

## Utility of $\alpha$ -Oxoketene Dithioacetals in Organic Synthesis: Synthesis of Some New Spiro Quinazolin-4-(3H)-one Derivatives

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**Abstract:** A convenient synthesis of a series of substituted 4'-oxo-3',4'-dihydro-(1'H)-spiro[pyran-4,2'-quinazoline]-3-carbonitrile and 4'-oxo-3',4'-dihydro-(1'H)-spiro[pyran-4,2'-quinazoline]-3-ethylcarboxylate *via* the reactions of versatile and readily accessible 3-(4-oxo-3,4-dihydroquinazolin-2(1H)-ylidene)pentane-2,4-dione **1** with the appropriate reagents, is described here.

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**Keywords:**  $\alpha$ -Oxoketene, dithioacetals, spiro, quinazolone.

### 1. Introduction

Quinazolines are considered to be important chemical synthons of various physiological significances and pharmaceutical utilities. They possess a variety of biological effects, including antihypertensive,<sup>1,2</sup> antimicrobial,<sup>3,4</sup> antihyperlipidemic,<sup>5,6</sup> antiinflammatory,<sup>7,8</sup> and anticonvulsant<sup>9-13</sup> activities. Moreover, many quinazolines contributed to the quest for an ultimate antitumor chemotherapeutic agent.<sup>14-18</sup> Moreover, the derivatives of quinazolin-4-one are potential drugs which can possess hypnotic, analgesic, antiallergic, anticonvulsant, antimalarial, and other effects.<sup>19</sup> On the other hand,  $\alpha$ -oxoketene dithioacetals and related compounds are versatile synthons in organic synthesis.<sup>20,21</sup> The substitution reaction of  $\alpha$ -oxoketene dimethylthioacetals with diamine is one of the important applications for the synthesis of the corresponding  $\alpha$ -oxoketene cyclic *N,N*-acetals.<sup>22</sup>

### 2. Materials and Methods

All melting points were determined on Kofler melting point apparatus and were uncorrected. IR spectra were obtained on a Nicolet 710-FT IR spectrophotometer. NMR spectra were recorded on Bruker avance 300 MHz spectrometer using TMS as internal reference (chemical shifts in  $\delta$ , ppm). Elemental analyses were carried out with an elemental analyzer model 240 C.

#### **Synthesis of 3-(4-oxo-3,4-dihydroquinazolin-2(1H)-ylidene)pentane-2,4-dione 1:**

A mixture of 3-[bis(methylthio)methylene]pentane-2,4-dione (4.0 mmol) and 2-aminobenzamide (4.1 mmol) was refluxed in 50 mL of absolute ethanol for 24 h. On cooling the precipitated product was filtered off and recrystallized from EtOH into pale yellow needles, mp: 242-244 °C; yield 82 %; IR (KBr, cm<sup>-1</sup>): 3341,

3283 (2NH), 1682, 1664 (2CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta$  8.83 (s, 1H, NH), 7.96 (s, 1H, NH), 7.64-7.26 (m, 4H, CH-arom.), 2.26 (s, 6H, 2CH<sub>3</sub>); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): 198.8, 159.6, 155.1, 142.2, 132.3, 128.2, 126.0, 118.6, 106.5, 98.9, 28.7.

#### **Synthesis of 2-(2-oxopropylidene)-2,3-dihydroquinazolin-4(1H)-one 2:**

An equivalent amount of compound **1** (10 mmol) and sodium methoxide (0.25g of sodium metal in 20 ml MeOH) was refluxed for 4 hrs. Water (20 ml) was then added and the mixture was extracted with CHCl<sub>3</sub> (3 x 50 ml). The organic extract was dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a solid precipitate which was recrystallized from EtOH into light brown powder, mp: 194-196 °C; yield 67%; IR (KBr, cm<sup>-1</sup>): 3361, 3280 (2NH), 1676 (CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta$  8.92 (s, 1H, NH), 8.11 (s, 1H, NH), 7.60-7.38 (m, 4H, CH-arom.), 5.2 (s, 1H, =CH) 2.25 (s, 3H, CH<sub>3</sub>).

