** tert-Butyl 2-(tert-butyldimethylsilyl)-2-oxoacetate**

(reagent used in various multicomponent coupling reactions typically for the synthesis of substituted glycolic acid derivatives)

**Physical Data:** bright yellow oil.

**Solubility:** soluble in most organic solvents.

**Form Supplied in:** bright yellow liquid. The most common impurity is silanol remaining from the final oxidation step.

**Analysis of Reagent Purity:** Rf: 0.49 (25% Et2O/Petroleum Ether); IR (thin film) cm−1: 2931, 2860, 1716, 1657, 1464, 1369, 1252, 1159, 993, 841, 785; 1H NMR (300 MHz, CDCl3) δ: 0.27 (s, 6H), 0.96 (s, 9H), 1.55 (s, 9H); 13C NMR (75 MHz, CDCl3) δ: −6.6, 17.1, 26.6, 28.1, 83.6, 163.0, 232.9; Anal. Calcd. for C12H24O3Si: C, 58.97; H, 9.90. Found: C, 58.81; H, 9.98.

**Preparative Methods:** the reagent is prepared by a three-step sequence starting from commercially available tert-butyl acetoacetate. Treating tert-butyl acetoacetate with p-acetamidobenzensulfonyl azide (1.0 equiv), tetrabutylammonium bromide (0.02 equiv), and sodium hydroxide (2.8 equiv) yields the requisite diazoacetate with the desired silyl triflate (1.2 equiv) in the presence of Hünig’s base (1.2 equiv) to provide the silyl diazoacetate as yellow oil. A silylation is performed on the unpurified diazoacetate with the desired silyl triflate (1.2 equiv) in the presence of Hünig’s base (1.2 equiv) to provide the silyl diazoacetate as yellow oils for a series of silyl triflates (TMS, TES, TBS, TBDPS). It is typically most convenient to proceed without purification after the C-silylation, since impurities are more easily rejected after the final step. Oxo transfer to the silyl diazoacetate is mediated by dimethylsulfonium formed in situ3 from Oxone® and acetone to provide the silyl glyoxylate as a yellow oil. The product is purified by flash chromatography in yields typically around 50% for the three-step sequence. This method allows for preparative quantities of silyl glyoxylates with varied silyl functionalities to be prepared. Other methods exist, but this preparation of silyl glyoxylates appears to be the most widely applicable at this time. Silyl glyoxylates with a benzyl ester (3δ) or an allylic ester6 functionality can be prepared by a modified procedure.

**Purification:** the final step in the protocol is an Oxone oxidation of the diazoacetate after which the product is purified by flash chromatography eluting with 5% EtOAc/hexanes. Since the product is yellow, the progress of elution can be visually monitored. No purification of the intermediates from the first two steps of the synthesis is required.

**Handling, Storage, and Precautions:** silyl glyoxylates can be stored for several months without significant decomposition if stored in a freezer away from light. The reagents decompose upon prolonged exposure to light and should be wrapped in aluminum foil. These reagents typically are stored at 0 °C to prevent thermal decomposition. The reagent is somewhat volatile and some may be lost by prolonged exposure to high vacuum (particularly the TMS silyl glyoxylates). Silyl glyoxylate toxicity has not been evaluated, but the reagents should be used with common precautions to limit exposure.

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**Introduction to Silyl Glyoxylate Chemistry and Reactivity Patterns.** Silyl glyoxylates are a specific subclass of acyl silanes that possess an attached ester; they are vicinal dicarbonyls. The effect of this functionality is to significantly increase the electrophilicity of the acyl silane and the rate at which tetrahedral addition intermediates undergo 1,2-Brook rearrangement. The unique reactivity of silyl glyoxylates has led to their use as conjunctive dipolarophiles in multicomponent couplings. Although silyl glyoxylate typically functions as a dipolar glycolic acid synthon for the union of nucleophilic and electrophilic partners, the scope of the reagent’s reactivity has been expanded to include glyoxylate anion3 and α-keto ester homoenolate synthons.8,9 An asset of silyl glyoxylate chemistry is the ability to “mix and match” a variety of complementary components into the reaction manifold enabling access to a diverse collection of complex molecular motifs.

