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Safe, Metal-Free, and Direct Synthesis of Dialkyl Acylmethylidenehydrazine-1,1-dicarboxylates from Dimethylsulfoxonium Acylmethylides and Dialkyl Azodicarboxylates

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Abstract. *N*-Acylhydrazones are versatile electrophiles for the synthesis of nitrogen-containing compounds. Dialkyl acylmethylidenehydrazine-1,1-dicarboxylates are a class of *N*-acylhydrazones and were prepared efficiently from dimethylsulfoxonium acylmethylides and dialkyl azodicarboxylates. The reaction is temperature-controlled, generating tetraalkyl 3,6-diacyl-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylates as major products accompanied by dialkyl acylmethylidenehydrazine-1,1-dicarboxylates as byproducts at low temperature, or dialkyl acylmethylidenehydrazine-1,1-dicarboxylates only at high temperature. The current direct synthetic method is a safe and transition-metal-free route for the synthesis of dialkyl acylmethylidenehydrazine-1,1-dicarboxylates.

Keywords: hydrazone; azodicarboxylate; sulfoxonium ylide; tetrazinane; green synthesis.

Introduction

N-Acylhydrazones are versatile electrophiles and have been widely applied in the synthesis of nitrogen-containing compounds, for example through reduction, the Mannich reaction, alkylation, cyanation, cycloaddition, radical addition, and phosphonation.[1] Dialkyl acylmethylidenehydrazine-1,1-dicarboxylates and 1,1-dicarboxamides are a class of *N*-acylhydrazone derivatives with more functional groups. Dialkyl acylmethylidenehydrazine-1,1-dicarboxylates were first prepared from dangerous and toxic diazomethyl ketones or ethyl diazoacetate with dialkyl azodicarboxylates in 1960s (Scheme 1, a).[2] During the last decade, Nair's group developed Ph_3P-mediated synthesis of dialkyl acylmethylidene- and alkylidenehydrazine-1,1-dicarboxylates, respectively, from diarylethane-1,2-diones or diarylmethanones and dialkyl azodicarboxylates with 1.2 to 1.5 equivalents of Ph_3P as an activating reagent (Scheme 1, b).[3] Shi's group realized a Ph_3P-mediated synthesis of dialkyl alkylidenehydrazine-1,1-dicarboxylates from acyl cyanides and dialkyl azodicarboxylates with an equivalent amount of Ph_3P as an activating reagent (Scheme 1, b).[4] Recently, Jiang's group prepared various alkylidenehydrazine-1,1-dicarboxamides through the palladium-catalyzed reaction of azodicarboxamides and *N*-tosylhydrazones, which generated carbenes under the catalysis of $Pd(TFA)_2$ in the presence of base Cs_2CO_3 (Scheme 1, c).[5] The base possibly limited the method as unsuitable in the preparation of dialkyl alkylidenehydrazine-1,1-dicarboxylates. Recently our research group has also worked on sulfur ylide chemistry[6] and dialkyl azodicarboxylate chemistry.[7] After analysis of the reactivities of sulfur ylides and dialkyl azodicarboxylates, we envisioned that the direct reaction of sulfur ylides and dialkyl azodicarboxlyates should be utilized for the synthesis of dialkyl acylmethylidenehydrazine-1,1-dicarboxylates efficiently. Herein, we present a safe, metal-free, and direct synthesis of dialkyl acylmethylidenehydrazine-1,1-dicarboxylates from dimethylsulfoxonium acylmethylides and dialkyl azodicarboxylates, and the temperature-controlled reactions of dimethylsulfoxonium acylmethylides and dialkyl azodicarboxylates (Scheme 1, d).

Results and Discussion

The optimization of reaction conditions was performed by using the reaction of dimethylsulfoxonium benzoylmethylide (**1a**) and diethyl azodicarboxylate (**2a**) as the model reaction. Initially, the reaction of **1a** and **2a** was conducted in a molar ratio of 1:1 in DCE at 20 °C for 12 h, affording **3a** in 13% yield as minor product and its dimeric isomeric product **4a** in 41% yield as major product (Table 1, entry 1). When **1a** was increased to 3

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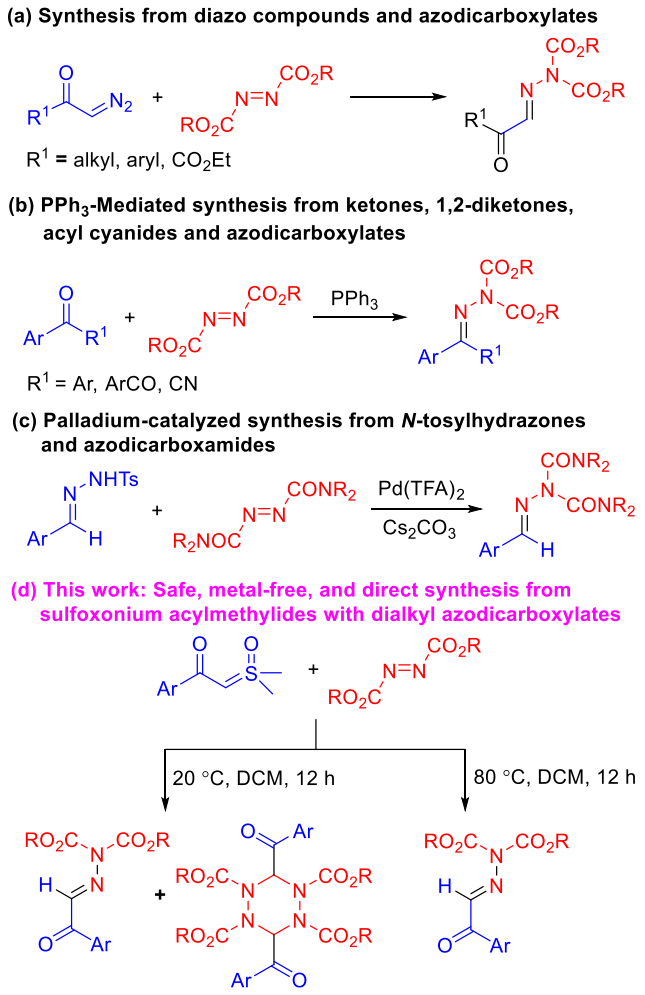
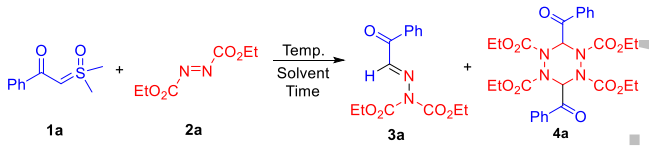


