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Efficient Synthesis of Quinolo-oxepanes Through [3+2] Cycloaddition Reaction of α,β-Unsaturated Ester with Unstabilized Azomethine Ylides

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New functionalized quinolo-oxepane were achieved by intramolecular 1,3-dipolar cycloaddition reaction of α,β-unsaturated ester with unstabilized azomethine ylides derived from various α-amino acids with high stereo selectivity and good yields. These derivatives were synthesized *via* Wittig reaction under mild, neutral conditions in a short duration and consistently good yields. The structures of final compounds were characterized by spectral analysis.

Keywords: Quinolines, 1,3-Dipolar cycloaddition, Azomethine ylides, Wittig reaction.

INTRODUCTION

Quinoline is a heterocyclic scaffold of paramount importance to human race. The utility of quinoline derivatives in the areas of medicine, food, catalyst, dye, materials, refineries and electronics is well established. As a result, the synthesis of quinoline core and its derivatives have been an attractive goal for the synthetic organic chemist. In the recent past there have been several new developments in the chemistry associated with quinolines. Quinoline nucleus occurs in several natural compounds (cinchona alkaloids)[1] and pharmacologically active substances displaying a broad range of biological activity. Quinoline has been found to possess antimicrobial[2], antituberculosis[3], anti-bacterial[4,5], antifungal[6,7], cytotoxicity[8], antiviral[9], antitumor[10], antidepressant[11] and analgesic[12] activity. Certain quinoline-based compounds also show effective antihistamine[13] activity. This broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of quinoline, which allows the generation of a large number of structurally diverse derivatives. Quinoline and its analogs have recently been examined for their modes of function in the inhibition of tyrosine kinases[14] and DNA repair[15]. Some of the quinoline derivatives such as dutadrupine, mepacrine and levofloxacin are in clinical use. In such sequence of study it is observed that the activity of such nucleus may be due to the presence of fused pyridine.

Examples of reduced oxepine-based natural products such as brevetoxin-like polyether marine metabolites[16] and dihydrooxepine epidithiodiketopiperazines are well known and have been the subject of synthetic studies. The oxepine natural products are not only interest in terms of their biological properties but are also intriguing from a biosynthetic viewpoint. Cycloaddition reactions are one of the most important class of reaction in synthetic organic chemistry. Within class, the 1,3-dipolar cycloaddition[17] reaction has found extensive use as a high-yielding and efficient, regio and stereo controlled method for the synthesis of five membered heterocyclic compounds[18,19]. Placing the ylide dipole and the alkene within the same molecule provides direct access to bicyclic or polycyclic product of considerable complexity. These cycloaddition reactions were performed by reacting α-amino acids and carbonyl compounds gave rise to *in situ* azomethine-ylide formation which leads to form a five member nitrogen heterocycles with regio and stereo control.

EXPERIMENTAL

Toluene was freshly distilled from sodium/benzophenone, DMF from CaO and 1,2-dimethoxy ethane from NaH. All the products were confirmed by their spectral data. ^{1}H NMR and ^{13}C spectra were recorded on a Bruker Biospin spectrometer at 400 MHz; Mass spectra were recorded on Agilent mass spectrometer. Flash column chromatography was performed on Merck silica gel (230-400 mesh).

General procedure for the synthesis of substituted quinoline carbaldehyde (1a-b): At 0 °C to a stirred solution of $POCl_3$ (39.6 g, 259 mmol) and anhydrous DMF (8 g, 111 mmol) was added acetanilide (5 g, 37 mmol). The mixture was then heated to 65 °C and the progress of the reaction was

monitored by TLC analysis. After 8 h the reaction mixture was then cooled to room temperature and added cautiously into ice-cold water. The solid precipitated was collected by filtration to isolate the compound **1a** as yellow solid.

2-Chloroquinolin-3-carbaldehyde (1a): Yield 6.2 g (87 %), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.58 (s, 1H), 8.78 (s, 1H), 8.10 (m, 1H), 8.01 (m, 1H), 7.91 (m, 1H), 7.67 (m, 1H); LCMS: *m/z* 192.0 (M^+).

2-Chloro-6-methylquinolin-3-carbaldehyde (1b): Yield 1.0 g (77 %), off yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.55 (s, 1H), 8.67 (s, 1H), 7.97 (d, *J* = 8.0, 1H), 7.73 (m, 2H), 2.57 (s, 3H); LCMS: *m/z* 206.2 (M^+).

