

An unusual dianion equivalent from acylsilanes for the synthesis of substituted β -keto esters†

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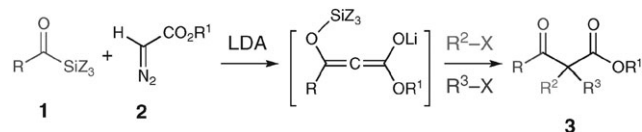
The reaction of lithiated diazo esters with acylsilanes generates a remarkable intermediate *en route* to highly substituted β -keto esters.

Reactions that combine multiple starting materials in a single flask are efficient methods for the rapid synthesis of target compounds.¹ Our own interest in developing new and efficient routes to biologically active or topologically diverse structures has led us to investigate processes with potential for constructing multiple carbon–carbon bonds in a single reaction flask.² Diazo compounds have wide-ranging reactivity patterns and synthetic utility that are potentially useful in the design of new multicomponent reactions. For example, many cycloaddition, cyclopropanation and C–H insertion processes involve metal–locarbenoid species derived from diazo decomposition catalyzed by a transition metal salt.³ Diazo esters and ketones have also been employed as nucleophiles in a variety of reaction manifolds. In this vein, Holmquist and Roskamp reported a stannous chloride-promoted homologation of aldehydes to *unsubstituted* β -ketoesters using diazoesters.⁴ Employing diazo compounds bearing alternative electron-withdrawing substituents including phosphoryl, phosphinoyl and toluenesulfonyl-groups has expanded the scope of this reaction. Padwa *et al.* have also disclosed the synthesis of 1,3-diketones by a similar method.⁵ The groups of Wang, Terada and more recently Hashimoto and Maruoka have all reported elegant and selective additions of diazo compounds to imines using chiral acid catalysis.⁶ In a related process the reaction of imines with diazo compounds yield aziridines as products.⁷ Yao and Wang have also reported additions to aldehydes catalyzed by a zirconium–BINOL complex, while Nishida and co-workers have independently reported the use of phase transfer catalysis to effect the addition of diazo esters to aldehydes.⁸

In connection with our research accessing unusual nucleophilic species, we became interested in pursuing the combination of acylsilanes (**1**) with the distinctive reactivity of diazo compounds (**2**).⁹ Our hypothesis was that the addition of a deprotonated diazo ester should induce a 1,2-Brook rearrangement¹⁰ followed by loss of dinitrogen.¹¹

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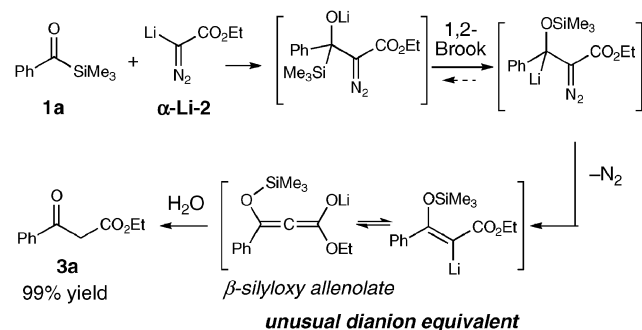
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for new compounds. See DOI: 10.1039/b801597j



The resulting intermediate could undergo *sequential* additions to two different electrophiles to generate substituted β -keto esters (**3**) in a single flask. In this communication, we report the realization of this multiple bond-forming reaction that accesses new and unusual dianion equivalent reactivity. The reactions of α -metallated diazoacetates with electrophiles are well known.¹² The deprotonation can be accomplished using several bases¹³ and the analogous zinc salt has also been employed in nucleophilic additions to aldehydes.¹⁴

To explore the potential reaction between diazo esters and acylsilanes, we treated benzoyltrimethylsilane **1a** with α -lithioethyl diazoacetate (α -Li-**2**) at -78°C (Scheme 1). Gratifyingly, ethyl benzoylacetate **3** was the sole product of this reaction (99% yield, entry 1). In contrast to the cases of ethyl diazoacetate anion additions to aldehydes and ketones, the normal carbinol product is not observed with acylsilanes. The tetrahedral intermediate most likely formed after the initial addition can undergo a 1,2-Brook rearrangement, which then precipitates the elimination of N_2 and potentially affords a novel β -silyloxy allenolate intermediate. This intriguing intermediate can be considered to be a new type of formal dianion equivalent.

Using this new process, various unsubstituted β -ketoesters can be prepared rapidly (Table 1, entries 1–5). We were pleased to discover that the substrate scope for the reaction accommodates three different diazo esters, (entries 1, 2 and 5) and both alkyl and aryl acylsilanes (entries 3 and 4). *A novel aspect of this new process is the ability to utilize the dianion equivalent in carbon–carbon bond forming reactions.* For



Scheme 1 Dianion equivalents from acylsilanes and diazo esters.

