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SOLVENT FREE ONE POT SYNTHESIS OF NOVEL NAPHTHO[1,8-GH] QUINAZOLINE-7,10-DIONE DERIVATIVES WITH $CuCl_2$

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ABSTRACT. The Biginelli-type reaction of phenalen-1,3-dione with urea, and benzaldehyde derivatives in the presence of $CuCl_2$ as a catalyst for the synthesis of naphtho[1,8-gh]quinazoline-7,10-diones in solvent free condition are reviewed. Excellent yields of the products, short reaction times and simple work-up are attractive features of this suitable protocol.

KEY WORDS: Synthesis, Naphtho[1,8-gh]quinazoline-7,10-diones, One pot, Solvent free

INTRODUCTION

Economic generation of bioactive compounds have major concerned in modern organic chemistry [1]. In this regard, development of novel compounds and especially diverse small molecule scaffolds caused higher attention of medicinal and biological chemists [2-4]. This has attributed to the growing requirement in assembling libraries of structurally complex substances to be evaluated as new compounds in drug discovery projects.

Polycyclic aromatic hydrocarbon (PAH) heterocycles are highly important structural units in a variety of pharmacologically active substances [5-8]. At first glance, rigid polycyclic structures seem to have role in the development of antitumor agents owing to their ability in insertion between stacked base pairs of oligonucleotides and action as intercalator [9-11]. Particularly important is that when these heterocycles with fused-PAHs bear appropriate side chains, further interactions with other important macromolecules may be envisaged [10].

In recent years, 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPs) and their derivatives have attracted considerable interest because of their therapeutic and pharmacological properties [12]. There is considerable current interest in the Biginelli-type reaction, because 3,4-dihydro-pyrimidin-2-(1H)-ones and their derivatives have attracted great attention recently in synthetic organic chemistry due to their pharmacological and therapeutic properties such as antibacterial and antihypertensive activity as well as behaving as calcium channel blockers, a-1a-antagonists and neuropeptides Y (NPY) antagonists [12, 13]. The Biginelli reaction is one of the multicomponent reactions (MCRs) and the most important procedures for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones.

Several improved procedures have been reported based on metal-catalyzed Biginelli reaction during the last decade. Among the simple metal/ammonium salts with nucleophilic anions, $ZrCl_4$ [14], NH_4Cl [15], $MgBr_2$ [16], LiBr [17], $Mn(OAc)_3.2H_2O$ [18], $InBr_3$ [19], $FeCl_3.6H_2O$ [20], $CdCl_2$ [21] and CuI [22] are attractive Lewis acid catalysts. The catalytic effect of metal cations are even more pronounced with methods based on metal salts with non-nucleophilic anions such as NH_4VO_3 [23], $KAl(SO_4)_2.12H_2O$ [24], $Bi(NO_3)_3$ [25], $Fe(CF_3CO_2)_3$ [26] which allow the preparation of DHPs in good to high yields. However, a number of the reported protocols for synthesis of DHPs and DHPs, require solvents and catalysts, are not acceptable in the context of green synthesis, utilize reagents and catalysts which are either toxic or expensive and stoichiometric use of reagents with respect to reactant.

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In connection with our ongoing work on multi-component condensations (MCCs) [27, 28] and an our interest to metal catalyzed reactions, we now wish to report a facile and rapid one-pot solvent free three component procedure preparation of DHPs derivatives with $CuCl_2$ as an non-toxic, inexpensive and easily available reagent, under solvent-free condition at the range of temperatures.

EXPERIMENTAL

Materials and instruments

All material compounds were purchased from chemical companies and used without further purification. Melting points were measured on the Electro thermal 9100 apparatus and are uncorrected. IR spectra were measured on a Bomen FT-IR-MB 100 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as internal standard. Mass spectra were recorded on a MS model 5973 Network apparatus at ionization potential of 70 eV. Elemental analysis for C, H, and N was performed using a Thermo Finnigan Flash EA 1112 (Thermo Fisher Scientific Inc, USA) instrument.

