Organic reactions are typically carried out in the presence of solvent. Therefore, isolation of the pure products requires separation and purification steps, which result in a substantial decrease in yield and can be environmentally hazardous processes. In solvent-based reactions, the weight ratio of waste to product, which is known as the E factor, is inevitably high. A simple and efficient way to increase yields and reduce environmental impact is to conduct the reaction in the absence of solvent, which includes solvent-free or solid-state reactions. Compared to conventional organic reaction, they have several advantages that include high reaction rate, cost savings, considerable process reduction, and minimal impact on the environment.\\n
Thus far, numerous efforts have been directed toward the development of novel solvent-free or solid-state reaction for the synthesis of a wide range of organic materials in high yields. Wang and Qin reported the synthesis of pyrazole derivatives by solvent-free reactions of diketones with hydrazine hydrate. The solid-state-grinding method has been directly applied to aldol condensation reactions between aldehydes and ketones in the solid state, which smoothly proceeded at ambient conditions in the absence of solvent. Kaupp and Schmeyers discovered the solid-state reactivity of hydrazine–hydroquinone complex toward carbonyl compounds and also investigated the reaction mechanism on the solid surface by atomic force microscopy.

Thus far, numerous green strategies have been developed as potential solutions to alleviate the problems associated with solvent-based reactions, suggesting that highly reactive and stable molecular precursors are necessary to make the routes synthetically efficient and environmentally benign.

We have recently isolated a hydrazinium carboxylate (H$_3$N$^+$NHCO$_2$\textsuperscript{−}, 1a) as a crystalline powder by reacting aqueous hydrazine with supercritical CO$_2$, which exhibited excellent reactivity toward aldehydes in the solid state at ambient conditions, producing only water and CO$_2$ as waste. The solid hydrazine (1a) proved to be a synthetic alternative to toxic liquid hydrazine (H$_2$NNH$_2$). Thus, we reasoned that 1a should be effective for the synthesis of other compounds containing the hydrazine motif through an efficient and green route. Herein, we report solid-state and solvent-free reactions between 1a and di-carbonyl compounds including α-, β-, and γ-keto derivatives. The reactions afford azines, pyrazoles, and pyridazonines in high yields with excellent selectivities (Scheme 1). These findings are significant because the reactions not only proceed at ambient conditions without solvents, but they also do not generate toxic waste.

We initially focused on the solid-state reactivity of 1a toward α-keto acid. A mixture of 1a and benzoyleformic acid (2a) with a...
Reactions of solid hydrazine (1a) with diketonic compounds in the presence of solvent.

Scheme 1. Formation of azines, pyrazoles, and pyridazinones via reactions of 1a with diketonic compounds.

The molar ratio of 1:2 was ground using a mortar and pestle at room temperature and then allowed to react in a vial. The reaction of 1a with 2a proceeded smoothly in the solid state to yield a mixture of 1a and 2a. Although the solid-state reaction proceeded even at 25 °C, an increased temperature was needed for the reaction to reach completion in a few hours. Complete conversion to 3a was achieved at 90 °C within 3 h (see Table 1, entry 1). The product was obtained as a pure, single phase as judged by both powder X-ray diffraction (XRD) and 1H NMR spectroscopy. The solid-state reactivity of 1a toward 2a was strongly dependent on the reaction temperature. At 50 °C, the reaction took longer and was complete in 24 h. The products of the reaction after 3, 6, 12, and 24 h were characterized by XRD and 1H NMR spectroscopy. The yields of 3a, determined from the 1H NMR spectra of the reaction mixture, gradually increased with increasing time, as shown in Figure 1. No byproducts were detected by XRD or 1H NMR spectroscopy.

