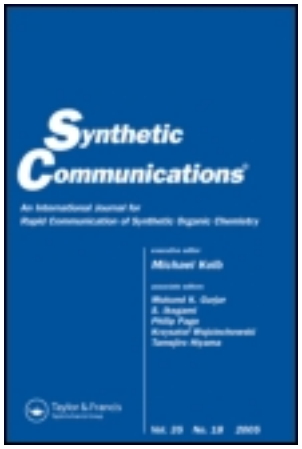

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Reaction of Isatoic Anhydride, Amine, and N,N′-Dialkyl Carbodiimides Under Solvent-Free Conditions: New and Efficient Synthesis of 3-Alkyl-2-(alkylamino)quinazolin-4(3H)-ones

Mehdi Asadi [a], Mostafa Ebrahimi [b], Mohammad Mahdavi [c], Mina Saeedi [c], Parviz Rashidi Ranjbar [a], Farshad Yazdani [b], Abbas Shafiee [c] & Alireza Foroumadi [c d]

[a] School of Chemistry, University College of Science, University of Tehran, Tehran, Iran

[b] Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran

[c] Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

[d] Drug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

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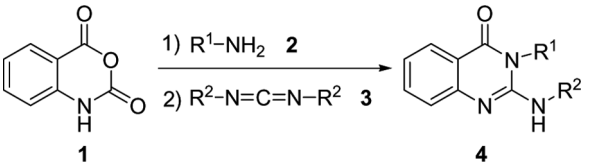
REACTION OF ISATOIC ANHYDRIDE, AMINE, AND *N,N′*-DIALKYL CARBODIIMIDES UNDER SOLVENT-FREE CONDITIONS: NEW AND EFFICIENT SYNTHESIS OF 3-ALKYL-2-(ALKYLAMINO) QUINAZOLIN-4(3*H*)-ONES

Mehdi Asadi,[1] Mostafa Ebrahimi,[2] Mohammad Mahdavi,[3] Mina Saeedi,[3] Parviz Rashidi Ranjbar,[1] Farshad Yazdani,[2] Abbas Shafiee,[3] and Alireza Foroumadi[3,4]

[1]*School of Chemistry, University College of Science, University of Tehran, Tehran, Iran*
[2]*Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran*
[3]*Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[4]*Drug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran*

GRAPHICAL ABSTRACT



Abstract *Heating a mixture of isatoic anhydride, amines, and N,N′-dialkyl carbodiimides under solvent-free conditions provided novel 3-alkyl-2-(alkylamino)quinazolin-4(3H)-one derivatives for the first time. The products were obtained in moderate to good yields without formation of any by-products.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords 3-Alkyl-2-(alkylamino)quinazolin-4(3*H*)-ones; isatoic anhydride; *N,N′*-dialkyl carbodiimides; solvent-free

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Address correspondence to Alireza Foroumadi, Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran. E-mail: aforoumadi@yahoo.com

INTRODUCTION

Quinazolin-4(3*H*)-one and their derivatives are very important heterocycles in medicinal chemistry and have notable pharmacological and therapeutic activities such as antiulcer,[1] anti-inflammatory,[2] anticancer,[3] hypolipidemic,[4] and anticonvulsant properties.[5] Also the quinazolin-4(3*H*)-one skeleton is found in a range of biologically important natural products including febrifugine and isofebrifugine (Fig. 1), which possess antimalarial activity.[6,7]

Because of the prevalent medicinal applications of quinazolin-4(3*H*)-ones, attempts to design new protocols for the synthesis of them has increased. So far, the most common synthetic methods for the preparation of quinazolin-4(3*H*)-ones involve (*i*) reaction of nitriles with lithiated anthranilamides;[8] (*ii*) condensation of aldehydes and anthranilamide or its derivatives in the presence of $CuCl_2$;[9] (*iii*) microwave-assisted condensation of anthranilic acids, carboxylic acids, and amines;[10] (*iv*) condensation of imidates with anthranilic acids;[11] (*v*) CuI-catalyzed coupling/condensative cyclization of *ortho*-haloarylcarboxamides with imidamides;[12] (*vi*) palladium-catalyzed cyclocarbonylation of *ortho*-iodoanilines with imidoyl chlorides and carbon monoxide;[13] (*vii*) silica sulfuric acid catalyzed reaction of isatoic anhydride, orthoesters, and primary amines;[14] and (*viii*) amine-induced thermal rearrangement of iminobenzoxazines.[15]

Among the various routes for the synthesis of complex scaffolds by cascade reactions, using green chemistry protocols has attracted synthetic organic chemists' interest. It offers efficient use of energy, hazard reduction, waste minimization, and the use of renewable resources.[16] Green chemistry was borne in mind and a novel route for the preparation of quinazolin-4(3*H*)-ones was designed according to Scheme 1.

