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Simple and Efficient Amberlite 15-catalyzed Synthesis of Dihydroquinazolinones

T. Krishnaji[a,*], V. N. Murthy[b,c], A. Raghunadh[b], and L. V. Rao[c]

[a] *Department of Chemistry, CHRIST (Deemed to be University), Hosur Road, Bangalore, 560029 India*
[b] *Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd., Hyderabad, 500049 India*
[c] *Department of Chemistry, GIS, GITAM University, Visakhapatnam, 530045 India*
**e-mail: krishnaji.tadiparthi@christuniversity.in*

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Abstract—The Amberlite 15 catalyzed synthesis of substituted 2,3-dihydroquinazolin-4(1*H*)-ones was reported. The reaction conditions were optimized by screening in different solvents and catalysts. The substrate scope of the reaction was also studied, and a plausible mechanism for the reaction was proposed.

Keywords: dihydroquinazolinones, Amberlite 15, one-pot synthesis, aza-Michael addition

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INTRODUCTION

The dihydroquinazolinone core is incorporated in various biologically important natural and synthetic compounds like Quinethazone, Benzouracil, Evodiamine, Fenquizone, NC1 substance 1D19143, and Proquazone (Fig. 1). Such compounds proved to be excellent pharmacores and exhibited numerous therapeutic properties, including anticancer [1, 2], antihypertension [3], anticonvulsant [4], antibacterial [5, 6], anti-inflammatory [7, 8], antianxietic [9], and antidiabetic [10]. In addition, the dihydroquinazolinone moiety is found in antidepressants, antihistamines, and vasodilating agents. Because of their biological activity, the synthesis of dihydroquinazolinones has always been of great interest to researchers, and many methods for synthesizing different derivatives of dihydroquinazolinone have been reported (Scheme 1) [11–24]. However, each method has its own limitations, such as harsh reaction conditions, use of expensive metal catalysts, or low yields. As a continuation