Scheme 1. Synthesis of Alkylidenehydrazine-1,1-dicarboxylic Acid Derivatives.

equivalents and the reaction was carried out at 20 °C, 10 °C, and 0 °C, the yield of **4a** was improved to 67%, 68%, and 67%, respectively, with **3a** in 12–13% yields (Table 1, entries 2–4). Further decreasing the reaction temperature resulted in obvious loss of the yields of both **3a** (5% yield) and **4a** (25% yield) (Table 1, entry 5). However, when the reaction temperature was raised to 40 °C, the yield of **3a** increased to 32% with no change of the yield of **4a** (Table 1, entry 6). The reaction was conducted in a molar ratio of 1:3 of **1a** and **2a**, affording **3a** in 45% yield and **4a** in 30% yield (Table 1, entry 7). When the reaction temperature was increased to 60 °C, the yield of **3a** was improved to 62%, while **4a** was reduced to 14% yield (Table 1, entry 8). Importantly, the reaction conducted at 80 °C gave **3a** in 80% yield as the sole product without **4a**. The results indicated that raising the reaction temperature promoted the generation of **3a** with decreasing yield of **4a** (Table 1, entries 7–9). Further increasing or decreasing the equivalent of **2a** resulted in decreasing the yield of **3a** (Table 1, entries 10 and 11). Prolonging or shortening the reaction time gave no further improvement in the yield of **3a** (Table 1, entries 12–14). Some other solvents, such as THF, chlorobenzene, toluene, and MeCN were screened, but the yield was not further improved (Table 1, entries 15–18). The results indicated that the reaction efficiency could be significantly affected by solvents. DCE was proven to be the optimal reaction medium among the various tested solvents. To shorten the reaction time, microwave heating was also tested in DCE and chlorobenzene for 0.5 h, affording **3a** in 47% and 57% yields, respectively (Table 1, entries 19 and 20). Thus, the conditions in entry 9 were selected as the optimal conditions.

Table 1. Optimization of the reaction conditions[a)]



Entry[a)]	1a:2a	Sol.	Temp. (°C)	Time (h)	Yield (%)[b)]	
					3a	**4a**
1	1:1	DCE	20	12	13	41
2	3:1	DCE	20	12	12	67
3	3:1	DCE	10	12	12	68
4	3:1	DCE	0	12	13	67
5	3:1	DCE	-40	12	5	25
6	3:1	DCE	40	12	32	25
7	1:3	DCE	40	12	45	30
8	1:3	DCE	60	12	62	14
9	**1:3**	DCE	**80**	12	**80**	**0**
10	1:4	DCE	80	12	74	0
11	1:2	DCE	80	12	53	0
12	1:3	DCE	80	24	64	0
13	1:3	DCE	80	6	70	0
14	1:3	DCE	80	4	52	0
15	1:3	THF	80	4	26	0
16	1:3	PhCl	80	4	36	0
17	1:3	PhMe	80	4	9	0
18	1:3	MeCN	80	4	17	66
19	1:3	DCE	80	0.5(MW)	47	0
20	1:3	PhCl	150	0.5(MW)	57	0

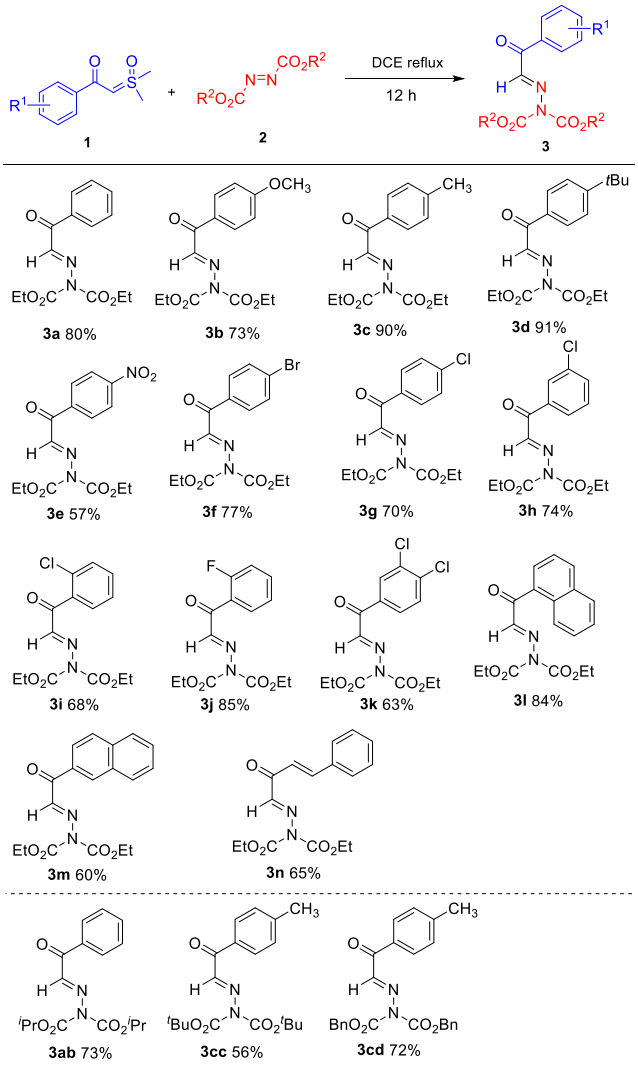
[a)] The reactions were run on a 0.2-mmol scale of **1a** (or **2a** for the 3:1 ratio) in reaction tubes. [b)] Isolated yields after column chromatography with petroleum ether and ethyl acetate (8:1, *v*/*v*) as eluent.