General procedure for the synthesis of substituted quinolyl α,β-unsaturated ester (2a-b): To a solution of compound **1** (1 g, 5.2 mmol) in anhydrous 1,2-dimethoxyethane was added methyl (triphenylphosphoranylidene)acetate (1.7 g, 5.2 mmol) and the mixture was heated to reflux for 8 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The solid thus obtained was purified by flash column chromatography on silica gel to yield the title compound **2** as white solid.

Methyl (E)-3-(2-chloroquinolin-3-yl)acrylate (2a): Yield 1.0 g (77 %), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (s, 1H), 8.14 (d, *J* = 16.0, 1H), 8.03 (d, *J* = 8.4, 1H), 7.87 (d, *J* = 8.0, 1H), 7.78 (m, 1H), 7.61 (m, 1H), 6.58 (d, *J* = 16.0, 1H), 3.87 (s, 3H); LCMS: *m/z* 248.2 (M^+).

Methyl (E)-3-(2-chloro-6-methylquinolin-3-yl)acrylate (2b): Yield 0.89 g (75 %), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (s, 1H), 8.14 (d, *J* = 16.0, 1H), 7.92 (m, 1H), 7.60 (m, 2H), 6.57 (d, *J* = 16.0, 1H), 3.88 (s, 3H), 2.56 (s, 3H); LCMS: *m/z* 262.2 (M^+).

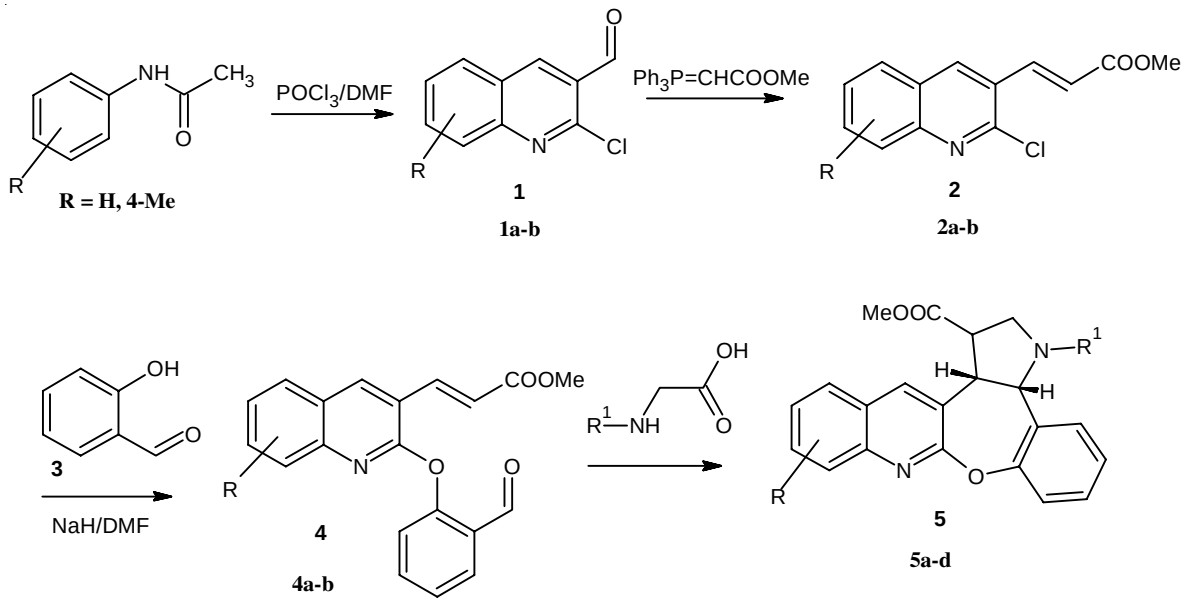
General procedure for the synthesis of 2-substituted quinolyl α,β-unsaturated ester (4a-b): At 0 °C, to a suspension of sodium hydride (0.12 g, 4.8 mmol) in anhydrous DMF (5 mL) were added salicylaldehyde (0.3 g, 2.4 mmol) and compound **2** (0.6 g, 2.4 mmol) in DMF solution. The mixture was heated to 80 °C and the progress of the reaction was monitored by TLC analysis. After 4 h, the reaction mixture was cooled to ambient temperature and added cautiously into ice-cold water. The contents were extracted with ethyl acetate washed with water, dried over sodium sulphate and filtered. The filtrate was concentrated under reduced pressure. The crude product thus obtained was purified by flash column chromatography on silica gel to the title compound **4a** as white solid.

