Synthesis of Azines in Solid State: Reactivity of Solid Hydrazine with Aldehydes and Ketones
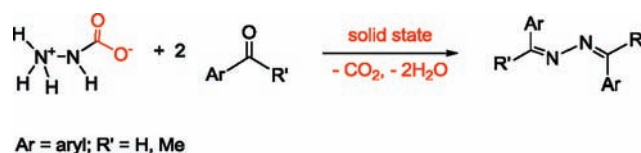
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ABSTRACT

Ar = aryl; R' = H, Me

Highly conjugated azines were prepared by solid state grinding of solid hydrazine and carbonyl compounds such as aldehydes and ketones, using a mortar and a pestle. Complete conversion to the azine product is generally achieved at room temperature within 24 h, without using solvents or additives. The solid-state reactions afford azines as the sole products with greater than 97% yield, producing only water and carbon dioxide as waste.

Recently, there has been growing research interest associated with the solvent-free synthesis of molecular materials *via* solid-state grinding. The solid-state grinding methodology utilizes mechanical forces to accelerate chemically driven reactions.[1−4] The reaction is performed by grinding the solid reactants using a mortar and pestle. The grinding induces a chemical reaction between the molecular reactants, which has been used in the synthesis of various materials such as pharmaceuticals,[1a,2] cocrystals,[1b−d,2] optical materials,[1e,2] and functional complexes.[1f−j,2] The solid-state reactions reported here proceed at room temperature, which is different from conventional solid-state reactions between inorganic solids that occur typically at > 800 °C.[4]

An important advantage of organic solid-state reactions is that neither solvent nor purification steps are required. Moreover, it is an environmentally benign process compared to solution-state reactions, which require solvents and separation processes. The simple grinding method is promising and provides a viable means for producing a wide range of molecular materials with high yield.[1−3] Despite the extensive use, application of solid-state grinding to prepare molecular solids still remains limited mainly due to the lack of appropriate solid precursors. To extend

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this technique to the synthesis of a wide range of materials, it is necessary to develop new molecular compounds that have weak intramolecular bonds while maintaining reactivity.
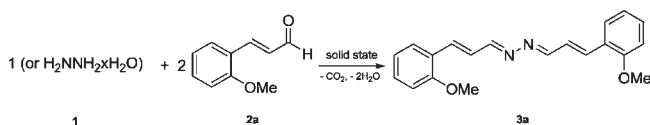
Scheme 1. Formation of Azines by the Solid State Reactions of **1** with Carbonyl Compounds

Ar = aryl; R' = H, Me
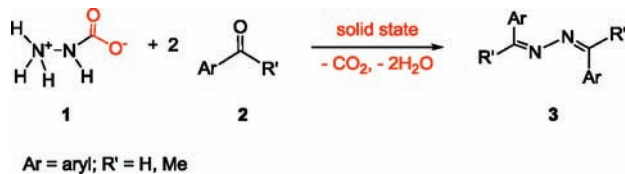
Very recently, we isolated the hydrazinium carboxylate ($H_3N^+NHCO_2^-$, **1**) under supercritical CO_2 conditions as a crystalline solid, which can be regarded as a new synthetic alternative to liquid hydrazine (NH_2NH_2).[5] Reported herein is the solid-state reactivity of solid hydrazine (**1**) toward various carbonyl compounds such as aldehydes and ketones. An important feature is that the azine derivatives were readily prepared in the absence of solvent using simple grinding. Moreover, the solid-state reaction shows high selectivity, which yields over 97% of the product and does not generate any waste other than water and CO_2 (Scheme1).