With the optimal reaction conditions in hand, the scope of sulfoxonium ylides **1** was investigated (Table 2). The reactions of benzoyl sulfoxonium ylides with electron-donating substituents (**1b**, **1c**, and **1d**) gave the desired products **3b**, **3c**, and **3d** in good yields of 73–91%, probably because the presence of the electron-donating groups increased the nucleophilicity of the carbanion in sulfoxonium ylides **1b-d**. On the other hand, this methodology was also successfully applied to sulfoxonium ylides bearing electron-withdrawing NO_2 (**1e**) and halogen substituents Br, Cl, and F (**1f-k**). As expected, compared with ylides with electron-donating groups, the yields of ylides with electron-withdrawing groups

were relatively lower due to their lower nucleophilicity, especially for one with the nitro group (**1e**). The structure of product **3e** was verified by X-ray single crystal diffraction analysis (Figure 1)(CCDC 1895643).[8] It was noted that there was no obvious influence of the position of substituents on the yield of the reaction (**3g**, **3h**, and **3i**). In addition, sulfoxonium ylides with naphthalenecarbonyl and cinnamonyl groups instead of benzoyl (**1l**, **1m**, and **1n**) also gave rise to the desired products **3l-n** in satisfactory to good yields of 60%−84%.

Substrate scope of azodicarboxylates **2** was also examined (Table 2), diisopropyl azodicarboxylate (**2b**) and dibenzyl azodicarboxylate (**2d**) were employed to give products **3ab** and **3cd** in 73% and 72% yields, respectively. It should be mentioned that a low yield was obtained when di-*tert*-butyl azodicarboxylate (**2c**) was used as a reagent possibly because the steric influence of the *tert*-butyl group blocked the migration of the ester group (**3cc**).

Table 2. Synthesis of dialkyl acylmethylidenehydrazine-1,1-dicarboxyates **3**[a)]

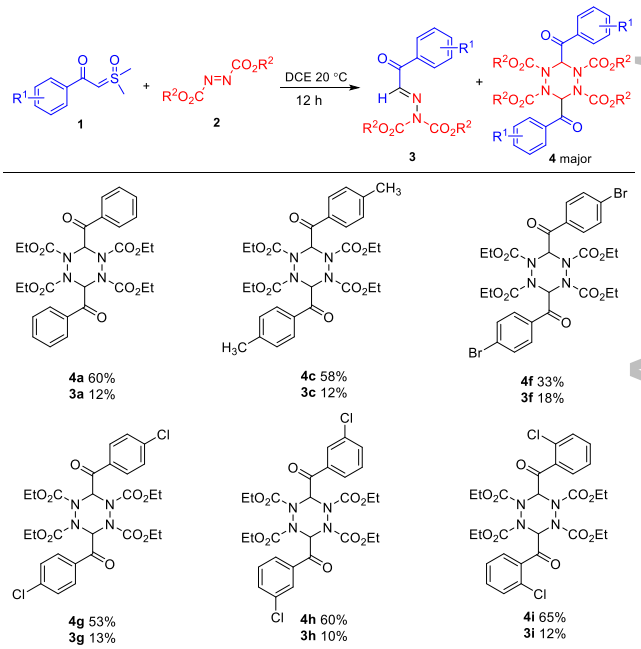


[a)] All reactions were carried out with **1** (0.20 mmol) and **2** (0.6 mmol) in DCE (2.0 mL) at 80 °C for 12 h. The yields are isolated yields by silica gel column chromatography.

Subsequently, the reactions of different sulfoxonium ylides **1** with diethyl azodicarboxylate **2** were tested at 10 °C, giving the desired products **4** in moderate yields of 33−65% (Table 3). It seemed that both electron-rich and electron-poor substrates showed similar reactivity to afford the corresponding products **4**. Product **4a** was generated from **1a** and **2a** in 60% yield as a major product. Sulfoxonium ylide bearing electron-donating group (**1c**) was attempted, affording **4c** in 58% yield. Furthermore, ylides with halo substituents (**1f** and **1g**) were also tested, resulting in the formation of the desired products **4f** and **4g** in 33% and 53% yields, respectively. The ylides (**4i** and **4h**) with Cl atom on the *ortho*- and *meta*-positions of their phenyl group were attempted, showing no significant difference compared to the ylide (**4g**) with Cl on the *para*-position of the phenyl group.

Figure 1. Single crystal structure of product **3e**.