Reacting silyl glyoxylates with nonstabilized nucleophiles results in addition to the acyl silane portion of the reagent, which triggers a facile [1,2]-Brook rearrangement to provide a transient secondary nucleophile that can react with a secondary electrophile (eq 1). Due to the high electrophilicity of the silyl glyoxylate, secondary electrophiles can often be present in the reaction mixture without significant side reactions occurring. Depending on the identity of the nucleophile and associated metal counteraction, silyl glyoxylates can undergo [1,2]-Brook rearrangement very
rapidly, even at low temperatures. For this reason, reactions with silyl glyoxylates are typically performed below 0 °C and often at −78 °C. Performing couplings at higher temperatures can result in uncontrolled oligomerization of the reagent. It is noteworthy that the controlled stereoselective dimerization of silyl glyoxylates is possible and was employed in the synthesis of zaragozic acid C.\textsuperscript{10}

\textbf{Silyl Glyoxylate Reactivity}

Silyl glyoxylates can typically be varied at the ester and the silyl portion of the reagent without significantly affecting the yield for various couplings. TES- and TBS-substituted silyl glyoxylates can often be used interchangeably. TMS-substituted silyl glyoxylates tend to perform poorest, since the [1,2]-Brook rearrangement is much faster for smaller silyl groups, which leads to uncontrolled oligomerization. The facile deprotection and/or migration of the TMS silyl ether can also lead to product mixtures.

\textbf{α-Coupling Aldol and Aldol-type Cascades.} Silyl glyoxylate 1 reacts with various aldehydes and alkynylzinc reagents to provide an alkynylation/[1,2]-Brook rearrangement/glycolate aldol sequence to afford orthogonally protected diol products with good diastereoselectivity (eq 2).\textsuperscript{11} Originally, the TMS-substituted silyl glyoxylate was utilized; however, this reagent resulted in mixtures of secondary and tertiary silyl ethers. Opting for the bulkier TBS group inhibited the undesired silyl migration and improved the diastereoselectivity. A single example employing vinyl Grignard instead of an alkynylzinc reagent was also performed that provided the analogous product with high diastereoselectivity.

\begin{equation}
\text{BuO}_2\text{C} \quad \text{TBS} + \quad \text{R}^1\text{C} = \quad \text{C} = \quad \text{H}
\end{equation}

An adaptation of this aldol-type silyl glyoxylate cascade involves replacing the ketone secondary electrophile with a stereodefined β-lactone; a terminating quaternary Claisen-type bond construction ensues (eq 4). In most cases, the reaction proceeds with high levels of 1,4-stereoinduction.\textsuperscript{12} The Reformatsky/Claisen methodology was also exploited in the formal synthesis of leustroducsin B.\textsuperscript{13}

\begin{equation}
\text{BnO}_2\text{C} \quad \text{TES} + \quad \text{R}^1\text{C} \quad \text{EtO} + \quad \text{CO}_2\text{R}^1
\end{equation}

Reactions of silyl glyoxylate 1 and 3 with metallated sulfonyl imidates and enantiopure sulfinyl aldimines provided good yields of cyclic N-sulfonylamidines with complete stereocontrol (eq 5).\textsuperscript{14} The reaction was amenable to scale-up and only a minor decrease in yield occurred when the reaction was run on a gram scale.
Silylglyoxylates and magnesium alkoxides react to provide \( \alpha,\beta \)-dihydroxysterter via a hydride addition/[1,2]-Brook rearrangement/aldol sequence (eq 6).\(^\text{15}\) The nucleophile initiator becomes the secondary electrophile via a Meerwein–Ponndorf–Verley/Oppenauer redox process. The magnesium alkoxide serves as the hydride source that triggers the [1,2]-Brook rearrangement to form the glycolate enolate; the latter attacks the newly formed carbonyl. Yields ranged from 63% to 97% with diastereomeric ratios up to 10:1.