Methyl (E)-3-[2-(2-formylphenoxy)quinolin-3-yl]acrylate (4a): Yield 0.54 g (67 %), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.01 (s, 1H), 8.41 (s, 1H), 8.11 (d, *J* = 16.0, 1H), 8.04 (m, 1H), 7.69 (m, 1H), 7.55 (m, 2H), 7.42 (m, 2H), 7.25 (m, 3H), 6.84 (d, *J* = 16.0, 1H), 3.85 (s, 3H); LCMS: *m/z* 334.2 (M^+).

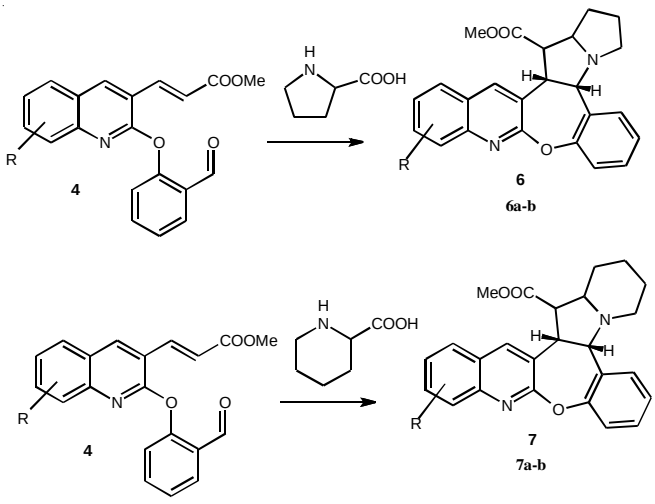
Methyl (E)-3-[2-(2-formylphenoxy)-6-methylquinolin-3-yl]acrylate (4b): Yield 0.92 g (76 %), off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.2 (s, 1H), 8.30 (s, 1H), 8.11 (d, *J* = 16.0, 1H), 8.03 (m, 1H), 7.71 (m, 1H), 7.69 (m, 2H), 7.44 (m, 2H), 6.83 (d, *J* = 16.0, 1H), 3.87 (s, 3H), 2.50 (s, 3H); MS: *m/z* 348.2 (M^+).

General procedure for the synthesis of quinolo-oxepane derivatives (5a-d, 6a-b and 7a-b): A mixture of compound **4a** (0.1 g, 0.3 mmol) and N-methyl glycine (0.05 g, 0.6 mmol) in anhydrous xylene (3 mL) was heated to reflux and the progress of the reaction was monitored by TLC analysis. The reaction mass was then cooled to ambient temperature and concentrated under reduced pressure. The crude product thus obtained was purified by flash column chromatography on silica gel to afford pure product **5a** (**Schemes I** and **II**).

Methyl 3-methyl-2,3,3a,14b,tetrahydro-1*H*-benzo[6,7]-pyrrolo[3',2':4,5]oxepino[2,3-b]quinoline-1-carboxylate (5a): Viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.12 (s, 1H), 8.01 (m, 1H), 7.74 (m, 1H), 7.69 (m, 1H), 7.49 (m, 3H), 7.30 (m, 2H), 4.07 (d, *J* = 11.0, 1H), 3.87 (s, 3H), 3.74 (m, 2H), 3.25 (m, 1H), 2.89 (m, 1H), 2.30 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 179.8, 172.3, 148.5, 144.2, 138.0, 135.2, 129.0, 127.4, 123.4 122.1 60.1 59.3, 52.1, 50.0, 42.4, 40.2; LCMS: *m/z* 361.0 (M^+).



Scheme-I



Scheme-II

Methyl 3-ethyl-2,3,3a,14b,tetrahydro-1*H*-benzo[6,7]-pyrrolo[3',2':4,5]oxepino[2,3-b]quinoline-1-carboxylate (5b): Viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.08 (s, 1H), 8.01 (m, 1H), 7.73 (m, 1H), 7.67 (m, 1H), 7.56 (m, 1H), 7.46 (m, 1H), 7.28 (m, 1H), 7.13 (m, 2H), 4.17 (d, *J* = 11.0, 1H), 3.82 (m, 1H), 3.66 (s, 3H), 3.48 (m, 2H), 2.75 (m, 1H), 2.45 (m, 1H), 2.33 (m, 1H), 1.09 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 179.2, 163.3, 149.5, 144.3, 137.6, 133.3, 129.4, 127.5, 123.3, 122.2, 60.8, 57.6, 52.4, 49.7, 47.5, 40.4, 12.4; LCMS: *m/z* 375.2 (M^+).

