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One-Step Multicomponent Synthesis of2-Oxo-Quinolin-3-yl-Dihydropyri-midinoneand 2-oxo-1,2-Dihydroquinolin-3-yl-tetrahydroquinazolinedioneDerivatives

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ABSTRACT

Many components bearing different pharmacophoric groups have been used in Biginelli condensation allowing the identification of marketed drugs active against different diseases. In this context, we describe herein, an efficient synthesis of some heterocyclic systems bearing two biologically active moieties 2-oxo-1,2-dihydroquinoline and 3,4-dihydropyrimidine-2(1*H*)-ones or octahydroquinazolinoneby the cyclocondensation reaction of the corresponding biologically active 2-chloro-1,2-dihydroquinoline-3-carbaldehydes**,**1,3-dicarbonyl compounds and ureain the presence of $NaNO_3$ as a high yielding catalyst.

Key words: Biginelli condensation, 2-oxo-1,2-dihydroquinoline, 3,4-dihydropyrimidine-2(1*H*)-ones, octahydroquinazolinone, DHPMs, $NaNO_3$

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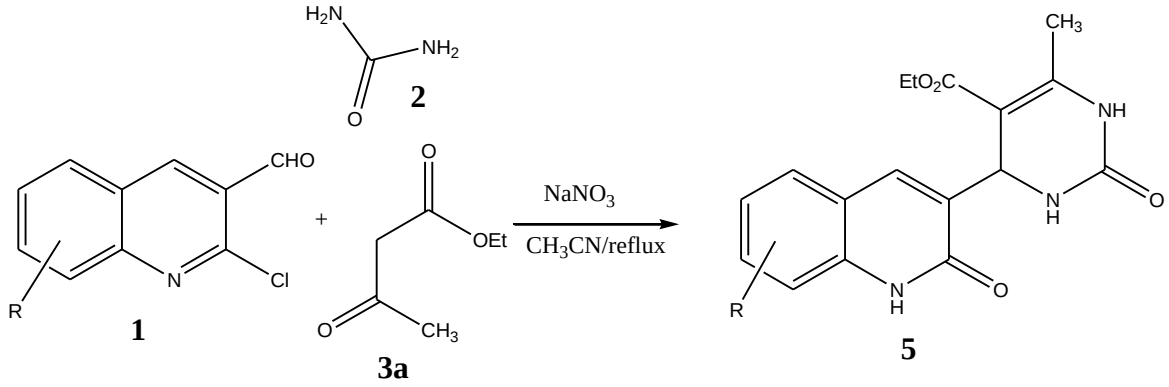
INTRODUCTION

In recent years, dihydropyrimidinones (DHPMs) are gaining increasingly importance due to their broad spectrum of biological activities such as antiviral, antitumor, anticancer, antibacterial, antifungal as well as anti-inflammatory actions [1-5] and antioxidative properties [6]. More recently, appropriately functionalized DHPMs have emerged as orally active antihypertensive agents [7-9], as calcium channel modulators, α1a-adrenergic antagonists, neuropeptide Y (NPY) antagonists, and compounds that target the mammalian mitotic machinery [10-12]. On the other hand, various substituted quinolone compounds are therapeutically potential in the area of human and animal health such as antibacterial [13-15], antimicrobia1[16], and antituberculosis activities [17-19]; as a result, several quinolones like Ciprofloxacin, Pefloxacin, Levofloxacin and Spafloxacin are released in the clinical world. Octahydroquinazolinone derivatives have, also, attracted considerable attention as they exhibit potent antibacterial [20, 21], and calcium antagonist activities [22].