In contrast to the excellent reactivity of 1a with 2a, inferior results were obtained when hydrazine hydrate (H₂NNH₂·H₂O, 1b) was used as the source of hydrazine. The solvent-free reaction of 1b with 2a performed at 90 °C for 3 h afforded about 50% yield to 3a (Table 1, entry 2) along with unidentified byproducts. Similar results were obtained when the same reaction was performed in the presence of THF, resulting in low conversion (~57%) even under reflux conditions (Table 1, entry 3). The low selectivity and low conversion in the two reactions might be due to the presence of water in 1b. Solid hydrazine 1a clearly showed better conversion and higher selectivity than 1b for the formation of 3a. This remarkable reactivity is presumably ascribed to the facile production of anhydrous hydrazine and evolution of CO₂ gas upon reaction of 1a. To further evaluate the solid-state reactivity of 1a, the substrate scope was extended to other α-keto compounds. Under similar reaction conditions, α-keto esters containing phenyl (3b) and methyl (3c) substituents resulted in the formation of the corresponding azines as the sole products (entries 4 and 5, Table 1).

Analysis by single crystal X-ray diffraction was conducted to confirm the solid-state structure of 3a. We obtained single crystals of the resulting powder by slow evaporation of a CH₃OH/CHCl₃ solution of 3a over a period of about 7 days. The ORTEP diagram of 3a is illustrated in Figure 2, showing a (2Z)-configuration with respect to the two C=N double bonds. The N1–N1 bond length (1.398 Å) of 3a is shorter than that of 1a (1.438 Å), but is similar to those of other azine compounds. The distance between C5 and N1 is 1.281 Å and the bond has a double bond character, which is similar to the C=N double bond. The C8–O1 bond length is 1.305 Å, which is close to the single C–O bond distance (1.315 Å). Details of the crystal structure of 3a including bond lengths and angles are given in Tables S1–S3.

Table 1
Reactions of solid hydrazine (1a) and liquid hydrazine (1b) with α-keto derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant (mp, °C)</th>
<th>Hydrazine</th>
<th>Product (mp, °C)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (66)</td>
<td>1a</td>
<td>3a (157-158)</td>
<td>3</td>
<td>90</td>
<td>&gt;96</td>
<td>Grinding</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>1b</td>
<td>3a (138-140)</td>
<td>3</td>
<td>90</td>
<td>50% (unknown ~50)</td>
<td>Neat (no grinding)</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>1b</td>
<td>3a</td>
<td>3</td>
<td>Reflux</td>
<td>53% (unknown ~45)</td>
<td>THF</td>
</tr>
<tr>
<td>4</td>
<td>2b (-)</td>
<td>1a</td>
<td>3b (138-140)</td>
<td>0.5</td>
<td>70</td>
<td>97</td>
<td>Neat (no grinding)</td>
</tr>
<tr>
<td>5</td>
<td>2c (-)</td>
<td>1a</td>
<td>3c (196)</td>
<td>0.5</td>
<td>70</td>
<td>97</td>
<td>Neat (no grinding)</td>
</tr>
</tbody>
</table>

a) Hydrazinium carboxylate 1a (5.2 mmol); α-keto acid 2 (10.0 mmol).
b) Isolated yield based on di-carbonyl compounds.
c) Not isolated, unknown compound(s): ~50% at 100% conversion based on 1H NMR (see Fig. S3 in Supplementary data).
d) Not isolated, unknown compound(s): ~8% at 57% conversion based on 1H NMR (see Fig. S4 in Supplementary data).
e) Liquid at 25 °C.
The reactivity of 1a was further explored using β-keto derivatives as di-carbonyl substrates. The reaction of 3-methylpentane-2,4-dione (4a) with 1a in the absence of solvent afforded greater than 97% conversion to 3,4,5-trimethyl-1H-pyrazole (5a). The solvent-free reaction was accomplished at 70 °C within 2 h without producing any byproducts other than CO₂ and water (Table 2, entry 1). When hydrazine hydrate (1b) was used as the source of hydrazine, however, the same reaction produced 5a in 77% yield along with unidentified byproducts (Table 2, entry 2). Unknown byproducts were also obtained when the same reaction was performed in the presence of THF (Table 2, entry 3). To confirm the reactivity of 1a toward other β-keto derivatives, a range of β-keto compounds were treated with 1a in the absence of solvent or in the solid state (Table 2, entries 4–7). All the reactions gave over 97% conversions to the corresponding pyrazoles. It is evident that solid hydrazine 1a proved to be the most effective reagent for the synthesis of pyrazoles.