Table 3. Synthesis of tetraalkyl 3,6-diacyl-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylates **4**[a)]



[a)] All reactions were carried out with **1** (0.20 mmol) and **2** (0.6 mmol) in DCE (2.0 mL) at 10 °C for 12 h. The yields are isolated yields by silica gel column chromatography.

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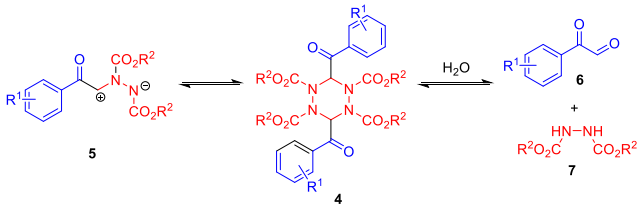
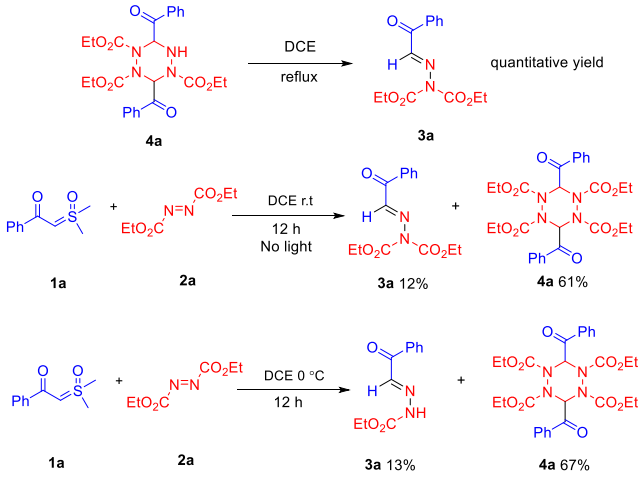
According to previous research,[2b] products **4** were proved unstable at room temperature. It was reported that a thermal balance between **4** and their hydrolytic products or two molecules of 1,3-zwitterionic intermediates **5** existed at room temperature. They could hydrolyze into the corresponding carbonyl compounds **6** and *N*,*N*-disubstituted hydrazines **7** (Scheme 2). But this phenomenon was not observed in our reaction system during workup. However, it was observed that **4a** could convert into more stable product acylmethylidenehydrazine-1,1-dicarboxyate **3a** when temperature was increased in our reaction system.



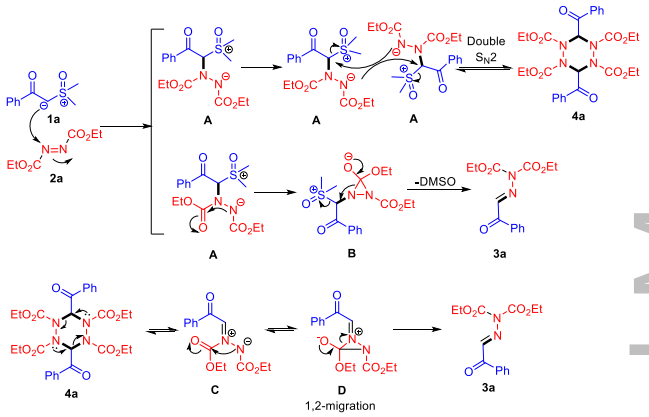
Scheme 2. Decomposition of products **4**

To test the conditions that caused **4** to convert to **3**, several control experiments were conducted (Scheme 3). First of all, **4a** was heated immediately in DCE at 80 °C after isolation from the reaction system. As expected, **4a** converted into **3a** completely without any other byproducts. The light-protected conditions were also tested, which showed no difference in the yields and ratio of **3a** and **4a** compared to those produced under standard reaction conditions. Low temperature conditions were carried out, product **3a** still was detected in the reaction system. Thus, we hypothesized that high temperature promoted the conversion of **4a** into **3a**. To verify the thermal conversion and to exclude the acidic effect of $CDCl_3$, pure **4a** was dissolved in DMSO-d_6 to obtain its pure NMR spectrum. A mixture of **4a** and **3a** appeared in DMSO-d_6 along with time. The same results were observed in DMSO-d_6 as those in $CDCl_3$, revealing that acidity of $CDCl_3$ was not the reason for the conversion.

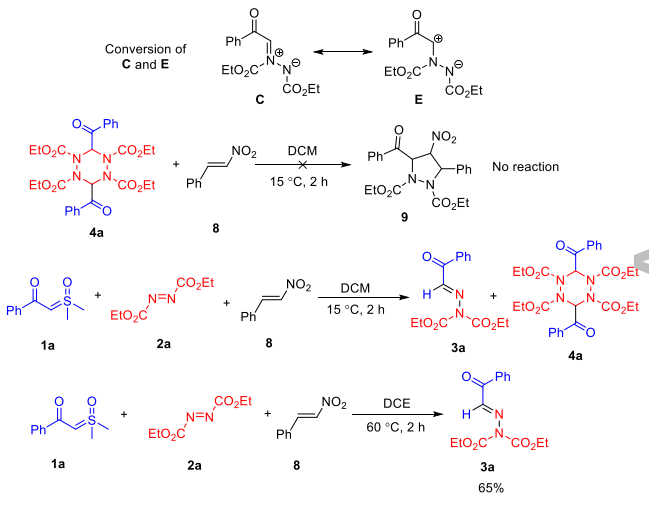


Scheme 3. Control experiments.