Literature investigation reveals that (un)sub. 2-chloro-1,2-dihydroquinoline-3-carbaldehydes were used in the synthesis of some DHPMs [23, 24], but, not a single reference referred to their use in the preparation of 2-oxo-quinolin-3-yl-dihydropyrimidinoneand 2-oxo-dihydroquinolin-3-yl tetrahydroquinazolinone derivatives in just one step-one pot Biginelli reaction. Based on these observations, we report in the present work the synthesis of the above mentioned compounds using some of (un)sub.2-chloro-1,2-dihydroquinoline-3-carbaldehyde derivatives **1,** urea and 1,3-dicarbonyl compounds in the presence of a catalytic amount of $NaNO_3$ (Scheme 1).



Scheme 1: General synthetic scheme of the obtained products 5

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MATERIALS AND METHODS

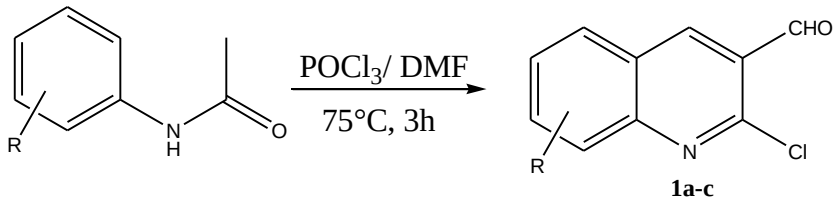
Experimental

General remarks

Melting points were measured using a fine control Electro thermal capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a BRUKER spectrometer (400 or 250 MHz) using $CDCl_3$ or DMSO-d_6.Chemical shifts are reported in parts per million (ppm) relative to TMS (0.00), as internal standard, and coupling constants (*J*) are reported in hertz (Hz). ^{13}C NMR spectra were recorded on a BRUKER spectrometer (200 or 62.9 MHz). High resolution mass spectral analyses (HR-MS) were performed by CRNS (centre de recherché,écolenationalesupérieure de chimie de Rennes, France) on a waters Q-TOF2 spectrometer and presented as m/z (relative intensity, assignment). IR spectra were obtained as potassium bromide (KBr) pellets with a Shimadzu FT IR-8201 PC spectrometer.

General Procedure for the Synthesis of 2-Chloro-3-quinolinecarbaldehydes (1a–c)

We initiated the present syntheses by the preparation of 2-Chloro-3-quinolinecarbaldehydes (**1a–c**) from the corresponding acetanilide via Meth-Cohn method [25] (Scheme 2).



Scheme 2: Synthesis of 2-Chloro-3-quinolinecarbaldehydes (1a-c)

General procedure for the synthesis of 4-[2oxo-1,2-dihydroquinlin-3-yl)]-3,4-dihydropyrimidin-2(1*H*)-onederivatives (5a–c)

A mixture of an appropriate 2-chloro-1,2-dihydroquinoline-3-carbaldehyde (2.5 mmol), urea (3.4 mmol) and ethyl acetoacetate (2.5mmol), in the presence of the catalyst $NaNO_3$ (10 mol%) in CH_3CN (5 ml), was refluxed for 3h as indicated by TLC. The reaction mixture was poured into ice water and the obtained residue was filtered and purified by recrystallization in EtOH. The aqueous layer was evaporated, under reduced pressure, and the catalyst was recovered.

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5-(Ethoxycarbonyl)-6-methyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-3,4-dihydropyrimidin-2(1H)-one(5a)