A catalytic variant of this aldol reaction utilizing strain release silacycles and silyl glyoxylates was developed (eq 7).\(^\text{16}\) The reductive aldol was catalyzed by various lanthanide trispropoxides. This is one of the few catalytic silyl glyoxylate cascades reported to date.

**Vinylogous Michael Coupling Cascades.** When \( \pi \)-nucleophiles (vinyl Grignard or alkynylzinc reagents) are added to silyl glyoxylates the [1,2]-Brook rearrangement provides a silyloxydiol intermediate. This diol intermediate can function as an \( \alpha \)-keto ester homoenolate synthetic equivalent by engaging an electrophile in vinylogous fashion. The identity of the secondary electrophile dictates whether an \( \alpha \)-coupling or vinylogous (\( \gamma \)-coupling) pathway will occur. If the secondary electrophile is a carbonyl the \( \alpha \)-coupling pathway predominates (vide supra); however, when electrophilic alkenes such as \( \alpha,\alpha \)-dicynoolefins and nitroalkenes are used, a \( \gamma \)-trapping or vinylogous mechanism predominates. In this manner, the secondary electrophile can function as a regioselective switch that determines which type of reactivity (\( \alpha \) vs. \( \gamma \)) will be observed.

When treated with vinyl Grignard as the nucleophilic initiator and various nitroalkenes as the secondary electrophile, silyl glyoxylates undergo a vinylation/[1,2]-Brook rearrangement/vinylogous Michael cascade to provide \( \text{Z} \)-enolsilanes with complete regioselectivity (eq 9).\(^\text{8}\) As with the \( \alpha \)-couplings, an excess of silyl glyoxylate is required to compensate for the oligomerization of silyl glyoxylate. The enolsilane product can be converted to nitrocyclopentanols via a silyl deprotection/Henry cyclization with complete diastereoselectivity in many cases (eq 10). This methodology enables the efficient construction of densely functionalized cyclopentenols in two steps from silyl glyoxylate.

**\( \alpha \)-Coupling Michael Cascades.** Silyl glyoxylates react with enolates and enones in a Michael-terminated cascade reaction to provide products with two contiguous stereocenters (eq 8).\(^\text{17}\) When lithium is used as the enolate countercation, the regioselectivity for this coupling is excellent (20:1) in favor of the Michael adduct over the 1,2-addition adduct. Replacing the enolate countercation with zinc provides complete regioselectivity for the 1,2-addition cascade.

A related methodology utilizes alkynylmagnesium bromide reagents instead of vinyl magnesium bromide reagents to achieve a tandem alkylation/[1,2]-Brook rearrangement/vinylogous Michael reaction to form silyloxyallenes with complete regio- and diastereoselectivity (eq 11).\(^\text{9}\) Density functional theory (DFT) calculations and control experiments suggested the regio- and diastereoselectivity arose from bidentate coordination of the nitro group to the MgBr cation of the \( \text{Z} \)-glycolate enolate. A Lewis acid-assisted Henry cyclization was also developed to access fully substituted cyclopentenols (eq 12).
Miscellaneous Reactions. The reaction of silyl glyoxylate 1 with aldehydes in the presence of a cyanide catalyst produces β-silyloxy-α-keto ester via a benzoin-type reaction. In this manner, the silyl glyoxylate functions as a glyoxylate anion synthetic equivalent. The coupling provides excellent yields ranging from 80% to 96% for aryl-, heteroaryl-, and alkyl-substituted aldehydes. The products can be converted to amino esters via a reductive amination with moderate levels of diastereoselectivity in favor of the syn-diastereomer.

Silyl glyoxylates that contain an allylic pendant ester can undergo a [1,2]-Brook rearrangement/Ireland-Claisen rearrangement leading to γ,δ-unsaturated α-silyloxy acid derivatives. The sequence provides the [3,3]-rearrangement products in moderate yields with variable diastereoselectivities. This cascade can also be used to form contiguous quaternary stereocenters with moderate diastereoselectivity. The predominance of the (Z)-glycolate enolate intermediate was inferred from the stereochemical outcome of the rearrangement.


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