Catalytic Alkylation Reactions of Weakly Acidic Carbonyl and Related Compounds Using Alkenes as Electrophiles

Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-COM-04-2018-000941.R1
Article Type:	Paper
Date Submitted by the Author:	06-Jun-2018

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Journal Name

ARTICLE

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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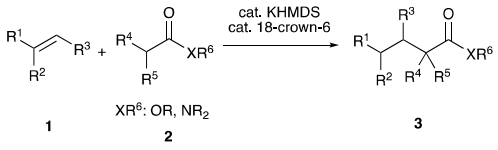
Catalytic alkylation reactions of weakly acidic carbonyl and related pronucleophiles such as amides, esters, and sulfonamides with substituted alkenes are reported. In the presence of a strong Brønsted base catalyst system, potassium hexamethyldisilazide and 18-crown-6 ether, the desired reactions proceeded in high yields at ambient temperature with wide substrate scope. These are atom-economical catalytic alkylation reactions of carbonyl and related compounds.

Introduction

In synthetic organic chemistry, carbon–carbon bond formation at an α-position of a carbonyl compound is a fundamental and important method for constructing basic carbon frameworks of target molecules. One of the most common methods for the introduction of a carbon unit at the α-position is an alkylation reaction of a metal enolate or an enamide with an alkane bearing a leaving group such as alkyl halides, alkyl tosylates, etc.[1] Although this is a powerful and reliable method for alkylation at the α-position of carbonyl compounds, at least one equivalent of base is required during the reaction, and undesired co-products such as metal salts are formed; hence, the atom economy of the reaction is always low.[2] On the other hand, a catalytic addition reaction of a carbonyl compound with an alkene is a simple and atom-economical reaction as alkylation of a carbonyl compound because only proton transfer occurs during the reaction. Although catalytic addition reactions of carbonyl compounds with alkenes bearing strong electron-withdrawing groups such as α,β-unsaturated carbonyl and related compounds have been well investigated as 1,4-addition reactions,[3] catalytic addition reactions with alkenes without strong electron-withdrawing groups (less activated alkenes) have been limited. Relatively acidic carbonyl compounds such as 1,3-diketones, β-keto esters, aldehydes, ketones, etc. have been employed,[4–6] but weakly acidic carbonyl compounds such as amides and esters bearing no activating functionality at the α-positions have not been well investigated. Pines *et al.* reported KO^{t}Bu-catalyzed addition reactions of lactams with less activated alkenes in a highly polar solvent, DMSO; however, relatively high catalyst loadings (20–30 mol%) are required, and the employed substrates are limited to only 5- and 6-membered lactams.[7] Obviously, more general methods for catalytic addition reactions of weakly acidic carbonyl compounds with less activated alkenes, such as atom-economical alkylation reactions, are required.[8]

Our recent focus was on strong Brønsted base-catalyzed addition reactions of weakly acidic carbon pronucleophiles (pK_a >30 in DMSO). We have reported catalytic Mannich-type reactions of simple esters and 1,4-addition reactions of simple amides, esters, alkylnitriles, etc. in less polar solvents by designing strongly basic reaction intermediates, product bases.[9] We have also developed catalytic addition reactions of alkylazaarenes with vinylsilanes.[10] In these reactions, a formed carbanion intermediate stabilized by a silicon atom functioned as a strong base in the catalytic cycle to promote the reaction. Based on this strategy, it should be possible to carry out catalytic addition reactions of weakly acidic carbonyl pronucleophiles with such less activated alkenes as alkylation reactions. Here, we report the development of this reaction using a strong Brønsted base as a catalyst under mild reaction conditions (Scheme 1).

Scheme 1 Catalytic alkylation reactions of weakly acidic carbonyl compounds with substituted alkenes



Results and Discussion

We initially investigated triphenylvinylsilane **1a** as an electrophile. The reaction of *N*,*N*-dimethyl propionamide **2a** as a weakly acidic carbonyl pronucleophile with **1a** was conducted in THF at 0 °C in the presence of 10 mol% of potassium hexamethyldisilazide (KHMDS) and 11 mol% of 18-crown-6 ether. It was pleasing to find that the desired α-alkylated product was obtained in 86% yield (Table 1, entry 1).

