

## Eco-friendly syntheses of 2,2-disubstituted- and 2-spiroquinazolinones

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Dedicated to the memory of a giant of heterocyclic chemistry:  
Professor Alan Roy Katritzky

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### Abstract

Environmentally friendly methods were applied to prepare quinazolin-4(1*H*)-one derivatives in either aqueous or solventless medium from anthranilamide and a number of ketones. With dialkyl-substituted ketones, acetophenone and cycloalkanones, the ring closure proceeded smoothly under either aqueous or solventless conditions. With poorly water-soluble cycloalkanones, the ring closure was carried out under mechanochemical ball-milling conditions, in the presence of molecular iodine as catalyst. The environmentally friendly protocols applied resulted in the corresponding quinazolinones in quantitative yields.

**Keywords:** Environmentally friendly methods, aqueous, solventless, mechanochemical, ball-milling reactions.

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### Introduction

Quinazolines are effective substances in medicinal chemistry that possess a broad spectrum of biological activities<sup>1</sup>, including antioxidant, antimicrobial,<sup>2</sup> anti-Alzheimer<sup>3</sup> and anticonvulsant<sup>4</sup> activities. Among the various quinazoline derivatives, 2-substituted and 2,2-disubstituted quinazolinone hybrids have been found to be good candidates for the treatment of leishmaniasis.<sup>5</sup> Incorporation of a spirocyclohexane moiety at position 2 of the quinazolinone heterocycle gives safer and potent anti-inflammatory and analgesic agents.<sup>6</sup> Some spiro[heterocycloalkyl-2'(1'*H*)-quinazolin]-4'(3'*H*)-ones demonstrate anti-amoebic activity *in vitro*<sup>7</sup> and have been investigated as central nervous system depressants.

A number of green methods have been reported for the preparation of 2(2,2)-(di)substituted quinazolin-4(1*H*)-ones, based mainly on the cyclocondensation of anthranilamide with various

aromatic aldehydes and (cyclo)alkanones in ionic liquids,<sup>8</sup> in/on water<sup>9</sup> or under solventless conditions, *i.e.* by heating at 60–70 °C<sup>10</sup> or by using a grinding technique<sup>11</sup>. Catalysts such as cyanuric chloride,<sup>12</sup> I<sub>2</sub>,<sup>13</sup> citric acid<sup>11</sup>, NH<sub>4</sub>Cl,<sup>14</sup> ZnCl<sub>2</sub>,<sup>15</sup> CuCl<sub>2</sub><sup>16</sup> and sulfamic acid<sup>17</sup> have been applied.

We recently demonstrated that the spirocyclization of carbocyclic 2-aminocarbohydrazides with *N*-benzylpiperidinone in water at room temperature (rt) in the absence of any additive led to 3'-aminospiropiperidine-quinazolinones. Environmentally benign spirocyclization in either aqueous or solventless medium has been developed for the preparation of spiro[cyclohexane-1,2'-(1'*H*)-quinazolin]-4'(3'*H*)-ones by the reaction of equivalent amounts of (saturated or partially saturated) anthranilamide and cyclohexanone.<sup>18</sup>

With the growing interest in environmentally friendly and atom-economic processes, the application of a green solvent (*i.e.* water)<sup>19</sup> or a solventless procedure<sup>20</sup> is considered a preferable route in organic chemistry. Aqueous chemistry protocols have attracted significant interest in synthetic processes.<sup>21</sup> Water-mediated reactions have recently been termed “in-water” or “on-water” reactions, depending on the nature of the reactants (solubility).<sup>22</sup> Water is the preferred reaction medium in the design of green chemical syntheses of heterocycles.<sup>23</sup> Significant efforts have been devoted to achieving organic syntheses in aqueous medium, one aim being “all-water chemistry”.<sup>24</sup>

In recent years, the solvent-free chemical synthesis of heterocycles has developed into powerful methodology: less toxic waste is produced, with less harm to the environment. Various new and innovative sustainable organic reactions and methodologies have made use of alternative energy input sources, such as microwaves, sonication, conventional and rt heating conditions, mechanochemical mixing and high-speed ball-milling.<sup>25</sup> The utilization of mechanical force for solventless organic syntheses, in the form of either mechanical grinding<sup>26</sup> or milling,<sup>27</sup> has been widely introduced. As a procedure for mechanochemical solid-state reactions (dry co-grinding),<sup>28</sup> a number of chemical transformations have been studied, including the formation of amides,<sup>29</sup> thioureas<sup>30</sup> and metallodrugs,<sup>31</sup> coupling chemistry<sup>32</sup> and asymmetric reactions.<sup>33</sup> A number of excellent reviews highlight the history and success of mechanochemistry.<sup>34</sup>

