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Rapid and Effective Synthesis of α-Acyloxy-α-alkynyltrimethylsilanes

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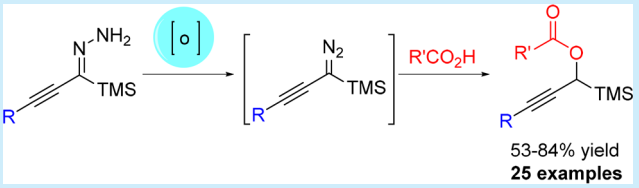
Supporting Information

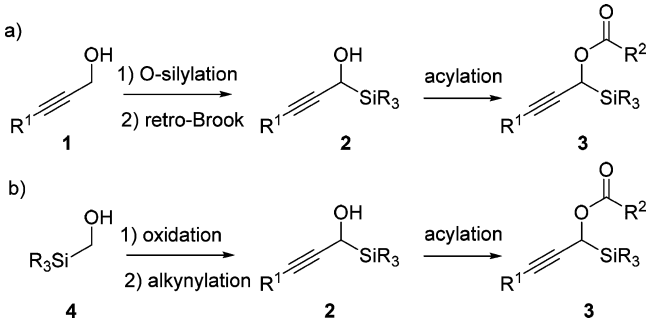
ABSTRACT: α-Alkynyl-α′-trimethylsilylhydrazones are readily oxidized into diazo compounds under simple experimental conditions. These stable diazo species can in turn react with a range of carboxylic acids via a protonation−nucleophilic substitution sequence, leading to valuable α-acyloxy-α-alkynyltrimethylsilanes. This procedure avoids the delicate preparation and manipulation of α-hydroxypropargyltrimethylsilanes.



α-Hydroxypropargylsilanes **2** and their corresponding esters **3** are interesting building blocks that have attracted much attention in organic synthesis. It has been shown that they can be used for the synthesis of new unnatural amino acids,[1] allyl-[2] or allenylsilanes,[3] as well as in total synthesis.[4] More recently, they have been described as valuable precursors of tetrasubstituted olefins via stereoselective halogen-induced 1,2-silyl migration.[5]

α-Acyloxy-α-alkynylsilanes are typically prepared starting from propargylic alcohols **1** via a silylation and reverse Brook rearrangement, followed by acylation (Scheme 1a).[6]

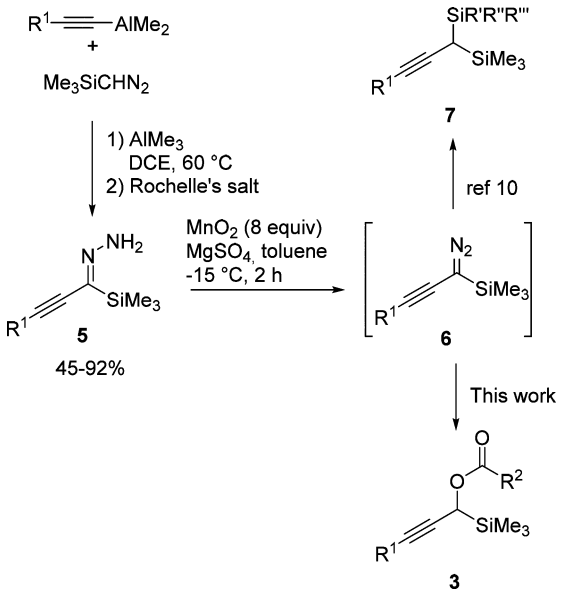
Scheme 1. Classical Syntheses of α-Acyloxy-α′-alkynylsilanes



Besides the need for low-temperature conditions, the major drawback of this synthetic route is the difficulty in handling TMS-substituted α-hydroxysilanes due to their instability against acidic conditions, as noticed by Ohfune and Sakaguchi.[6b] As a consequence, this route is generally used for the preparation of more stable silanes such as *tert*-butyldimethylsilyl derivatives. An alternative approach based on nucleophilic addition of alkynyllithium reagents to formylsilanes has also been reported (Scheme 1b).[7] This procedure requires a careful control of the temperature both for the oxidation step of (trimethylsilyl)-methanol **4** and the nucleophilic addition. Once again, the instability of TMS-substituted α-hydroxysilanes **2** has been reported.

In our ongoing work on studying the reactivity of mixed dimethylalkynylaluminum reagents,[8] we have recently reported that these organometallic species react with trimethylsilyl (TMS) diazomethane to provide propargylic hydrazones **5** (Scheme 2).[9] These hydrazones can in turn be oxidized with

Scheme 2



MnO_2 to give the corresponding diazo derivatives **6** that proved to be efficient Rh(II)-carbenoid precursors, leading to propargylic geminal bis(silanes) **7**.[10] Herein, we describe a new synthesis of **3** exploiting the reactivity of diazo derivatives toward carboxylic acids. This synthetic route provides a general access to α-acyloxy-α-propargyltrimethylsilanes without the need to prepare unstable TMS-substituted α-hydroxysilane intermediates **2**.