It is worth mentioning that pyrazole motifs are essential components of many agrochemicals and pharmaceuticals. They are typically synthesized by the condensation of 1,3-diketones with hydrazine derivatives in the presence of solvents and acid. However, the solvent-based reactions afford moderate yields of pyrazoles along with unknown byproducts. Thus, separation and purification steps are necessary to obtain the pure products. The additional processes lead to a substantial decrease in the yields of the pyrazole products and are environmentally hazardous processes. In contrast, our method based on solid hydrazine 1a gave pyrazoles as the sole products with excellent yields, and the method is found to be an effective and environmentally benign process.

The scope of the reaction of 1a was further investigated using γ-keto acids as di-carbonyl substrates. Grinding γ-keto acids with one molar equivalent of 1a led to the formation of pyridazinones in the solid state, even at 25 °C. A long reaction time or high reaction temperature was necessary for the reactions to reach completion. Almost complete conversions were accomplished at 90 °C within 3 h and the reactions gave excellent yields (Table 3, entries 1–5). Clearly, our solvent-free reaction based on solid hydrazine 1a gave pyrazoles as the sole products with excellent yields, and the method is found to be an effective and environmentally benign process.

In summary, solid hydrazine played a major role in the development of the environmentally benign methodology described herein, and it reacted efficiently with a range of di-carbonyl compounds under solvent-free conditions. The resulting products, including azines, pyrazoles, and pyridazinones, which are not readily synthesized by conventional solvent-based reactions were obtained in high yields with excellent selectivities. In particular, pyrazoles are not easily synthesized using the solution-phase methodology. Moreover, the reactions proceeded without the need for any additives such as catalysts and did not produce any toxic waste. These advantages make this simple methodology based on solid hydrazine attractive for industrial applications and provide the opportunity to synthesize a wide range of organic materials with excellent selectivity in a much greener way.

**Experimental section**

**Instrumentation**

A Thermo Scientific Nicolet 205 spectrometer was used to measure infrared spectra. Absorption spectra were recorded on an Agilent 8453 UV–visible spectrophotometer. Melting points were measured with a Barnstead IAP1900 Digital Melting Point Apparatus. GC/MS data were recorded on an Agilent 5973 N and elemental analyses were conducted using a Carlo Erba EA11180 at the Organic Chemistry Research Center at Sogang University.
University. High resolution mass spectra were recorded on a 4.7 Tesla Ion Spec ESI-TOFMS and a JEOL (JMS-700). The 1H NMR and 13C NMR spectra were recorded in solution on a Varian 400-MHz Gemini operating at 400 MHz for 1H and 100 MHz for 13C. Some NMR spectra were also recorded on a Varian UNITY INOVA 500 at 500 MHz for 1H and 125 MHz for 13C. All chemical shifts were referenced to tetramethylsilane. Single crystal X-ray diffraction data were collected using a Bruker SMART AXS diffractometer equipped with a monochromator with a Mo Kα (λ = 0.71073 Å) incident beam.

