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A clean procedure for synthesis of phenylquinoline derivatives

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ABSTRACT

In this investigation the reaction of cyclohexanone 1 with benzaldehyde 2 yielded (E)-2-benzylidenecyclohexanone 3, which on reaction with 3-oxo-N-phenylbutanamide afforded 1-(1, 4, 5, 6, 7, 8-hexahydro-2-hydroxy-1, 4-diphenylquinolin-3-yl) ethanone.4. While the treatment of 4 with ethylbromoacetate and bromophenylethanone afforded the compounds 5 and 6 respectively. However, treatment of 4 with phosphoryltrichloride gave the corresponding compound 7. The reaction of compound 4 with hydrazine hydrate in ethanol led to the formation 4, 5, 6, 7, 8, 9-hexahydro-3-methyl-4,9-diphenyl-1H-pyrazolo [3, 4-b] quinoline 8. 1, 2, 3, 4, 5, 6, 7, 8-Octahydro-2-oxo-4-phenylquinoline-3-carbonitrile 9 was prepared followed by reacting with ethyl chloroacetate in the presence of anhydrous sodium acetate to produce carbonitrile derivative 10. Compound 10 was reacted with hydrazine hydrate in ethanol to give the corresponding hydrazides 11, which was reacted with D-glucose in acetic acid to afford nucleoside derivative 12. The biological activity of the prepared compounds was also described.

Key words: Quinoline, hydrazine hydrate, ethylbromoacetate.

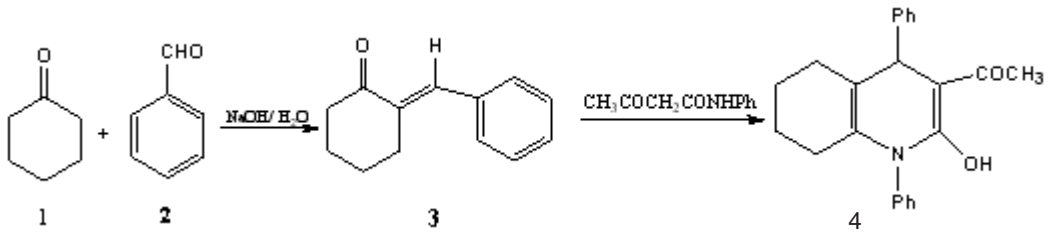
INTRODUCTION

α,β-Unsaturated ketones are versatile and convenient intermediates for the synthesis of a wide variety of heterocyclic compounds. The α,β-enone moiety of the molecule is a favorable unit for dipolar cycloaddition with numerous reagents providing heterocyclic compounds of different ring sizes with one or several heteroatoms. Their reactions with dinucleophiles usually result in the formation of polycyclic ring systems which may be the skeleton of important heterocyclic compounds. Among the α,β–unsaturated ketones, chalcones and their analogues are especially important starting materials or intermediates for the synthesis of naturally occurring flavonoids[1-5] and various nitrogen-containing heterocyclic compounds. For this reason, their syntheses have been compiled and discussed in various accounts.[6,7] Exocyclic α,β-unsaturated ketones are convenient starting materials for the synthesis of heterocyclic compounds of polycyclic skeletons. The 5, 6-dihydro-4H-pyrrolo [3, 2, 1-ij] quinoline ring constitutes the central core of different series of compounds exerting platelet activating factor production inhibition[8]or acting as 5-hydroxytryptamine (5-HT2c) receptor agonists and exerting antiepileptic or anti-obesity activities[9].