Azines exhibit interesting optical,[6] biological,[7] and conductive[8] properties and are extensively used as synthetic intermediates.[9] Typically, azines are prepared by reacting 2 equiv of a carbonyl compound with 1 equiv of hydrazine hydrate ($NH_2NH_2 \cdot H_2O$) in solution under refluxing conditions or with promoters such as acid or iodine. The solution reaction proceeds rapidly but often yields byproducts, which require product separation.[3,6a,7a,8a,9a] As an alternative, Kaupp and Schmeyers employed hydrazine-hydroquinone powder as a source of hydrazine; the powder was ball-milled with a solid carbonyl compound to yield an azine product. Although the mechanochemical reaction was carried out in the solid state, it called for the elimination of hydroquinone from

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Table 1. Reaction of Hydrazines with 2-Methoxycinnamalde-hyde (**2a**)[a]

entry	hydrazine (mmol)	solvent	temp (°C)	time (h)	product	yield (%)	remark
1	**1** (5.0 mmol)	no	25	<20	**3a** only	>97[b]	yellow crystal
2	**1** (50.0 mmol)	no	60	<3	**3a** only	>97[b]	yellow crystal
3	$H_2NNH_2 \cdot xH_2O$ (5.0 mmol)	ether (10 mL)	25	5	**3a** + unknown	~75[c,d]	
4	$H_2NNH_2 \cdot xH_2O$ (10.0 mmof)	no	25	2	**3a** + unknown	<40[e,e]	

[a] 2-Methoxycinnamaldehyde(**2a**)/hydrazine = 2/1. [b] Isolated yield based on **1** (hydrazinium carboxylate, $H_3N^+NHCO_2^-$) was determined using ^{1}H NMR. [c] Not isolated, the yield is based on ^{1}H NMR. [d] Product-(s) resulting from the reaction(s) at the olefin group in **2a** with possible hydrazine formation. The starting aldehyde, **2a**, is detected, which is ca. 13%. [e] Highly exothermic. Product(s) resulting from the reaction(s) at the olefin group in **2a** with possible hydrazine formation. The starting aldehyde, **2a**, is detected, which is ca. 48%.

the product.[3d] Unlike the hydrazinium salt,[3b,c] our solid hydrazine (**1**) dissociates into hydrazine and CO_2.

Therefore, the solid-state reactions of aldehydes or ketones with **1** using the simple grinding method did not require further separation. The reaction is a single-step process, and the evolution of CO_2 gas stimulates the forward reaction to produce the desired azine complexes. This is the first report on the waste-free synthesis of azine derivatives using solid-state grinding under ambient conditions, which also provides a novel green approach for preparing various azines on a large scale and in the absence of solvents. Notably, the solid-state reaction provides new opportunities for large-scale production in a small vessel: for example, the current system was scaled to prepare more than 16 g of the azine product within a 50 mL vial (see Table 1, entry 2).

A 1:2 mixture of **1** and an aromatic aldehyde (Table 1, entry 1) was ground at room temperature using a mortar and pestle.[10] The physical grinding resulted in a distinctive color change from white to yellow within 5 min. The ground powder was placed in a vial without any agitation. Near-complete conversion to an azine compound (**3a**) with the formula $C_{20}H_{20}N_2O_2$ was achieved within 20 h; the process was carefully monitored using both powder X-ray diffraction (XRD) and ^{1}H NMR spectroscopy. The solid-state reaction was complete within 2 h at a reaction temperature of 60 °C.

(10) *Precaution.* The solid hydrazine, hydrazinium carboxylate (**1**), could be harmful for health due to its sublimation character. The equipment of effective ventilation is highly recommended for handling the solid hydrazine to avoid vapor inhalation.

For comparison, liquid hydrazine ($NH_2NH_2 \cdot H_2O$) instead of **1** was employed to react with an aldehyde (Table 1, entry 2). The selectivity toward the azine compound was relatively low in the presence of solvent ($<75\%$) or in neat ($<40\%$) conditions (Table 1, entries 3 and 4), presumably due to the presence of water in liquid hydrazine.[11] These results suggest that the solid state reaction between **1** and the aromatic aldehyde may provide increased selectivity toward azine formation as compared with conventional solution-based methods.