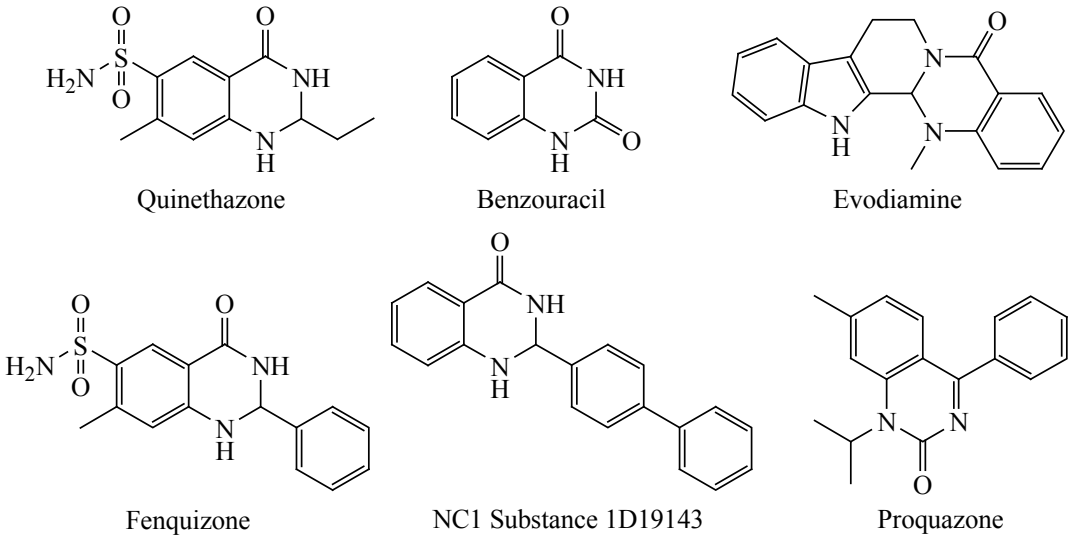
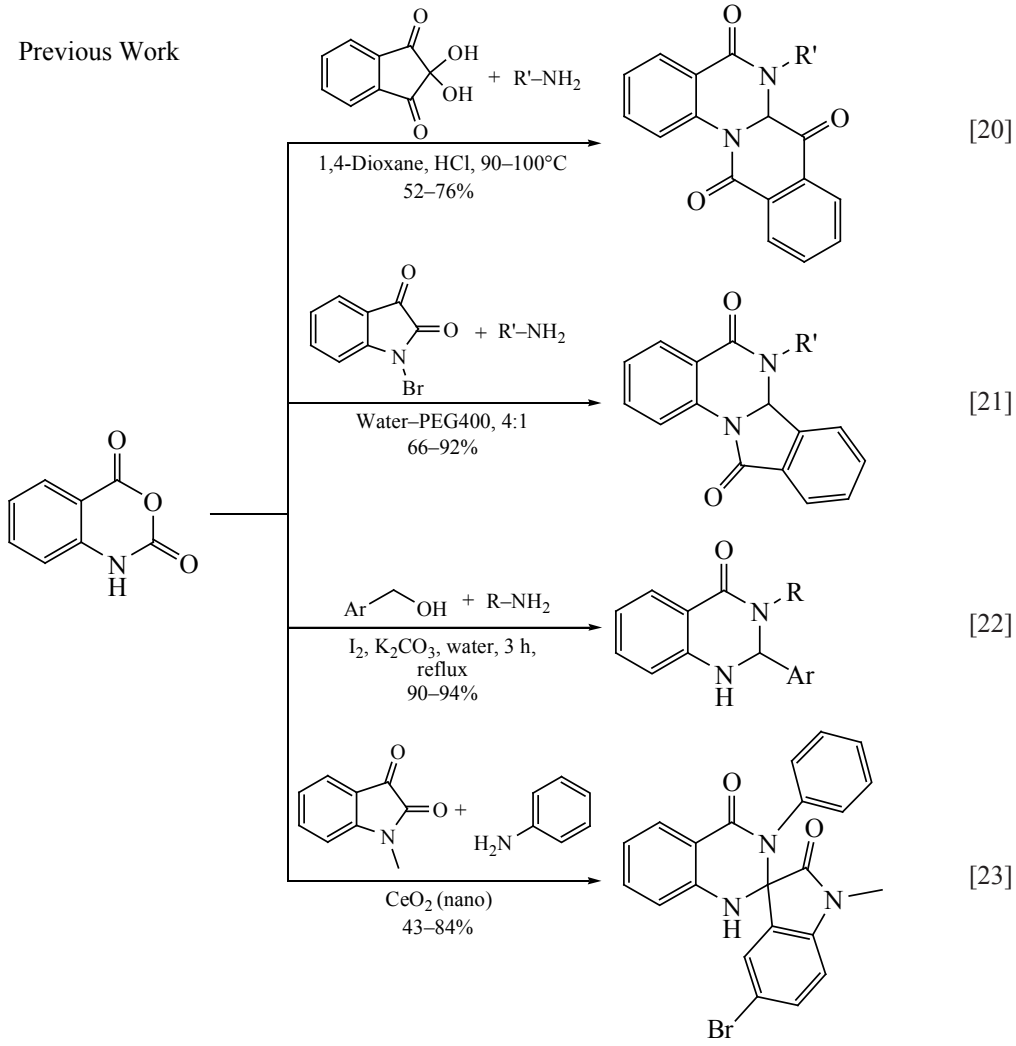
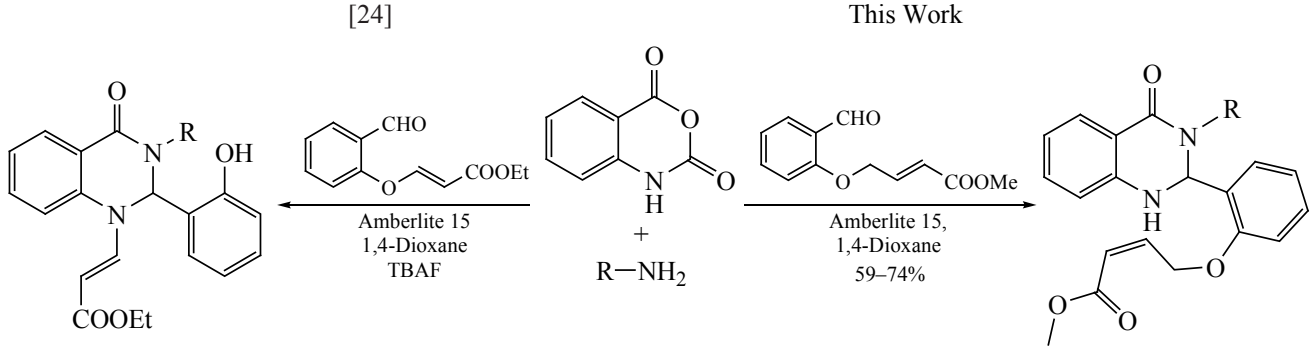


