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# A Convenient Synthesis of Masked β-Ketoaldehydes by the Controlled Addition of Nucleophiles to (Trimethylsilyl)ethynyl Ketones

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# A CONVENIENT SYNTHESIS OF MASKED β-KETOALDEHYDES BY THE CONTROLLED ADDITION OF NUCLEOPHILES TO (TRIMETHYLSILYL)ETHYNYL KETONES

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**ABSTRACT :** The controlled addition of nucleophiles to (trimethylsilyl)ethynyl ketones provides a facile route to β–ketoacetals, β–alkoxy-α,β–unsaturated ketones or vinylogous amides depending on the choice of reaction conditions.

β–Ketoaldehydes are important intermediates that are widely used in heterocyclic synthesis.[1] Masked equivalents such as β–ketoacetals,[2] β–alkoxy-α,β–unsaturated ketones[3] or vinylogous amides[4] are often preferred due to greater ease of handling and the scope they provide for regio-control of reaction.

A well established route to β-ketoacetals is the addition of alcohols to terminal ethynyl ketones, a procedure that invariably yields the acetal without isolation of the mono-addition product.[5] A limitation on this approach, however, is the difficulty associated with the preparation and handling of terminal ethynyl ketones.[6a, 7]

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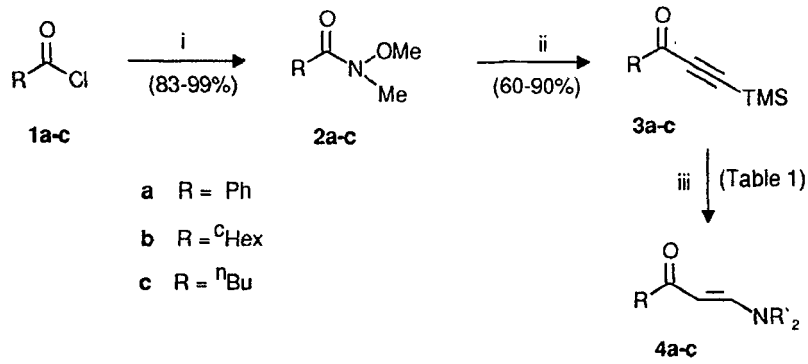
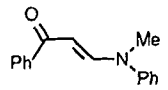
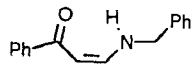
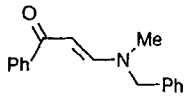
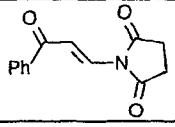
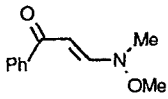
(Trimethylsilyl)ethynyl ketones are more stable than the parent ynones, but a review of the literature revealed that their reactions with nucleophiles have received scant attention. A report by Wilbur and Wilbur[8] appeared during the course of our own studies claiming the first example of a one-pot synthesis of vinylogous amides involving the direct reaction of primary or secondary aryl amines with (trimethylsilyl)ethynyl ketones. These additions were carried out using one equivalent of base in solvents such as benzene, DMF, *m*-cresol or N,N-dimethylacetamide at 90-110°C and it was claimed that the presence of methanol or ethanol was essential for desilylation and amine addition. There are, in fact, earlier reports of this reaction in the Russian literature with the addition of one to two equivalents of simple alkyl amines to 4-trimethylsilylbut-3-yne-2-one, or to 3-trimethylsilylpropynal, reported to give vinylogous amides in moderate yields.[9,10] The reactions were carried out at room temperature either in the absence of solvent or in diethyl ether or hexane and although the authors[9] postulated a mechanism that required an equivalent of base to promote desilylation the actual amounts used were not consistent with this theory.