General procedure

Both solid and liquid compounds were used as di-carbonyl substrates. Typical procedures are as follows. For solid substrate, a mixture of solid α-keto acid (10.0 mmol, entry 1 in Table 1) and 1a (5.2 mmol) was ground using a pestle and a mortar. Although the solid-state reaction proceeded at 25 °C without any agitation, heating was necessary to achieve complete conversion within a few hours. Therefore, the ground powder was placed in a vial and heated in an oil bath. The reaction temperature was adjusted depending on the nature of the di-carbonyl compound. For liquid substrate, a 5.2 mmol of 1a was added to a neat solution of α-keto acid (10.0 mmol, entry 2 in Table 1). The neat reaction also proceeded smoothly at 25 °C but heating was necessary to achieve complete conversion within a few hours. Water and CO₂ were produced during the reaction. Note: a 1:1 molar ratio was used for the reactions of β-diketones (5.0 mmol) or γ-keto acids (5.0 mmol) with 1a (5.2 mmol). All products were initially characterized by 1H and 13C NMR spectroscopy. Both yields and selectivities were determined by 1H NMR spectroscopy.

Acknowledgments

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Supplementary data

Supplementary data (X-ray crystallographic data and NMR data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.106.

### Table 2
Reactions of solid hydrazine (1a) and liquid hydrazine (1b) with β-keto derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant (mp, °C)</th>
<th>Hydrazine</th>
<th>Product (mp, °C)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a (-)</td>
<td>1a</td>
<td>5a</td>
<td>2</td>
<td>70</td>
<td>96</td>
<td>Neat (no grinding)</td>
</tr>
<tr>
<td>2</td>
<td>4a (-)</td>
<td>1b</td>
<td>5a</td>
<td>2</td>
<td>70</td>
<td>77 (unknown ~23%)</td>
<td>Neat (no grinding)</td>
</tr>
<tr>
<td>3</td>
<td>4b (-)</td>
<td>1a</td>
<td>5b</td>
<td>0.3</td>
<td>70</td>
<td>99</td>
<td>Neat (no grinding)</td>
</tr>
<tr>
<td>4</td>
<td>4c (-)</td>
<td>1b</td>
<td>5c</td>
<td>1</td>
<td>70</td>
<td>97</td>
<td>Neat (no grinding)</td>
</tr>
<tr>
<td>5</td>
<td>4d (57)</td>
<td>1a</td>
<td>5d</td>
<td>3</td>
<td>90</td>
<td>98</td>
<td>Grinding</td>
</tr>
<tr>
<td>6</td>
<td>4e (78)</td>
<td>1a</td>
<td>5e</td>
<td>5</td>
<td>90</td>
<td>98</td>
<td>Grinding</td>
</tr>
</tbody>
</table>

a Solid hydrazine (1a, 5.2 mmol); β-diketone 5 (5.0 mmol).
b Isolated yield based on di-carbonyl compounds.
c Liquid at 25 °C.
d Not isolated, based on 1H NMR (see Figs. S14 and S15 in Supplementary data).
### References and notes


### Table 3

**Solid state reactions of solid hydrazine (1a) with γ-keto derivatives**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant (mp, °C)</th>
<th>Product (mp, °C)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a (30-33)</td>
<td>7a (103)</td>
<td>1.5</td>
<td>90</td>
<td>98</td>
<td>Grinding</td>
</tr>
<tr>
<td>2</td>
<td>6b (116)</td>
<td>7b (196)</td>
<td>3</td>
<td>90</td>
<td>99</td>
<td>Grinding</td>
</tr>
<tr>
<td>3</td>
<td>6c (118)</td>
<td>7c (226)</td>
<td>3</td>
<td>90</td>
<td>97</td>
<td>Grinding</td>
</tr>
<tr>
<td>4</td>
<td>6d (149)</td>
<td>7d (150-151)</td>
<td>3</td>
<td>90</td>
<td>98</td>
<td>Grinding</td>
</tr>
<tr>
<td>5</td>
<td>6e (128)</td>
<td>7e (241-243)</td>
<td>3</td>
<td>90</td>
<td>98</td>
<td>Grinding</td>
</tr>
</tbody>
</table>

*Hydrazinium carboxylate 1a (5.2 mmol), γ-keto acid 6 (5.0 mmol).*  

*b* Isolated yield based on di-carbonyl compounds.