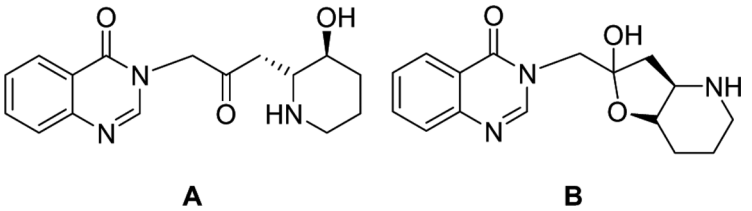
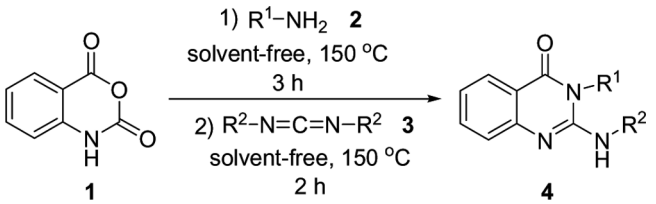


Figure 1. Febrifugine (A) and isofebrifugine (B).



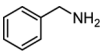
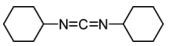
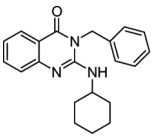
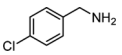
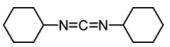
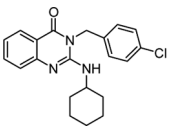
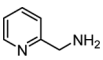
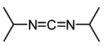
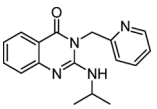
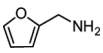
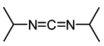
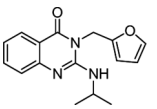
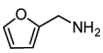
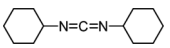
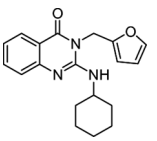
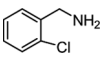
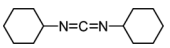
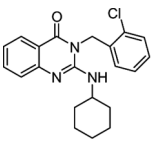
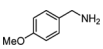
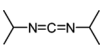
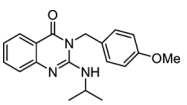
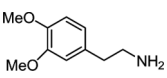
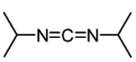
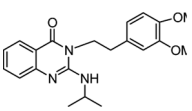
Scheme 1. Synthesis of 3-alkyl-2-(alkylamino)quinazolin-4(3*H*)-ones **4**.

RESULTS AND DISCUSSION

In continuation of our ongoing efforts to develop novel routes to synthesize new heterocycles and bioactive compounds,[17–19] herein, we have described green synthesis of quinazolin-4(3*H*)-one derivatives **4** by the solvent-free reaction of isotonic anhydride **1**, amines **2**, and *N,N′*-dialkyl carbodiimides **3** (Scheme 1).

Chemistry of isatoic anhydride and its reaction with amines has been investigated in detail.[20,21] We found that isatoic anhydride undergoes ring opening upon heating with various amines (Table 1) to produce 2-amino-*N*-alkylbenzamides. Moreover, benzamides can easily react with *N,N′*-dialkyl carbodiimides as potential

Table 1. Synthesis of 3-alkyl-2-(alkylamino)quinazolin-4(3*H*)-ones **4**

Entry	R^1-NH_2	R^2-N=C=N-R^2	Product		Yield (%)[a]
1				**4a**	85
2				**4b**	82
3				**4c**	80
4				**4d**	78
5				**4e**	86
6				**4f**	74
7				**4g**	77
8				**4h**	84