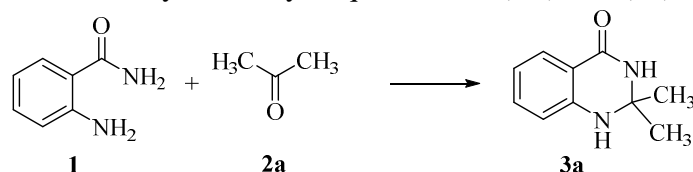
In this context, we set out to study the condensation of anthranilamide with (cyclo)alkanones for the synthesis of 2,2-disubstituted- and 2-spiroquinazolinones either in aqueous medium or under solventless conditions.

## Results and Discussion

We initially studied the influence of solventless and catalyst-free conditions in the reaction of anthranilamide (**1**) and acetone (**2a**) as standard and model. From a mixture of **1** and **2a** after 2 days at rt, only 2% of 2,2-dimethyl-2,3-dihydro-1*H*-quinazolin-4-one (**3a**) was obtained. This

low yield could be explained by the fact that aromatic amines are less potent nucleophiles than the (cyclo)aliphatic derivatives.

**Table 1.** Synthesis of 2,2-dimethyl-2,3-dihydroquinazolin-4(1*H*)-one (**3a**)



Entry	Solvent	Temp. [°C]	Time [h]	Catalyst	Acetone equiv.	Yield <sup>a</sup> [%]	Ref.
1	acetone	56	15	HCl	27	ng	35
2	acetone	40–50	0.25	HCl	9	83	36
3	ethanol	78	6	<i>p</i> -TSA	2	ng	37
4	methanol	65	3	<i>p</i> -TSA	6.8	60	38
5	acetone	56	15	HCl	27	35	39
6	acetone	ng	ng	HCl	ng	56	40
7	acetone	56	1	<i>p</i> -TSA	18	96	41
8	TFE	74	24	–	3	97	42
9	acetone	MW	0.08	<i>p</i> -TSA	40	91	43
10	methanol	25	0.17	H <sub>2</sub> SO <sub>4</sub> -silica	13	97	44
11	[BMIm][BF <sub>4</sub> ]	50	4	I <sub>2</sub>	1.05	92	8
12	water	70	0.5	NH <sub>2</sub> SO <sub>3</sub> H	1	92	17
13	acetic acid	115	0.5	–	1	92	45
14	water	70	3	MNPs-PSA	1	71	46
15	CH <sub>3</sub> CN	25	2	HCNC-4 <sup>b</sup>	1	57	47
17	water	25	12	I <sub>2</sub> /KI	1.1	76	present work
18	–	25	12	I <sub>2</sub>	1.1	~100	present work

<sup>a</sup> ng = not given; <sup>b</sup> Heteropolyacid–clay(montmorillonite-K10) nano composite.

The synthesis of **3a** *via* the above starting compounds has been extensively studied. The most useful classical and modern methods for the preparation, presented in Table 1, reveal only a few examples involving green methodologies.

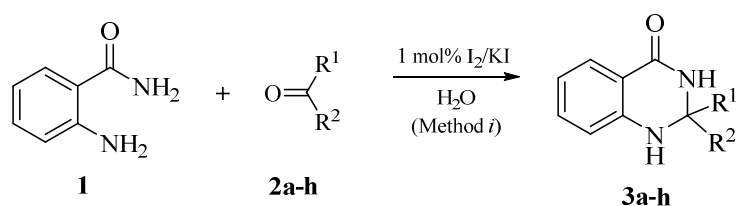
To overcome the limitations in our model reaction, we envisaged the use of a catalyst that could promote the cyclization process. Several research groups have implemented various strategies for the synthesis of nitrogen heterocycles where I<sub>2</sub> plays a key role as a mild Lewis

acid in the Schiff-base formation and intramolecular ring closure by polarizing the carbonyl group.<sup>13</sup> Some of these procedures comprised I<sub>2</sub>-catalysed multicomponent reactions.<sup>48</sup> We chose solid I<sub>2</sub> as catalyst.