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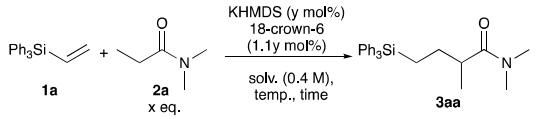
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

We further investigated the use of less polar solvents and found that ether solvents were effective (entries 2–7). Among them, cyclopentyl methyl ether (CPME) was found to be the best, and the desired reaction proceeded smoothly at 0 °C to afford the desired product **3aa** in excellent yield (entry 6). Furthermore, we examined reduction of the catalyst loading and the amount of the pronucleophile. It was found that 5 mol% of KHMDS and 1.2 equivalents of **2a** were enough to promote this reaction efficiently (entry 9). The reaction using 2.5 mol% of the catalyst also proceeded well to afford the product in high yield (entry 10).

Table 1 Optimization of the reaction conditions[a]

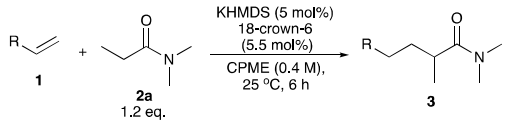


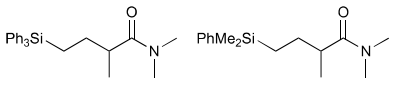
entry	x	y	solvent	temp. (°C)	time (h)	yield (%)
1	2	10	THF	0	18	86
2	2	10	THF	0	6	72
3	2	10	toluene	0	6	72
4	2	10	PhEt	0	6	45
5	2	10	Et_2O	0	6	90
6	2	10	CPME	0	6	quant.
7	2	10	TBME[b]	0	6	86
8	1.2	5	CPME	0	6	81
9	1.2	5	CPME	25	6	93
10	1.2	2.5	CPME	25	6	89

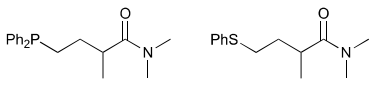
[a] The reaction of **1a** (0.400 mmol) with **2a** (0.800 or 0.480 mmol) was conducted in the presence of KHMDS and 18-crown-6 ether in the solvent shown in the table. Yields are isolated yields. [b] *t*-Butyl methyl ether.

We then examined other alkenes as electrophiles. Firstly heteroatom-substituted alkenes were employed (Table 2). The reaction of **2a** with dimethylphenylvinylsilane (**1b**) proceeded to afford the product **3ba**, but a slightly lower reactivity was observed compared to the reaction with **1a**. Alkenes bearing other heteroatoms were also available. Diphenylvinylphosphine **1c** reacted with **2a** to afford the product **3ca** in high yield. Phenyl vinyl sulfide **1d** also worked, and the desired adduct **3da** was obtained.

Table 2 Catalytic addition reactions of heteroatom-substituted alkenes with *N*,*N*-dimethyl propionamide (**2a**) [a]



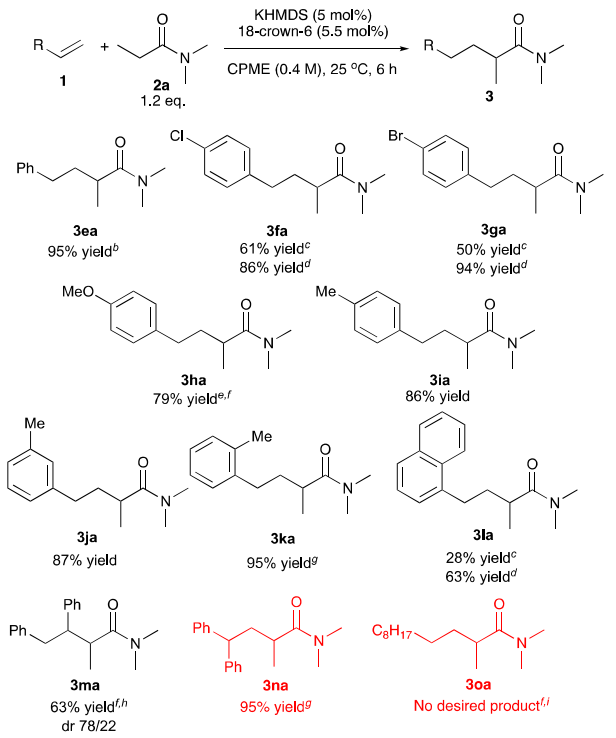




[a] The reaction of **1** (0.400 mmol) with **2a** (0.480 mmol) was conducted in the presence of KHMDS (0.020 mmol, 5.0 mol%) and 18-crown-6 ether (0.022 mmol, 5.5 mol%) in CPME at 25 °C for 6 h unless otherwise noted. Yields are isolated yields. [b] 10 mol% of the KHMDS and 11 mol% of the 18-crown-6 ether and 2 eq. of pronucleophile were used.