On the basis of these experimental results and previous literature,[2b] we tentatively proposed the reaction mechanism as outlined in Scheme 4. At first, the carbanion of sulfoxonium ylide **1a** nucleophilically attacks the N=N bond of diethyl azodicarboxylate (**2a**), affording zwitterionic intermediate **A**. Product **4a** is its dimer after loss of DMSO. Two molecules of intermediate **A** undergo intermolecularly double S_N2 reactions to afford **4a**. Regarding the other product **3a**, the amide anion in intermediate **A** nucleophilically attacks the carbonyl group of the neighboring carbamate group to generate intermediate **B**, which undergoes an isomerization to release DMSO, affording final product **3a**. The reaction proceeds via a nitrogen to nitrogen migration of a carboethoxy group through an intramolecular aminolysis followed by elimination of DMSO. In addition, the mechanism on the conversion of **4a** into **3a** was also proposed. It is probably the decomposition of **4a** that leads to the formation of 1,2-zwitterionic intermediate **C**, which processes a similar 1,2-carboxylate group migration to afford final product **3a** (Scheme 4).



Scheme 4. Proposed mechanism.



Scheme 5. 1,3-Dipole intermediate capture experiments.

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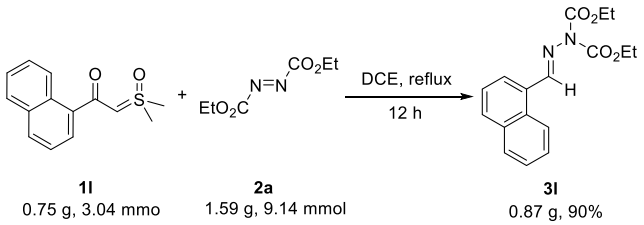
We proposed that **4a** converted into 1,2-zwitterionic intermediate **C**, which undergoes an intramolecular nucleophilic addition followed by elimination, giving rise to **3a** through a similar 1,2-carboxylate group migration as the intermediate **A** to **3a**.

Scheckenbach and co-workers previously assumed that 1,3-zwitterionic intermediate **E** was an intermediate in the conversion of **4a** to **3a**.[2a] Although our proposed intermediate **C** and the Scheckenbach-assumed intermediate **E** are resonance forms of each other, our proposed intermediate **C** should be more stable and plausible, because its non-hydrogen atoms all have a full octet of electrons, whereas intermediate **E** has a sextet carbocation adjacent to an electron-withdrawing benzoyl group. Thus, intermediate **E** should be less stable.

To verify the conversion mechanism, the capture of the zwitterionic intermediates **C** or **E** with nitroolefin **8** as an electrophile was attempted, in the hope of obtaining adduct **9** (Scheme 5). To this end, pure **4a** and nitroolefin **8** were mixed and stirred at room temperature. However, no adduct **9** was observed. Subsequently, the reaction of sulfur ylide **1a**, azodicarboxylate **2a**, and nitroolefin **8** when stirred in DCE at 15 °C was carried out, affording a mixture of hydrazine **3a** and tetrazinane **4a**, as well as in the absence of nitroolefin **8**. Under the conditions at 60 °C, product **3a** was generated in 65% yield. Based on the current results, the possibility of the reaction passing through zwitterionic intermediates **C** and **E** was not verified, but not excluded either. The intramolecular nucleophilic addition was possibly too fast compared to the intermolecular addition with nitroolefin **8**.

A larger-scale experiment was conducted with sulfur ylide **1l** and azodicarboxylate **2a**, affording product **3l** as white solid 0.87 g, 90% yield (Scheme 6).



Scheme 6. Larger-scale experiment.

Conclusion

In summary, we have developed the direct reaction of sulfoxonium ylides and azodicarboxylates, a new method for the preparation of hydrazone-1,1-dicarboxylates and 1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylates without additives or metal-catalysts. The major products of the reaction were effectively controlled by changing reaction temperature. Tetrazinane compounds were generated as the major products at room temperature, while hydrazone compounds can be obtained chemospecifally under high temperature conditions. This method is safe, metal-free, and convenient. Tetrazinane compounds decomposed into more stable hydrazones due to their instability, indicating that heating is the major factor to promote the decomposition of tetrazinane compounds.

Experimental Section

General Information. Unless otherwise noted, all starting materials were purchased from commercial suppliers. Dichloromethane and 1,2-dichloroethane were refluxed over CaH_2; THF was refluxed over lithium aluminum hydride. The solvents were freshly distilled prior to use. Column chromatography was performed using silica gel (normal phase, 200-300 mesh) from Branch of Qingdao Haiyang Chemical, with petroleum ether (PE, 60–90 °C fraction) and ethyl acetate (EA) as eluent. Reactions were monitored by thin-layer chromatography on GF254 silica gel plates (0.2 mm) from Institute of Yantai Chemical Industry. The plates were visualized under UV light, as well as other TLC stains (10% phosphomolybdic acid in ethanol; 1% potassium permanganate in water; 10 g of iodine absorbed on 30 g of silica gel). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer, usually in $CDCl_3$ as an internal standard, and the chemical shifts (δ) are reported in parts per million (ppm). And multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet). Coupling constants (J) are reported in Hertz (Hz). HRMS measurements were carried out on an Agilent LC/MSD TOF mass spectrometer. Melting points were obtained on a Yanaco MP-500 melting point apparatus and are uncorrected.

