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Highly *Z*-selective synthesis of α,β-unsaturated amides with the Peterson reaction between α-silylamides and aldehydes†

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The Peterson reaction of triphenylsilylacetamide $Ph_3SiCH_2CONBn_2$ with aromatic aldehydes and certain aliphatic aldehydes proceeded to give the corresponding *α,β*-unsaturated amide with high *Z* selectivity (up to $Z{:}E$ = $>97{:}<3$).

Geometry-defined olefins serve as good building blocks in organic synthesis. Of particular utility are olefins bearing electron-withdrawing groups, such as the ester group, since not only are these groups viable of further functionalization, but they also activate the olefin moiety for reactions such as Michael addition and pericyclic reactions. While it is rather facile to obtain disubstituted *E*-olefins bearing an electron-withdrawing group with high selectivity from aldehydes, only a few methods are available for moderate to highly selective preparation of the thermodynamically less stable *Z*-olefins, and so far they have been limited to the ester,[1–5] the cyano,[6,7] and the recently reported methyl ketone group.[8] For disubstituted *Z*-olefins bearing an amide group, it would be desirable to have a direct method of preparation from an aldehyde, especially for multifunctional carbonyl compounds. Peterson olefination with reagents bearing a trimethylsilyl (TMS) group has been widely utilized as a useful complementary reaction to that of Wittig type.[9] However, for disubstituted olefins with electron-withdrawing groups, the selectivity observed for this reaction is generally low (even for *E*-olefins) compared with its phosphorus counterpart. Previous amide formation with Peterson reagents bearing the TMS group is no exception.[10] Thus, based upon the notion that a more bulky and more electronegative silyl group would shift the selectivity towards the *Z*-olefin, we examined a reagent bearing the triphenylsilyl group, which had previously proved to be effective in combination with the cyano group.[6] In accordance with expectations, we have realized the first highly *Z*-selective preparation of α,β-unsaturated amides. Herein we describe our results.

The Peterson reagents **1a**,**b** examined for the reactions were prepared by treating the lithium enolate of *N*,*N*-dibenzylacetamide with Ph_3SiCl or Me_3SiCl, regioselectively giving the *C*-silylated products in moderate yield.[10,11] The results of using the triphenylsilyl reagent **1a** are given in Table 1. Since a countercation effect is usually observed for the analogous Horner–Wadsworth–Emmons (HWE) reaction, the examination of various metal-containing bases was first carried out in the reaction with benzaldehyde. The effect of the countercation proved to be quite significant as the ratio of *Z*-amide increased from 54 : 46 with *n*-BuLi to 80 : 20 with NaHMDS, and an exclusive $>97{:}<3$ with KHMDS‡ (entry 1). In the case of *n*-BuLi, the reaction temperature was gradually raised from −78 to 0 °C in order to effect reaction. More common bases such as NaH and *t*-BuOK were found to be unsuitable. The reaction of **1a** and 3-phenylpropionaldehyde with KHMDS as base (entry 8) was also found to be *Z*-selective, although not quite as high as with benzaldehyde. In seeking a possible improvement in selectivity, an examination of solvents was carried out. However, neither a decrease (ether, 74 : 26, 15%) or increase (THF–HMPA mixture, 71 : 29, 64%) in polarity proved fruitful. Lowering of the reaction temperature to −95 °C led to a slight increase in selectivity to 94:6 but with a lower yield of 58%.

Table 1 Peterson reaction of $Ph_3SiCH_2CONBn_2$ (**1a**) with various aldehydes[a]

Entry	R	$Z{:}E$[b]	Yield (%)[c]
1	Ph	$>97{:}<3$	88
2	*p*-$MeOC_6H_4$	$>97{:}<3$	87
3	*o*-$MeOC_6H_4$	81 : 19	72
4	*p*-ClC_6H_4	88 : 12	91
5	2-Furyl	91 : 9	92
6	2-Pyridyl	59 : 41	47
7	(*E*)-PhCH = CH	81 : 19	99
8	$PhCH_2CH_2$	91 : 9	77
9	*c*-Hexyl	83 : 17	82

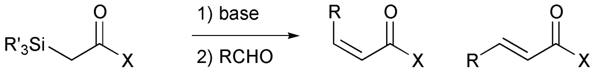
[a] All reactions were carried out in THF at −78 °C with KHMDS as base. [b] Determined by 500 MHz ^1H NMR measurement of crude mixture. [c] Combined isolated yield of *E* and *Z* olefins.