#### **Synthesis of 4'-oxo-3',4'-dihydro-1'H-spiro[pyran-4,2'-quinazoline] derivatives 3-7: General Procedure**

Compound **1** (2.68 g, 0.01 mol) in EtOH (40 mL) was treated with the appropriate active methylene compound (0.01 mol) and piperidine (1 mL) was then added. The reaction mixture was refluxed for different periods of time (30 min - 3hrs) and then left to cool. The obtained solids were collected by filtration and recrystallized from the proper solvent to afford the desired product in pure form.

**2-Amino-6-methyl-4'-oxo-3',4'-dihydro-1'H-spiro[pyran-4,2'-quinazoline]-3-carbonitrile 3.** Dark yellow crystals; yield 82%, mp: 206-208 °C; IR (KBr, cm<sup>-1</sup>): 3389, 3312, 3266 (NH<sub>2</sub> and 2 NH), 2212 (CN), 1672 (CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta$  9.05 (s, 1H, NH), 8.20 (s, 1H, NH), 7.68-7.42 (m, 4H, CH-arom.), 6.15 (br, 2H, NH<sub>2</sub>), 5.16 (s, 1H, =CH), 2.32 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): 168.2, 151.4, 147.8,

141.6, 133.5, 130.4, 128.7, 117.6, 113.2, 101.3, 96.7, 67.8.

**Ethyl 2-amino-6-methyl-4'-oxo-3',4'-dihydro-1'H-spiro[pyran-4,2'-quinazoline]-3-carboxylate 4.**

Yellow needles; yield 78%; mp: 243-245 °C; IR (KBr, cm<sup>-1</sup>): 3374, 3316, 3252 (NH<sub>2</sub> and 2 NH), 1748 (CO), 1668 (CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 9.12 (s, 1H, NH), 8.18 (s, 1H, NH), 7.77-7.45 (m, 4H, CH-arom.), 5.85 (br, 2H, NH<sub>2</sub>), 5.09 (s, 1H, =CH), 3.86 (q, 2H, CH<sub>2</sub>), 2.27 (s, 3H, CH<sub>3</sub>), 1.22 (t, 3H, CH<sub>3</sub>).

**2-Amino-6-methyl-4'-oxo-3',4'-dihydro-1'H-spiro[pyran-4,2'-quinazoline]-3-carboxamide 5.**

White powder; yield 76%; mp: 210-212 °C; IR (KBr, cm<sup>-1</sup>): 3412, 3341, 3312, 3276 (2 NH<sub>2</sub> and 2 NH), 1668 (CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 8.87 (s, 1H, NH), 7.96 (s, 1H, NH), 7.62-7.41 (m, 4H, CH-arom.), 6.12 (br, 2H, NH<sub>2</sub>), 5.05 (s, 1H, =CH), 4.24 (br, 2H, NH<sub>2</sub>), 2.36 (s, 3H, CH<sub>3</sub>).

**6-Methyl-1H, 1'H-spiro[pyrano(2,3-c)pyrazole-4,2'-quinazoline]-3,4'-(2H,3;H)-dione 6.**

Light brown crystals; yield 68%; mp: 224-226 °C; IR (KBr, cm<sup>-1</sup>): 3375, 3323, 3286, 3250 (4 NH), 1668 (CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 9.15 (s, 1H, NH), 8.76 (s, 1H, NH), 7.88 (s, 1H, NH), 7.58-7.35 (m, 4H, CH-arom.), 5.25 (s, 1H, =CH), 4.44 (s, 1H, NH), 2.32 (s, 3H, CH<sub>3</sub>).

**Ethyl 2,6-dimethyl-4'-oxo-3',4'-dihydro-1'H-spiro[pyran-4,2'-quinazoline]-3-carboxylate 7.**

Pale yellow crystals; yield 87%; mp: 192-194 °C; IR (KBr, cm<sup>-1</sup>): 3363, 3275 (2NH), 1745 (CO), 1665 (CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 8.88 (s, 1H, NH), 8.4 (s, 1H, NH), 7.66-7.43 (m, 4H, CH-arom.), 5.17 (s, 1H, =CH), 4.12 (q, 2H, CH<sub>2</sub>), 2.38 (s, 3H, CH<sub>3</sub>), 1.25 (t, 3H, CH<sub>3</sub>).