General procedure for the synthesis of dialkyl 2-acylmethylidenehydrazine-1,1-dicarboxylates 3

Sulfoxonium ylide **1** (2.0 mmol) was added into a flame dried reaction tube. A solution of dialkyl azodicarboxylate **2** (6 mmol) in freshly distilled DCE (2 mL) was added. The reaction tube was sealed and put in an oil bath. The reaction mixture was allowed to stir overnight at 80 °C. Upon completion of reaction, the reaction mixture was cooled to room temperature. After removal of solvent in vacuum, the residue was subjected directly to flash chromatography on silica gel with petroleum ether and EtOAc (10:1, *v*/*v*) as eluent, affording the corresponding product **3**.

Diethyl (*E*)-2-(2-oxo-2-phenylethylidene)hydrazine-1,1-dicarboxylate (3a)

Colorless oil, yield: 46 mg, 80%; R_f = 0.45 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.21 (d, J = 7.7 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 4.41 (q, J = 7.1 Hz, 4H), 1.39 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.3, 151.2, 147.2, 135.2, 133.4, 130.6, 128.3, 64.6, 14.1. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_5^+$: 293.1132, found: 293.1140.

Diethyl (*E*)-2-(2-(4-methoxyphenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3b)

Colorless oil, petroleum ether:EtOAc (8:1, *v*/*v*) as eluent, yield: 46 mg, 73%; R_f = 0.26 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 9.0 Hz, 2H), 8.10 (s, 1H), 6.94 (d, J = 9.0 Hz, 2H), 4.40 (q, J = 7.1 Hz, 4H), 3.87 (s, 3H), 1.39 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.4, 164.0, 151.2, 148.4, 133.1, 128.2, 113.7, 64.5, 55.5, 14.1. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{19}N_2O_6^+$: 323.1238, found: 323.1242.

Diethyl (*E*)-2-(2-oxo-2-(4-methylphenyl) ethylidene)hydrazine-1,1-dicarboxylate (3c)
Colorless oil, yield: 55 mg, 90%; R_f = 0.45 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.14 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 4.41 (q, J = 7.1 Hz, 4H), 2.42 (s, 3H), 1.40 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.6, 151.1, 147.7, 144.4, 132.6, 130.7, 129.0, 64.5, 21.7, 14.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{19}N_2O_5^+$: 307.1288, found: 307.1293.

Diethyl (*E*)-2-(2-(4-(*tert*-butyl)phenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3d)
Yellow oil, yield: 63 mg, 91%; R_f = 0.50 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 4.26 (q, J = 7.1 Hz, 4H), 1.35 (s, 9H), 1.29 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.1, 158.8, 153.7, 151.4, 131.8, 128.9, 126.0, 64.1, 35.4, 31.0, 14.1. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{25}N_2O_5^+$: 349.1758, found: 349.1762.

Diethyl (*E*)-2-(2-(4-nitrophenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3e)
Colorless solid, yield: 37 mg, 57%; M.p. 104–106 °C, R_f = 0.34 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.8 Hz, 2H), 8.29 (d, J = 8.8 Hz, 2H), 8.23 (s, 1H), 4.43 (q, J = 7.1 Hz, 4H), 1.41 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.2, 150. 9, 150.2, 145.2, 140.1, 131.8, 123.2, 64.9, 14.1. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}N_3O_7^+$: 338.0983, found: 338.0984.

Diethyl (*E*)-2-(2-(4-bromophenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3f)
White solid, yield: 57 mg, 77%; M.p. 90–92 °C, R_f = 0.34 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 4.41 (q, J = 7.1 Hz, 4H), 1.40 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.3, 151.0, 146.4, 133.9, 132.2, 131.6, 128.8, 64.7, 14.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}BrN_2O_5^+$: 371.0237, found: 371.0237.

Diethyl (*E*)-2-(2-(4-chlorophenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3g)
White solid, yield: 47 mg, 70%; M.p. 80–82 °C, R_f = 0.34 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.6 Hz, 2H), 8.19 (s, 1H), 7.44 (d, J = 8.6 Hz, 2H), 4.42 (q, J = 7.1 Hz, 4H), 1.40 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.1, 151.0, 146.5, 140.0, 133.5, 132.1, 128.6, 64.7, 14.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}ClN_2O_5^+$: 327.0742, found: 327.0740.

Diethyl (*E*)-2-(2-(3-chlorophenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3h)
Colorless oil, yield: 48 mg, 74%; R_f = 0.53 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.18 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 4.42 (q, J = 7.1 Hz, 4H), 1.40 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.9, 151.0, 146.0, 136.6, 134.3, 133.1, 130.7, 129.5, 128.6, 64.7, 14.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}ClN_2O_5^+$: 327.0742, found: 327.0738.

Diethyl (*E*)-2-(2-(2-chlorophenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3i)
Colorless oil, yield: 44 mg, 68%; R_f = 0.45 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.43 – 7.37 (m, 2H), 7.36 – 7.28 (m, 2H), 4.34 (q, J = 7.1 Hz, 4H), 1.32 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 151.0, 145.4, 136.6, 132.2, 131.7, 130.4, 130.0, 126.2, 64.6, 13.9. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}ClN_2O_5^+$: 327.0742, found: 327.0750.

Diethyl (*E*)-2-(2-(2-fluorophenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3j)
Colorless oil, yield: 53 mg, 85%; R_f = 0.45 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 1.4 Hz, 1H), 7.78 (td, J = 7.7, 1.6 Hz, 1H), 7.64 – 7.49 (m, 1H), 7.38 – 7.25 (m, 1H), 7.20 – 7.12 (m, 1H), 4.41 (q, J = 7.1 Hz, 4H), 1.38 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0, 161.2 (d, J = 255.3 Hz), 151.1, 145.7, 134.2 (d, J = 8.8 Hz), 131.4, 125.1 (d, J = 12.9 Hz), 124.0 (d, J = 3.2 Hz), 116.3 (d, J = 22.3 Hz). 64.6, 14.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}FN_2O_5^+$: 311.1038, found: 311.1044.