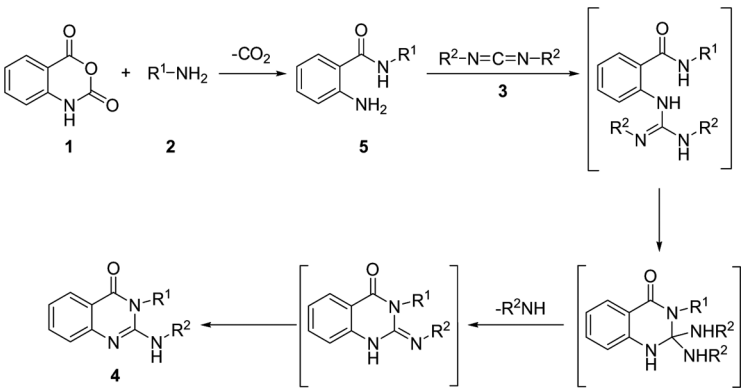
[a]Isolated yields.

precursors for nucleophilic attack. Hence, to obtain the best reaction conditions we initialized with reaction of isatoic anhydride (1 mmol) and benzylamine (1 mmol) at 150 °C under solvent-free conditions. After the completion of reaction (checked by thin-layer chromatography TLC), *N,N′*-dicyclohexyl carbodiimide (1.3 mmol) was added to the reaction mixture, which continued at the same temperature, and after 2 h the related product was obtained in 85% yield. It should be noted that using a stoichiometric amount of *N,N′*-dicyclohexyl carbodiimide led to a lower yield, and excess amount of it is needed.

The structure of product **4a** was elucidated by usual spectroscopic analysis. In the infrared (IR) spectrum, the amide carbonyls showed absorption at 1660 cm^{-1} and the imine group displayed its characteristic signal at 1615 cm^{-1}. In the ^1H NMR spectrum, the cyclohexyl protons were observed as multiplets at $\delta = 1.09$–1.80 (10H) and $\delta = 1.09$–1.80 (1H, NCH) ppm. Doublet signals for cyclohexyl NH group and singlet signal associated with the two protons of CH_2 were visible at $\delta = 6.41$ and 5.40 ppm, respectively. Multiplet signals related to nine aromatic protons were observed around 7.09–7.96 ppm. The ^{13}C spectrum showed 18 distinct resonances. The structure was also confirmed by mass spectroscopy fragmentation pattern analysis, which displayed the molecular ion peak at 333 for $C_{21}H_{23}N_3O$. The spectrum showed a strong peak at 251, which is related to elimination of the cyclohexyl ring. The peaks at 222 and 149 have been resulted from loss of carbonyl and phenyl groups respectively from the latter ion. They are related to the formation of benzylidene-2-phenylguanidine ion and benzylguanidine radical cation.

After confirmation of **4a** and with the optimized conditions in hand for the synthesis of 3-benzyl-2-(cyclohexylamino)quinazolin-4(3*H*)-one, we next set out to explore the scope of our reaction. To our delight, various amines and *N,N′*-dialkyl carbodiimides produced diverse quinazolin-4(3*H*)-one derivatives in good to excellent yields (Table 1).

Sequences in the formation of compounds **4** are given in Scheme 2. It is believed that the initial event is the formation of 2-amino-*N*-alkylbenzamides **5** from the reaction of isatoic anhydride **1** and amines **2**. Then *N,N′*-dialkyl carbodiimides **3** is added to **5**. Cyclization of the intermediate, omission of -NHR^2, and tautomerization lead to the formation of 3-alkyl-2-(alkylamino)quinazolin-4(3*H*)-ones **4**.



Scheme 2. Steps of the formation of 3-alkyl-2-(alkylamino)quinazolin-4(3*H*)-ones **4**.

In conclusion, we have developed a simple and highly efficient green protocol for the synthesis of potential pharmaceutically active quinazolin-4(3*H*)-one derivatives by reaction of isatoic anhydride, amines, and *N,N′*-dialkyl carbodiimides under solvent-free conditions. The advantages of this work are green procedure, simple workup, good yields, and versatility, which make it one of the most convenient methods for the synthesis of this class of heterocycles.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker FT-500, using tetramethylsilane (TMS) as an internal standard. The infrared (IR) spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disks). Mass spectra were documented on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. The elemental analysis was performed with an Elemetar Analysensystem GmbH VarioEL CHNS mode.

Synthesis of 3-Alkyl-2-(alkylamino)quinazolin-4(3*H*)-ones: General Procedure

A mixture of isotonic anhydride **1** (1 mmol) and appropriate amine **2** (1 mmol) was stirred at 150 °C for 3 h. Then, *N,N′*-dialkyl carbodiimide **3** (1.3 mmol) was added to the reaction mixture and stirring continued at 150 °C for 2 h. After completion of the reaction, it was cooled to room temperature and the residue was purified by column chromatography using petrolume ether–ethyl acetate (2:1) as eluent.