RESULTS AND DISCUSSION

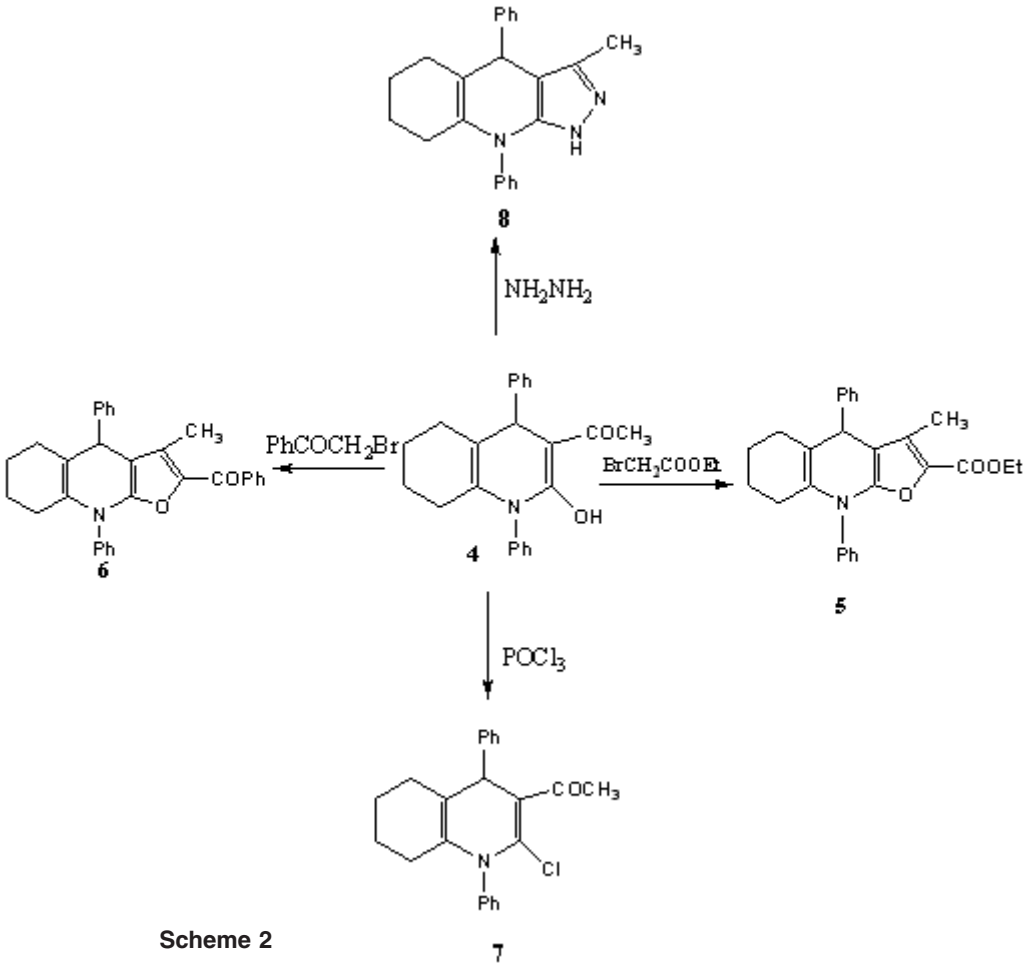
Arylidenecyclanones are frequently used α,β–unsaturated ketones. Their most important synthesis is based on the reaction of the appropriate cyclic ketone with aldehydes, the well known aldol reaction, which was discussed in detail by Nielsen and Houliham[10]. For this reason, in this review article examples will be shown only for the synthesis of selected groups, arylidenecyclohexanones and some hetero-analogues. Cyclohexanone **1** was allowed to react with benzaldehyde **2** in sodium hydroxide solution was formed 2-

benzylidenecyclohexanone **3**[11] which allowed to react with 3-oxo-N-phenylbutanamide afforded 1-(1, 4,5,6,7,8-hexahydro-2-hydroxy-1,4-diphenyl-quinolin-3-yl) ethanone **4.** (Scheme 1). The structure of compound **4** was characterized by IR, ^{1}H NMR and MS spectral data