Single crystals of **3a** were obtained by recrystallization of the initial yellow solid product from a $CHCl_3$/ether (1:1) solution. The solid-state structure of **3a** was determined using single-crystal X-ray diffraction, and the ORTEP diagram is shown in Figure 1. An interesting feature is that the structure is composed of two crystallographically independent azine molecules. The structure of **3a** shows a N—N *trans* conformation with respect to the N—N bond.
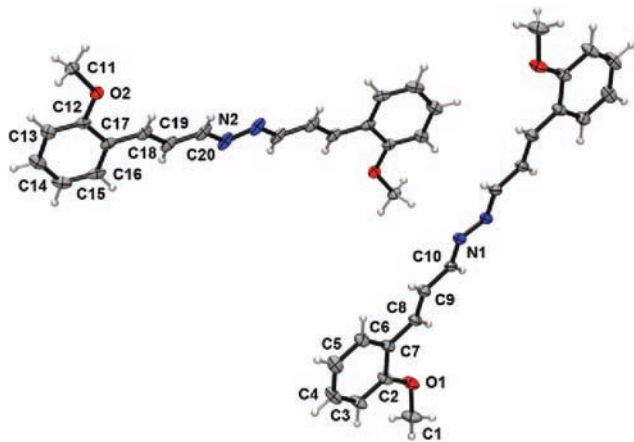

Figure 1. Schematic of asymmetric unit of **3a**. ORTEP drawings of **3a** with the numbering scheme, which indicate that the thermal ellipsoids have 30% probability.

The bond distances and angles of the two molecules are slightly different owing to their subtle differences in the geometric parameters, which are given in the Supporting Information. The N—N bond length (1.398 Å) of **3a** is shorter than that of **1** (1.438 Å)[5] but is similar to that of other azine compounds.[6a,d,9c,12] Notably, the C=C and C=N bonds in the π-conjugated bridge (—C=C—C=N—N=C—C=C—) were virtually identical to those in other organic molecules.[12] Alternatively, the C—C bond (1.336 Å) in the π-conjugated bridge was much shorter than a typical C—C single bond (1.54 Å), as found in the conjugated system.

To display the general and innovative application of the solid hydrazine molecule, we investigated the solid-state

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Table 2. Reaction of Hydrazinium Carboxylate (**1**) with Solid Carbonyl Compounds[a]

entry	reactant	product[b]	reaction time (h)	yield (%)[c]	remark[d]
1			5	**3b**, >97	pale yellow
2			5	**3c**, >97	pale yellow
3			10	**3d**, >97	pale yellow
4			3	**3e**, >97	beige powder
5			5	**3f**, >97	pale yellow
6			5	**3g**, >97	deep yellow
7			5	**3h**, >97	yellow
8			24	**3i**, >97	yellow
9			24	**3j**, >97	yellow

[a] Reaction conditions: **1** (5.0 mmol, 0.38 g), reactant, **2** (10.0 mmol), no solvent, the reactant was mixed with **1** by grinding in a mortar and a pestle, which were heated to 60 °C. [b] All products, **3b**–**3j**, are known compounds (see Supporting Information). [c] Isolated yield based on **1** was determined using ¹H NMR. [d] Crystals were obtained from recrystallization of powders (0.1 g) in chloroform/ether (10 mL/10 mL) at 25 °C.

reactions of **1** with other aldehydes under the same conditions (Table 2, entries 1–7). In all reactions, the grinding alone resulted in azine formation, although complete conversion requires approximately 24 h at room temperature. To increase the reaction rate, the powder was allowed to react at 60 °C after grinding the mixture of **1** and the aldehyde at room temperature. Nearly complete conversion to the azine product ($>97\%$) was accomplished within 5 h. Only azines were obtained from the solid-state reactions.