3-Benzyl-2-(cyclohexylamino)quinazolin-4(3*H*)-one (4a)

White powder (0.28 g, 85%), mp 148–150 °C. IR (KBr) (ν_{max}/cm^{-1}): 3403, 3109, 2929, 2853, 1660, 1615, 1531, 1473. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.96–7.10 (m, 9H, ArH), 6.40 (d, $J = 7.4$ Hz, 1H, NH), 5.40 (s, 2H, CH_2), 3.97 (m, 1H, NCH), 1.80–1.09 (m, 10H, cyclohexyl). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.0, 149.3, 149.0, 136.4, 134.2, 128.4, 127.1, 126.7, 126.6, 124.5, 121.6, 116.1, 50.0, 42.8, 33.4, 31.9, 25.3, 24.7. Mass, m/z (%): 333 (M^+, 31), 251 (100), 222 (30), 91 (50). Anal. calcd. for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60%. Found: C, 75.50; H, 7.10; N, 12.55.

3-(4-Chlorobenzyl)-2-(cyclohexylamino)quinazolin-4(3*H*)-one (4b)

White powder (0.30 g, 82%), mp 177–178 °C. IR (KBr) (ν_{max}/cm^{-1}): 3370, 3056, 2926, 2851, 1661, 1613, 1535, 1470. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.94–7.10 (m, 8H, ArH), 6.44 (d, $J = 7.5$ Hz, 1H, NH), 5.37 (s, 2H, CH_2), 3.954 (m, 1H, NCH), 1.82–1.11 (m, 10H, cyclohexyl). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.9, 149.3, 148.9, 135.4, 134.2, 131.7, 128.6, 128.3, 126.5, 124.5, 121.6, 116.0, 50.0, 42.2, 33.3, 31.9, 25.3, 24.7, 24.4. Mass, m/z (%): 369 ($[M+2]^+$, 19), 367 (M^+, 57), 285 (100), 256 (55), 224 (45), 125 (96). Anal. calcd. for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42%. Found: C, 68.20; H, 6.15; N, 11.71.

2-(Isopropylamino)-3-((pyridin-2-yl)methyl)quinazolin-4(3*H*)-one (4c)

White powder (0.23 g, 80%), mp 165–167 °C. IR (KBr) (ν_{max}/cm^{-1}): 3402, 3050, 2928, 2850, 1660, 1615, 1531, 1475. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.51–7.10 (8H, m, ArH), 7.00 (1H, d, $J = 7.1$ Hz, NH), 5.38 (2H, s, CH_2), 4.27 (1H, q, $J = 6.5$ Hz, CH), 1.16 (6H, d, $J = 6.5$ Hz, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.8, 155.5, 149.8, 149.4, 148.7, 137.3, 134.2, 126.5, 124.5, 122.8, 122.4, 121.6, 116.2, 45.5, 42.9, 22.2. Mass, m/z (%): 294 (M^+, 54), 251 (44), 235 (42), 202 (100), 93 (85). Anal. calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03%. Found: C, 69.50; H, 6.22; N, 19.15.

3-((Furan-2-yl)methyl)-2-(isopropylamino)quinazolin-4(3*H*)-one (4d)

White powder (0.22 g, 78%), mp 170–172 °C. IR (KBr) (ν_{max}/cm^{-1}): 3407, 2925, 3056, 1665, 1530, 1475. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.93–6.60 (m, 7H, ArH), 6.40 (d, $J = 7.0$ Hz, 1H, NH), 5.38 (d, $J = 14.5$ Hz, 2H, CH_2), 4.30 (q, $J = 6.5$ Hz, 1H, CH), 1.20 (d, $J = 6.5$ Hz, 3H, CH_3), 1.12 (d, $J = 6.5$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.5, 149.3, 149.0, 148.8, 128.7, 128.4, 126.5, 124.5, 124.4, 121.7, 110.5, 108.4, 43.1, 42.3, 22.1, 22.0. Mass, m/z (%): 283 (M^+, 50), 240 (40), 225 (35) 202 (100). Anal. calcd. for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83%. Found: C, 67.70; H, 6.30; N, 14.60.