General procedure for preparation of naphtho[1,8-gh]quinazoline-7,10-diones

A mixture containing an appropriate phenalen-1,3-dione (3 mmol), corresponding aldehydes (3 mmol), thio (urea) (6 mmol) and $CuCl_2$ (0.04 g) were heated in oil bath at 80 ^{o}C for the required time period. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, chloroform (10 mL) was added and filtered through a sinter funnel, then was washed with cold water and recrystallized from ethanol to afford pure products.

Charactristic data for synthesized compounds

*8,9-Dihydro-8-phenyl-11H-naphtho[1,8-gh]quinazoline-7,10-dione (**4a**)*. m.p. 170–173 ^{o}C. IR spectrum, ν, cm^{-1}: 3200, 3120, 1730, 1650, 850; ^{1}H NMR spectrum, δ, ppm: 5.46 (1H, s, CH); 6.72 (2H, s, N-H); 7-7.25 (5H, m, Ph); 7.51-7.92 (6H, m, Phenalen). ^{13}C NMR spectrum, δ, ppm: 43.3; 107.5; 120.4; 121.3; 122.3; 123.4; 124.9; 125.5; 126.6; 127.8; 129.0; 131.5; 130.2; 132.7; 133.5; 136.5; 137.3; 137.6; 140.4; 144.4; 165.3; 167.7. Mass spectrum, m/z (I, rel, %): 326 $[M+H]^+$ (100). Found, %: C: 77.37, H 4.39, N 8.45, O 9.73. $C_{21}H_{14}N_2O_2$ calculated, %: C 77.36, H 4.37, N 8.49, O 9.78.

*8,9-Dihydro-8-(4-nitrophenyl)-11H-naphtho[1,8-gh]quinazoline-7,10-dione (**4b**)*. m.p. 174–177 ^{o}C. IR spectrum, ν, cm^{-1}: 835; 1650; 1710; 3170; 3250. ^{1}H NMR spectrum, δ, ppm *(J, H)*: 5.23 (s, 1H, CH); 7.44-7.78 (6H, m, Phenalen), 7.23-7.45 (4H, m, Ph,), 6.63 (s, 2H, N-H). ^{13}C NMR spectrum, δ, ppm: 44.5; 107.2; 121.2; 122.0; 122.9; 123.1; 124.5; 126.2; 127.8; 128.7; 129.1; 130.5; 131.2; 131.7; 132.3; 133.2; 136.8; 137.1; 142.4; 143.6; 164.4; 168.2. Mass spectrum, m/z (I rel, %): 67 $[M+H]^+$ (100). Found, %: C: 67.97, H: 3.49, N: 11.37, O: 17.28. $C_{21}H_{13}N_3O_4$ calculated, %: C: 67.92, H: 3.53, N: 11.32, O: 17.23.

*8,9-Dihydro-8-(3-nitrophenyl)-11H-naphtho[1,8-gh]quinazoline-7,10-dione (**4c**)*. m.p. 165–168 ^{o}C. IR spectrum, ν, cm^{-1}: 3257, 865; 1630; 1710; 3146. ^{1}H NMR spectrum, δ, ppm: 5.64 (s, 1H, CH); 7.13-7.45 (4H, m, Ph) 7.4-7.71 (6H, m, Phenalen), 7.51 (s, 1H, Ph-H). ^{13}C NMR spectrum, δ, ppm: 44.5; 108.1; 122.2; 122.2; 122.3; 123.1; 124.5; 126.2; 127.8; 128.7; 128.5; 130.8; 131.7; 132.3; 133.9; 135.4; 138.5; 142.4; 143.6; 166.3; 171.3. Mass spectrum, m/z (I rel, %): 371 $[M+H]^+$ (100). Found, %: C: 67.88, H: 3.46, N: 11.25, O: 17.36. $C_{21}H_{13}N_3O_4$ calculated, %: C: 67.92 , H: 3.53, N: 11.32, O: 17.3.