**Synthesis of (4-oxo-3,4-dihydroquinazolin-2(1H)-ylidene)malononitrile 8.**

A mixture of [bis (methylthio) methylene] malononitrile (4.0 mmol) and 2-aminobenzamide (4.1 mmol) was refluxed in 50 mL of absolute ethanol for 24 h. On cooling the precipitated product was filtered

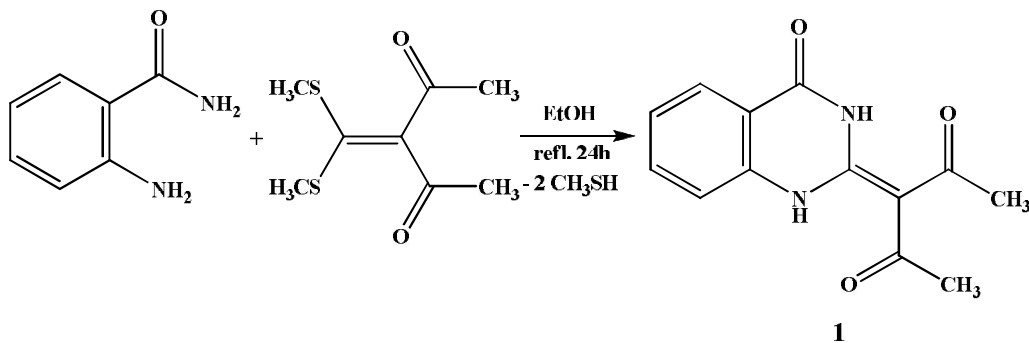
off and recrystallized from EtOH into yellow needles, mp: 192-194 °C; IR (KBr, cm<sup>-1</sup>): 3312, 3276 (2 NH), 2202 (CN), 1670 (CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 8.92 (s, 1H, NH), 7.88 (s, 1H, NH), 7.62-7.41 (m, 4H, CH-arom.).

**Synthesis of 5-acetyl-2-amino-6-methyl-4'-oxo-3',4'-dihydro-1'H-spiro[pyran-4,2'-quinazoline]-3-carbonitrile 9.**

A mixture of compound 8 (0.21 g, 1 mmol) and acetylacetone (0.1 mL, 1 mmol) in 40 mL absolute ethanol was treated with 1 drop piperidine and then was refluxed for 3h. Solvent was removed under vacuum and the solid mass was treated with 50 mL distilled water and left overnight. The formed solid was filtered off and recrystallized from ethanol into white solid; mp: 168-170 °C; IR (KBr, cm<sup>-1</sup>): 3385, 3294, 3250 (NH<sub>2</sub> and NH); 2198 (CN), 1698, 1668 (2CO); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 9.15 (s, 1H, NH), 8.07 (br, 1H, NH), 7.66-7.43 (m, 4H, CH-arom.), 6.22 (br, 2H, NH<sub>2</sub>), 2.20 (s, 3H, CH<sub>3</sub>), 1.24 (s, 3H, CH<sub>3</sub>).