Next, we conducted the reactions of styrene and its derivatives which were expected to be good electrophiles because the aromatic groups could stabilize the formed carbanion, while an undesired side reaction such as an anionic polymerization to form polystyrene derivatives was a negative concern (Table 3). It was found that the catalytic addition reaction of **2a** with styrene **1e** proceeded smoothly at 0 °C to afford the desired product **3ea** in high yield. The lower reaction temperature was effective, and the product was obtained in high yield. Other substituted styrenes were useful. Styrenes bearing electron-withdrawing groups (**1f** and **1g**) gave low yields of the products (**3fa** and **3ga**), even at low temperature, because of the undesired anionic polymerization. However, it was found that addition of a proton source, hexamethydisilazane (H-HMDS), was effective in preventing the polymerization, and yields were improved even at a higher reaction temperature. On the other hand, styrenes with electron-donating groups (**1h**–**1k**) also worked well. The desired products (**3ha**–**3ka**) were obtained in high yields. 1-Vinylnaphthalene (**1l**) was also employed; however, the yield of **3la** was low because of the anionic polymerization. In this case, again, the addition of H-HMDS was effective. The reaction with trans-stilbene (**1m**) proceeded to afford the product **3ma** in good yield and diastereoselectivity. 1,1-Diphenylethylene (**1n**)

Table 3 Catalytic addition reactions of substituted alkenes with *N*,*N*-dimethyl propionamide (**2a**) [a]

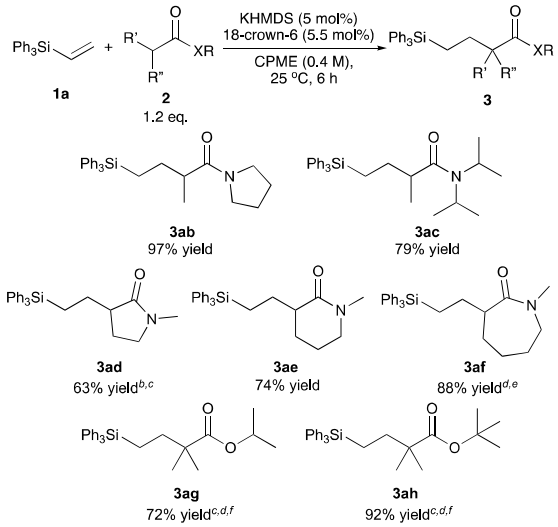


[a] The reaction of **1** (0.400 mmol) with **2a** (0.480 mmol) was conducted in the presence of KHMDS (0.020 mmol, 5.0 mol%) and 18-crown-6 ether (0.022 mmol, 5.5 mol%) in CPME at 25 °C for 6 h unless otherwise noted. Yields are isolated yields. [b] The reaction temperature was 0 °C. [c] The reaction temperature was −40 °C. [d] H-HMDS (20 mol%) was used. [e] The reaction was conducted for 72 h. [f] 10 mol% of the KHMDS and 11 mol% of the 18-crown-6 ether were used. [g] The reaction was conducted for 9 h. [h] The reaction was conducted for 24 h. [i] 2 eq. of **2a** were used. The reaction temperature was 50 °C.

was also found to be a good electrophile, and the desired product **3na** was obtained in high yield. Alkyl-substituted alkene **1o** was employed; however, no desired product was obtained due to low stabilizing effect of the alkyl substituent. It was determined that catalytic addition reactions of **2a** with various kinds of less activated alkenes proceeded smoothly in the presence of the strong base catalyst.

We then employed other weakly acidic carbonyl pronucleophiles, amides and esters, in the reactions of **1a** (Table 4). The less hindered propionamide **2b** bearing a pyrrolidine group reacted smoothly to afford the product **3ab** in high yield, but the hindered propionamide **2c** afforded **3ac** in a slightly lower yield. *N*-Methyllactams **2d**, **2e**, and **2f** were also successfully employed; *N*-methyl-2-pyrrolidone (**2d**) and *N*-methyl-2-piperidone (**2e**) reacted with **1a** to afford the desired adducts **3ad** and **3ae** in moderate to good yields. In both reactions, undesired by-products, bis(2-triphenylsilylethyl)lactams, formed during the reactions to reduce the yields. *N*-Methylcaprolactam **2f** also reacted to afford the product **3af**. It is noted that **2f** did not react under the reaction conditions given in a previous report of Pines *et al*. Besides the amide derivatives, the ester derivatives, isobutyrates, also reacted with **1a** to afford the adducts **3ag** and **3ah** in good to high yields.