8,9-Dihydro-8-(3,4-dinitrophenyl)-11H-naphtho[1,8-gh]quinazoline-7,10-dione ***(4d)***. m.p. 173–175 °C. IR spectrum, ν, cm^{-1}: 815, 1643, 1725, 3140, 3270.^{1}H NMR spectrum, δ, ppm *(J, H)*: 5.37 (s, 1H, CH,); 6.43 (s, 2H, N-H); 7.23-7.45 (2H, d, Ph, *J* = 7.8); 7.32-7.65 (6H, m, Phenalen), 7.57 (1H, s, Ph-H). ^{13}C NMR spectrum, δ, ppm: 44.8; 107.7; 122.2; 122.2; 122.3; 123.8; 125.7; 126.8; 127.1; 127.8; 128.0; 128.5; 131.1; 131.4; 132.3; 133.9; 134.8; 137.5; 146.2; 166.3; 172.3. Mass spectrum, m/z (I rel, %): 416 $[M+H]^+$ (100). Found, %: C: 60.5, H: 2.84, N: 13.4, O: 23.15. $C_{21}H_{12}N_4O_6$ calculated, %: C: 60.58, H: 2.91, N: 13.46, O: 23.06.

8,9-Dihydro-8-p-tolyl-11H-naphtho[1,8-gh]quinazoline-7,10-dione ***(4e)***. m.p. 162–165 °C. IR spectrum, ν, cm^{-1}: 810, 1550, 1630, 1720, 3114, 3250. ^{1}H NMR spectrum, δ, ppm *(J, H)*: 2.28 (3H, s, CH_3); 5.32 (1H, s, CH); 6.25 (2H, t, N-H); 7.13-7.42 (4H, dd, , Ph, *J* = 7.7, *J* = 7.8); 7.32-7.65 (6H, m, Phenalen). ^{13}C NMR spectrum, δ, ppm: 30.3; 107.7; 120.6; 121.3; 121.9; 122.3; 123.3; 124.2; 125.4; 126.3; 127.1; 128.0; 129.2; 131.1; 131.4; 132.9; 133.9; 135.4; 137.2; 146.2; 166.3, 168.6. Mass spectrum, m/z (I rel, %): 340 $[M+H]^+$ (100). Found, %: C: 77.56, H: 4.7, N: 8.29, O: 9.32. $C_{22}H_{16}N_2O_2$ calculated, %: C: 77.63, H: 4.74, N: 8.23, O: 9.40.

8,9-Dihydro-8-m-tolyl-11H-naphtho[1,8-gh]quinazoline-7,10-dione ***(4f)***. m.p. 177–179 °C. IR spectrum, ν, cm^{-1}: 865; 1536; 1620; 1732; 3188. ^{1}H NMR spectrum, δ, ppm *(J, H)*: 2.73 (s, 3H, CH_3); 5.28 (s, 1H, CH); 6.46 (t, 2H, N-H); 7.17-7.33 (m, 4H, Ph); 7.35-7.68 (m, 6H, Phenalen); 7.42 (s, 1H, Ph-H). ^{13}C NMR spectrum, δ, ppm: 31.9; 106.3; 121.3; 122.2; 122.6; 123.7; 125.1; 126.0; 126.4; 127.3; 128.0; 128.5; 129.8; 131.5; 131.9; 132.9; 133.9; 135.4; 137.2; 146.2; 166.3; 170.3. Mass spectrum, m/z (I rel, %): 340 $[M+H]^+$ (100). Found, %: C: 77.56, H: 4.68, N: 8.28, O: 9.34. $C_{22}H_{16}N_2O_2$ calculated, %: C: 77.63, H: 4.74, N: 8.23, O: 9.40.

8-(4-Chlorophenyl)-8, 9-dihydro-11H-naphtho[1,8-gh]quinazoline-7,10-dione ***(4g)***. m.p. 171–173 °C. IR spectrum, ν, cm^{-1}: 720, 810, 1614, 1720, 3154, 3200. ^{1}H NMR spectrum, δ, ppm *(J, H)*: 5.44 (s, 1H, CH); 6.25 (t, 2H, N-H); 7.21-7.47 (m, 6H, Phenalen), 7.28-7.41 (dd, 4H, Ph, *J* = 7.5, *J* = 7.8). ^{13}C NMR spectrum, δ, ppm: 45.2; 107.0; 121.4; 121.8; 122.5; 123.1; 124.5; 126.2; 127.8; 128.7; 129.1; 131.2; 131.7; 132.3; 133.2; 136.8; 137; 142.4; 143.8; 166.8; 171.5 Mass spectrum, m/z (I rel, %): 340 $[M+H]^+$ (100). Found, %: C: 69.86, H: 3.57, N: 7.66, O: 8.85. $C_{21}H_{13}ClN_2O_2$ calculated, %: C: 69.91, H: 3.63, N: 7.76, O: 8.87.