When the model reaction was performed under magnetic stirring in the presence of 1 mol% of I<sub>2</sub>, the reaction mixture solidified in 20–25 min. A 76% yield was obtained at rt in 35 min, and **3a** was formed quantitatively after 12 h. Alternatively, **3a** was prepared in aqueous medium. Because of the insufficient solubility of I<sub>2</sub> in water, 1 mol% of I<sub>2</sub> as Lugol's solution (I<sub>2</sub>/KI) was used. After stirring for 12 h at ambient temperature, the precipitated **3a** was isolated by simple filtration in a yield of 76%.

With a successful procedure available, we first examined the aqueous condensation of ketones **2b–2h** with **1**. In 4 ml of water, a mixture of 4 mmol of **1**, 1 ml of 1% I<sub>2</sub>/KI (Lugol's) solution and 1.1 equivalents of **2a–2c** or 1 equivalent of **2d–2h** was stirred in a closed vessel at rt for 12 h. **3a–3c**, **3e** and **3f** started to precipitated in about 30 min. After stirring for 12 h, **3a–3c** and **3e**, **3f** were isolated by filtration (Table 2) [Method (i)]. The in-water syntheses of **3d**, **3g** and **3h** were carried out under reflux. The less water-soluble **2h** gave **3h** in moderate yield only under reflux in ethanol. The poor solubility of the alkanone in water appeared to restrict the water-mediated quinazolinone synthesis.

**Table 2.** Syntheses of 2,2-disubstituted- and 2'-spiro-2,3-dihydroquinazolin-4(1*H*)-ones (**3a–3h**) in aqueous media

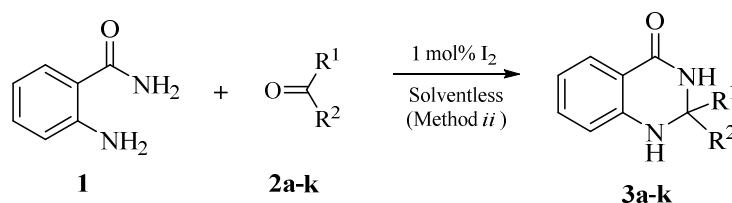


Entry	R <sup>1</sup>	R <sup>2</sup>	Solubility of <b>2a-h</b> [g/100 mL water] <sup>a</sup>	Ketone equiv.	Temp. [°C]	Time [h]	Product	Yield [%] <sup>b</sup>	Mp [°C] <sup>c</sup>
1	CH <sub>3</sub>	CH <sub>3</sub>	<b>2a</b> [∞]	1.1	25	12	<b>3a</b>	76	183–185
2	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	<b>2b</b> [4.7]	1.1	25	12	<b>3b</b>	95	186–188
3	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	<b>2c</b> [2.2]	1.1	25	12	<b>3c</b>	47	202–204
4	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	<b>2d</b> [0.24]	1	100	3	<b>3d</b>	51	226–230
5	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>4</sub>		<b>2e</b> [2.3]	1	25	12	<b>3e</b>	71	262–264
6	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>5</sub>		<b>2f</b> [1.5]	1	25	12	<b>3f</b>	90	234–235
7	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>6</sub>		<b>2g</b> [0.89]	1	100	3	<b>3g</b>	88	200–204
8	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>7</sub>		<b>2h</b> [0.54]	1	100 78	3 2	<b>3h</b>	26 67	194–198 193–196 <sup>d</sup>

<sup>a</sup> at 25 °C; <sup>b</sup> Isolated yields; <sup>c</sup> from aqueous suspension; <sup>d</sup> from ethanolic solution.

In view of the above observations, we further investigated the I<sub>2</sub>-catalysed solventless ring-closure reactions of various (cyclo)alkanones with **1**. I<sub>2</sub> was dissolved in liquid (cyclo)alkanones **2b**, **2c** or **2e–2g**; and **1** was then added. The reactions were complete in 12 h at rt (Table 3).