Diethyl (*E*)-2-(2-(3,4-dichlorophenyl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3k)
Colorless oil, yield: 45 mg, 63%; R_f = 0.45 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 1.5 Hz, 1H), 8.16 (s, 1H), 8.08 (dd, J = 8.4, 1.5 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 4.43 (q, J = 7.1 Hz, 4H), 1.41 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.9, 150.9, 145.6, 138.0, 134.6, 132.8, 132.7, 130.3, 129.7, 64.8, 14.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}Cl_2N_2O_5^+$: 361.0353, found: 361.0357.

Diethyl (*E*)-2-(2-(naphthalen-1-yl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3l)
White solid, yield: 57 mg, 84%; M.p. 80–81 °C, R_f = 0.45 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 8.4 Hz, 1H), 8.35 (s, 1H), 8.08 – 7.98 (m, 2H), 7.89 (d, J = 7.9 Hz, 1H), 7.68 – 7.46 (m, 3H), 4.37 (q, J = 7.1 Hz, 4H), 1.34 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 151.2, 148.4, 133.8, 133.1, 132.6, 131.2, 131.0, 128.5, 127.9, 126.4, 125.5, 124.1, 64.5, 14.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_5^+$: 343.1288, found: 343.1293.

Diethyl (*E*)-2-(2-(naphthalen-2-yl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3m)
Colorless oil, yield: 41 mg, 60%; R_f = 0.45 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.31 (s, 1H), 8.19 (dd, J = 8.7, 1.4 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.88 (t, J = 8.7 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 4.44 (q, J = 7.1 Hz, 4H), 1.41 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0, 151.3, 147.4, 135.8, 133.4, 132.5, 132.4, 130.0, 128.8, 128.1, 127.8, 126.7, 125.5, 64.7, 14.1. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_5^+$: 343.1288, found: 343.1291.

Diethyl (*E*)-2-((*E*)-2-oxo-4-phenylbut-3-en-1-ylidene)hydrazine-1,1-dicarboxylate (3n)
Yellow oil, yield: 41 mg, 65%; R_f = 0.45 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.84 (d, J = 16.1 Hz, 1H), 7.67 (d, J = 16.0 Hz, 1H), 7.65 – 7.62 (m, 2H), 7.42 – 7.37 (m, 3H), 4.43 (q, J = 7.1 Hz, 4H), 1.41 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.5, 151.2, 146.7, 144.5, 134.8, 130.7, 128.9, 128.7, 120.0, 64.6, 14.1. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_5^+$: 319.1288, found: 319.1297.

Diisopropyl (*E*)-2-(2-oxo-2-phenylethylidene)hydrazine-1,1-dicarboxylate (3ab)
Colorless oil, yield: 48 mg, 73%; R_f = 0.50 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.2 Hz, 2H), 8.16 (s, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 5.16 (hept, J = 6.3 Hz, 2H), 1.38 (d, J = 6.3 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4, 150.6, 146.0, 135.3, 133.3, 130.7, 128.2, 73.1, 21.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}N_2O_5^+$: 321.1445, found: 321.1445.

Di(*tert*-butyl) (*E*)-2-(2-oxo-2-phenylethylidene)hydrazine-1,1-dicarboxylate (3cc)
Colorless oil, yield: 41 mg, 56%; R_f = 0.65 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 2H), 7.97 (s, 1H), 7.25 (d, *J* = 7.7 Hz, 2H), 2.41 (s, 3H), 1.58 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0, 149.5, 144.13, 144.07, 132.8, 130.7, 128.9, 85.1, 27.8, 21.7. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{27}N_2O_5^+$: 363.1914, found: 363.1919.

Dibenzyl (*E*)-2-(2-oxo-2-(4-methylphenyl)ethylidene) hydrazine-1,1-dicarboxylate (3cd)
Colorless oil, yield: 62 mg, 72%; R_f = 0.50 (petroleum ether/EtOAc 5:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.26 (m, 10H), 7.19 (d, *J* = 8.1 Hz, 2H), 5.18 (s, 4H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.0, 155.6, 151.0, 145.8, 134.5, 131.7, 129.6, 129.0, 128.44, 128.41, 128.3, 69.4, 21.8. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{23}N_2O_5^+$: 431.1601, found: 431.1605.

General procedure for the synthesis of tetraethyl 3,6-dibenzoyl-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylates 4

A mixture of sulfoxonium ylide **1** (6.0 mmol) and dialkyl azodicarboxylate **2** (2 mmol) in freshly distilled DCE (2 mL) was stirred overnight at room temperature until the starting material **2** was completely consumed (monitored by TLC). After removal of solvent under reduced pressure, the residue was subjected directly to flash chromatography on silica gel with petroleum ether and EtOAc (5:1, *v*/*v*) as eluent, affording the corresponding product **4**. The NMR analysis of product **4** must be conducted within one hour, otherwise decomposition of **4** would occur.

Tetraethyl 3,6-dibenzoyl-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylate (4a)
Colorless oil, yield: 35 mg, 60%; R_f = 0.35 (petroleum ether/EtOAc 3:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 4H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 4H), 6.96 (s, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 4H), 1.42 (t, *J* = 7.2 Hz, 6H), 1.29 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.5, 159.8, 153.4, 134.4, 133.1, 129.2, 128. 9, 87.9, 69.0, 62.8, 14.5, 14.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{33}N_4O_{10}^+$: 585.2191, found: 585.2195.

