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Use of *N*-Allylidene-1,1-diphenylethanamine as a Latent Acrolein Synthon in the Double Nucleophilic Addition Reaction of Ketene Silyl (Thio)acetals and Allylborolanes

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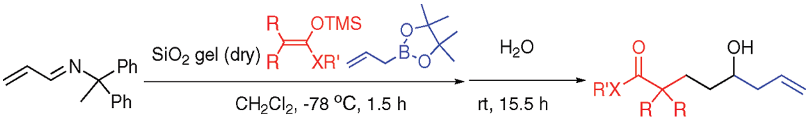
ABSTRACT



In the presence of silica gel and water, a mixture of ketene silyl acetals and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane underwent 1,4- and subsequently 1,2-addition with *N*-allylidene-1,1-diphenylethanamine to give *δ*-hydroxyesters in good yields, where the allylideneamine was successfully used as an acrolein equivalent.

Although acrolein has received considerable attention as a useful unit for the synthesis of a variety of novel and functional materials as well as biologically important molecules, it is not always easy to use this particular compound as a conjugate addition acceptor of carbon nucleophiles.[1] This is due in part to the high reactivity of the carbonyl and olefin functional groups to induce 1,2-addition and/or polymerization. During an investigation into double nucleophilic addition to α,*β*-unsaturated imines,[2] two practical methods were developed for the preparation of *N*-allylideneamines **1a,b**, which in turn were used as efficient substrates for 1,4- and 1,2-double nucleophilic additions.[2a] Several years ago, we also found that the aldimines **2** and **3** derived from enals and alkynals acted as latent unsaturated aldehydes to promote the 1,4-addition of thiolates or azide and 1,2-addition of tetraallyltin to the parent unsaturated aldehydes under the influence of $SnCl_4{\cdot}5H_2O$, where in situ hydrolysis of the imino moieties to the parent aldehydes was crucial for the success of the double addition.[3] However, in contrast to these results using heteroatom nucleophiles for the 1,4-

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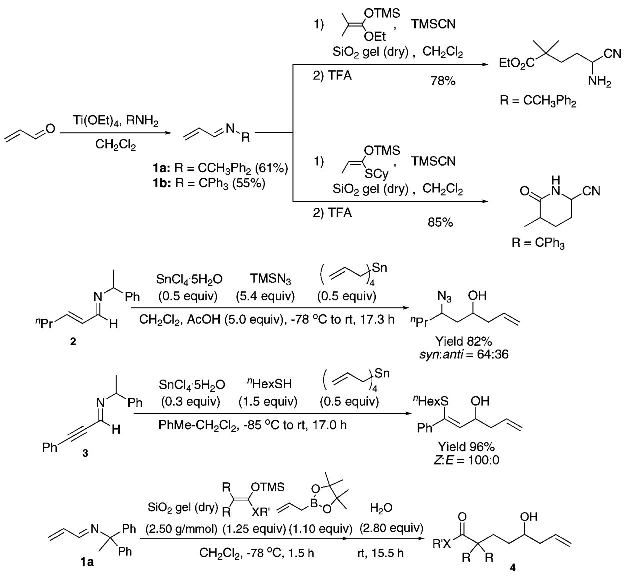
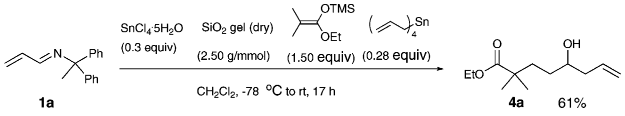
addition reaction, difficulties were always encountered for the use of carbon nucleophiles in the initial conjugate addition reaction. The accessibility of the allylideneamine recently developed,[2a,c] coupled with the need to use acrolein as conjugate addition acceptor, has prompted us to report an efficient method for the use of *N*-allylidene-1,1-diphenylethanamine **1a** as a latent acrolein (Scheme 1).

