



Addition of silylated nucleophiles to α -oxoketenes†

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A general evaluation of silylated nucleophiles to intercept transient α -oxoketenes generated by microwave-assisted Wolff rearrangement of 2-diazo-1,3-dicarbonyl compounds is presented. Original scaffolds and synthetic intermediates are accessed in a rapid, efficient and easy-to-handle way. Mechanistic studies by DFT calculations and some post-functionalizations are discussed.

The 1,2-Wolff rearrangement, *i.e.* the conversion of easily available α -diazocarbonyl derivatives into ketenes with extrusion of dinitrogen, is a venerable and useful synthetic tool (Scheme 1).^{1,2} It has been extensively used for the functionalization and variation of carbon backbones, especially for the ring contraction of cyclic molecules and the Arndt–Eistert homologation of carboxylic acids.³ Starting from 2-diazo-1,3-dicarbonyl compounds **1**,⁴ the Wolff rearrangement produces strongly electrophilic α -oxoketene species **2**,⁵ which are usually not isolable and must be generated *in situ*. α -Oxoketenes can react with a variety of heteroatomic or carbon-centered nucleophiles to produce the corresponding 1,3-dicarbonyl products,^{6,7} and with various unsaturated compounds to afford stereodefined polycyclic molecules following pericyclic processes (Scheme 1, left).⁸ Microwave-assisted heating was shown to be highly beneficial in terms of efficiency and practicability in these transformations.⁹ However, the chemoselective interception of α -oxoketenes with simple nucleophiles such as dihydrogen, hydrogen azide or ammonia remains unknown (Scheme 1, upper right). We identified the following issues as possible explanations: (i) reactivity and chemoselectivity, since the nucleophile has to react with the α -oxoketene but not with the ketones of the starting materials; (ii) practicability for reactions at elevated temperature at the lab-scale, as most of

those nucleophiles are gases, often with high toxicities; (iii) product stability since the resulting naked functionalities in the products (*e.g.* aldehydes and acyl azides) might be unstable under the reaction conditions. The alternative anionic species (such as mineral cyanide or azide sources) can barely be used since they are hardly soluble in the unpolar organic reaction media commonly used to carry out the Wolff rearrangement.

Despite the widespread application of silylated nucleophiles in organic chemistry (hydrosilylation,¹⁰ Mukaiyama aldol reaction,¹¹ Peterson elimination,¹² Hiyama–Denmark cross-coupling¹³ *etc.*), they have hardly been reacted with ketene species. Indeed, there are only a single example of trapping of a ketene with hexamethyldisilazane (HMDS) to afford the corresponding primary amide in a context of total synthesis,¹⁴ and a study on the hydrosilylation of bench-stable polyfluoroketenes under Pt-catalysis.¹⁵ Additionally, a recent report presents the coupling of 1,3-dioxin-2-ones with silyl enol ethers.¹⁶ In the present work, we describe the first chemoselective addition of a variety of easy-to-handle silylated nucleophiles to α -oxoketenes generated by microwave-assisted Wolff rearrangement of either acyclic or cyclic 2-diazo-1,3-dicarbonyl compounds, to prepare building blocks that are hard or impossible to access by alternative existing methods (Scheme 1, bottom right). Triethylsilane and trimethylsilyl azide were used as sources of hydride and azide, to synthesize masked β -ketoaldehydes **3** and a β -ketoacyl azide **5**, respectively. In addition, HMDS acted as a liquid anhydrous ammonia surrogate and trimethylsilyldiazomethane as a source of methylene to afford upon desilylation primary β -ketoamides **4** and fused bicyclic furan-3-ones **6**, respectively. In these reactions, the silyl group remarkably enabled the *in situ* protection of sensitive functionalities avoiding their degradation during the reaction.

We started our investigation by mixing triethylsilane and 2-diazo-5,5-dimethylcyclohexane-1,3-dione in toluene at 160 °C under microwave irradiation during 3 minutes (Table 1). Pleasingly, analysis of the clean crude reaction mixture showed only the masked β -ketoaldehyde **3a** as a single diastereomer (98% yield), which was identified by comparison with known related compounds.¹⁷ This methodology could be applied to