**3. Results and Discussion**

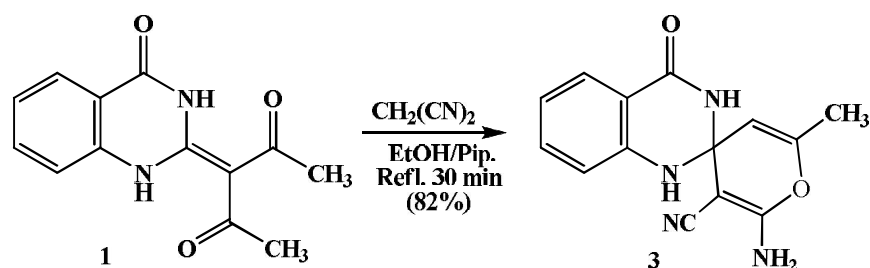
α-Oxoketene dithioacetals have been extensively used as three carbon synthons in the synthesis of a variety of five-membered and six-membered heterocycles due to their 1,3-bielectrophilic character<sup>20</sup>. Considering the above reports, we wish here to report a simple, convenient, and high-yielding method for the synthesis of some new spiro heterocycles bearing the quinazolone moiety. The starting 3-(4-oxo-3,4-dihydroquinazolin-2(1H)-ylidene) pentane-2,4-dione **1** was obtained from the reaction of 2-aminobenzamide (anthranilamide) with 3-[bis(methylthio)methylene]pentane-2,4-dione in refluxing ethanol for 24 hours. The reaction was assumed to proceed through a nucleophilic attack of both -NH<sub>2</sub> groups of 2-aminobenzamide to the ethylenic bond followed by elimination of two molecules of methyl mercaptan, Scheme 1.



Scheme 1

Compound **1** was then allowed to react with malononitrile in refluxing ethanol in the presence of piperidine as a catalyst where 2-amino-6-methyl-4'-

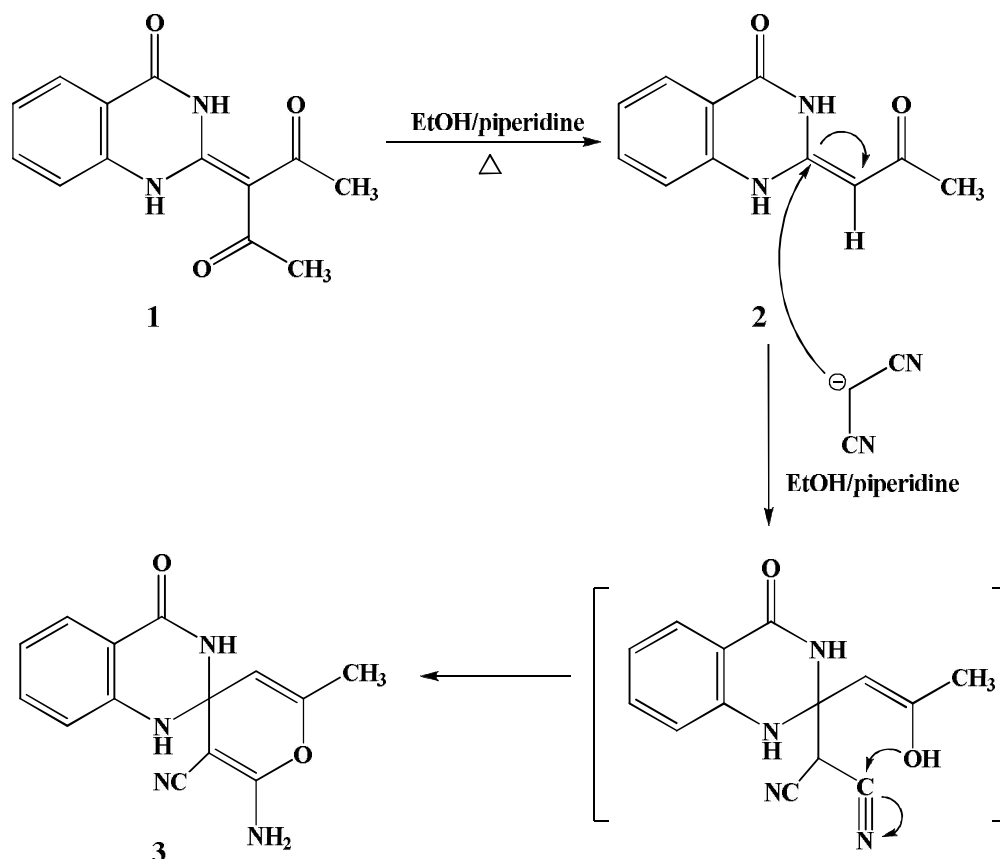
oxo-3',4'-dihydro-1'*H*-spiro[pyran-4,2'-quinazoline]-3-carbonitrile **3** was formed in good yield, Scheme 2.