Scheme 1. 1,4- and 1,2- Double Addition Reactions



The initial examination was carried out to check the use of the allylideneamine **1a** to act as a latent acrolein synthon to accept a carbon nucleophile in the initial 1,4-addition under similar conditions previously reported.[3]

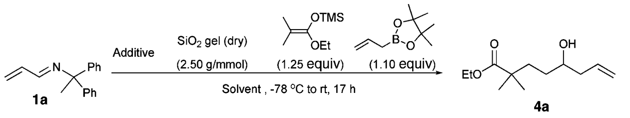
Scheme 2. Double Addition Reaction to the Latent Acrolein



As shown, the 1,4-addition of the ketene silyl acetal actually proceeded followed by hydrolysis of the imino moiety and the subsequent 1,2-allylation to give the adduct **4a** in 61% yield. However, the recent need to use more environmentally benign reagents induced us to investigate other conditions, e.g., without the use of $SnCl_4{\cdot}5H_2O$ and tetraallylstannane. Table 1 summarizes the results.

As can be seen from Table 1, regarding the solvent, both dichloromethane and toluene gave comparable results (entries 1−4). Among the metal salt hydrates, $SnCl_4{\cdot}5H_2O$ and $CeCl_3{\cdot}7H_2O$ promoted the desired double addition to give the adduct **4a** in moderate yields (entries 4 and 8). In the absence of added water the reaction gave the adduct in poor yield, while addition of water increased the formation of the double addition product in moderate yields (entries 10 and 11). The presence of a limited amount of water absorbed in molecular sieves 4Å as previously reported[2j] increased the product yield (entry 12). The best result was obtained when the reaction was conducted by initially mixing all of the reagents in dichloromethane at −78 °C for 1.5 h and then adding water (2.8 equiv) at −78 °C followed by allowing the whole mixture to stand at room temperature for 15.5 h to give the desired adduct in 81% yield (entry 14). Under the best conditions a variety of ketene silyl acetals or ketene silyl thioacetals and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[4] underwent the 1,4- and 1,2-double addition reaction to give the adduct in good yields. Table 2 summarizes the results.

Table 1. Double Nucleophilic Addition to the Latent Acrolein under Various Conditions[a]



entry	solvent	additive (equiv)	**4a** yield (%)
1	CH_2Cl_2	$SnCl_4{\cdot}5H_2O$ (0.24)	67
2	CH_2Cl_2	$SnCl_4{\cdot}5H_2O$ (0.24)[b]	52
3	PhMe	$SnCl_4{\cdot}5H_2O$ (0.24)[c]	79
4	PhMe	$SnCl_4{\cdot}5H_2O$ (0.20)	68
5	PhMe	$Cu(OAc)_2{\cdot}H_2O$ (1.00)[d]	41
6	PhMe	$Na_2SO_4{\cdot}10H_2O$ (1.00)	58
7	PhMe	$Al_2Cl_3{\cdot}6H_2O$ (0.20)	54
8	PhMe	$CeCl_3{\cdot}7H_2O$ (0.14)	65
9	PhMe	$SmCl_3{\cdot}6H_2O$ (0.20)	53
10	PhMe	none	38
11	PhMe	H_2O (2.80)	51
12	PhMe	MS 4A/H_2O (2.80)	69
13	PhMe	H_2O (2.80)[e]	73
14	CH_2Cl_2	H_2O (2.80)[e]	81

[a] The reaction was carried out according to the typical procedure. [b] Ketene silyl acetal (1.0 equiv) was used. [c] Ketene silyl acetal (1.5 equiv) was used. [d] The reaction was carried out for 38 h. [e] Water was added after 1.5 h of the initial reaction.

As shown in Table 2, among the tetrasubstituted ketene silyl acetals, ethoxy and benzyloxy derivatives provided good yields of the adducts (entries 1−5 and 12−14), whereas the cyclohexylthio derivative gave better results regarding the tri- and disubstitued analogues (entries 6−11). When crotylboronates **3c,d** were used as the second nucleophile, the reaction proceeded with good to excellent diastereoselectivities with respect to the C5−C6 carbons, where the (*E*)-derivative **3c** gave *anti*-adducts and (*Z*)-isomer **3d** effected the formation of the *syn*-isomers (entries 13, 14, 16, 17, 19, and 20). However, the diastereoselectivities regarding the C2−C5 carbons were not high.

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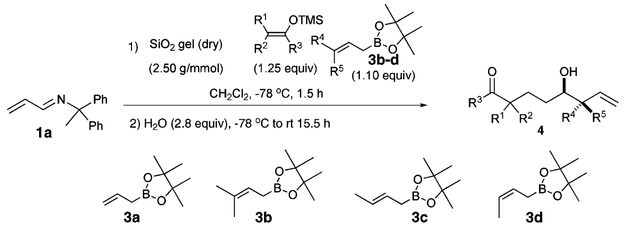
(5) For determination of the relative stereochemistry, see: Yamamoto, Y.; Asao, N. *Chem. Rev* **1993**, *93*, 2207, and references therein.