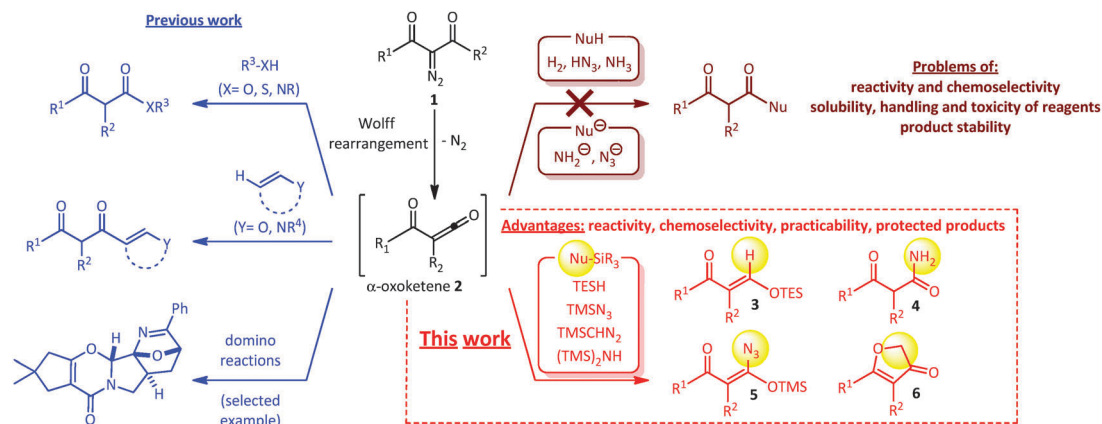
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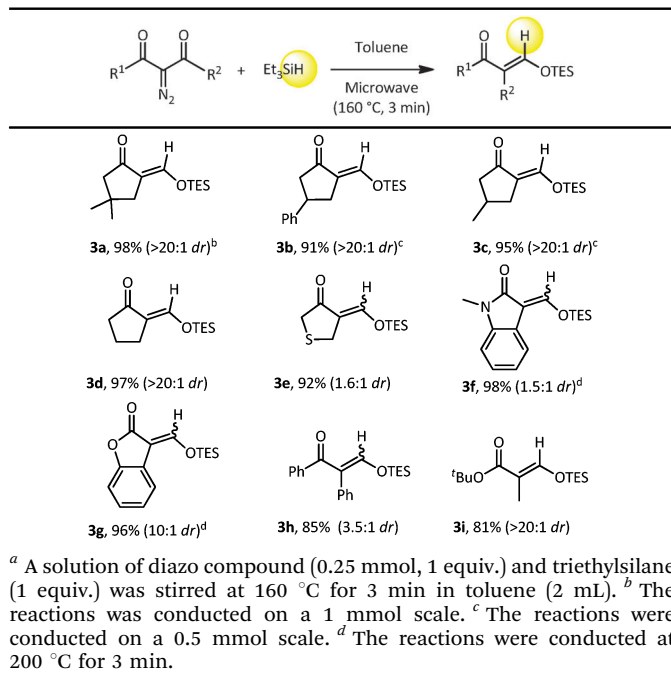
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Scheme 1 Previous and new applications of the microwave-assisted Wolff rearrangement.

Table 1 Synthesis of masked β -ketoaldehydes by triethylsilane addition^a



the synthesis of various cyclic masked β -ketoaldehydes by ring contraction (products **3b** to **3g**), such as functionalized thiolanone **3e**, oxindole **3f** and benzoxofurane **3g**. The acyclic products **3h** and **3i** could also be prepared from the corresponding acyclic diazo compounds. Notably, all those compounds were obtained with good to excellent yields in a practical and expeditious manner (reaction time = 3 min, no work-up, no purification). Generally, only the (*E*)-diastereomer was observed, but for several examples, the (*Z*) diastereomer could also be detected. The use of less nucleophilic silicon hydrides (Ph_3SiH , Ph_2SiH_2 and $(\text{EtO})_3\text{SiH}$) resulted in complex reaction mixtures.¹⁸ Remarkably, with this methodology, the position of the protected aldehyde functionality in compounds **3a–c** and **3e** is fully controlled since the starting diazo compounds are symmetric molecules, whereas other existing methods to prepare this motif, such as the formylation of enolate, are plagued with problems of regioselectivity.^{17h}