**Table 3.** Solventless syntheses of 2,2-disubstituted- and 2'-spiro-2,3-dihydroquinazolin-4(1*H*)-ones (**3a–3k**)



Entry	R <sup>1</sup>	R <sup>2</sup>	Ketone	equiv.	Temp. [°C]	Time [h]	Product	Yield [%] <sup>a</sup>	Mp (lit. Mp) [°C] <sup>b</sup>
1	CH <sub>3</sub>	CH <sub>3</sub>	<b>2a</b>	1.1	25	12	<b>3a</b>	99 (81) <sup>d</sup>	183–185 <sup>c</sup> (182–183) <sup>45</sup>
2	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	<b>2b</b>	1.1	25	12	<b>3b</b>	98 (85) <sup>d</sup>	186–188 <sup>c</sup> (184–185) <sup>8</sup>
3	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	<b>2c</b>	1.1	25	12	<b>3c</b>	96 (92) <sup>d</sup>	198–201 <sup>c</sup> (190–191) <sup>49</sup>
4	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	<b>2d</b>	1	60	2	<b>3d</b>	97 (86) <sup>d</sup>	227–230 <sup>c</sup> (224–225) <sup>8</sup>
5	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>4</sub>		<b>2e</b>	1	25	12	<b>3e</b>	99 (78) <sup>d</sup>	268–271 <sup>c</sup> (265–267) <sup>8</sup>
6	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>5</sub>		<b>2f</b>	1	25	12	<b>3f</b>	99 (87) <sup>d</sup>	227–230 <sup>c</sup> (221–223) <sup>8</sup>
7	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>6</sub>		<b>2g</b>	1	25	12	<b>3g</b>	98 (91) <sup>d</sup>	198–202 <sup>c</sup> (204–205) <sup>39</sup>
8	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>7</sub>		<b>2h</b>	1	60	2	<b>3h</b>	97 (90) <sup>d</sup>	189–192 <sup>c</sup> (178–179) <sup>8</sup>
9	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>11</sub>		<b>2i</b>	1	60	2	<b>3i</b>	96 (91) <sup>d</sup>	200–204 <sup>c</sup> (206–207) <sup>8</sup>
10	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>14</sub>		<b>2j</b>	1	60	2	<b>3j</b>	96 (89) <sup>d</sup>	175–179 <sup>c</sup> –
11	R <sup>1</sup> + R <sup>2</sup> = 1-indane		<b>2k</b>	1	60	2	<b>3k</b>	97 (91) <sup>d</sup>	220–224 <sup>c</sup> (224–226) <sup>14</sup>

<sup>a</sup> Conversion yields determined on the basis of <sup>1</sup>H NMR spectra. <sup>b</sup> The spectral data and the mp's of the products corresponded well with literature values. <sup>c</sup> Melting points of crude products after aqueous work-up. <sup>d</sup> Isolated yields after aqueous work-up.

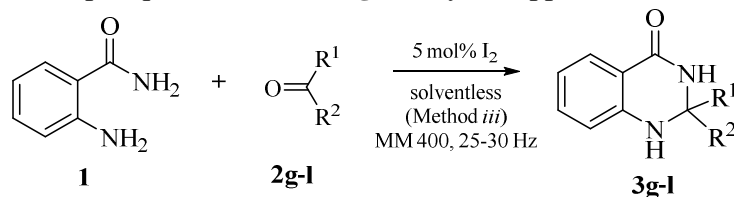
Melt reactions were applied for the preparation of **3d** and **3h–3k**. Reaction mixtures of **2d** or solid **2h–2k**, I<sub>2</sub> and **1** were heated at 60 °C for 2 h. After 10–20 min, these mixtures solidified and the reactions gave 96–97% yields [Method *ii*].

As mechanical ball-milling is an emerging solventless technique that can promote eco-friendly organic reactions,<sup>50</sup> we next investigated the mechanochemical synthesis of spirocyclic quinazolinones. The liquid–solid and solid–solid condensations of **2g–2k** with **1** were carried out in a mixing ball-mill. The solid-state spirocyclization of **1** and **2l** was also studied. All these reactions were performed at a 1:1 stoichiometric ratio of the reactants, in the presence of 5 mol% of I<sub>2</sub>. 4.0 mmol of **1** and **2g–2l** were placed in a 25 mL stainless-steel jar with two stainless-steel balls 15 mm in diameter, the vessel was closed, and milling was started at rt at 25 Hz. During the mechanochemical experiments, the temperature of the reaction vessel reached 60–70 °C. After a 60 min milling time, the formation of liquid eutectics (**3h** and **3k**), *eutectic melts*<sup>51</sup> (**3g** and **3i**) or powders (**3j** and **3l**) was observed. The progress of the spirocyclization was monitored by TLC. On a silica gel plate developed with EtOAc–*n*-hexane (1:1, v/v), the following amounts of heterocycles were detected: **3h** ~60%, **3k** ~40%, **3g** and **3i** ~70–80%, and **3j** and **3l** ~90%. Milling was continued for an additional 1 h under the same conditions, leading to the formation of powder-like products, except in the case of **3k**, which was in a liquid phase. Further mechanochemical treatment of the mixture of **1** and **2k** for 1.5 h at 30 Hz yielded crude **3k** in a yield of 97% as a powder. The ball-milling reactions therefore always led to powdery products (Table 4).