Tetraethyl 3,6-bis(4-methylbenzoyl)-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylate (4c)
Orange oil, yield: 35.5 mg, 58%; R_f = 0.35 (petroleum ether/EtOAc 3:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 4H), 7.31 (d, *J* = 8.1 Hz, 4H), 6.92 (s, 2H), 4.40 (d, *J* = 7.2 Hz, 2H), 4.39 (d, *J* = 7.2 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 4H), 2.43 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 6H), 1.33 – 1.16 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.0, 159.8, 154.0, 145.6, 130.6, 129.6, 129.4, 87.8, 68.9, 62.7, 21.8, 14.5, 14.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{37}N_4O_{10}^+$: 613.2504, found: 613.2503.

Tetraethyl 3,6-bis(4-bromobenzoyl)-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylate (4f)
Colorless oil, yield: 25 mg, 33%; R_f = 0.35 (petroleum ether/EtOAc 3:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 6.7 Hz, 4H), 7.60 (d, *J* = 6.7 Hz, 4H), 6.82 (s, 2H), 4.39 – 4.29 (m, 4H), 4.25 – 4.15 (m, 4H), 1.38 – 1.29 (m, 6H), 1.26 – 1.15 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.8, 159.9, 153.8, 132.3, 131.8, 130.7, 130.0, 87.8, 69.13, 63.0, 14.5, 14.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{31}Br_2N_4O_{10}^+$: 741.0401, found: 741.0413.

Tetraethyl 3,6-bis(4-chlorobenzoyl)-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylate (4g)
Colorless oil, yield: 35 mg, 53%; R_f = 0.35 (petroleum ether/EtOAc 3:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 4H), 7.49 (d, *J* = 8.5 Hz, 4H), 6.89 (s, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.27 (q, *J* = 7.0 Hz, 4H), 1.41 (t, *J* = 7.2 Hz, 6H), 1.21 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.6, 159.9, 151.0, 141.2, 131.4, 130.7, 129.3, 87.8, 69.1, 62.9, 14.5, 14.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{31}Cl_2N_4O_{10}^+$: 653.1412, found: 653.1422.

Tetraethyl 3,6-bis(3-chlorobenzoyl)-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylate (4h)
Colorless oil, yield: 39 mg, 60%; R_f = 0.35 (petroleum ether/EtOAc 3:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, *J* = 1.8 Hz, 2H), 7.97 (d, *J* = 7.8 Hz, 2H), 7.61 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 2H), 7.46 (t, *J* = 7.9 Hz, 2H), 6.86 (s, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 4H), 1.40 (t, *J* = 7.2 Hz, 6H), 1.28 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.6, 159.8, 153.1, 135.3, 134.6, 134.4, 130.2, 129.2, 127.3, 87.8, 69.1, 62.9, 14.5, 14.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{31}Cl_2N_4O_{10}^+$: 653.1412, found: 653.1422.

Tetraethyl 3,6-bis(2-chlorobenzoyl)-1,2,4,5-tetrazinane-1,2,4,5-tetracarboxylate (4i)
Colorless oil, yield: 42 mg, 65%; R_f = 0.35 (petroleum ether/EtOAc 3:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.54 (m, 2H), 7.48 – 7.44 (m, 2H), 7.43 – 7.41 (m, 2H), 7.39 – 7.33 (m, 2H), 6.85 (s, 2H), 4.39 (q, *J* = 7.4 Hz, 2H), 4.38 (q, *J* = 7.4 Hz, 2H), 4.19 (q, *J* = 7.4 Hz, 4H), 1.39 (t, *J* = 7.4 Hz, 6H), 1.21 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 159.6, 154.5, 135.0, 133.1, 132.1, 130.5, 130.4, 127.0, 88.8, 69.0, 62.7, 14.4, 14.1. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{31}Cl_2N_4O_{10}^+$: 653.1412, found: 653.1422.

Larger-scale synthesis of diethyl (*E*)-2-(2-(naphthalen-1-yl)-2-oxoethylidene)hydrazine-1,1-dicarboxylate (3l)

Sulfoxonum ylide **1l** (0.75 g, 3.04 mmol) and diethyl azodicarboxylate (**2a**) (1.59 g, 9.14 mmol) were dissolved in 20 mL of DCE. The mixture was allowed to stir overnight at 80 °C. Upon completion of reaction, the reaction mixture was cooled to room temperature. After removal of solvent in vacuum, the residue was subjected directly to flash chromatography on silica gel with petroleum ether and EtOAc (8:1, *v*/*v*) as eluent, affording the corresponding product **3l** as white solid (0.87 g, 90%).

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[8] CCDC 1895643 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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FULL PAPER

Safe, Metal-Free, and Direct Synthesis of Dialkyl Acylmethylidenehydrazine-1,1-Dicarboxylates from Dimethylsulfoxonium Acylmethylides and Dialkyl Azodicarboxylates

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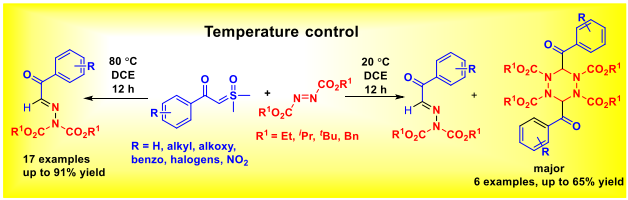

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