The outcome of the reaction raised mechanistic considerations, which were investigated by computational DFT methods in the case of the model reaction between the conformationally constrained α -oxoketene and trimethylsilane (**A**, Fig. 1).¹⁹ In early calculations, both the *endo* and *exo* direct 1,2-hydrosilylation of the ketene carbonyl group reaction paths were computed, and the formation of the (*E*) isomer **C** was found both kinetically and thermodynamically favored over the (*Z*) isomer **B** at the studied level of theory (Fig. 1a). However, in both cases activation barriers are high (134 and 110 kJ mol^{-1} , respectively), and an alternative reaction pathway was investigated (Fig. 1b). The hydrosilylation reactions described in Table 1 are believed to occur *via* a three-step mechanism: (i) a concerted kinetically favored 1,4-hydrosilylation of the α -oxoketene produces intermediate **D** through a six-membered transition state TS_{AD} ,²⁰ (ii) a 1,5-shift of the silyl group from the ketone enol ether oxygen atom to the aldehyde one in **D** is possible through another six-membered transition state TS_{DB} to give the (*Z*) isomer **B**; (iii) the thermodynamic (*E*) isomer of product **C** can be obtained by an isomerization of the (*Z*) isomer **B**. The unusual **B** \rightarrow **C** isomerization has a reasonable energy barrier due to the marked polarization of the enol ether double bond with a “push–pull” motif allowing for a transition state similar to an enolate/silyl-stabilized oxonium system.^{21,22}

We then turned our attention to nitrogen-centered silylated nucleophiles, using HMDS and trimethylsilyl azide (TMSN_3). The reactions of representative α -oxoketenes with HMDS afforded relatively complex crude reaction mixtures, which after purification by silica gel chromatography delivered the corresponding cyclic and acyclic primary β -ketoamides **4a–4e** in satisfactory yields (Table 2).²³ The reaction with TMSN_3 was less straightforward but, after optimization of the reaction conditions involving the portion-wise addition of the diazo compound deriving from dimedone, the previously unknown masked β -ketoacyl azide **5** was obtained diastereoselectively with 86% yield (Scheme 2).¹⁹

To complete the study, carbon-centered silylated nucleophiles were investigated through the reactions with trimethylsilyl cyanide (TMSCN), trimethyl(trifluoromethyl)silane (TMSCF_3) and trimethylsilyldiazomethane (TMSCHN_2). With TMSCN , the expected product could be observed but it was not possible to optimize the reaction to a reasonable level of selectivity (not depicted). As to the reaction with TMSCF_3 , only the α -oxoketene dimer was obtained,



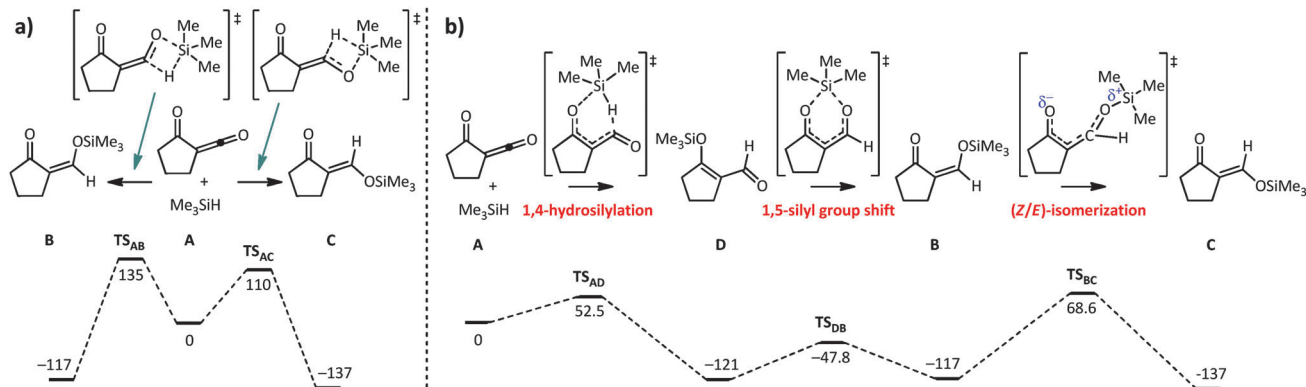
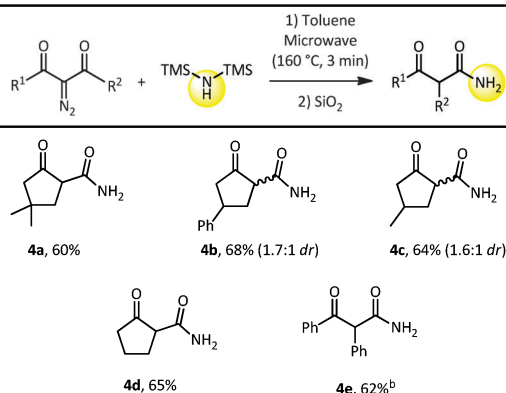