Methyl 3,12-dimethyl-2,3,3a,14b,tetrahydro-1*H*-benzo[6,7]pyrrolo[3',2':4,5]oxepino[2,3-b]quinoline-1-carboxylate (5c): Gummy liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.01 (s, 1H), 7.88 (d, *J* = 8.8 *Hz*, 1H), 7.52 (m, 2H), 7.44 (m, 4H), 4.01 (d, *J* = 11.0 *Hz*,1H), 3.86 (s, 3H), 3.75 (m, 2H), 3.25 (m, 1H), 2.85 (m, 1H), 2.52 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 176.3, 172.3, 149.3, 140.0, 136.4, 135.3, 128.3, 125.4, 122.0, 120.1, 103.3, 60.5, 58.6, 49.3, 42.3, 40.2; LCMS: *m/z* 375.2 (M^+).

Methyl 3-ethyl,12-methyl-2,3,3a,14b,tetrahydro-1*H*-benzo[6,7]pyrrolo[3',2':4,5]oxepino[2,3-b]quinoline-1-carboxylate (5d): Gummy solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.99 (s, 1H), 7.90 (d, *J* = 8.8 *Hz*, 1H), 7.53 (m, 1H), 7.46 (m, 2H), 7.27 (m, 1H), 7.16 (m, 2H), 4.20 (m, 2H), 3.74 (s, 3H), 3.45 (m, 2H), 2.85 (m 1H), 2.49 (s, 6H), 2.35 (m, 2H), 1.11 (t, *J* = 8.0 *Hz*, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 178.3, 173.2, 155.0, 149.6, 140.1, 135.3, 133.2, 128.4, 127.5, 123.2, 119.0, 104.3, 60.2, 58.5, 53.3, 47.2, 40.2, 14.4; LCMS: *m/z* 389.2 (M^+).

Methyl 2,3,4a,15b,16,16a-hexahydro-1*H*-benzo[6,7]-pyrrolizino[2',3'4,5]oxepino[2,3-b]quinoline-16-carboxylate (6a): Gummy liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.95 (s, 1H), 7.80 (m, 1H), 7.65 (m, 2H), 7.44 (m, 1H), 7.25 (m, 1H), 7.11 (m, 1H), 7.02 (m, 1H), 6.89 (m, 1H), 4.07 (d, *J* = 11.0, 1H), 3.88 (m, 1H), 3.72 (s, 3H), 2.88 (m, 1H), 2.70 (m, 1H), 2.35 (m, 2H), 1.60 (m, 2H), 1.45 (m, 2H); LCMS: *m/z* 387.2 (M^+).

Methyl13-methyl-2,3,4a,15b,16,16a-hexahydro-1*H*-benzo[6,7]pyrrolizino[2',3'4,5]oxepino[2,3-b]quinoline-16-carboxylate (6b): Gummy liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.98 (m, 1H), 7.90 (m, 1H), 7.55 (m, 1H), 7.42 (m, 2H), 7.22 (m, 1H), 7.18 (m, 2H), 4.21 (m, 2H), 3.72 (s, 3H), 3.42 (m, 2H), 2.85 (m, 1H), 2.50 (s, 6H), 2.45 (m, 1H), 1.63 (m, 2H), 1.40 (m, 2H); LCMS: *m/z* 401.2 (M^+).

Methyl 1,2,3,4,5a,16b,17,17a-octahydrobenzo[6,7]-indolizino[2',3'4,5]oxepino[2,3-b]quinoline-17-carboxylate (7a): Viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (m, 2H), 7.58 (m, 1H), 7.49 (m, 3H), 7.28 (m, 1H), 7.13 (m, 2H), 4.20 (m, 1H), 3.90 (m, 1H), 3.68 (s, 3H), 3.01 (m, 1H), 2.90 (m, 1H), 2.34 (m, 2H), 1.56 (m, 2H), 1.46 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 179.8, 173.4, 160.5, 156.4, 144.2, 139.4, 135.8, 132.0, 129.7, 127.6, 125.9, 124.8, 123.4, 68.3, 66.2, 57.5, 51.8, 46.5, 29.7, 23.9, 21.4; LCMS: *m/z* 401.0 (M^+).