Table 2. Double Nucleophilic Addition to the Latent Acrolein with Various Nucleophiles[a]



entry	R^1	R^2	R^3	R^4	R^5	**4** yield (%) (*anti*:*syn*)[b]
1	Me	Me	OEt	H	H	81
2	Me	Me	OBn	H	H	72[c]
3	Me	Me	OPh	H	H	0
4	Me	Me	SEt	H	H	17
5	Me	Me	SCy	H	H	8
6	H	Me	OCy	H	H	8[d]
7	H	Me	SCy	H	H	73[e,f]
8	H	Me	SPh	H	H	13[d]
9	H	H	OCy	H	H	0
10	H	H	SCy	H	H	40
11	H	H	SCy	H	H	54[g]
12	Me	Me	OEt	Me	Me	75
13	Me	Me	OEt	Me	H	79 (94:6)
14	Me	Me	OEt	H	Me	70 (<1:>99)
15	H	Me	SCy	Me	Me	58[e,f]
16	H	Me	SCy	Me	H	62[e] (>99:<1)
17	H	Me	SCy	H	Me	63[e] (<1:>99)
18	H	H	SCy	Me	Me	52[g]
19	H	H	SCy	Me	H	67[g] (>99:<1)
20	H	H	SCy	H	Me	54[g] (<1:>99)

[a] The reaction was carried out according to the typical procedure. [b] Ratio regarding C5/C6 diastereomers.[5] [c] Ketene silyl acetal (5.0 equiv) was used. [d] Diastereomer ratio was not determined. [e] Ketene silyl acetal (*E*/*Z* = 55/45) was used. [f] 1:1 ratio of diastereomers was obtained. [g] Ketene silyl acetal (2.0 equiv) was used.

Although more experimental results are needed to propose a plausible reaction mechanism, facile hydrolysis of an intermediary 1,4-addition product **A** or an iminium salt **B**[6] to the aldehyde **C**[7] is responsible for the success of the present tandem addition (Figure 1).

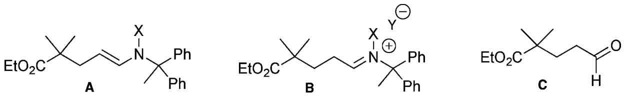
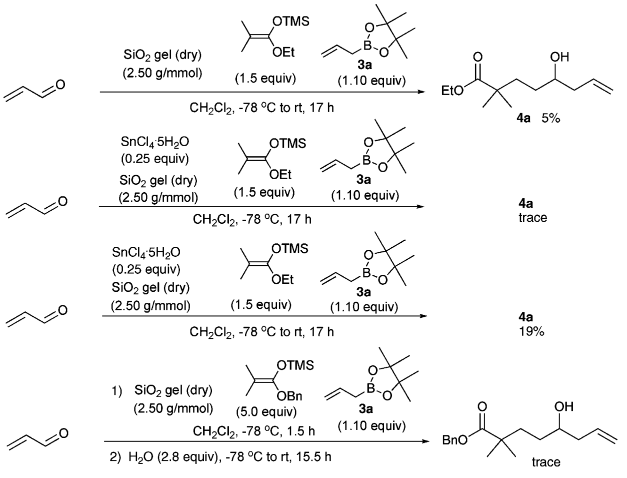


Figure 1. Possible intermediates for hydrolysis to aldehyde.

Control experiments were carried out using acrolein under essentially the same conditions used in the present study to give the 1,4- and 1,2-double addition products in only low yields, indicating that the present procedure offers a convenient acrolein source for the double addition reactions (Scheme 3).

Scheme 3. Control Experiments Using Acrolein



In conclusion, we have found that the use of *N*-allylideneamine as a latent acrolein can be successfully carried out in the presence of silica gel and a limited amount of water to effect the 1,4- and 1,2- double nucleophilic addition of two different kinds of nucleophiles. Since the *N*-allylideneamine used for the present study is readily prepared by the previously published method[2a,c] and the double addition reaction is readily carried out, the present method offers a convenient and useful procedure for the use of a conjunctive C3 unit.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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