Brown solid, M.P > 300°C. ^{1}H NMR (400 MHz, $CDCl_3$,δ ppm, *J* Hz): δ = 11.89 (s, 1H, NH of quinolone), 9.23 (d, 1H, *J* = 1.4 Hz, NH of DHPM), 7.70 (dd, 1H, *J* = 7.9, 1.3 Hz, H-C_5), 7.57 (s, 1H, C_4), 7.48 (ddd, 1H, *J* = 8.3, 7.1, 1.3 Hz, H-C_7), 7.31 (broad d (dd after resolution improving with Traficante), 1H, *J* = 8.3, 0.7 Hz, H-C_8), 7.16 (ddd, 1H, *J* = 7.9, 7.1, 1.1 Hz, H-C_6), 7.11 (broad t, 1H, *J* = 2.3 Hz, NH of DHPM), 5.37 (d, 1H, *J* = 3.1 Hz, C<u>H</u>-N), 3.97 (q, 2H, *J* = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 2.34 (s, 3H, C<u>H</u>$_3$-C=), 1.05 (t, 3H, *J* = 7.1 Hz, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$,δ ppm): δ = 165.09 (C_{quat}, <u>C</u>O of ester), 161.10 (C_{quat}, C_2 e.g. <u>C</u>O of quinolone), 152.00 (C_{quat}, NH<u>C</u>ONH), 150.03 (C_{quat}, C_{8a}), 138.02 (C_{quat}, C=<u>C</u>-Me), 134.69 (<u>C</u>H, C_4), 133.43 (C_{quat}, C_3), 130.05 (<u>C</u>H, C_7), 127.99 (<u>C</u>H, C_5), 121.80 (<u>C</u>H, C_6), 118.79 (C_{quat}, C_{4a}), 114.71 (<u>C</u>H, C_8), 95.93 (C_{quat}, <u>C</u>=C-Me), 58.98 (O<u>C</u>H$_2$CH$_3$), 49.39 (<u>C</u>H-N), 17.80 (<u>C</u>H$_3$-C=), 14.02 (OCH$_2$<u>C</u>H$_3$).

4-(7-chloro-2-oxo-1,2-dihydroquinolin-3-yl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (5b)

Orange solid, M.P > 300°C.^{1}H NMR (250 MHz, DMSO-d_6, δ ppm, *J* Hz):δ = 12.20 (s, 1H, NH of quinolone), 9.25 (d, 1H, *J* = 1.4 Hz, NH of DHPM), 7.78 (dd, 1H, *J* = 7.9, 1.3 Hz, H-C_5), 7.62 (s, 1H, C_4), 7.33 (s, H-C_8), 7.19 (m, 1H, H-C_6), 7.11 (broad t, 1H, *J* = 2.3 Hz, NH of DHPM), 5.35 (d, 1H, *J* = 3.1 Hz, C<u>H</u>-N), 3.94 (q, 2H, *J* = 6.41 Hz, OC<u>H</u>$_2$CH$_3$), 2.32 (s, 3H, C<u>H</u>$_3$-C=), 1.04 (t, 3H, *J* = 7.1 Hz, OCH$_2$C<u>H</u>$_3$). ^{13}C RMN (62.9 MHz, DMSO-d_6, δ ppm): δ = 165.58 (C_{quat}, <u>C</u>O of ester), 161.64 (C_{quat}, C_2 e.g. <u>C</u>O of quinolone), 152.60 (C_{quat}, NH<u>C</u>ONH), 150.67 (C_{quat}, C_{8a}), 139.45 (C_{quat}, C=<u>C</u>-Me), 137.50 (<u>C</u>Cl, C_7), 134.93 (<u>C</u>H, C_4), 133.43 (C_{quat}, C_3), 130.05 (<u>C</u>H, C_5), 128.02 (<u>C</u>H, C_6), 121.52 (<u>C</u>H, C_8), 118.22 (C_{quat}, C_{4a}), 95.93 (C_{quat}, <u>C</u>=C-Me), 59.54 (O<u>C</u>H$_2$CH$_3$), 49.93 (<u>C</u>H-N), 18.50 (<u>C</u>H$_3$-C=), 14.34 (OCH$_2$<u>C</u>H$_3$).