Methyl 14-methyl-1,2,3,4,5a,16b,17,17a-octahydro-benzo[6,7]indolizino[2',3'4,5]oxepino[2,3-b]quinoline-17-carboxylate (7b): Viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (m, 2H), 7.88 (d, *J* = 8.8, 1H), 7.45 (m, 3H), 7.26 (m, 2H), 7.19 (m, 2H), 4.15 (m, 1H), 3.89 (m, 2H), 3.74 (s, 3H), 3.01 (m, 1H), 2.80 (m, 1H), 2.45 (s, 6H), 2.40 (m, 1H), 2.12 (m, 1H), 1.50 (m, 2H), 1.20 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 179.3, 173.4, 160.5, 156.4, 144.2, 139.9, 135.8, 132.0, 129.7, 127.8, 125.9, 124.8, 123.4, 68.3, 66.2, 57.5, 51.8, 50.8, 46.5, 29.7, 24.8, 23.9, 21.4; LCMS: *m/z* 415.4 (M^+).

RESULTS AND DISCUSSION

In the course of our ongoing research the synthesis of quinolo-oxepane were prepared through intramolecular 1,3-diploar cycloaddition reaction with Wittig products. To our best knowledge pyrrolidines and benzo-oxepanes which are present in biologically active molecules have never been combined with quinolines subunits. 2-Chloro 3-formyl quinolines were obtained by subjecting the suitable acetanilide with Vilsmeier reagent ($POCl_3$/DMF)[20]. Further the quinoline skeleton was extended by Wittig reaction with phosphonium ylides[21] (Ph_3P=CHCOOMe) in refluxing 1,2-dimethoxy ethane gave the corresponding α,β-unsaturated ester (**2**) with high stereoslectivity in good yields. Subsequent reaction of Wittig product with salicylaldehyde in presence of NaH/DMF yields compound **4**.

With these activated alkenes we turned our attention to the synthesis of cycloadducts[22,23] through azomethine ylides with various α-amino acids[24,25]. This reaction was conducted in refluxing anhydrous xylene to afford quinolo-oxepane in good yields. The yields of the reaction are tabulated in (Tables 1 and 2). The formation of the cyclo-adducts was confirmed by spectral analysis.

Conclusion

The structures and the regiochemistry of the cycloadducts **5a-d, 6a, b and 7a, b** were confirmed by spectroscopic data. The reaction were found to be highly regioselective leading to the formation of only one product in which ring junction protons were found to be *cis*. In conclusion, this paper describes the cycloaddition reactions of unstable azomethine ylides generated *in situ* by the decarboxylative condensation of the O-alkylated salicylaldehyde (**4**) with N-substituted glycine in xylene to afford the novel quinolo-oxepane. This simple method utilizes commercially available materials and is performed under neutral conditions.

TABLE-1
YIELDS OF QUINOLO-OXEPANE DERIVATIVES

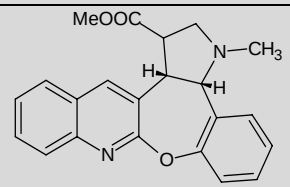
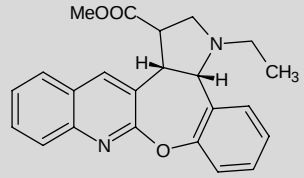
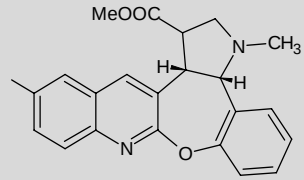
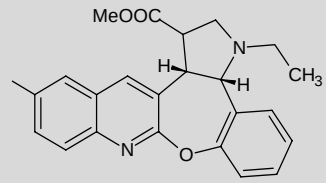
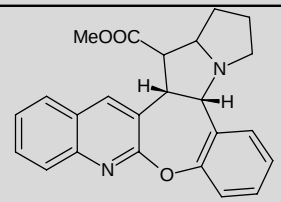
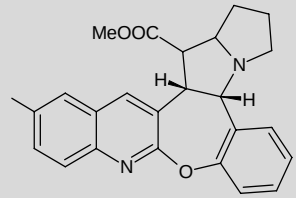
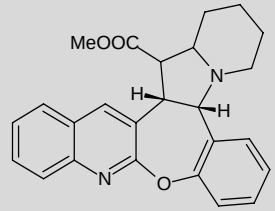
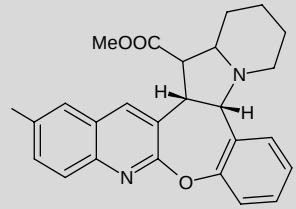
Compd. No.	Product	Time (min)	Yield (%)
5a		30	82
5b		25	88
5c		40	79
5d		50	84

TABLE-2
YIELDS OF QUINOLO-OXEPANE DERIVATIVES

Compd. No.	Product	Time (min)	Yield (%)
6a		40	78
6b		45	79
7a		55	82
7b		50	85

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