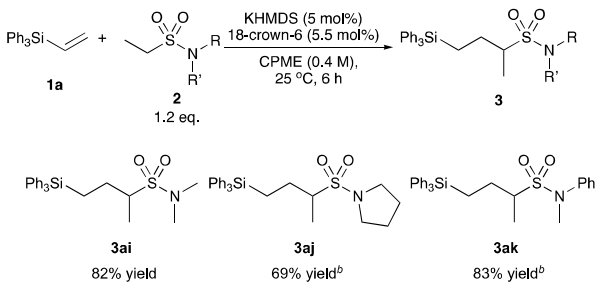
Table 4 Catalytic addition reactions of triphenylvinylsilane (**1a**) with weakly acidic amides and esters[a]



[a] The reaction of **1** (0.400 mmol) with **2** (0.480 mmol) was conducted in the presence of KHMDS (0.020 mmol, 5.0 mol%) and 18-crown-6 ether (0.022 mmol, 5.5 mol%) in CPME at 25 °C for 6 h unless otherwise noted. Yields are isolated yields. [b] The reaction temperature was −20 °C, and 4 eq. of the pronucleophile were used. [c] The reaction was conducted for 18 h. [d] 10 mol% of the KHMDS and 11 mol% of the 18-crown-6 ether were used. [e] The reaction was conducted for 24 h, and the reaction temperature was 50 °C. [f] The reaction temperature was 0 °C, and the reaction was conducted in THF.

The related weakly acidic pronucleophiles, alkanesulfonamides, were found to be applicable for the current reaction (Table 5). The desired adducts **3ai–3ak** were obtained in good to high yields. It was found that several kinds of weakly acidic carbonyl and related pronucleophiles were also applicable for this reaction.

Table 5 Catalytic addition reactions of triphenylvinylsilane (**1a**) with alkanesulfonamides[a]

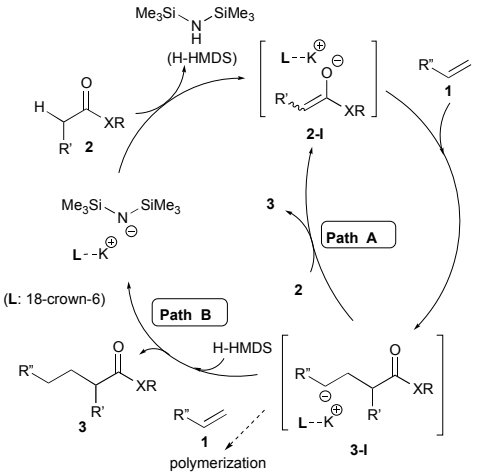


[a] The reaction of **1a** (0.400 mmol) with **2** (0.480 mmol) was conducted in the presence of KHMDS (0.020 mmol, 5.0 mol%) and 18-crown-6 ether (0.022 mmol, 5.5 mol%) in CPME at 25 °C for 6 h unless otherwise noted. Yields are isolated yields. [b]The reaction was conducted for 18 h.

A plausible catalytic cycle for the addition reactions is shown in Figure 1. A KHMDS–18-crown-6 complex deprotonates weakly acidic pronucleophile **2** to form a

nucleophilic anion specie **2-I** such as an enolate, and it attacks C=C double bond to generate a strongly basic reaction intermediate **3-I** (product base). After the formation of **3-I**, two reaction pathways can be considered. One is direct deprotonation of the next pronucleophile **2** by the reaction intermediate to regenerate the nucleophilic anion specie **2-I** (Path A). The second path involves regeneration of the KHMDS–18-crown-6 species through deprotonation of H-HMDS by the intermediate **3-I** (Path B). It is difficult to clarify the actual catalytic pathway in this kind of reaction, but in the reactions with styrene derivatives with the propionamide **2a**, the undesired polymerization was suppressed by using additional H-HMDS, which indicates that the Path B was the major pathway in the reactions.

Figure 1 Plausible catalytic cycle



Conclusions

We have developed catalytic alkylation reactions of weakly acidic carbonyl and related pronucleophiles such as amides, esters, and sulfonamides with substituted alkenes under mild reaction conditions in the presence of a strong Brønsted base system KHMDS and 18-crown-6 ether as a catalyst. The reactions proceeded smoothly to afford the desired products in high yields at ambient temperature, and wide substrate scope was obtained. It is noteworthy that atom-economical alkylation reactions of carbonyl compounds have been attained. Further investigations into enantioselective reactions are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgement

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS) and Ministry of Education, Culture, Sports, Science and Technology (MEXT), and the Japan Science and Technology Agency (JST). H.S. thanks the MERIT program, The University of Tokyo, and JSPS Research Fellowships for Young Scientists for financial support.

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