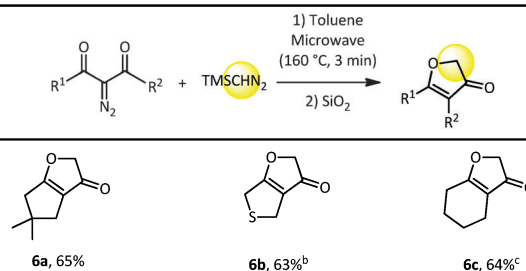
Fig. 1 (a) Model study for the direct 1,2-hydrosilylation pathway. (b) Simplified model study for the 1,4-hydrosilylation/1,5-shift of the Me₃Si group/isomerization pathway. The energy profiles were obtained by DFT calculations at the B3LYP/6-311++G(d,p) level of theory with the IEFPCM solvation model for toluene (free energies in kJ mol⁻¹; see ESI,† for full details).

Table 2 Synthesis of β-ketoamides by HMDS addition^a

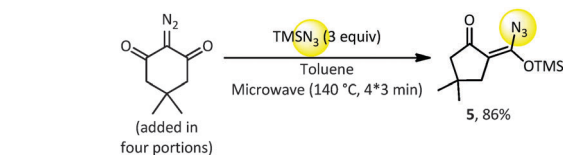


^a A solution of diazo compound (0.1 mmol, 1 equiv.) and HMDS (1 equiv.) was stirred at 160 °C for 3 min in toluene (2 mL). Yields of isolated pure products after purification by flash chromatography on silica gel. ^b This reaction was conducted on a 0.25 mmol scale.

Table 3 Synthesis of bicyclicfuran-3-ones by TMSCHN₂ addition^a



^a A solution of diazo compound (1 equiv.) and TMSCHN₂ (1 equiv.) was stirred at 160 °C for 3 min in toluene (2 mL). Yields of isolated pure products after purification by flash chromatography on silica gel. ^b This reaction was conducted on a 0.5 mmol scale. ^c This reaction was conducted on a 0.25 mmol scale.



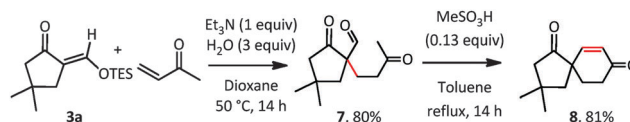
Scheme 2 Addition of TMSN₃.

presumably because of its too weak nucleophilicity (not depicted). On the opposite, TMSCHN₂ behaved as a convenient source of methylene (Table 3): indeed, after initial nucleophilic trapping, the second diazo function underwent an insertion reaction to deliver original fused bicyclic furan-3-ones **6a–c**, whose synthesis has scarcely been reported,²⁴ with satisfactory yield after purification by silica gel chromatography. It is worth noting that related preliminary evaluation of the coupling between two different diazo species can be found in the literature but yields of products were low because of other competing pathways.²⁵ The present results highlight the beneficial effect of the silyl group to prevent over-reaction of the product under the reaction conditions.

Moreover this transformation represents a selective cross-coupling of two different diazo compounds.

With this set of original structures in hand, we briefly investigated their potential post-functionalization to obtain more structurally diverse scaffolds (Scheme 3). Starting from masked β-ketoaldehyde **3a**, Michael addition on methyl vinyl ketone in slightly basic hydro-organic reaction conditions¹⁹ delivered with good yield product **7**, which could be further functionalized into spiro-cyclohexenone **8** by Robinson annulation, also with good yield.

In conclusion, we have successfully developed a versatile method for the addition of silylated nucleophiles to α-oxoketenes generated by microwave-assisted Wolff rearrangement of 2-diazo-1,3-dicarbonyl compounds to synthesize valuable building blocks that are hard or impossible to access by existing methods. This methodology is a rapid, efficient and user-friendly way to prepare original scaffolds and synthetic intermediates that are likely to



Scheme 3 Post-functionalization of masked β-ketoaldehyde **3a**.



find interesting applications in synthetic organic chemistry. Additionally, DFT calculations are in agreement with an initial 1,4-hydrosilylation with participation of the ketone's oxygen atom. Our current efforts aim to find applications for these promising substrates in enantioselective organocatalysis.

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