Scheme 1

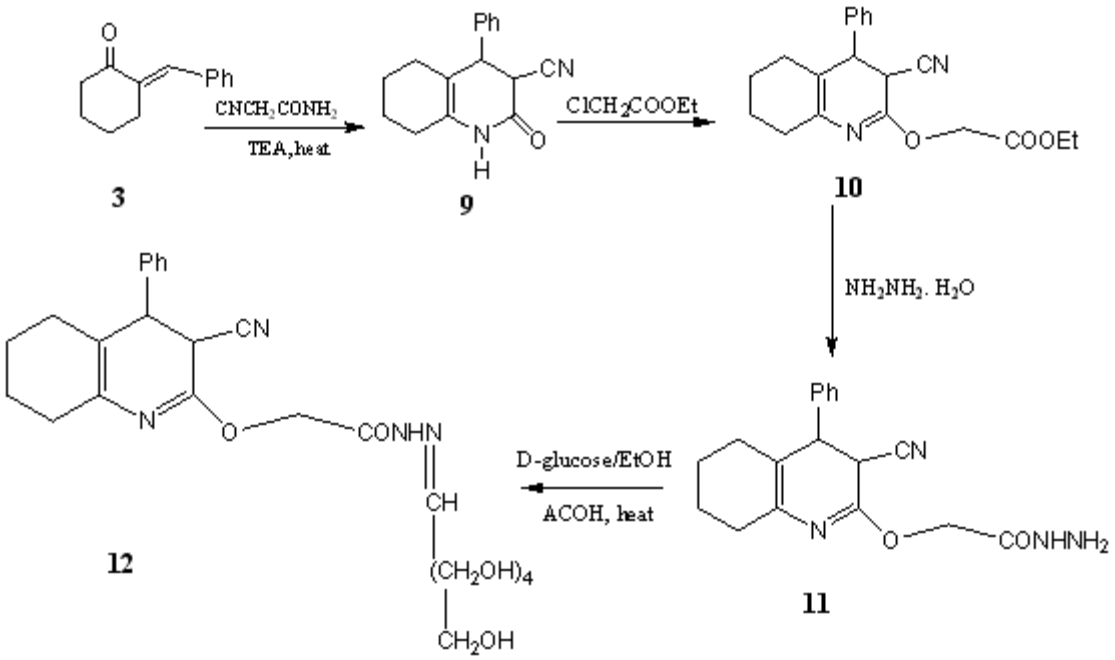
Ethyl - 4, 5, 6,7, 8, 9- hexahydro-3-methyl-4, 9-diphenylfuro [2,3-b] quinoline-2-carboxylate **5** and 4, 5, 6,7, 8, 9- hexahydro-3- methyl- 4, 9-diphenylfuro[2, 3-b] quinoline-2-yl- (phenyl) mehanone **6** were synthesized by the reaction of compound **4** with ethylbromoacetate and bromophenylethanone respectively in the presence of sodium ethoxide. (Scheme 2). The structures of the products were established on the basis of spectroscopic (IR, ^{1}H NMR, and MS) data of the pure compounds.



Scheme 2

The compound **7** was prepared by the reaction of compound **4** with phosphoryltrichloride in refluxing. Compound **4** was readily cyclized into pyrazolo [3, 4-b] quinoline derivative **8** on refluxing in ethanol (Scheme 3). The structures of the products were established on the basis of spectroscopic (IR, ^{1}H NMR, and MS) data of the pure compounds.

In this case, treatment of (E)-2-benzylidenecyclohexanone **3** with cyanoacetamid in ethanol yield 1, 2, 3, 4, 5, 6, 7, 8-Octahydro-2-oxo-4-phenylquinoline-3-carbonitrile **9** followed by reacting with ethyl chloroacetate in the presence of anhydrous sodium acetate to produce carbonitrile derivative **10**. Compound **10** was reacted with hydrazine hydrate in ethanol to give the corresponding hydrazides **11**, which was reacted with D-glucose in acetic acid to afford nucleoside derivative **12**. The structures of the products were established on the basis of spectroscopic (IR, ^{1}H NMR, and MS) data of the pure compounds.



Scheme 3

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-iR 8201 PC spectrophotometer. 'H NMR spectra were recorded in CDCI3 and (CDi)2S0 solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in *8* units using TMS as an internal reference.