Fig. 1. Some biologically important dihydroquinazolinone compounds.

Scheme 1.



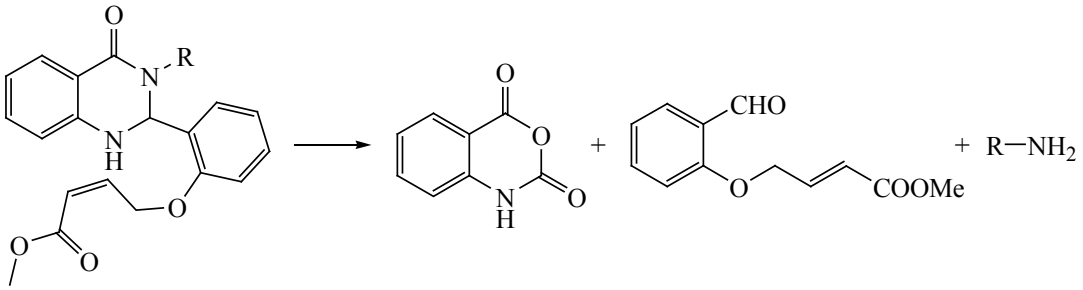


of our earlier efforts [25–29] toward the synthesis of various heterocyclic compounds, in the present work we developed a simple and efficient Amberlite 15-catalyzed one-pot synthesis of α,β-unsaturated esters of dihydroquinazolinone.

RESULTS AND DISCUSSION

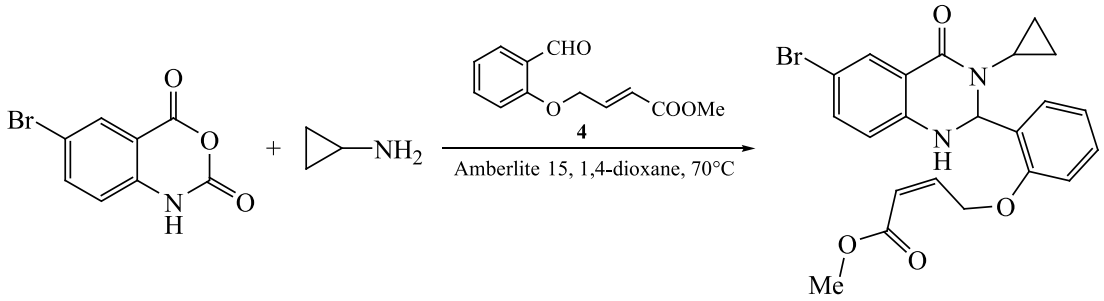
The retrosynthetic analysis of the proposed molecule of dihyroquinazolinone is depicted in Scheme 2. Accordingly, we developed our method for the synthesizing these compounds, using the

Scheme 2.