Under the standard conditions of using THF and KHMDS at −78 °C, other aldehydes were examined.§ For 4-substituted benzaldehyde derivatives, a drop-off in selectivity was observed with the electronegative Cl substituent (entry 4), but remained high with the electron-donating MeO group (entry 2). Although sterically hindered 2-substituted aromatic aldehydes are usually more *Z*-selective than their 4-substituted counterparts in HWE reactions, with the MeO group the Peterson reaction here gave lower selectivity (entry 3). With heterocyclic aldehydes, the highly electronegative pyridylaldehyde showed very low selectivity (entry 6), whereas that of furfural was highly *Z*-selective (entry 5). The conjugated *E*-cinnamaldehyde also furnished the *Z*-product as the predominant isomer (entry 7).

As for other aliphatic aldehydes, whereas α-branched 2-phenylpropionaldehyde did not react, the same α-branched cyclohexanecarboxyaldehyde did, giving the *Z*-olefin as the major product (entry 9). This indicates that with readily enolizable aldehydes, enolization is favoured over the olefination reaction. Apparently due to steric factors, pivalaldehyde was unreactive.

The 4-substituent effect observed with KHMDS as base was more profound upon using *n*-BuLi as base, with the *Z*-selectivity decreasing with increasing electron-withdrawing ability; from 69 : 31 with *p*-$MeOC_6H_4CHO$ to 54 : 46 with benzaldehyde and 43 : 57 with *p*-ClC_6H_4CHO.

The efficacy of the triphenylsilyl group was confirmed by making comparisons with reactions of trimethylsilyl reagent **1b**



1a: R'=Ph, X=NBn_2
1b: R'=Me, X=NBn_2
2: R'=Ph, X=OEt

***Z*-3**

***E*-3**

Scheme 1

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† Electronic supplementary information (ESI) available: synthesis and characterisation data for **1a**,**b** and **3a–i**. See http://www.rsc.org/suppdata/cc/b0/b004416o/

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Table 2 Comparison between differently substituted reagents **1a**, **b**, and **2**[a]

Entry	Reagent	R	Z:E[b]	Yield (%)[c]
1	$Ph_3SiCH_2CONBn_2$	Ph	> 97 : < 3	88
2	$Me_3SiCH_2CONBn_2$	Ph	27:73	63
3	$Ph_3SiCH_2CO_2Et$	Ph	71:29	82
4	$Ph_3SiCH_2CONBn_2$	$PhCH_2CH_2$	91:9	77
5	$Me_3SiCH_2CONBn_2$	$PhCH_2CH_2$	—	0
6	$Ph_3SiCH_2CO_2Et$	$PhCH_2CH_2$	77:23	78

[a] All reactions were carried out in THF at −78 °C with KHMDS as base. [b] Determined by 500 MHz ^1H NMR measurement of crude mixture. [c] Combined isolated yield of *E* and *Z* olefins.

using KHMDS as base, as shown in Table 2.[10] The reaction of **1b** with benzaldehyde resulted in a complete turnaround in selectivity, favouring *E*-olefin formation (entry 2) while that with 3-phenylpropionaldehyde gave no olefin product (entry 5). The effectiveness of the amide group for high *Z*-selectivity was exhibited by comparing corresponding reactions of an ester analogue **2**. The reaction of ethyl triphenylsilylacetate with benzaldehyde (entry 3) and 3-phenylpropionaldehyde (entry 6) with KHMDS as base gave the corresponding electron-deficient olefin as Z:E = 71:29 and 77:23 mixtures, respectively, which are clearly inferior ratios compared with those of corresponding amide reactions (entries 1, 4). Thus, we have the general trend in which the larger the electron-donating ability of the group directly attached to the carbonyl group in both the aldehyde and the silyl reagent, the higher the *Z*-selectivity tends to be. Considering these electronic effects, the results we have obtained here fit in well with the generally accepted mechanism which involves an intermediate formed by rearrangement of the silyl group from a carbon to an oxygen atom, preceding olefin formation.[12]

In summary, we have developed a highly geometry-selective method of preparing *Z*-unsaturated amides based upon the Peterson reaction. Further examination of substituent effects are underway.

Notes and references

‡ Olefin geometries were determined by the coupling constants and chemical shifts of the olefinic protons, and were verified by NOE experiments for representative products.

§ The general procedure for the Peterson reaction is given as follows as the example of the reaction of benzaldehyde. To a solution of **1a** (206 mg, 0.415 mmol) in THF (4 mL) cooled to −78 °C was added KHMDS (0.5 M in toluene, 0.98 mL, 0.49 mmol). After stirring for 30 min at 0 °C, the solution was recooled to −78 °C. To this solution was added benzaldehyde (39.0 mg, 0.368 mmol) in THF (2.5 mL), and stirring was continued for 3 h. Water was then added to quench the solution, and extraction was carried out with ether. After the usual workup and chromatographic purification by preparative TLC (SiO_2; hexane : ethyl acetate = 5 : 1), (*Z*)-*N*,*N*-dibenzylcinnamamide (106 mg) was obtained as a viscous oil in 88% yield.

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