5-Ethoxycarbonyl-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (5c)

Orange solid, M.P > 300°C. ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm, *J* Hz): δ = 11.84 (s, 1H, NH of quinolone), 9.23 (d, 1H, *J* = 1.4 Hz, NH of DHPM), 7.50 (s, 1H, H-C_5), 7.50 (s, 1H, C_4), 7.30 (d 1H, *J* = 7.89 Hz, H-C_8), 7.20 (d, 1H, *J* = 8.54 Hz, H-C_7), 7.11 (broad t, 1H, *J* = 2.3 Hz, NH of DHPM), 5.37 (d, 1H, *J* = 3.1 Hz, C<u>H</u>-N), 3.98 (q, 2H, *J* = 11.0 Hz, OC<u>H</u>$_2$CH$_3$), 2.33 (s, 3H, C<u>H</u>$_3$-C=), 2.20 (s, 3H C<u>H</u>$_3$-C=), 1.05 (t, 3H, *J* = 11.0 Hz, OCH$_2$C<u>H</u>$_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6, δ ppm): δ = 165.64 (C_{quat}, <u>C</u>O of ester), 161.64 (C_{quat}, C_2 e.g. <u>C</u>O of quinolone), 152.60 (C_{quat}, NH<u>C</u>ONH), 150.57 (C_{quat}, <u>C</u>$_{8a}$), 135.00 (C_{quat}, C=<u>C</u>-Me), 134.80 (<u>C</u>H, C_4), 132.43 (C_{quat}, C_6), 128.00 (C_{quat}, C_3), 118.00 (C_{quat}, C_{4a}), 115.00 (<u>C</u>H, C_7), 112.00 (<u>C</u>H, C_5), 111.00(<u>C</u>H, C_8), 96.00

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(C_{quat}, C=C-Me), 59.50 (OCH_2CH_3), 48.59 (CH-N), 22.10 (CH_3-Aro), 18.20 (CH_3-C=), 14.50 (OCH_2CH_3).

General procedure for the synthesis of 7,7-dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8 tetrahydroquinazoline-2, 5(1*H*,6*H*)-dione (6a–c)

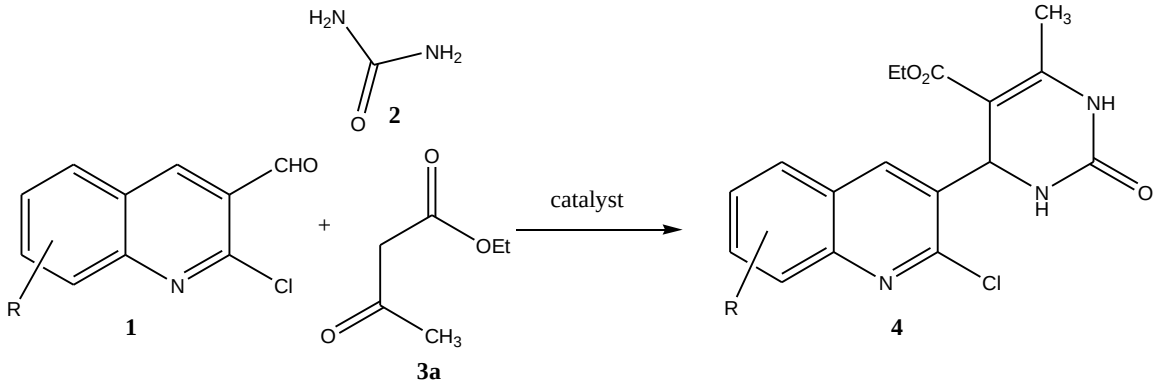
2-chloro-1,2-dihydroquinoline- 3-carbaldehyde (2.5 mmol), dimedone (2.5 mmol), urea (2.5 mmol), and $NaNO_3$ (20 mol%) in methanol and water (3 ml, 1:1)) were charged in a 100 ml round-bottomed flask with magnetic stirrer and condenser. The reaction mixture was slowly heated and refluxed for 8 h. On completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature and the separated solid was filtered and washed with a mixture of chloroform and methanol (1:1) to obtain the pure compounds **6a–c**.