2-(Cyclohexylamino)-3-((furan-2-y)methyl)quinazolin-4(3*H*)-one (4e)

White powder (0.28 g, 86%), mp 130–131 °C. IR (KBr) (ν_{max}/cm^{-1}): 3403, 3106, 2929, 2853, 1656, 1612, 1558, 1472. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.93–7.08 (m, 5H, ArH), 6.50 (d, $J = 7.5$ Hz, 1H, NH), 6.41–6.38 (m, 2H, furan), 5.41 (s, 2H, CH_2), 3.99 (m, 1H, NCH), 1.90–1.04 (m, 10H, cyclohexyl). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.5, 149.4, 149.2, 148.7, 142.5, 134.2, 126.5, 124.4, 121.5, 116.0, 110.4, 108.4, 50.0, 36.5, 33.3, 32.0, 25.3, 24.7, 24.4. Mass, m/z (%): 323 (M^+, 52), 241 (90), 212 (100), 143 (37). Anal. calcd. for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99%. Found: C, 70.75; H, 6.73; N, 13.10.

3-(2-Chlorobenzyl)-2-(cyclohexylamino)quinazolin-4(3*H*)-one (4f)

White powder (0.27 g, 74%), mp 129–130 °C. IR (KBr) (ν_{max}/cm^{-1}): 3439, 3060, 2933, 2855, 1678, 1606, 1568, 1475. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.89–6.73 (8H, m, ArH), 6.66 (1H, d, $J = 7.5$ Hz, NH), 5.35 (2H, s, CH_2), 4.05 (1H, m, NCH), 1.92–1.06 (10H, m, cyclohexyl). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.7, 149.4, 149.3, 134.3, 133.7, 131.9, 129.4, 128.5, 127.3, 126.4, 126.1, 125.6, 124.6, 115.9, 50.1, 41.9, 32.0, 28.1, 25.6, 25.3, 24.9. Mass, m/z (%): 369 ($[M+2]^+$, 17), 367 (M^+, 23), 336 (92), 303 (42), 149 (34), 125 (100). Anal. calcd. for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42%. Found: C, 68.44; H, 6.20; N, 11.33.

3-(4-Methoxybenzyl)-2-(isopropylamino)quinazolin-4(3*H*)-one (4g)

White powder (0.25 g, 77%), mp 169–170 °C. IR (KBr) (ν_{max}/cm^{-1}): 3440, 3050, 2925, 2855, 1670, 1612, 1560, 1475. ^{1}H NMR (DMSO-d_6): δ 7.93–6.88

(m, 8H, ArH), 6.52 (d, $J = 6.7$ Hz, 1H, NH), 5.29 (s, 2H, CH_2), 4.27 (q, $J = 6.0$ Hz, 1H, NCH), 3.70 (s, 3H, OCH_3), 1.14 (d, $J = 6.0$ Hz, 6H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.9, 158.4, 149.2, 149.0, 134.2, 128.4, 126.5, 124.4, 121.6, 116.1, 113.8, 55.0, 43.0, 42.1, 40.6, 22.0. Mass, m/z (%): 323 (M^+, 50), 280 (45), 265 (40), 202 (100). Anal. calcd. for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99%. Found: C, 70.40; H, 6.84; N, 12.84.

3-(3,4-Dimethoxyphenylethyl)-2-(isopropylamino)quinazolin-4(3*H*)-one (4h)

White powder (0.31 g, 84%), mp 178–180 °C. IR (KBr) (ν_{max}/cm^{-1}): 3435, 3055, 2920, 2850, 1668, 1610, 1565, 1470. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.91–6.72 (7H, m, ArH), 6.38 (1H, d, $J = 7.5$ Hz, NH), 4.32 (2H, t, $J = 7.2$ Hz, CH_2), 4.26 (1H, q, $J = 6.5$ Hz, NCH), 3.70 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.82 (2H, t, $J = 7.2$ Hz, CH_2), 1.17 (6H, d, $J = 6.5$ Hz, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.8, 155.6, 149.8, 149.4, 148.7, 137.3, 134.2, 126.5, 124.5, 122.8, 122.4, 121.6, 116.2, 45.5, 42.9, 31.8, 22.2. Mass, m/z (%): 367 (M^+, 50), 324 (45), 308 (45), 202 (100). Anal. calcd. for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44%. Found: C, 68.54; H, 7.05; N, 11.70.

SUPPORTING INFORMATION

Full experimental details and ^{1}H and ^{13}C NMR spectra are available online.

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