synthesis of dihyroquinazolinone **1a** by the reaction of 6-bromoisatoic anhydride (**2a**), cyclopropylamine (**3a**), and (*E*)-methyl-4-(2-formylphenoxy)but-2-enoate (**4**) as model substrates. During optimization we carried out the reaction in various solvents and catalysts and after fine tuning we found a good conversion rate with Amberlite 15 in 1,4-dioxane under reflux conditions (Table 1). However the yield of compound **1a** was low, when the reaction was conducted at room temperature. In addition few more experiments were conducted by varying the amount of Amberlite 15 (0.05–0.5 wt %) and good yields were obtained with Amberlite 15 (0.1 wt %) under similar conditions. The reaction was further tried to undergo aza-Michael reaction with tetrabutylammoniumfluoride (TBAF), but this attempt may have failed due to the lack of electrophilicity at the allylic carbon atom [24]. However the obtained α,β-unsaturated ester **1a** was characterized by ^{1}H and ^{13}C NMR. Furthermore, the substrate scope of this reaction has been studied by varying different types of amines and

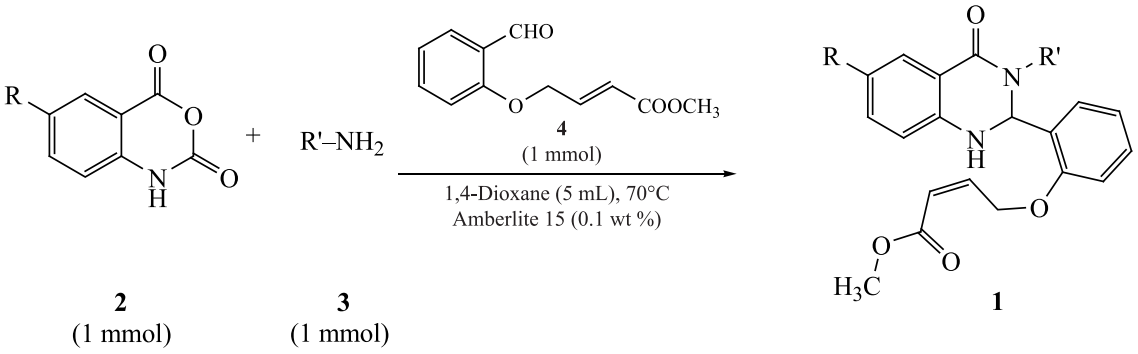
Table 1. Solvent and catalyst screening for the synthesis of dihyroquinazolinone **1a**