We were somewhat surprised to observe that the spirocyclization of **1** (mp 111–113 °C) with **2l** (mp 256–258 °C) proceeded without the formation of a visible liquid state. This can be explained by the formation of instant “hot spots” during the mechanical process.

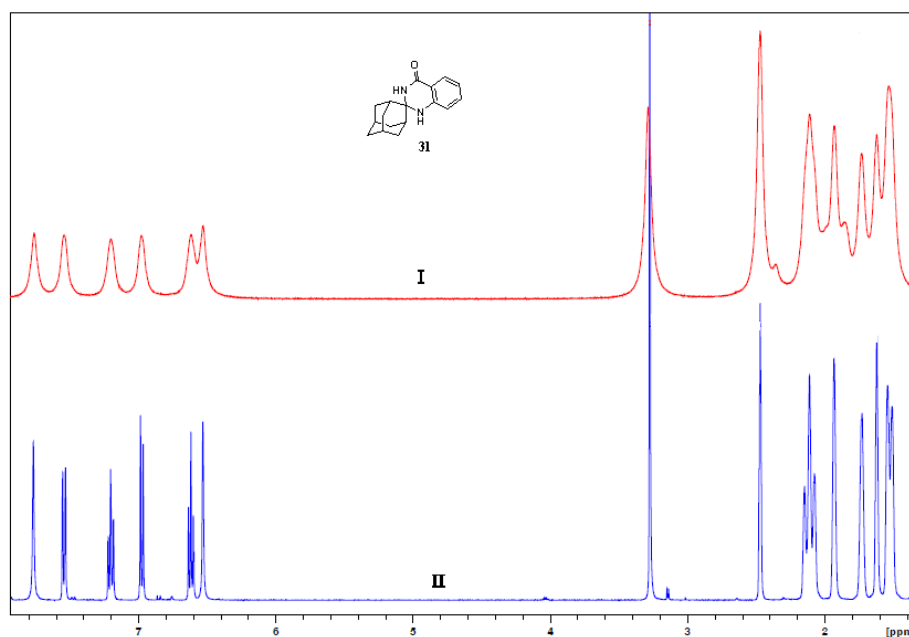
<sup>1</sup>H NMR spectroscopy demonstrated that the yields of powders **3g–3l** were nearly quantitative. It is important to note that paramagnetic iron particles abraded from the stainless-steel balls led to extreme broadening of the lines in the NMR spectra. To eliminate this contamination, ZrO<sub>2</sub> milling balls were applied in a further mechanochemical study. The proton spectra of iron-polluted and crude ZrO<sub>2</sub> ball-milled **3l** are compared in Figure 1.

When elimination of the I<sub>2</sub> catalyst was essential, a simple aqueous work-up procedure was applied. Products prepared by Method *ii* were suspended by use of a magnetic stirrer in a mixture of 1 mL of 2% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> and 9 mL of water for 10 min, then filtered and air-dried. In the mechanosynthesis (Method *iii*) of **3g–3l**, 5 mL of 2% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> and 5 mL of water were added to the milling jar and ball-mill mixing for 5 min furnished a fine suspension, which was filtered off, washed with 5 mL of water and air-dried.