Optimization of the reaction conditions was first conducted starting from hydrazone **5a**. The corresponding diazo compound

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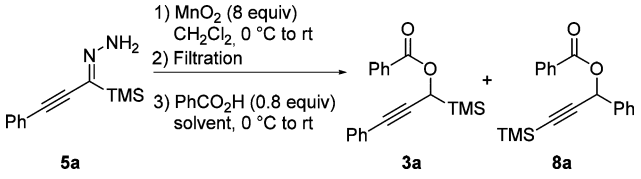
was prepared by oxidation in CH_2Cl_2 using 8 equiv of MnO_2. The resulting mixture was then filtered to remove the oxidant. A solution of benzoic acid was finally added to the filtrate (entry 1, Table 1), leading to a 87:13 regioisomeric mixture of **3a** and **8a**

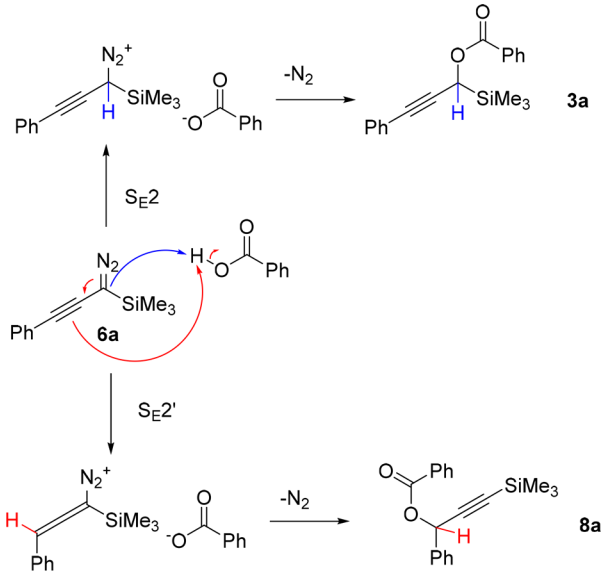
Table 1. Optimization of the Reaction with Benzoic Acid[a]



entry	solvent	time (h)	method[b]	3a/8a[c]	yield[d] (%)
1	CH_2Cl_2	3	A	87:13	74
2	CH_2Cl_2	3	B	90:10	81 (66)[e]
3[f,g]	CH_2Cl_2	3	-	85:15	33
4[g]	CH_2Cl_2	3	B	87:13	59
5	DCE	2	A	89:11	71
6	DCE	2	B	88:12	66
7	toluene	2	A	90:10	74
8	THF	1	A	88:12	37[h]
9	THF	1	B	87:13	58[h]
10	MeCN	1	A	nd	nd[i]
11	MeOH	1	A	89:11	62
12	water	20	B	83:17	54

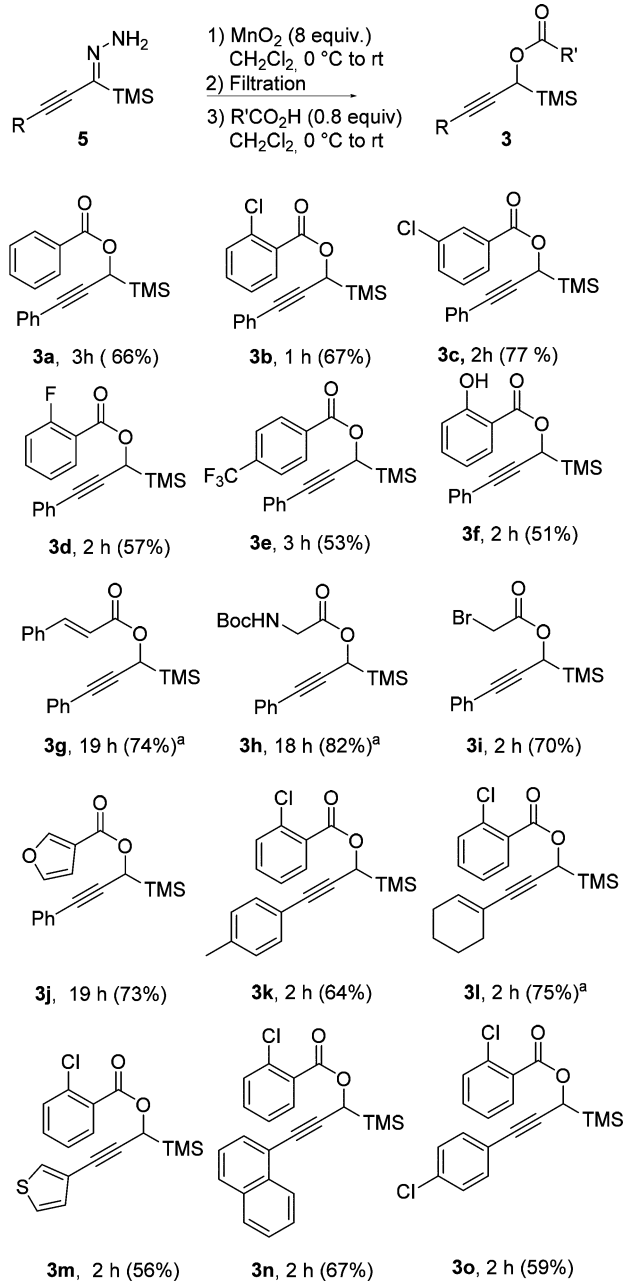
[a]Oxidation reaction was carried out with **5a** (0.5 mmol) and MnO_2 (4.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C for 1 and 2 h at rt. The resulting mixture was filtered and mixed to a solution of benzoic acid (0.4 mmol) in the desired solvent (5 mL) at 0 °C to rt. [b]Method A: a solution of the acid is added to the solution of the diazo derivative. Method B: the solution of the formed diazo derivative is added to the solution of the acid. [c]Ratio determined by ^{1}H NMR of the crude product. [d]Isolated yield of the mixture of the two regioisomers. [e]Yield of isolated **3a**, on 5.0 mmol scale. [f]Reaction conducted in one pot without removing the MnO_2. [g]Reaction conducted using 1 mmol of benzoic acid. [h]Partial desilylation was observed. [i]Only desilylated product was observed.