**Scheme 1** *Reagents and conditions:* **i**, NHMeOMe.HCl, pyridine; **ii**, LiC≡CTMS; **iii**, 2eq. $NHR`_2$ ,THF

**Table 1** Addition of Nitrogen Nucleophiles to **3a**

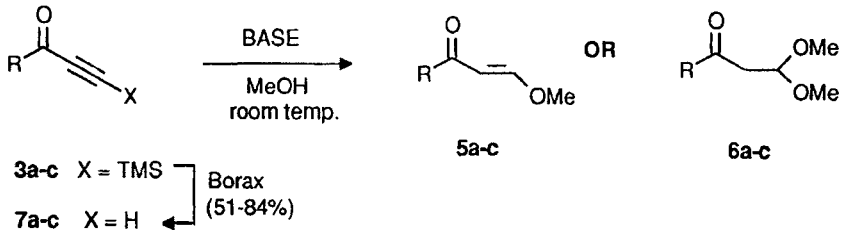
| Nucleophile | Structure of product[a] | Yield[b] | Conditions |
|---|---|---|---|
| N-methylaniline |  | 40% | 17 hrs reflux |
| Benzylamine* |  | 96% | 4 days room temp. |
| N-methyl benzylamine |  | 95% | 2 hrs reflux |
| Succinimide |  | 90% | 2 hrs reflux (KO$^t$Bu added) |
| N,O-dimethyl hydroxylamine |  | 37% | 5 hrs reflux |

[a]The stereochemistry of the adducts was determined by $^1H$ nmr. With the exception of the entry marked with an asterix, which was *cis* presumably due to intramolecular hydrogen bonding, all the adducts were exclusively *trans*.
[b]Reactions were carried out with 2eq. of the nucleophile in THF. Products were isolated by evaporation of the reaction mixture followed by aqueous work-up and chromatography on silica.

These apparent discrepancies led us to investigate this reaction further. We obtained moderate to high yields of vinylogous amides **4** by simply treating the (trimethylsilyl)ethynyl ketones **3** with two equivalents of a variety of amines in dichloromethane or THF (Scheme 1). The versatility of this approach was established by its successful extension to a variety of nitrogen nucleophiles and representative examples of these additions to 1-phenyl-3-trimethylsilylprop-2-yne-1-one **3a** are shown in Table 1.

The (trimethylsilyl)ethynyl ketones **3** were readily prepared[6] by the addition of lithium (trimethylsilyl)acetylide to N-methyl-N-methoxyamides **2**, which are themselves derived[11] from the corresponding acid chlorides **1** (Scheme 1).

It has also been reported that the addition of alcohols to (trimethylsilyl)ethynyl ketones using either triethylamine or sodium alkoxide as base yields β–ketoacetals.[8,9,12] However, attempts by Wilbur and Wilbur to control the addition by the use of one equivalent of methanol in the presence of triethylamine resulted in polymerisation.[8] We have discovered that, by judicious choice of base and reaction conditions, it is possible to isolate either the β-alkoxy-α,β-unsaturated ketones **5** or the β–ketoacetals **6** in good yields (Scheme 2). Interestingly, generation of the β-alkoxy-α,β-unsaturated ketones **5** using low concentrations of methanol in THF was sensitive to the nature of the base. Under each set of conditions used, nucleophilic bases such as quinuclidine or DABCO afforded better yields of the monoadduct **5a** than triethylamine, which required longer reaction times and gave significant amounts of side products. The hindered non-nucleophilic Hunigs base (N-ethyldiisopropylamine) produced no reaction or a slow desilylation followed by decomposition. In contrast, with methanol as solvent we obtained good yields of the acetal **6a** irrespective of the base used (Table2).




**Scheme 2**

**Table 2** Products from Addition of Methanol to **3a** under Various Conditions[a]

| BASE | 2-3 eq. MeOH in THF, 0.2 eq. base | 8 eq. MeOH in THF, 2 eq. base | MeOH solvent 2 eq. base, overnight |
|---|---|---|---|
| Quinuclidine | **5a** (67%) | **5a** (96%) | **6a** (83%) |
| Triethylamine | **5a** (22%) | **5a** (74%) | **6a** (79%) |
| Hunigs base ($NEt^iPr_2$) | No reaction | Slow desilylation | **6a** (99%) |

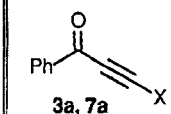
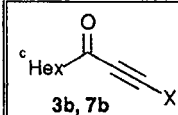
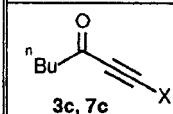
[a]All reactions were carried out at room temperature and monitored by tlc, mono-additions were generally complete within one hour, other reactions were left overnight. The products were isolated by evaporation of the reaction mixture followed by aqueous work-up and distillation under reduced pressure.