7,7-Dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline 2,5(1*H*,6*H*)-dione (6a)

Yellowish compound, M.P.280-283 °C.^{1}H NMR (250 MHz, DMSO-d_6,δ ppm, *J* Hz): δ = 1.05 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.08–2.44 (m, 4H, $2CH_2$), 5.31 (s, 1H, quinazolinone H4), 7.00 (s, 1H, NH), 7.04–7.70 (m, 5H, Ar–H), 9.48 (s, 1H, NH), 11.84 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6, δ ppm): δ = 27.80 (CH_3), 29.03 (CH_3), 32.74 ($C(CH_3)_2$), 39.09 (CH_2), 48.65 (CH_2–CO), 50.12 (quinazolinone C4), 105.62, 115.57, 119.03, 128.10, 131.85, 132.70, 132.92, 136.37, 136.74, 150.55 (10C, Ar–C), 156.57 (C_{quat}, NHCONH), 161.64 (C=O of quinolone), 193.64 (C=O of quinazolinone).

RESULTS AND DISCUSSION

The presence of two or more different heterocyclic moieties in a single molecule often enhances the biological activities remarkably [26]. Therefore, we investigated the model multicomponent reaction of 2-chloro-3-formylquinoline **1a** (R = H**)** with urea **2** and ethyl acetoacetate **3a**with the expectation of synthesizing compounds of type **4** (Scheme-3).



Scheme 3: General synthetic scheme of Biginelli compounds

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To determine the optimum conditions of the reaction, we attempted a plethora of catalysts and media. After some experimentation, we set up that the appropriate promoter system was the use of CH_3CN as solvent and $NaNO_3$ as catalyst (Table 1).

Table 1Effect of different catalysts on the yield of 4a

catalyst	Catalyst (mol%)	Time (h)	Yield(%)[a]
$Pb(NO_3)_2$	10	3	70
$Ni(NO_3)_2.6H_2O$	10	5	60
$NaNO_3$	10	3	75
$FeCl_3.6H_2O$	10	5	≤20
$NiCp_2Cl_2$	10	5	35

When we analyzed the spectral data of the product **4a** (Scheme 3, R= H), IR spectrum showed absorption at 1660 cm^{-1} for the 2-quinolinone group [24b, 27]. ^{1}HNMR spectrum showed the characteristic up field absorption of quinolin-CONH (s, 11.89) and quinolinone carbonyl resonance at δ161.10 in ^{13}C-NMR spectrum.

These data are in favor of 2-oxoquinoline product **5a** (Scheme 1, R= H**)** formation rather than 2-chloroquinoline product **4a** (Scheme 3, R = H**)**. The structure of **5a** was further confirmed by the existence of the molecular ion peak at m/z 350.1115 $[M + Na]^+$in mass spectral studies corresponding to molecular formula $C_{17}H_{17}N_3O_4Na$. Moreover, the bass resolution spectrum showed no chloride isotopic corresponding to molecular formula $C_{17}H_{17}N_3O_3Cl$ **4a**.

These unexpected results prompted us to use different substituted 2-chloro-3-formylquinoline, under the above mentioned reaction conditions, in order to synthesize some products containing both quinolone and DHPM moieties in one molecular framework in one step reaction (Scheme 1). Delightedly, all the reactions gave exclusively the desired products**5**. The results are summarized in Table 2.

Table 2: The yield (%) of 4-[2oxo-1,2-dihydroquinolin-3-yl)]-3,4-dihydropyrimidin-2(1*H*)-one derivatives 5

Product[a]	R		Yield[b](%)
5a	H		75
5b	7-Cl		70
5c	6-CH_3		75

Reaction conditions: Aldehyde (2.5 mmol), urea (3.4 mmol), ethyl acetoacetate (2.5 mmol),$NaNO_3$ (10 mol %), CH_3CN ((5.0 ml) at reflux temperature.
[a] All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.
[b] Isolated yields.