8-(4-Bromophenyl)-8,9-dihydro-11H-naphtho[1,8-gh]quinazoline-7,10-dione ***(4h)***. m.p. 181–183 °C. IR spectrum, ν, cm^{-1}: 715; 853; 1614; 1712; 3123; 3234. ^{1}H NMR spectrum, δ, ppm *(J, H)*: 5.57 (s, 1H, CH); 6.22 (t, 2H, N-H); 7.2-7.41 (m, 6H, Phenalen), 7.34-7.46 (dd, 4H, Ph, *J* = 7.8, *J* = 8.2). ^{13}C NMR spectrum, δ, ppm: 44.1; 107.4; 121.2; 121.8; 122.5; 123.1; 125.4; 126.2; 127.8; 128.7; 129.8; 131.2, 131.3; 132.3; 133.2; 136.8; 137; 142.4; 143.8; 162.8; 169.3. Mass spectrum, m/z (I rel, %): 340 $[M+H]^+$ (100). Found, %: C: 62.28, H: 3.28, N: 6.86, O: 7.68. $C_{21}H_{13}BrN_2O_2$ calculated, %: C: 62.24, H: 3.23, N: 6.91, O: 7.9.

8-(2-Chloro-4-methylphenyl)-8,9-dihydro-11H-naphtho[1,8-gh]quinazoline-7,10-dione ***(4i)***. m.p. 167–170 °C. IR spectrum, ν, cm^{-1}: 705, 821, 1619, 1732, 3117, 3230. ^{1}H NMR spectrum, δ, ppm *(J, H)*: 5.38 (s, 1H, CH); 6.1 (t, 2H, N-H); 6.85 (s, 1H, Ph); 7.34-7.46 (dd, 4H, Ph, *J* = 7.4, *J* = 7.8); 7.33-7.53 (m, 6H, Phenalen). ^{13}C NMR spectrum, δ, ppm: 45.2; 107.0; 121.4; 122.5; 123.1; 124.5; 126.2; 127.8; 128.7; 129.1; 131.2; 131.7; 132.3; 132.7; 133.1; 135.3; 137.5; 142.1; 143.8; 165.4. 170.7. Mass spectrum, m/z (I rel, %): 374 $[M+H]^+$ (100). Found, %: C: 70.33, H: 4.17, N: 7.26, O: 8.67. $C_{22}H_{15}ClN_2O_2$ calculated, %: C: 70.50, H: 4.03, N: 7.47, O: 8.54.

4-(8,9,10,11-Tetrahydro-7,10-dioxo-7H-naphtho[1,8-gh]quinazolin-8-yl)benzaldehyde ***(4j)***. m.p. 187–190 °C. IR spectrum, ν, cm^{-1}: 850; 1650; 1711; 1730; 3120; 3200. ^{1}H NMR spectrum, δ, ppm *(J, H)*: 5.35 (s, 1H, CH); 6.42 (t, 2H, N-H); 7.19-7.35 (dd, 4H, Ph, *J* = 7.6, *J* = 7.8); 7.45-7.68 (m, 6H, Phenalen); 9.21(s, 1H, CHO). ^{13}C NMR spectrum, δ, ppm: 42.3; 108.8; 121.5;

122.7; 122.9; 123.1; 124.5; 126.2; 127.8; 128.7; 129.1; 131.2; 131.7; 132.3; 133.8; 134.5; 136.1; 137.7; 143.2; 162.6; 167.5; 178.8. Mass spectrum, m/z (I rel, %): 374 $[M+H]^+$ (100). Found, %: C: 70.55, H: 4.1, N: 7.41, O: 8.49. $C_{22}H_{14}N_2O_2$ calculated, %: C: 70.50, H: 4.03, N: 7.47, O: 8.54.