**Table 4.** Syntheses of 2-spiroquinazolinones (**3g–3l**) by the application of mechanical forces

Entry	R <sup>1</sup>	R <sup>2</sup>	Ketone	equiv.	Temp. [°C]	Time [h]	Product	Yield [%] <sup>a</sup>	Mp [°C] <sup>b</sup>
1	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>6</sub>		<b>2g</b>	1	25	2	<b>3g</b>	98 (95) <sup>d</sup>	195–199 (198–202) <sup>e</sup>
2	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>7</sub>		<b>2h</b>	1	25	2	<b>3h</b>	97 (93) <sup>d</sup>	185–190 (189–192) <sup>e</sup>
3	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>11</sub>		<b>2i</b>	1	25	2	<b>3i</b>	98 (94) <sup>d</sup>	201–205 (203–205) <sup>e</sup>
4	R <sup>1</sup> + R <sup>2</sup> = (CH <sub>2</sub> ) <sub>14</sub>		<b>2j</b>	1	25	2	<b>3j</b>	98 (91) <sup>d</sup>	164–168 (180–182) <sup>f</sup>
5	R <sup>1</sup> + R <sup>2</sup> = 1-indane		<b>2k</b>	1	25	2+1.5 <sup>c</sup>	<b>3k</b>	97 (94) <sup>d</sup>	212–216 (221–224) <sup>e</sup>
6	R <sup>1</sup> + R <sup>2</sup> = 2'-adamantane		<b>2l</b>	1	25	2	<b>3l</b>	99 (90) <sup>d</sup>	270–274 (281–283) <sup>f</sup>

<sup>a</sup> On the basis of <sup>1</sup>H NMR; <sup>b</sup> melting points of crude products; <sup>c</sup> at 30 Hz; <sup>d</sup> isolated yields from aqueous work-up; <sup>e</sup> from aqueous suspension; <sup>f</sup> recrystallized from EtOAc.

**Figure 1.** <sup>1</sup>H NMR spectra of crude **3l** after stainless-steel (I) and ZrO<sub>2</sub> (II) ball-milling.

In conclusion, we have developed I<sub>2</sub>-mediated solvent-free and aqueous green syntheses of known and new quinazolinones. The condensations of anthranilamide with (cyclo)alkanones proceeded efficiently in/on water to provide convenient syntheses of **3a–3g** in good to excellent yields without the need for further work-up. As new green methodology, we have demonstrated that various 2,2-disubstituted- or 2-spiroquinazolines can be prepared almost quantitatively under solventless conditions. We have also shown that ball-milling can be a useful method for the preparation of diverse 2-spiroquinazolinones from liquid/solid or solid/solid reactants. These methods have a number of advantages over other methods: the reaction techniques are very simple, and the syntheses occur under mild, green reaction conditions without the need for costly, highly sensitive catalysts.

## Experimental Section

**General.** The products were characterized by comparison of their spectral data and melting points with those reported in the literature. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of the dried crude mixtures were taken in *d*<sub>6</sub>-DMSO to confirm the formation of **3a–3l**. <sup>1</sup>H NMR (400 Hz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded on a Bruker Avance DRX 400 spectrometer with TMS as internal reference. Analytically pure samples of new compounds (**3j** and **3l**) were prepared by crystallization from EtOAc.

Melting points were determined on a Kofler apparatus. FT-IR spectra were recorded in KBr pellets on a Perkin-Elmer 100 FT-IR spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyser. Mass spectra were recorded on a Finnigan MAT 95S spectrometer.

The ball-milling experiments were performed in a Retsch MM400 mixer mill with two stainless-steel or ZrO<sub>2</sub> balls 15 mm in diameter in a stainless-steel jar (25 mL) at 25 Hz or 30 Hz at rt.

### Preparation of 2,2-disubstituted- and 2'-spiro-2,3-dihydroquinazolin-4(1*H*)-ones (**3a–3l**)

**Method i:** To a stirred mixture of **1** (0.54 g, 4.0 mmol) in 1 mL of 1% I<sub>2</sub>/KI (1 g of I<sub>2</sub> and 1.6 g of KI in 100 ml of aqueous solvent) and 4 mL of water in a round-bottomed flask (25 mL), **2a–2c** (4.4 mmol) or **2d–2h** (4 mmol) was added in portions. The flask was sealed with a teflon cap. After vigorous stirring at rt for 12 h (for **3d**, **3g** and **3h**, the aqueous suspension was heated under reflux for 3 h), **3a–3h** precipitated. The products were filtered off, washed with water (2 mL) and dried. The purities of **3a–3h** were established by <sup>1</sup>H NMR measurements.