Scheme 2

The reaction pathway was assumed to follow a preliminary elimination of one of the two acetyl groups followed by a nucleophilic addition of malononitrile to the ethylenic bond with subsequent cyclization. This suggested mechanism was confirmed by a two-step reaction: compound **1** was

hydrolyzed in the presence of piperidine or sodium methoxide to the intermediate product (2*E*)-2-(2-oxopropylidene)-2,3-dihydroquinazolin-4(1*H*)-one **2**, which was refluxed with malononitrile in boiling ethanol in the presence of piperidine to afford compound **3**, Scheme 3.



Scheme 3

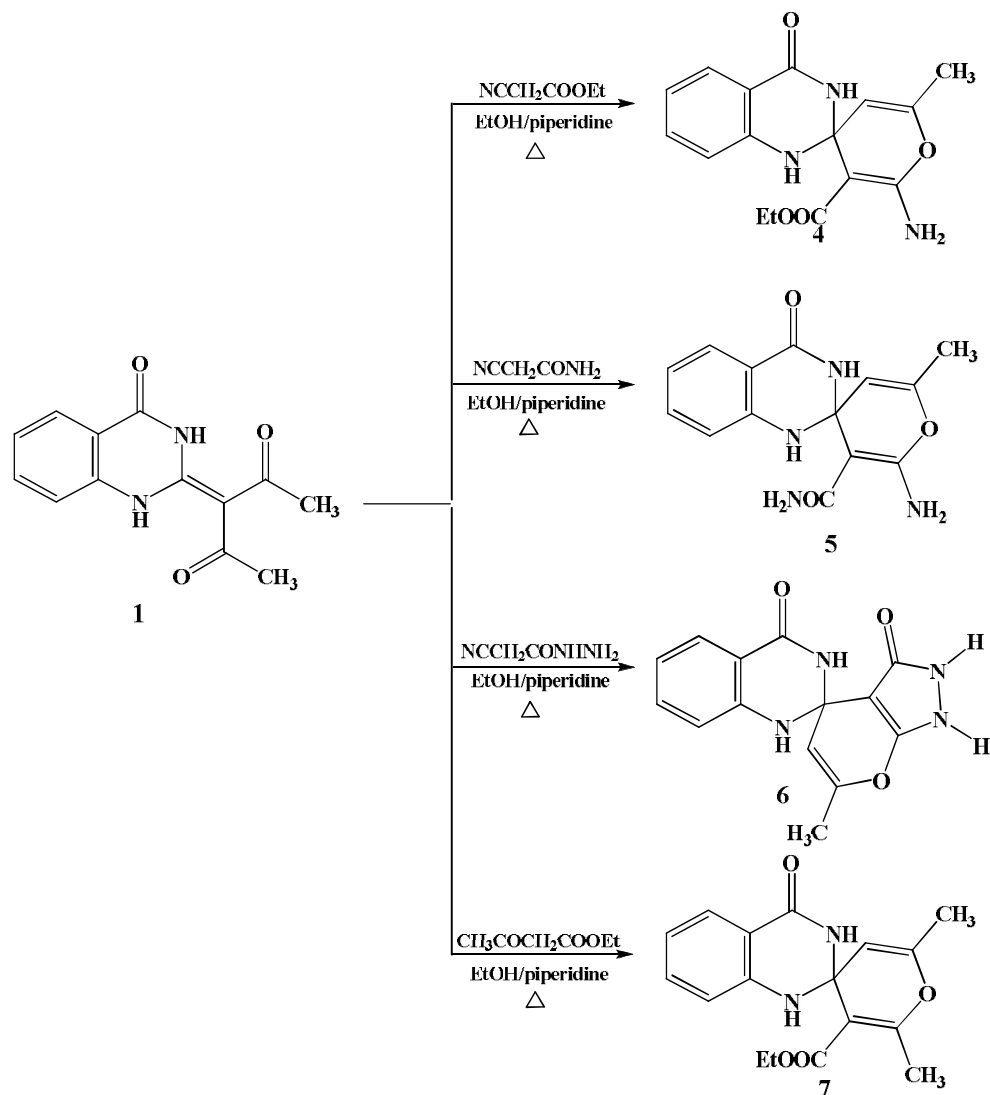
Compound **1** was subsequently reacted with a variety of active methylene compounds including: ethyl cyanoacetate, cyanoacetamide,