*8,9-Dihydro-8-(5-methylthiophen-2-yl)-11H-naphtho[1,8-gh]quinazoline-7,10-dione (**4k**)*. m.p. 194–196 ^oC. IR spectrum, ν, cm^{-1}: 850; 1650; 1713; 3127; 3230. ^1H NMR spectrum, δ, ppm *(J, H)*: 2.55 (s, 3H, CH_3); 5.19 (s, 1H, CH); 6.37 (t, 2H, N-H); 6.61 (dd, 4H, thiophen, J = 7.9, J = 8.4); 7.37-7.56 (m, 6H, Phenalen) .^{13}C NMR spectrum, δ, ppm: 42.3; 56.2; 108.8; 122.7; 122.9; 124.5; 126.2; 127.8; 128.7; 129.1; 131.2; 131.7; 132.3; 133.8; 136.1; 137; 138.3; 143.2; 161.8; 169.2. Mass spectrum, m/z (I rel, %): 346 $[M+H]^+$ (100). Found, %: C: 69.56, H: 4.23, N: 8.16, O: 9.37. $C_{20}H_{14}N_2O_2S$ calculated, %: C: 69.35, H: 4.07, N: 8.09, O: 9.24.

*8,9-Dihydro-8-(1H-pyrrol-2-yl)-11H-naphtho[1,8-gh]quinazoline-7,10-dione (**4l**)*. m.p. 184–185 ^oC. IR spectrum, ν, cm^{-1}: 814, 1638; 1710; 3134; 3204. ^1H NMR spectrum, δ, ppm: 4.86 (t, 1H, NH); 5.14 (s, 1H, CH); 6.22 (t, 2H, N-H); 6.57-6.36 (m, 3H, pyrol); 7.37-7.56 (m, 6H, Phenalen). ^{13}C NMR spectrum, δ, ppm: 56.2; 108.8; 122.7; 123.6; 124.5; 126.2; 127.8; 128.7; 129.1; 131.2; 131.7; 132.3; 133.8; 136.1; 137.2; 141.3; 142.8; 165.4; 167.6. Mass spectrum, m/z (I rel, %): 315 $[M+H]^+$ (100). Found, %: C: 72.42, H: 4.17, N: 13.28, O: 10.2. $C_{19}H_{13}N_3O_2$ calculated, %: C: 72.37, H: 4.16, N: 13.33, O: 10.15.

RESULTS AND DISSCUSSION

The results of optimization experiments for the three component Biginelli condensation involving phenalen-1,3-dione (1), urea/thio urea (2), benzaldehydes (3) and with $CuCl_2$ without any solvents are presented in Table 1. It is remarkable to note that the condensation proceeded with a low catalyst concentration (0.04 g) with heating in oil bath conditions that produce a naphtho[1,8-gh]quinazoline-7,10-diones 4a-l in high yields. We examined the proceeding of the reaction in four temperature (80, 90, 100, 110) ^oC and cleared that the optimized temperature is 80 ^oC and the reaction did not significantly proceed at lower temperatures.

We increased the temperature up to 90 ^oC but final product was not appreciable. We examined the reactions with different amount of catalysts that listed in Table 1. According to these results, the best amount of catalyst was 0.04 g. Because of the low melting point of urea, we used two equivalent of this material. The additional amount of urea in the end of the reaction, removed with washing with cool water. The reaction extended to aromatic and heteroaromatic to produce the expected 1,4-DHPs **4a–l** in high to excellent yields (Table 1).

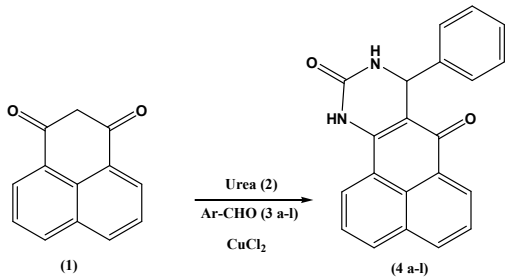
Table 1. Condensation reaction for the synthesis of naphtho[1,8-gh]quinazoline-7,10-diones in the presence of different loading of catalyst under solvent free condition.

Entry	Catalyst loading	Temperature (^oC)	Time (h)	Yield (%)
1	-	Room temperature	12	Trace
2	-	70	12	<25
3	0.01	80	2	45
4	0.02	80	2	63
5	0.03	80	2	77
6	0.04	80	2	94

Reaction conditions: 4-choloro benzaldehyde (3 mmol), phenalen-1,3-dione (3 mmol), urea (6 mmol).