2a **3a** **4** **1a**

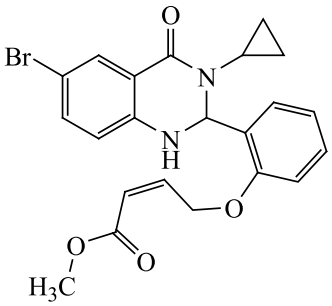
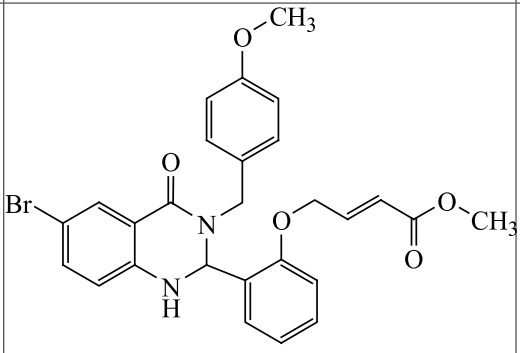
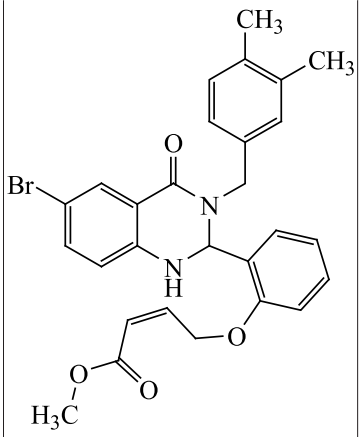
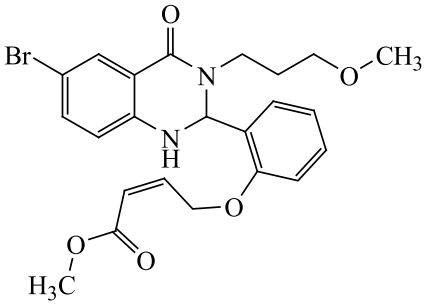
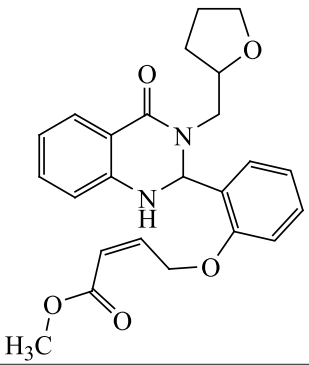
Entry	Solvent	Catalyst	Yield of **1a**, %
1	DMSO	Amberlite 15	35
2	1,4-Dioxane	Amberlite 15	74
3	DMF	Amberlite 15	36
4	Acetonitrile	Amberlite 15	55
5	Toluene	Amberlite 15	45
6	THF	Amberlite 15	50
7	Ethanol	Amberlite 15	10
8	1,4-Dioxane	Acetic acid	55
9	1,4-Dioxane	$BF_3{\cdot}OEt_2$	50
10	1,4-Dioxane	$TiCl_4$	63
11	1,4-Dioxane	$FeCl_3$	65

Table 2. Substrate scope for the synthesis of dihydroquinazolinones



2 (1 mmol) **3** (1 mmol)

R = H, Br; R' = cyclopropyl, aryl, alkoxy.

Comp. no.	Formula	Yield, %	Comp. no.	Formula	Yield, %
1a		65	**1d**		68
1b		72	**1e**		74
1c		59			

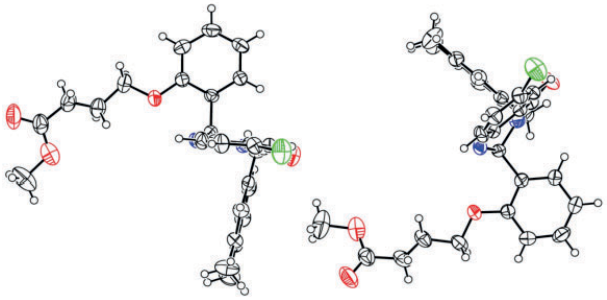
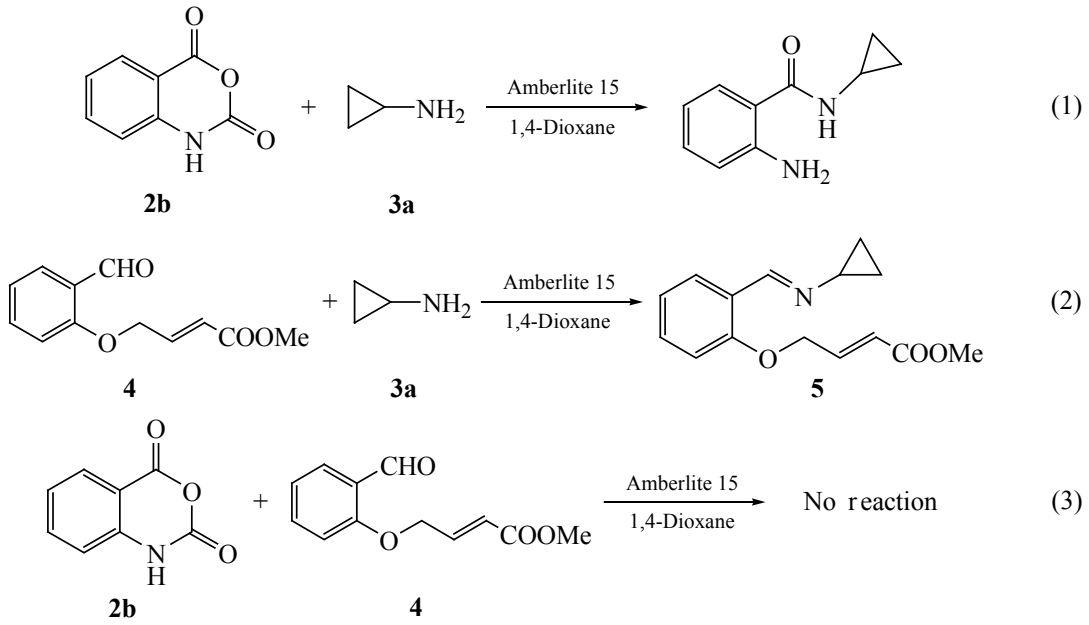