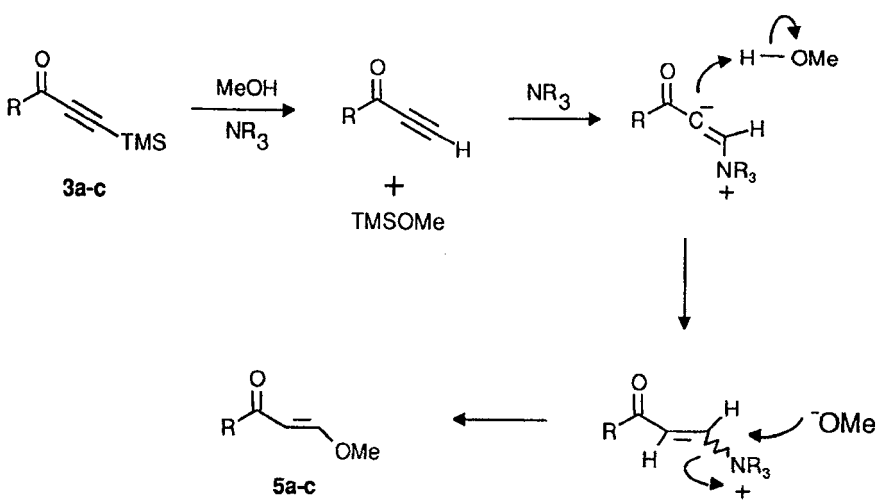
This reaction was extended to a range of model (trimethylsilyl)ethynyl ketones **3a-c** and to the corresponding unsubstituted ethynyl ketones **7a-c**, which were readily obtained from **3a-c** by treatment with aqueous borax in methanol.[13] This is the first reported example of a single Michael addition of methanol to a terminal ethynyl ketone, and the optimum general conditions for the additions are shown in Table 3.

The observations that nucleophilic bases give best results for the controlled additions and that (trimethylsilyl)ethynyl ketones **3** and unsubstituted ethynyl ketones **7** react in a similar manner have led us to propose the mechanism shown in Scheme 3. It seems likely that desilylation is the initial step, followed by reversible nucleophilic addition of the amine facilitating methanol addition.[14] However, when methanol is used as solvent with non-nucleophilic bases, such as Hunigs base, it is more plausible that the acetal **6** is formed by base-assisted addition of methanol.

**Table 3** Products from Addition of Methanol to Ethynyl ketones Under Optimum Conditions[a]

| SUBSTRATE | X = TMS | | X = H |
|---|---|---|---|
| | 2eq. DABCO 30eq. MeOH, 1hr. | 2eq. Hunigs MeOH sol., overnight | 2eq. DABCO 10eq. MeOH, 10 min. |
|  **3a, 7a** | **5a** (89%) | **6a** (99%) | **5a** (75%) |
|  **3b, 7b** | **5b** (68%) | **6b** (79%) | **5b** (68%) |
|  **3c, 7c** | **5c** (82%) | **6c** (83%) | **5c** (67%) |

[a]All reactions were carried out at room temperature. The products were isolated by evaporation of the reaction mixture followed by aqueous work-up and distillation under reduced pressure.




**Scheme 3** Proposed Mechanism for Mono-addition of Methanol to **3a-c**

In conclusion (trimethylsilyl)ethynyl ketones are readily available, versatile intermediates, which can be transformed easily into β-alkoxy-α,β–unsaturated ketones, β-ketoacetals or vinylogous amides depending on the choice of reaction conditions. The nucleophilic addition of methanol to terminal ethynyl ketones can also be controlled to yield the mono-adduct.



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