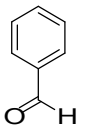
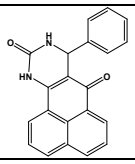
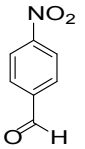
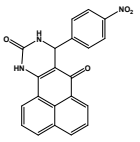
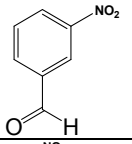
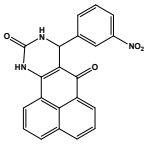
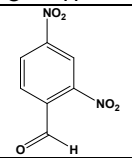
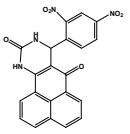
In summary, we have described a successful strategy, efficient and convenient green synthesis for the preparation of 3,4-dihdro pyrimidin-2(1H)-ones in valuing cyclocondensation reaction of 1,3-dicarbonyl compounds, aldehydes and urea using the inexpensive, non-toxic and

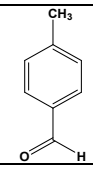
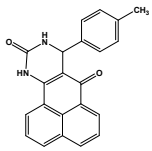
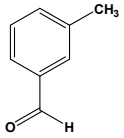
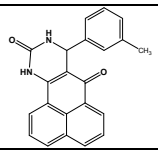
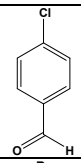
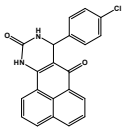
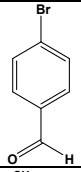
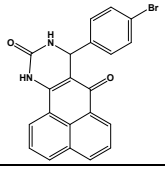
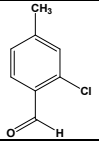
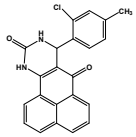
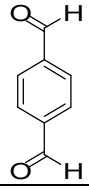
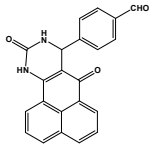
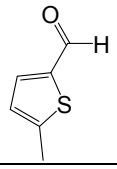
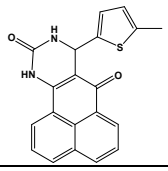
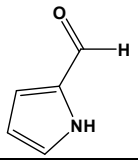
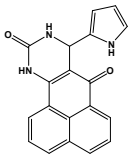
easily available $CuCl_2$ as a catalyst. $CuCl_2$ as a catalyst compare to other metal catalyst, have some benefits like inexpensive, easily prepare, reaction without any side products and easily separate from the reaction medium and finally easily reuse twice after the end of the reactions with solvation in ethanol. The method offers several advantages including high yield of products and easy experimental work-up procedure, which makes it a useful process for the synthesis of naphtho[1,8-gh]quinazoline-7,10-diones. We can see in Table 1 and 2 that the reaction times with this reagent and this condition, reduce from hours to minutes. Although the products yield improve and increase with this reaction condition as compare to other reagents [14, 16, 17].



Scheme 1. Synthesis of novel naphtho[1,8-gh]quinazoline-7,10-diones in solvent free condition.

Table 2. Synthesis of naphtho [1,8-gh]quinazoline-7,10-dione derivatives.

Entry	**3(a-l)**	**4(a-l)**	Time (min)	Yield (%)	m.p. (°C)
4a			54	75	170-173
4b			50	79	174-177
4c			75	83	165-168
4d			40	80	173-175

4e			45	78	162-165
4f			55	72	177-179
4g			50	77	171-173
4h			62	74	181-183
4i			65	70	167-170
4j			58	77	187-190
4k			70	75	194-196
4l			75	68	184-185

CONCLISION

The easy procedure, simple work-up, short reaction times and excellent yields of the products make this protocol as an useful addition to other routes for the synthesis of new dihydropyrimidones. Also, it emphasizes that the reactions can perform cleanly. We report a procedure where the reaction performs in solvent free condition, with the little amount of $CuCl_2$ as an catalyst in order to prevent problems that connected with conventional heating (cost, handling, safety, pollution, and decreases in reactivity by dilution of the reactants). In this work, we use the one-pot reaction procedure for the synthesis of naphtho[1,8-gh]quinazoline-7,10-diones by reaction of phenalen dione, benzaldehyde derivatives, urea and $CuCl_2$ as a catalyst. We obtained desired products with high yields. Therefore this method is simple, efficient, and easy separation of product.

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