Perkin-Elmer FTIR instrument. The mass spectra were obtained on a Micromass Quattro II mass spectrometer (electrospray ionization). The purity of products and the progress of reactions were monitored by TLC on Merck silica gel plates.

Experimental Procedure:

2-Chloro-6-methylquinolin-3ylmethanol (2b). Sodium borohydride, 0.2 g (5.2 mmol) was slowly added under stirring at room temperature to a solution of 1.5 g (7.2 mmol) of 2-chloro-6-methyl-quinoline carbaldehyde (**1b**) in 10 ml of methanol. The progress of the reaction was monitored by TLC using hexane–ethyl acetate as eluent. When the reaction was complete (10 min),the mixture was concentrated under reduced pressure, the residue was treated with ice water, and the precipitate was filtered off, washed with water, and dried in an oven at 50°C for 8.0 h. Yield 1.44g (95.4%), mp 144–146°C.

Es-MS m/z: 207.8 [M+1], 209.9[M+3].

Compounds **2a** and **2c–h** were synthesized in a similar way.

***O*-(2-Chloro-6-methylquinolin-3-yl)methyl*O,O*-diethyl phosphorothioate (3b):** *O,O*-Diethyl phosphorochloridothioate, 1.5 g (7.9mmol), was added under stirring to a solution of 1.0 g (4.8 mmol) of 2-chloromethylquinolin-3-ylmethanol and 0.5 g of DBU in 10 ml of acetone, and the mixture was stirred until the reaction was complete (10 min; TLC, hexane–ethyl acetate, 8: 2).The mixture was poured on crushed ice, and the precipitate was filtered off, washed with water, and dried in a vacuum oven at 40°C. Yield 1.70 g (98.5%), mp. 71–73°C.

IR (cm^{-1}):2989(C–H), 1242 (P=S), 1021 (P–O–C).

^{1}HNMR (δppm): 1.31–1.40 (t, 6H, CH_2CH_3), 2.53 (s, 3H, Ar-CH_3), 4.14-4.22 (m, 4H, OCH_2CH_3), 5.27 (d, 2H, CH_2), 7.56 (d, 1H, Ar-H), 7.61 (s, 1H, Ar-H), 7.92 (d, 1H, Ar-H), 8.20 (s, 1H, Ar-H). **Es-MS m/z:** 360.1 [M+1], 362.1 [M+3].

Compounds **3a** and **3c–h** were synthesized in a similar way.

***O*-(2-Chloroquinolin-3-yl)methyl*O,O*-diethyl phosphorothioate (3a).**

IR (cm^{-1}): 2992 (C–H), 1234 (P=S), 1032 (P–O–C).

^{1}H NMR (δppm): 1.31–1.35 (t, 6H, CH_2CH_3), 4.14– 4.22 (m, 4H, OCH_2CH_3), 5.29 (d, 2H, -CH_2), 7.56 (t, 1H, Ar-H), 7.72 (t, 1H, Ar-H), 7.84 (d, 1H, Ar-H), 8.00 (d, 1H, Ar-H), 8.28 (s, 1H, Ar-H).

Es-MS m/z: 346.0 [M+1], 348.0 [M+3].

***O*-(2-Chloro-7-methylquinolin-3-yl)methyl*O*,*O*-diethyl phosphorothioate (3c):**

IR (cm^{-1}): 2981 (C–H), 1231 (P=S), 1028 (P–O–C).

^{1}H NMR (δ ppm): 1.30–1.34 (t ,6H, CH_2CH_3), 2.55 (s, 3H, Ar-CH_3), 4.13–4.20 (m, 4H, OCH_2-CH_3), 5.27 (d, 2H,-CH_2), 7.39 (d, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 8.22 (s, 1H, Ar-H).

Es-MS m/z: 360.1 [M+1], 362.0[M+3].

***O*-(2-Chloro-8-methylquinolin-3-yl)methyl*O*,*O*-diethyl phosphorothioate (3d).**

IR (cm^{-1}): 2986 (C–H), 1223 (P=S), 1027(P–O–C).

^{1}H NMR (δ ppm): 1.31–1.39 (t, 6H, OCH_2- CH_3), 2.74 (s, 3H, Ar-CH_3), 4.13–4.21 (m, 4H, OCH_2CH_3), 5.27 (d, 2H, CH_2), 7.42 (t, 1H, Ar-H), 7.55 (d, 1H, Ar-H), 7.64 (d, 1H, Ar-H), 8.22 (s,1H, Ar-H).

Es-MS m/z: 360.1 [M+1], 362.1 [M + 3].

***O*-(2-Chloro-6-methoxyquinolin-3-yl)methyl*O*,*O*-diethyl phosphorothioate (3e).**

IR (cm^{-1}): 2983 (C–H), 1228 (P=S), 1022 (P–O–C).