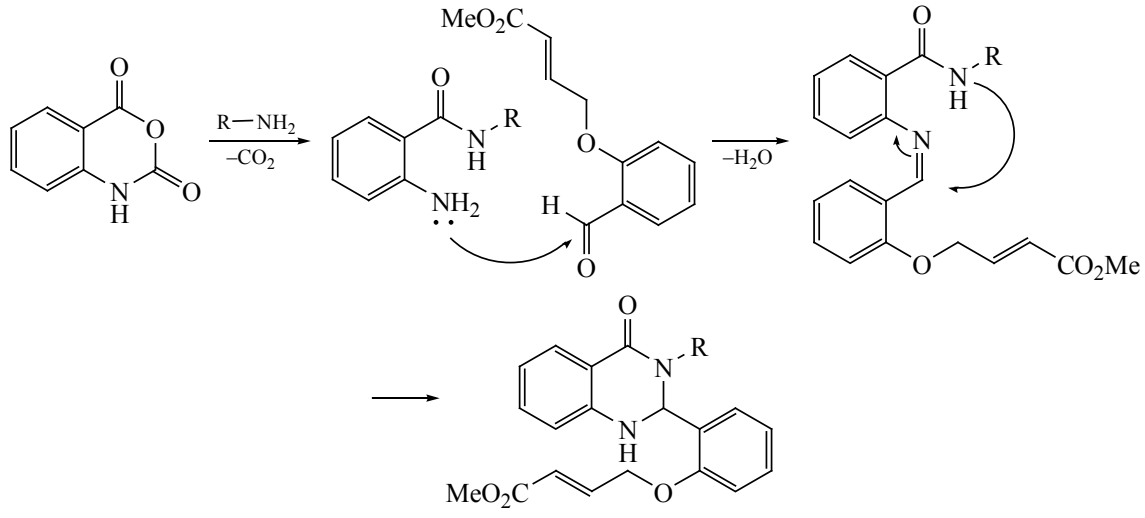
Fig. 2. ORTEP diagram of compound **1b** (the thermal ellipsoids of non-hydrogen atoms are drawn at a 50% probability level).

to our delight all the substrates have been well tolerated under the given optimized reaction conditions in order to get novel functionalized dihyroquinazolinones with reasonably good yields (Table 2). In addition the single crystal X-ray diffraction analysis of dihyroquinazolinone **1b** was used to confirm the structure (for details of the XRD experiment, see Supporting Information). The ORTEP diagram of the molecule (Fig. 2) provides clear evidence for the presence of the bromine atom, three phenyl rings, and methyl groups attached to aromatic ring.

Scheme 3.



Scheme 4.



To gain insight to the mechanism of the reaction, we performed few control experiments (Scheme 3). First we treated isatoic anhydride (**2b**) with cyclopropylamine (**3a**), the reaction involved ring opening to form an amide [Scheme 3, reaction (1)]. Cyclopropylamine (**3a**) was further treated with aldehyde **4** to form imine **5** [Scheme 3, reaction (2)]. However, no product formation was observed, when isatoic anhydride (**2b**) was reacted with aldehyde **4** [Scheme 3, reaction (3)]. The results of the control experiments clear evidence to suggest initial amide formation followed by imine formation and, finally, *aza*-Michael addition and allowed us to propose the reaction mechanism which is depicted in Scheme 4.