cyanoaceto-hydrazone and ethyl acetoacetate in refluxing ethanol in the presence of a catalytic amount of piperidine as catalyst, where in each

reaction a preliminary elimination of one of the two acetyl groups occurred followed by nucleophilic addition of the formed carbanion to the ethylenic bond and subsequent cyclization to give the corresponding spiro quinazolones 4-7, Scheme 4.

In the case of the reaction of compound 1 with cyanoacetohydrazide a clear evolution of NH<sub>3</sub>

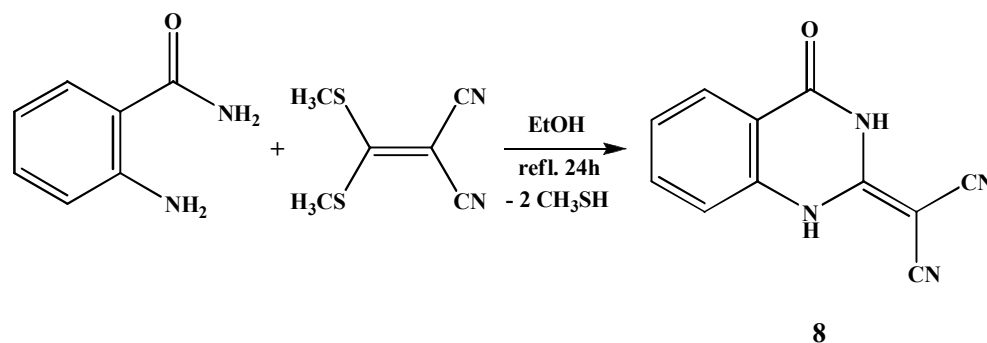
gas was observed. The analytical and spectral data of the obtained product revealed that the fused pyrazolone ring was formed most probably *via* nucleophilic attack of the -NHNH<sub>2</sub> to the C-NH<sub>2</sub> linkage of the  $\gamma$ -pyran nucleus followed by cyclization to compound 6, Scheme 4.



Scheme 4

In an extension to our work (4-oxo-3,4-dihydroquinazolin-2(1H)-ylidene)malononitrile 8 was obtained from the reaction of 2-aminobenzamide with [bis(methylthio) methylene] malononitrile in

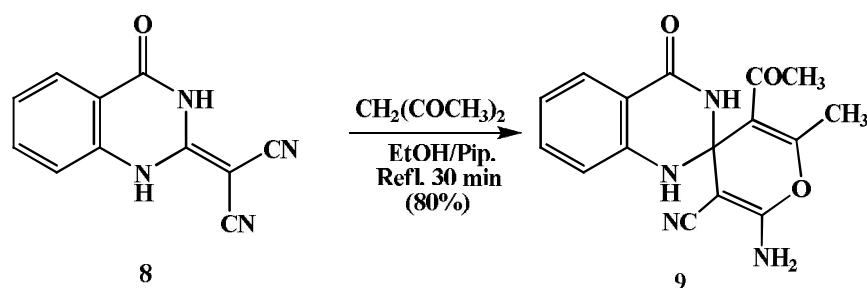
refluxing ethanol for 24 hours, Scheme 5. The reaction was assumed to proceed *via* the same mechanism as mentioned previously.



Scheme 5

Compound **8** was then reacted with acetylacetone under the same experimental conditions (ethanol/piperidine/reflux) where 5-acetyl-2-amino-6-

methyl-4'-oxo-3',4'-dihydro-1'*H*-spiro[pyran-4,2'-quinazoline]-3-carbonitrile **9** was obtained, Scheme 6.



Scheme 6

Structures of the obtained products were confirmed by their melting and mixed melting points, spectral measurements, FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and Elemental analyses.

In conclusion, the synthetic methodology described in this communication is productive and useful for obtaining different heterocycles under simple experimental conditions.

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