Table 1 Multicomponent synthesis of β -ketoesters^a

Entry	R	R ¹	R ² -X	Yield ^b (%)	Compound
1	Ph	Et	H-OM	99	3a
2	Ph	<i>t</i> -Bu	H-OMe ^b	98	4
3	4-CH ₃ C ₆ H ₄	Et	H-OMe	98	5
4	CH ₃	Et	H-OMe	79	6
5	Ph	Cinnamyl	H-OMe	95	7
6	Ph	Et	Me-I	93	8
7	Ph	Et	Bn-Br	95	9
8	CH ₃	Et	Bn-Br	76	10


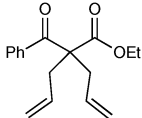
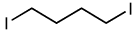
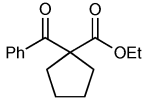
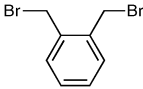
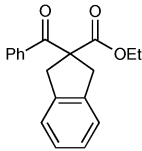
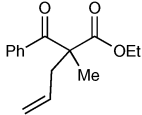
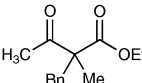
^a See ESI† for further reaction details. ^b Isolated yield.

example, the addition of MeI to the reaction in place of a proton results in 93% yield of monomethyl β -ketoester **8** (entry 6). The addition of a variety of alkylating agents (entries 6–10) allows for the three-component preparation of substituted β -ketoesters in a single flask.

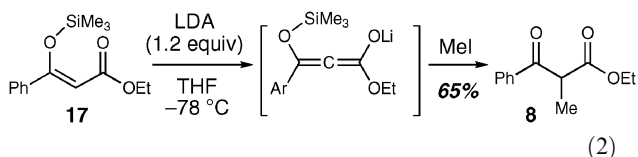
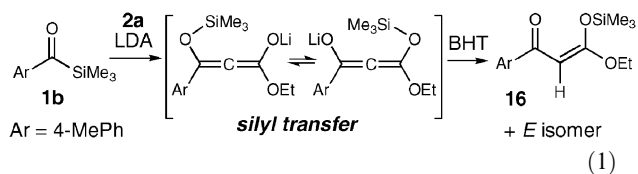
We were also able to prepare β -ketoesters possessing quaternary centers by utilizing two electrophilic partners (Table 2). Using an excess of allyl iodide or tethered alkyl bis-halides constructs three new carbon–carbon bonds at the same time in high yield (Table 2, entries 1–3). To highlight the versatility of the putative β -silyloxy allenolate, differentially substituted β -ketoesters can be accessed in a single-flask operation by the sequential addition of electrophiles (Table 2, entries 4 and 5).

While the α -deprotonation of vinyl or allenyl ketones leading to allenolate or cumulenolate intermediates is preceded, *this approach does not work when active protons are present*.^{15,16} This restriction underscores the potential utility of accessing a β -silyloxyallene from simple starting materials as described herein. To probe the identity of the potential intermediate(s) in our reaction, we combined *p*-methyl benzoylsilane **1b** and α -lithio-ethyl diazoacetate (α -Li-**2**) in C₆D₆ at 5 °C, and added a proton source (2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) for 30 min). The ¹H NMR spectrum of the reaction mixture provides data consistent with both silylketene acetal isomers (**16**, eqn (1)).¹⁷ This observation supports a β -silyloxy allenolate intermediate and suggests that silyl transfer between oxygen atoms is also operative under these conditions.

Table 2 Double alkylation of dianion equivalent^a

<div><div><div><div><div>$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{SiZ}_3$</div><div>1</div></div><div><div>$\text{H}-\overset{\text{N}_2}{\parallel}{\text{C}}-\text{CO}_2\text{R}^1$</div><div>2</div></div></div><div><div>$\xrightarrow[2. \text{R}^2-\text{X}, \text{R}^3-\text{X}]{1. \text{i-Pr}_2\text{NLi}}$</div></div><div><div><div><div>$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{C}(\text{R}^2)(\text{R}^3)-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}^1$</div><div>11-15</div></div></div></div></div></div>				
Entry	Electrophile	Product	Yield ^b (%)	Compound
1			91	11
2			84	12
3			77	13
4	MeI, followed by allyl iodide		81	14
5	BnBr, followed by MeI		69	15

^a See ESI† for further reaction details. ^b Isolated yield.



Further evidence for a β -silyloxy allenolate generated in this process is obtained when silyl enol ether **17** was treated with LDA and then exposed to MeI (eqn (2)), with compound **8** isolated as the product. Additionally, when we employ cinamyl diazoacetate **2c** in the reaction, smooth conversion to the β -ketoester **7** is obtained in 95% yield with no products resulting from a possible carbenoid intermediate (Table 1, entry 5).

The combination of lithiated diazo esters and acylsilanes provides a new and general way to access a useful and unprecedented dianion equivalent. This straightforward combination is presumed to generate a β -silyloxy allenolate intermediate by a 1,2-Brook rearrangement followed by loss of nitrogen gas. The addition of two electrophiles, either simultaneously or sequentially, results in a multicomponent synthesis of substituted β -keto esters. The dual anion aspects of this process are unique and have potential for the efficient synthesis of highly functionalized 1,3-carbonyl compounds. The combination of reactive nucleophiles and acylsilanes continues to provide innovative routes to atypical nucleophiles which facilitate the synthesis of target molecules by unconventional means.

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