The electrophilic character of the carbonyl carbon of the aldehydes **1** might be increased by forming the intermolecular bonding between Na^+cation, which facilitates the formation of imines species (**Int-1**) that lead to the N-acyliminium intermediates (**Int-2**) by splitting the acid proton of 1,3-dicarbonyl compounds**3**. Further, the enolic ethyl acetoacetate, stabilized by the interaction with Na^+cation, reacts as nucleophile on N-acyliminium species leading to the intermediates (**Int-3**), which yieldBiginelli compounds **4** after subsequent cyclodehydration. The

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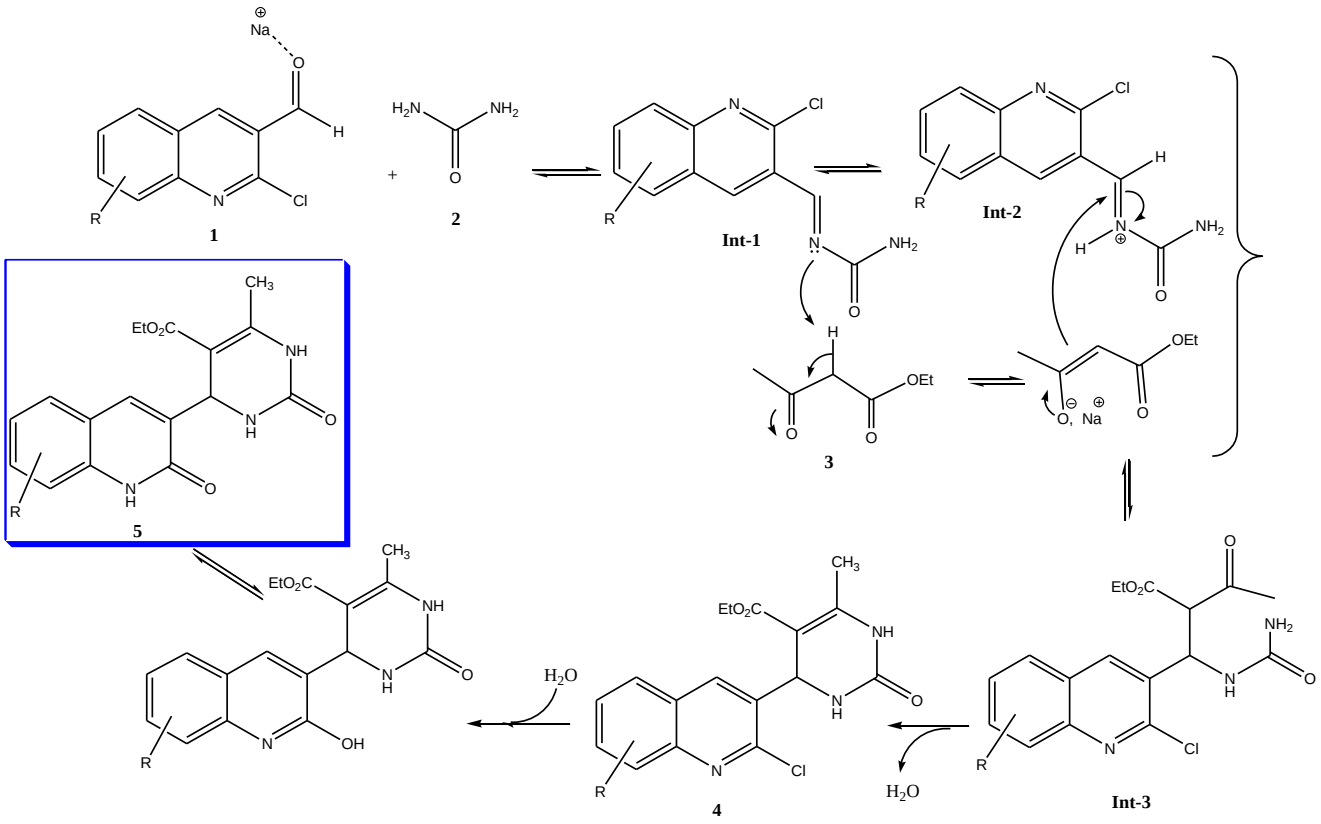
presence of water in the reaction mixture reacts as nucleophile and substitutes the chlorine to give the corresponding quinolones **5**. Hence, a tandem reaction: Biginelli/ hydrolysis. The plausible mechanism for the formation of DHPMs using $NaNO_3$is depicted in Scheme 4.