Scheme 3. Possible Mechanisms for the Formation of Compounds 3a and 8b



in 74% overall yield. When the order of the addition was reversed, the yield was improved (entry 2). The use of one-pot

Scheme 4. Scope of the Reaction with Carboxylic Acid and Aromatic Derivatives



[a]Isolated as an inseparable 83:17 to 90:10 mixture of regioisomers.

conditions previously described by Shaw and co-workers[11] led to a lower yield (entry 3).

In the presence of cosolvents such as DCE (entries 5 and 6) or toluene (entry 7), similar results were obtained, whereas partial or total desilylation could be observed with THF (entries 8 and 9) or acetonitrile (entry 10). Interestingly, protic solvent such as MeOH (entry 11) or even water (entry 12) were tolerated, with no competitive reaction of the transient diazonium with these nucleophiles.

In all cases, the formation of the desired ester **3a** was accompanied by about 10−17% of undesirable isomer **8a**.[12] Compound **3a** can be obtained in pure form after chromatographic purification (entry 2) in 66% overall yield.

Formation of compound **8a** can be explained by a competitive S_E2' protonation step (Scheme 3). The α/γ protonation rate is

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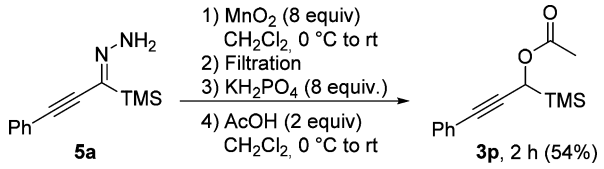
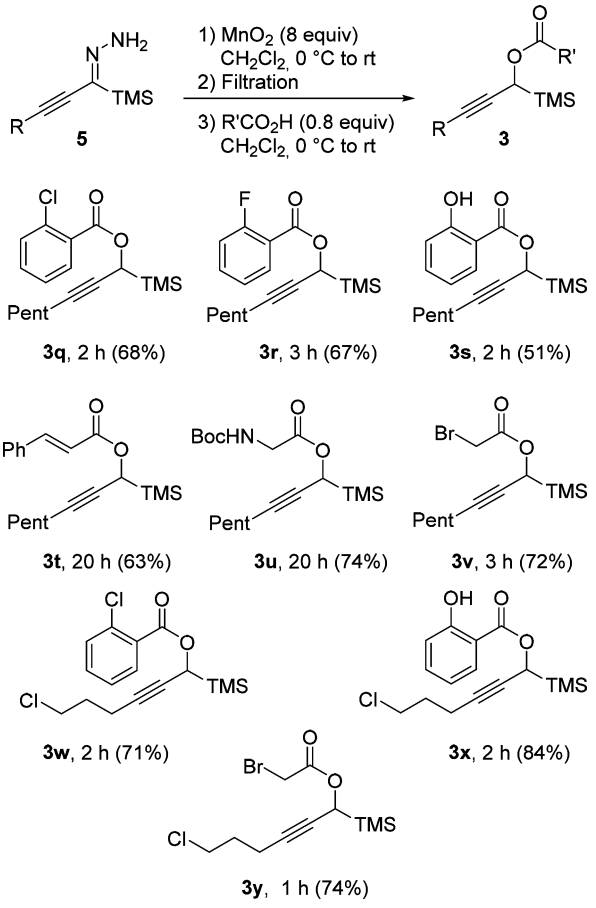
Scheme 5. Preparation of the Acetate Ester 3p



Scheme 6. Scope of the Reaction with Carboxylic Acids and Aliphatic Derivatives



expected to be mostly influenced by the substitution of the alkyne (see below).