EXPERIMENTAL

All reactions were carried out in oven or flame-dried glassware under an argon atmosphere, employing standard techniques for handling air-sensitive materials. All solvents were reagent grade. All other reagents were used as received. Unless otherwise noted, reactions were magnetically stirred and monitored by TLC on Merck-Kiesegel 60 F plates. Flash chromatography was performed on silica gel (230–400 mesh) using distilled hexane and ethyl acetate. The yields refer to chromatographically and spectroscopically pure compounds. The ^{1}H and ^{13}C NMR spectra were recorded using a Bruker instrument at 400 and 100 MHz, respectively, from solutions in DMSO-d_6 with tetramethylsilane as internal standard.

Synthesis of dihydroquinazolin-4(1*H*)-ones 1a–1e (*general procedure*). To a solution of isatoic anhydride **2a** or **2b** (1 mmol) in 1,4-dioxane (5 mL), amine **3a–3e** (1 mmol) was added and stirred for 1 h at 70°C. (*E*)-Methyl-4-(2-formylphenoxy)but-2-enoate **4** (1 mmol) and Amberlite 15 (0.1 wt %) were added to the reaction mixture at room temperature and the was stirred for 4 h at 70°C. After completion of the reaction, the solvent in the reaction mass was evaporated under vacuum and the crude residue was purified by column chromatography (ethylacetate–hexane, 3 : 7) to get pure product **1a–1e**.

Methyl-(*Z*)-4-[2-(6-bromo-3-cyclopropyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)phenoxy]but-2-enoate (1a). White solid, yield 65%, mp 221–223°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 0.59–0.66 m (2H), 0.85–0.90 m (1H), 1.10–1.23 m (1H), 2.33–2.39 m (1H), 3.69 s (3H), 4.89 s (2H), 6.08 s (1H), 6.16 d (1H, *J* 16.0 Hz), 6.66 d (1H, *J* 8.4 Hz), 6.89–6.93 m (1H), 7.04–7.12 m (3H), 7.29–7.31 m (3H), 7.73 s (1H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 5.3, 9.1, 27.9, 51.5, 66.5 (2C), 107.5, 112.6, 115.8, 116.7, 120.7, 120.9, 125.9, 128.2, 129.1, 129.8, 135.6, 143.8, 144.8, 154.5, 163.2, 165.7. Mass spectrum, *m/z*: 457.10 [*M* + 1].

Methyl-(*Z*)-4-{2-[3-(3,4-dimethylbenzyl)-6-bromo-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl]-phenoxy}but-2-enoate (1b). Yellow solid, yield 72%, mp 199–201°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.15 s (3H), 2.17 s (3H), 3.52 d (1H, *J* 14.8 Hz), 3.67 s (3H), 4.73–4.86 m (2H), 5.31 d (1H, *J* 17.6 Hz), 5.97 d (*J* 13.6 Hz, 1H), 6.01 d (1H, *J* 2.8 Hz), 6.63 d (1H, *J* 8.8 Hz), 6.91–6.95 m (2H), 6.99–7.01 m (2H), 7.02–7.06 m (2H), 7.11–7.14 d.d (1H, J_1 7.6, J_2 4.0 Hz), 7.22 d (1H, *J* 2.0 Hz), 7.29–7.35 m (2H), 7.79 d (1H, *J* 2.4 Hz). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 19.0 (2C), 26.8, 46.1, 51.5, 63.8, 66.5, 107.7, 112.6, 115.6, 116.7, 120.6, 127.6, 128.9, 129.6, 130.0, 133.9, 135.3, 135.7, 136.3, 143.5, 145.3, 154.7, 161.2, 165.7. Mass spectrum, *m/z*: 537.20 [*M* + 1].