Scheme 4: Plausible mechanism for the formation of compounds 5

Prompted by the effectiveness of $NaNO_3$ as catalyst, we have applied, the present one-step method in the synthesis of some octahydroquinazolinone derivatives from 2-chloro-1,2-dihydroquinoline-3-carbaldehyde derivatives **1**, urea **2** and dimedone**3b,** prepared in previous reports by M. Pushpak*et al.*in two steps [24](Scheme 5).

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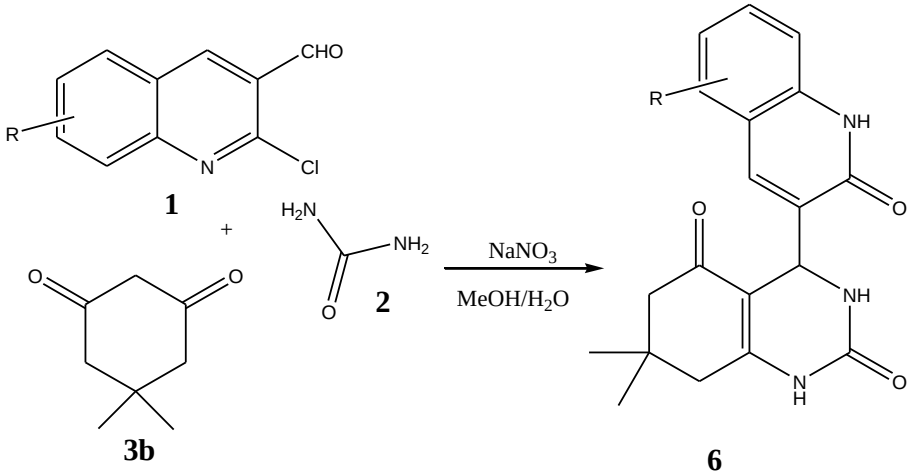

Scheme 5: One-pot synthesis of substituted octahydroquinazolinone6 catalyzed by $NaNO_3$

Interestingly, we found that $NaNO_3$ worked well, and the condensation took place efficiently to give the expected products **6** (Table 3).

Table 3: The yield (%) of tetrahydroquinazoline-2, 5(1*H*,6*H*)-dione derivatives6

Product[a]	R	Yield (%)	Mp (°C)	
			Found	Reported
6a	H	87	280-283	284-286[24]
6b	6-Me	80	294-297	293-295[24]
6c	6-OMe	78	292-295	294–296[24]

Reaction conditions: Aldehyde (2.5 mmol), dimedone (2.5 mmol), urea (2.5 mmol), $NaNO_3$ (20 mol %), methanol/water (3.0 ml, 1/1) at reflux temperature.
[a]All compounds are known and are identified by their melting points and spectral data

CONCLUSION

We have developed a novel, simple and convergent one pot reaction for the construction of 4-[2-oxo-1,2-dihydroquinolin-3-yl)]-3,4-dihydropyrimidin-2(1*H*)-ones and some 4-(2-oxo-1,2-dihydroquinolin-3-yl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione derivatives from the corresponding 2-chloro-3-formylquinoline derivatives which were obtainable only with sequenced linear processes.

The present procedure offers several advantages including mild reaction conditions, good yields of products, and a recoverable catalyst which make it an alternative, and an attractive process for the synthesis of such heterocyclic compounds.

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