^{1}H NMR (δ ppm): 1.31–1.35 (t, 6H, OCH_2CH_3), 3.93 (s, 3H, Ar-OCH_3), 4.14–4.22 (m, 4H, OCH_2-CH_3), 5.27 (d, 2H,-CH_2), 7.10 (d, 1H, Ar-H), 7.36 (d.d, 1H, Ar-H,), 7.89 (d, 1H, Ar-H), 8.19 (s, 1H, Ar-H). **Es-MS m/z:** 376.0 [M+1], 378.1 [M+3].

***O*-(2-Chloro-7-methoxyquinolin-3-yl)methyl*O*,*O*-diethyl phosphorothioate (3f).**

IR (cm^{-1}): 2987 (C–H), 1234 (P=S), 1032 (P–O–C).

^{1}H NMR (δ ppm): 1.30–1.40 (t, 6H, OCH_2-CH_3), 3.93 (s, 3H, Ar-OCH_3), 4.13–4.21 (m, 4H, OCH_2CH_3), 5.26 (d, 2H, Ar-CH_2), 7.15(d.d, 1H, Ar-H), 7.29 (d, 1H, Ar-H), 7.65(d, 1H, Ar-H), 8.14 (s 1H, Ar-H).

Es-MS m/z: 376.1 [M+1], 378.1 [M+3].

***O*-(2-Chloro-8-ethylquinolin-3-yl)methyl*O*,*O*-diethyl phosphorothioate (3g).**

IR (cm^{-1}): 2985 (C–H), 1220 (P=S), 1026(P–O–C).

^{1}H NMR (δ ppm): 1.23–1.41 (m, 9H, OCH_2- CH_3, -CH_2CH_3), 3.19 (q, 2H, -CH_2), 4.13–4.21 (m, 4H, OCH_2CH_3), 5.27 (d, 2H, -CH_2), 7.45 (t, 1H, Ar-H), 7.55 (d, 1H, Ar-H), 7.64 (d, 1H, Ar-H), 8.22 (s, 1H, Ar-H).

Es-MS m/z: 374.1 [M+1], 376.1 [M+3].

***O*-(2-Chloro-6-ethoxyquinolin-3-yl)methyl*O*,*O*-diethyl phosphorothioate (3h).**

IR (cm^{-1}): 2989 (C–H), 1227 (P=S), 1020 (P–O–C).

^{1}H NMR (δ ppm): 1.31–1.34 (t, 6H, OCH_2CH_3), 1.46 (t, 3H, -OCH_2CH_3), 4.11–4.21 (m, 6H, OCH_2CH_3), 5.26 (d, 2H, -CH_2), 7.07 (d, 1H, Ar-H), 7.35 (d.d, 1H, Ar-H), 7.88(d, 1H, Ar-H), 8.15 (s, 1H, Ar-H).

Es-MS m/z: 390.1 [M+1]392.1 [M+3].

Conclusion:

Thus the proposed procedure ensures synthesis of new *O*,*O*-diethyl phosphorothioates from (2-chloro- quinolin-3-yl)methanol derivatives using *O*,*O*-diethyl phosphorochloridothioate in the presence of sodium hydroxide under mild conditions in a short time and with almost quantitative yields. It may be useful for combinatorial chemistry.

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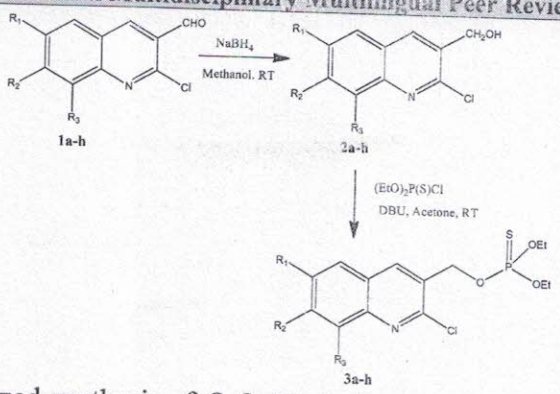

Scheme-1: DBU catalyzed synthesis of *O,O*- Diethyl Phosphorothioates

Table-1: DBU catalyzed *O,O*- Diethyl Phosphorothioates

Entry	R_1	R_2	R_3	Time (min)	Yield (%)	MP/BP (°C)
3a	H	H	H	15	97	52-54
3b	CH_3	H	H	10	98	71-73
3c	H	CH_3	H	15	98	53-55
3d	H	H	CH_3	10	98	164 Liq
3e	OCH_3	H	H	10	98	82-84
3f	H	OCH_3	H	10	98	165Liq
3g	OEt	H	H	10	98	183Liq
3h	H	H	C_2H_5	15	98	76-78

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