Methyl-(*Z*)-4-(2-{4-oxo-3-[(tetrahydrofuran-2-yl)methyl]-1,2,3,4-tetrahydroquinazolin-2-yl}-phenoxy)but-2-enoate (1c). Yellow solid, yield 59%, mp 215–217°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 0.82–0.85 m (0.5H), 1.10–1.14 m (1H), 1.39–1.47 m (0.5H), 1.59–1.61 m (0.5H), 1.76–1.93 m (4H), 2.75 d.d (0.5H, J_1 10.4, J_2 3.2 Hz), 3.60–3.83 m (5H), 4.01–4.10 m (2H), 4.88 s (2H), 6.17 d.d (1H, J_1 9.2, J_2 2.6 Hz), 6.42 d (1H, *J* 19.6 Hz), 6.67 t (1H, *J* 9.2 Hz), 6.91 t (1H, *J* 7.2 Hz), 7.00–7.13 m (3H), 7.23–7.33 m (3H), 7.72 s (1H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 15.1 (2C), 25.4, 28.8, 47.9, 59.0, 65.6, 67.2 (2C), 67.3, 77.8, 107.6, 112.6, 115.9, 116.8, 120.7, 125.9, 129.4, 129.8, 135.6, 145.2, 154.6, 162.0, 165.7. Mass spectrum, *m/z*: 423.10 [*M* + 1].

Methyl-(*Z*)-4-{2-[3-(4-methoxybenzyl)-6-bromo-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl]-cyclohexyloxy}but-2-enoate (1d). White solid, yield 59%, mp 215–217°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 3.56–3.66 m (2H), 3.69 s (3H), 3.72 s (3H), 4.76–4.88 m (2H), 5.28 d (1H, *J* 14.8 Hz), 5.97–6.03 m (2H), 6.64 d (1H, *J* 8.8 Hz), 6.85–6.87 m (2H), 6.89–6.94 m (1H), 6.94–7.00 m (2H), 7.04–7.13 m (2H), 7.22 m (1H), 7.28–7.35 m (2H), 7.79 d (*J* 2.4 Hz, 1H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6),

δ, ppm: 29.6, 45.9, 51.5, 54.9, 64.0, 66.5, 107.8, 112.6, 113.9 (2C), 115.6, 116.7, 120.9, 126.2, 127.6, 128.6 (2C), 129.6, 130.3, 135.3, 135.7, 143.5, 145.3, 154.7, 158.6, 161.2, 165.7. Mass spectrum, *m/z*: 537.20 [*M* + 1].

Methyl-(*Z*)-4-{2-[6-bromo-3-(3-methoxypropyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl]phenoxy}-but-2-enoate (1e). White solid, yield 74%, mp 232–234°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.61–1.71 m (1H), 3.34–3.37 m (1H), 3.70 s (3H), 3.77–3.85 m (1H), 4.82–4.91 m (2H), 6.14–6.17 m (2H), 6.67 d (1H, *J* 8.8 Hz, 1H), 6.91 d (1H, *J* 6.8 Hz), 7.03–7.08 m (2H), 7.11 t (1H, *J* 4.4 Hz), 7.20 d (1H, *J* 2.4 Hz), 7.30–7.33 m (2H), 7.71 d (1H, *J* 2.0 Hz). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 27.5, 41.9, 51.5, 57.8, 65.7, 66.6, 69.3, 107.7, 112.6, 116.0, 116.7, 120.8, 120.9, 126.2, 128.1, 129.2, 129.9, 135.5, 143.7, 145.3, 154.8, 161.3, 165.8. Mass spectrum, *m/z*: 489.20 [*M* + 1].

CONCLUSIONS

In conclusion, we have developed a simple procedure for the preparation of different dihyroquinazolinones by employing Amberlite 15 as a catalyst. The scope of the reaction has been demonstrated with various amines, and the plausible mechanism of the reaction has been proposed based on control experiments.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S1070428020080199 and are accessible for authorized users.

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