Mass spectra were recorded on a GC-MS QPIOOO EX Shimadzu. Elemental analyses were carried out at the Micro analytical Center of the Cairo University.

1-(1, 4, 5, 6, 7, 8-hexahydro-2-hydroxy-1, 4-diphenylquinolin-3-yl) ethanone (4)

A mixture of (E)-2-benzylidenecyclohexanone **3** (1 mmol) , sodium

ethoxide (0.02 g) and 3-oxo-N-phenylbutanamide (1mmol) in ethanol was heated under reflux for 6 hrs, then allowed to cool, poured into water, the solid product formed was filtrated off and recrystallized from ethanol to afford a pale yellow crystals. mp 210 °C; IR: (KBr) 3438 brs, 3025,1695,1631, 1576, 1440 cm^{-1}; ^{1}H-NMR (DMSO-d6) δ13.43 (s, 1H, OH); 7.04-7.15 (m, 10H, H-Ar-H); 4.34 (s, 1H, CH), 2.43 (s,3H, CH_3), 1.72-2.13 (s, 8H,CH_2); Anal. Calcad. For $C_{23}H_{23}NO_2$ (345.43): C, 79.97; H, 6.71; N, 4.05; found C, 79.80; H, 6.42; N, 3.97.

Ethyl-4, 5, 6, 7, 8, 9-hexahydro-3-methyl-4, 9-diphenylfuro [2, 3-b] quinoline-2-carboxylate (5)

To a solution of **3** (1mmol) in absolute ethanol sodium ethoxide (30ml) was added (10mmol) sodium in 20 ml absolute ethanol), followed by (1mmol) of ethyl bromoacetate. The reaction mixture was refluxed under anhydrous condition for 3hr. and filtered; the filtrate was poured on to 100ml of ice –water. The separated ester was extracted with ether and dried over anhydrous magnesium sulphate. Excess ether was removed by distillation the remaining crude was 45% (mp 216 °C) crystallized from ethanol ; IR (KBr): 3120, 1692, 1631, 1460, 1440 cm^{-1}; ^{1}H-NMR(DMSO-d6) δ 7.01-7.14 (m, 10H, H) 5.30 (s, 1H,CH), 2.52 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.67-1.98 (s, 8H, CH_2); Anal. Calcad. For $C_{27}H_{27}NO_3$ (413.51): C, 78.42; H, 6.58; N, 3.39; Found C, 78.51; H, 6.27; N, 3.05.

4, 5, 6, 7, 8, 9- hexahydro-3- methyl- 4, 9-diphenylfuro [2, 3-b] quinoline-2-yl-(phenyl)mehanone (6)

To a solution of **3** (1mmol) in absolute ethanol, sodium ethoxide (30 ml) was added (10 mmol) sodium in 20 ml absolute ethanol), followed by (1 mmol) of bromophenylethanone. The reaction mixture was refluxed under anhydrous condition for 6hr. and filtered; the filtrate was poured on to 100 ml of ice –water. The separated ester was extracted with ether and dried over anhydrous magnesium sulphate. Excess ether was removed by distillation the remaining crude was 45% (mp 245 °C) crystallized from ethanol ; IR (KBr): 3112, 1664, 1631, 1430 cm^{-1}; ^{1}H-NMR (DMSO-d6) δ 6.64-7.14 (m, 15H, H), 4.50 (s, 1H, CH), 2.42 (s, 3H, CH_3), 1.67-1.98 (s, 8H, CH_2); Anal. Calcad. For $C_{31}H_{27}NO_2$ (445.55): C, 83.57; H, 6.11; N, 3.14; Found C, 83.46; H, 5.98; N, 3.00.