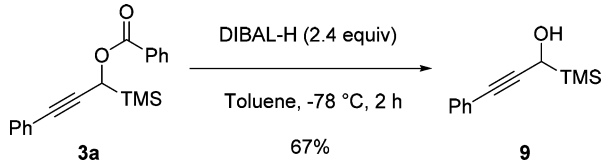
The scope of the reaction with aryl-substituted alkynyl diazo species was then investigated (Scheme 4). A wide range of α-acyloxy-α-alkynylsilanes could be obtained in 53−75% yields. In each case, the formation of roughly 10% of regioisomeric compound was observed in the crude reaction mixture. Compounds **3a−o** could be obtained in pure form after chromatographic purification, except for compounds **3g**, **3h**, and **3l**. Naphthyl-substituted derivative **3n** was isolated as a single isomer. Various aromatic or heterocyclic carboxylic acids were able to react with silylated diazoalkynes, regardless of their substitution pattern (**3a−e**). Remarkably, salicylic acid exclusively reacted with its carboxylic function (**3f**). Cinnamic acid led to the unsaturated ester **3g** in 74% yield, albeit being contaminated by 10% of its regioisomer. Purification of N-Boc-glycine adduct **3h** also proved to be difficult, despite the good overall yield of the reaction. In the case of aliphatic acids, bromoacetic acid reacted efficiently with the diazo compound to give **3i**, whereas acetic acid did not react under these conditions. Heterocyclic carboxylic acid can also be a valuable nucleophile in this transformation (**3j**). Variation of the aromatic substituent of the alkyne did not affect the reaction (**3k**, **3m**, **3n**, **3o**).

To circumvent the low reactivity of acetic acid, we added KH_2PO_4 to the diazo solution, as proposed by Shaw and co-workers.[11] This allowed isolating **3p** in acceptable yield using 2 equiv of acetic acid (Scheme 5).

The reaction was then conducted using hydrazones bearing aliphatic substituents. To our delight, the reaction proved to be fully regioselective, delivering the propargylic silylated esters as single isomers (in the crude reaction mixtures). Pure esters were obtained from 51 to 84% yields using this procedure (Scheme 6).

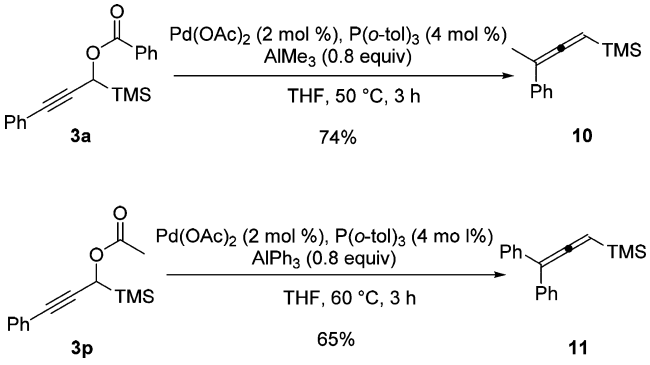
Because α-silylated propargyl alcohols are also an interesting class of compounds, we investigated the way to obtain them starting from esters. After the reduction in the presence of DIBAL-H at −78 °C, the resulting hemiacetal was hydrolyzed to afford the desired compound **9**. These conditions were compatible with the presence of a triple bond (Scheme 7).

Scheme 7. Preparation of α-Hydroxypropargyltrimethylsilane 9



Finally, compound **3a** was engaged in palladium-catalyzed allene formation with trimethylaluminum using the conditions reported by Li and co-workers.[13] The reaction afforded **10** in 74% yield. Under similar conditions, no reaction could be observed in the presence of $AlPh_3$. However, the use of a more reactive ester such as **3p** and higher temperatures enabled us to get the desired allenylsilane **11** in 65% yield (Scheme 8).

Scheme 8. Allene Synthesis



In conclusion, we have shown that trimethylsilylalkynylhydrazones are valuable precursors for the general synthesis of α-acyloxy-α-propargyltrimethylsilane using the reactivity of diazo compounds. This new route avoids the delicate preparation of α-hydroxypropargyltrimethylsilanes and delivers in a simple manner a full range of propargyl esters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02165.

General experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Compound **8a** was prepared following a different route to confirm its structure. For further details, see Supporting Information.

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