To further explore the solid-state reactivity of **1**, the reaction between **1** and ketones (Table 2, entries 8 and 9) using solid-state grinding was investigated. Complete conversion was achieved after reacting for 24 h at 60 °C, clearly demonstrating that **1** also reacts with ketones to yield ketazines in the solid state and confirming the broader application and impact of solid hydrazine.
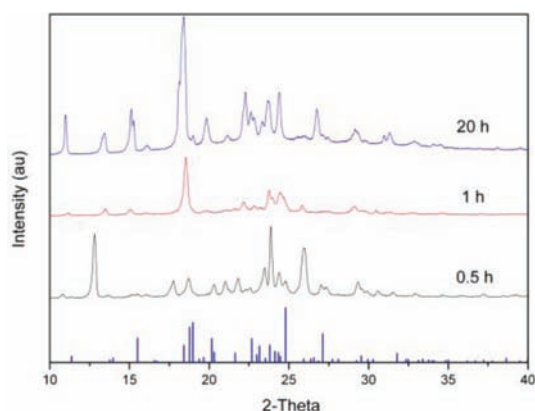
Figure 2. Powder XRD patterns of products obtained from grinding a mixture of **1** and aromatic aldehyde **2a** (Table 1, entry 1) at intervals of 0.5, 1, and 20 h at room temperature. Vertical bars are the theoretical diffraction peaks of **3a**.
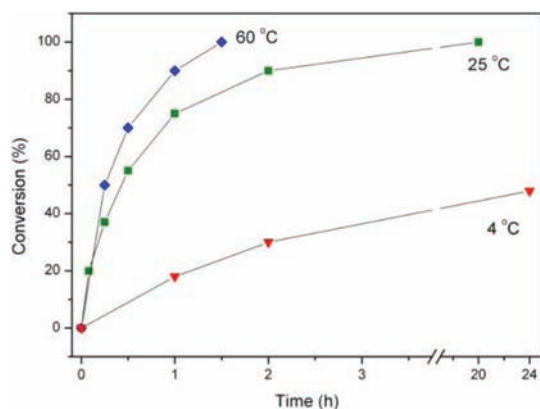

Figure 3. Yields of **3a** (Table 1, entry 1) as function of time for three reactions performed at 4, 25, and 60 °C, where yield was determined using ^{1}H NMR spectroscopy. The red triangles, green squares, and blue diamonds represent yields corresponding to reactions at 4, 25, and 60 °C, respectively.

It is worthy to mention that an acid catalyst and/or water removers are required during ketone and hydrazine solution reactions.[11]

To understand the nature of the interfacial reaction between the solid reactants induced by grinding, we se-

lected the reaction between **1** and 2-methoxycinnamalde-hyde (**2a**, Table 1, entry 1) as a model and investigated the reaction progress. The products at each interval were analyzed using XRD and ^{1}H NMR spectroscopy. Figure 2 shows powder XRD patterns of the ground mixture, which were collected as a function of reaction time. New reflections corresponding to the azine (**3a**) appeared in the XRD pattern after 0.5 h at room temperature, providing direct evidence of **3a** formation. Their intensities increased with increasing reaction time. We performed two control experiments to determine that the reaction occurs truly in the solid state rather than in a possible solution pathway. The first experiment was completed at 4 °C, and it clearly demonstrates that the yellow azine product forms although the reaction is very slow (Figure 3). The results implicate that the solid-state reaction takes place without the formation of liquid intermediates. When the ground mixture is reacted at 60 °C, the formation of **3a** is greatly accelerated. It is suggested that the high-temperature annealing enhances the reactivity. The results of the temperature-dependent experiments indicate that the reaction appears to proceed via a solid-state process rather than a liquid-mediated pathway.

In summary, we have demonstrated the excellent reactivity of a newly synthesized solid hydrazine toward carbonyl compounds in the solid state. The solid hydrazine was found to be a very valuable alternative for the toxic liquid hydrazine. It was also demonstrated that the solid-state reaction method can have a broad substrate scope and the azine products were obtained from the ground mixture in high yields with excellent selectivity. The reaction proceeds smoothly at room temperature, yielding only CO_2 and H_2O waste. The grinding method does not require any solvent and/or additives, which affords an admirable atom economy and provides a novel, environmentally benign process for preparing various compounds.

Supporting Information Available. Experimental procedures; full characterization for all compounds (including X-ray diffraction data). This material is available free of charge via the Internet at http://pubs.acs.org.