**Method ii:** 10 mg (1 mol%) of iodine was dissolved in 4.4 mmol of **2a–2c** or 4.0 mmol of **2d–2k** at rt or 60 °C (Table 2) in a round-bottomed flask (25 mL), which was sealed with a teflon cap. To the resulting solution, 0.54 g (4.0 mmol) of **1** was added and the mixture was stirred for 15 min. After standing at rt for 12 h (**3a–3c** and **3e–3g**) or at 60 °C for 2 h (**3d**, **3h–3k**), the excess of **2a–2c** was removed by evaporation. The <sup>1</sup>H NMR data on the solidified products proved the presence of **3a–3k** in 96–99% purity.



In the aqueous work-up procedure, the reaction mixture was suspended in a mixture of 1 ml of 2% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> and 9 ml of water, and the resulting solid was filtered off, washed with water (2 mL) and dried.

**Method iii:** **2g–2l** (4.0 mmol), **1** (0.54 g, 4.0 mmol), 50 mg (5 mol%) of I<sub>2</sub> and two stainless-steel or ZrO<sub>2</sub> balls 15 mm in diameter were placed in a stainless-steel jar. The vessel was vibrated at 25 Hz for 2 h. The reaction progress was monitored by TLC. The milling of the reaction mixture of **1** and **2k** was continued for 1.5 h at 30 Hz (Table 4). The products were recovered as solids (directly from the jar) and dried. Crude **3g–3l** were characterized by the determination of melting points and <sup>1</sup>H NMR.

In the aqueous work-up procedure, 5 mL of 2% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> solution and 5 mL of water were added to the reaction mixture in the jar. The aqueous suspension was mixed at 25 Hz for 5 min, filtered off, washed with water (5 mL) and dried. The isolated yields were determined after the aqueous work-up. Analytically pure samples of new compounds **3j** and **3l** (entries 4 and 6, Table 4) were recrystallized from EtOAc. Analytical and spectroscopic data on **3j** and **3l** are given below.

**Spiro[cyclopentadecane-1,2'(1'H)-quinazolin]-4'(3'H)-one (3j).** Slightly beige crystals, mp 180–182 °C (EtOAc); IR (cm<sup>-1</sup>): 3343, 3193, 3054, 2930, 2854, 1646, 1614, 1512, 749. <sup>1</sup>H NMR δ (ppm): 1.10–1.70 (m, 28 H, cycloalkyl), 6.46 (br s, 1 H, NH), 6.56 (t, *J* 7.3 Hz, 1 H, ArH), 6.68 (d, *J* 8.1 Hz, 1 H, ArH), 7.16 (m, 1 H, ArH), 7.51 (m, 1 H, ArH), 7.84 (br s, 1 H, NHCO); <sup>13</sup>C NMR δ (ppm): 21.77 (2×C), 26.76 (2×C), 27.03 (2×C), 27.06 (2×C), 27.33 (2×C), 27.92 (2×C), 38.70 (2×C), 72.06 (C-2'), 115.01, 115.22, 117.11, 127.93, 133.97, 147.90, 163.89; Anal. calcd. for C<sub>22</sub>H<sub>34</sub>N<sub>2</sub>O (342.52) (%): C, 77.14; H, 10.01; N, 8.18. Found: C, 76.95; H, 10.31; N, 8.21; MS: (ESI) *m/z* = 343 [M+H]<sup>+</sup>**Spiro[tricyclo[3.3.1.1<sup>3,7</sup>]decane-2,2'(1'H)-quinazolin]-4'(3'H)-one (3l).** Colourless crystals, mp 281–283 °C (EtOAc); IR (cm<sup>-1</sup>): 3421, 3217, 3082, 2918, 2859, 1647, 1610, 1500, 1485, 754. <sup>1</sup>H NMR δ (ppm): 1.47–2.18 (m, 14 H, adamantyl), 6.53 (br s, 1 H, NH), 6.62 (t, *J* 7.3 Hz, 1H, ArH), 6.97 (d, *J* 8.1 Hz, 1 H, ArH), 7.20 (m, 1H, ArH), 7.54 (m, 1 H, ArH), 7.77 (br s, 1 H, NHCO); <sup>13</sup>C NMR δ (ppm): 26.81 27.08, 32.60 (2×C), 33.05 (2×C), 36.66 (2×C), 38.47, 72.08 (C-2'), 115.96, 115.99, 117.67, 127.89, 133.98, 147.21, 164.11; Anal. calcd. for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O (268.35) (%): C, 76.09; H, 7.51; N, 10.44. Found: C, 75.95; H, 7.31; N, 10.25; MS: (ESI) *m/z* = 269 [M+H]<sup>+</sup>

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