1-(2-Chloro-1, 4, 5, 6, 7, 8-hexahydro-1, 4-diphenylquinolin-3-yl) ethanone (7)

A mixture of the compound 3 and phosphoryltrichloride (30 ml) was refluxed with stirring for 4hr. On cooling, the yellowish green precipitate with ether (50ml) and crystallized from large quantily of dioxane. mp 225 °C IR (KBr): 3154, 1702, 1641, 1443 cm^{-1}; ^{1}H-NMR (DMSO-d6) δ 7.00-7.24 (m, 10H, H), 5.30 (s, 1H, CH), 2.12 (s, 3H, CH_3), 1.67-1.98 (s, 8H, CH_2); Anal. Calcad. For $C_{23}H_{22}ClNO$ (363.88): C, 75.92; H, 6.59; N, 3.85; Found C, 75.80; H, 6.38; N, 3.71.

4, 5, 6, 7, 8, 9-Hehahydro-3-methyl-4, 9-diphenyl-1H-pyrazolo [3, 4-b] quinoline (8)

A mixture of compound **3** (0.01 mol) and hydrazine hydrate in (30 ml) ethanol was refluxed for 4 h, and then left to cool. The solid product so formed was collected by filtration and recrystallized from ethanol mp 234 °C; IR (KBr) : 3304-3150, 1630, 1460, 1398 cm^{-1}; ^{1}H-NMR (DMSO-d6) δ12.23 (s, 1H, NH), 6.64-7.15 (m, 10H, Ar-H), 4.74 (s, 1H, CH), 2.53 (s, 3H, CH_3), 1.72 - 2.13 (s, 8H,CH_2); Anal. Calcad. For $C_{23}H_{23}N_3$ (341.45): C, 80.90; H, 6.79; N, 12.31; found C, 80.76; H, 6.82; N, 12.02.

1, 2, 3, 4, 5, 6, 7, 8-Octahydro-2-oxo-4-phenylquinoline-carbonitrile (9)

A mixture of compound **3** (0.3 g, 1.27 mmole), triethylamine (0.02 g) and cyanoacetamide (0.1 g) in ethanol was heated under reflux for 6 hrs, then allowed to cool, poured into water, the solid product formed was filtrated off and recrystallized from ethanol to afford a pale yellow crystals mp 310 °C IR (KBr): 3450-3200, 3020, 2215, 1675, 1664, 1631 cm^{-1}; ^{1}H- ^{1}H-NMR (DMSO-d6) δ 9.6 (s, IH, NH), 7.12-7.21 (m, 6H, H-aromatic), 3.62 (d.1H, CH-CN), 3.51 (d, 1H, CH), 1.65-1.95 (s, 8H, CH_2) Anal. Calcad. For $C_{16}H_{16}N_2O$ (252.31): C, 76.16; H, 6.39; N, 11.10; Found C, 76.76; H, 6.82; N, 11.02.

Ethyl-2-(3-cyano-3, 4, 5, 6, 7, 8-hexahydeo-4-phenylquinolin-2-yloxy) acetate (10)

To a solution of **9** (4.6 g, 10 mmol) in absolute ethanol and sodium acetate anhydrous, followed by (10 mmol) of ethylchloroacetate the

reaction mixture was refluxed under anhydrous condition, and filtered, the filtrate was poured into (100 ml) water of ice cold water. The separated ester was extracted with ether and dried over anhydrous magnesium sulphate. mp 198-201 °C IR (KBr) : 3342, 2981, 2221, 1702, 1637, cm^{-1}; ^{1}H-NMR (DMSO-d6) δ 7.08-7.21 (m, 6H, aromatic-H), 4.49 (s, 2H, CH_2), 4.12(s, 2H, CH_2), 1.82-2.21 (s, 8H, CH_2), 1.35 (s, 3H, CH_3) Anal. Calcad. For $C_{20}H_{22}N_2O_3$ (338.16): C, 70.99; H, 6.55; N, 8.28; found C, 70.76; H, 6.82; N, 8.02.

2-(3-Cyano -3, 4, 5, 6, 7, 8-hexahydro-4-phenylquinolin-2-yloxy) acetohydrazide (11)

A solution of **10** (3.8 g, 10 mmol) and hydrazine hydrate (0.015 mol) in 50 ml of ethanol was refluxed for 3 hr. the hydrazide which separated on cooling, was collected by filtration m.p. 280-283°C IR (KBr): 3340-3200, 2960, 2231, 1680, 1645 cm^{-1}; ^{1}H-NMR (DMSO-d6) δ 6.6-6.8 (br, 3H, $NHNH_2$), 7.2-7.9 (m, 6H, aromatic-H), 4.24 (s, 2H, CH_2), 3.62 (d, 1H, CH-CN), 2.51 (d, 1H, CH), 1.85-2.95 (s, 8H, CH_2) Anal. Calcad. For $C_{18}H_{20}N_4O_2$ (324.38): C, 66.65; H, 6.21; N, 17.27; found C, 66.76; H, 6.82; N, 17.02.

2-(3-Cyano -3, 4, 5, 6, 7, 8-hexahydro-4-phenylquinolin-2-yloxy) acetohydrazono- D-glucose (12)

A solution of **11** (0.32 g, 2.03 mmole) dissolved in warm methanol (30 ml) and acetic acid (2 ml) was added to D-glucose (0.653 g, 1.67 mmole). The reaction mixture was stirred for 6 hrs and then allowed to cool to room temperature. Then the solvent was removed by evaporation in vacuo to dryness, the residue was dissolved in water and washed with aqueous sodium bicarbonate. The organic layer was dried in vacuo, and the residue was recrystallized from ethanol to give yellow crystal yield, 51%, m.p. 210-220°C; ^{1}H-NMR (DMSO-d6) δ 10.23 (s, 1H, NH), 7.12-7.29 (m, 6H, aromatic-H), 7.50 (s, 1H, CH), 6.82 (s, 1H, N=CH), 5.24 (s, 2H, OH-1, OH-2), 5.03(s, 1H, OH-3), 3.89-3.55 (m, 4H, H-2,3,4,5) 4.53 (s, 2H, CH_2), 3.62 (d, 1H, CH-CN), 2.51 (d, 1H, CH), 1.85-2.95 (s, 8H, CH_2). Anal. Calcad. For $C_{24}H_{34}N_4O_7$ (490.55): C, 58.76; H, 6.99; N, 11.42; found C, 58.96; H, 6.82; N, 11.32.

Antimicrobial activity

The activity of the synthesized products was tested by the disk diffusion method. The cup-plate technique was used for the determination of these antimicrobial effects. Antibacterial and antifungal assays using Whatman No. 4 filter paper discs (0.5 cm diameter) were soaked in the tested sample. The samples were dissolved in DMSO (dimethyl sulfoxide). 0.24 µg of each sample was dissolved in 0.1 ml DMSO**,** then 0.1 ml of each sample was used with some gram positive bacteria such as (*Sarcina lutea, Staphylococcus aureus* and *Bacillus subtilis*) , gram negative bacteria such as (*Pseudomonas aeuroginosa*, *Esherishia coli, Agrobacterium and Erwinia sp*.) and fungi (*Aspergillus niger, Penicillium funiculosum*) under aseptic conditions. The medium for cultivation of the test organisms was nutrient agar, and the Petri-dishes were incubated at 30°C for 24 hrs. The results were obtained by measuring the inhibition zones (in mm) caused by the various compounds on the microorganisms. From the results**,** it is obvious that most of the tested compounds posses slight or no activity at all towards the tested microorganisms. However**,** some compounds showed considerable activity against the tested bacteria such as **4, 5 and 6.** Others exhibit moderate or slight activity against the fungi such as **7, 8.**

Table 1: Antimicrobial activity of the compounds considered

Compd.	** Microorganisms zone of inhibition (mm)				
	1	2	3	4	5
4	15	-	15	-	-
5	15	13	-	-	-
6	23	-	14	-	-
7	-	20	15	-	-
8	-	14	14	-	-

* The solvent is dimethylsulfoxide (DMSO)
** 1: *Staphylococcus aureus*
2: *Pseudomonas aeuroginosa*
3: *Bacillus subtilis* 4: *Aspergillus niger*
5: *Penicillium funiculosum*
The values are in mm diameter

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