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# A Practical Protocol for the Highly *E*-Selective Formation of Aryl-Substituted Silylketene Acetals

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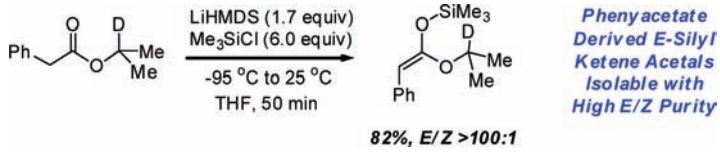
## ABSTRACT




**The *E*/*Z*-selectivity in the formation of silylketene acetals derived from phenylacetate esters, mediated by LiHMDS, has been studied by in situ NMR techniques. The formation is seen to be highly *E*-selective with use of the newly developed protocol. Isolated aryl-substituted silylketene acetals are now attainable with high levels of *E*-geometrical purity in excellent yield.**

Silylketene acetals are versatile and reactive nucleophiles which find widespread use in organic synthesis,[1] and in particular, *C*−*C* bond forming contexts such as aldol[2] and Ireland−Claisen [3,3]-sigmatropic rearrangement reactions.[3] In many situations the diastereoselectivity and/or enantioselectivity of the studied transformation is dependent upon the *E*/*Z* ratio of the silylketene acetal.[4] Therefore, controlling the *E*/*Z* ratio during the formation of the silylketene acetal unit can be crucial for a successful and stereoselective reaction.

As aromatic functionality is ubiquitous in organic chemistry, the controlled formation of silylketene acetals bearing aromatic substituents and their subsequent transformations can be regarded as an important issue. However, in the majority of instances, aryl-substituted silylketene acetals are typically formed and used with moderate levels of *E*/*Z* purity. A number of recent transformations with phenylacetate derived silylketene acetals have done so with levels of *E*/*Z* purity between 2:1 and 4:1.[5−7] Studies have concluded that, although the *E*-enolate from phenylacetate esters forms kinetically, unsuitable and impractical *E*/*Z* mixtures are ultimately isolated.[8,9] The inability to prepare aryl-substituted

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(1) For selected recent synthetic usage of silylketene acetals, see: (a) Nishiyama, Y.; Kaiba, K.; Umeda, R. *Tetrahedron Lett.* **2010**, *51*, 793. (b) Le Engers, J.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, 6109. (c) Shiina, I.; Iizumi, T.; Yamai, Y.; Kawakita, Y.; Yokoyama, K.; Yamada, Y. *Synthesis* **2009**, 2915. (d) Kise, N.; Isemoto, S.; Sakurai, T. *Org. Lett.* **2009**, *11*, 4902. (e) Denmark, S. E.; Eklov, B. M.; Yao, P. J.; Eastgate, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 11770. (f) Alaimo, P. J.; O'Brien, R.; Johnson, A. W.; Slauson, S. R.; O'Brien, J. M.; Tyson, E. L.; Marshall, A.-L.; Ottinger, C. E.; Chacon, J. G.; Wallace, L.; Paulino, C.; Connell, Y. S. *Org. Lett.* **2008**, *10*, 5111. (g) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*, 4951. (h) Zikou, L. C.; Igglessi-Markopoulou, O. *Synthesis* **2008**, 1861. (i) Denmark, S. E.; Chung, W. *J. Org. Chem.* **2008**, *73*, 4582. (j) Cho, D. W.; Lee, H.-Y.; Oh, S. W.; Choi, J. H.; Park, H. J.; Mariano, P. S.; Yoon, U. C. *J. Org. Chem.* **2008**, *73*, 9. (k) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (l) Notte, G. T.; Leighton, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 6676. (m) Denmark, S. E.; Chung, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1890. (n) Song, J. J.; Tan, Z.; Reeves, J. T.; Fandrick, D. R.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 877. (o) Cho, S. W.; Romo, D. *Org. Lett.* **2007**, *9*, 1537.

(2) For an overview, see: *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004.

(3) For recent reviews concerning the Ireland−Claisen rearrangement, see: (a) Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Chai, Y. H.; Hong, S. P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (c) McFarland, C. M.; McIntosh, M. C. *The Claisen Rearrangement*; Hiersemann, M. N., Nubbemeyer, U. , Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007; p117.

(4) For a specific discussion regarding the relevance of *E*/*Z* silylketene acetal geometry to diastereoselection in the Ireland−Claisen [3,3]-sigmatropic rearrangement, see: Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

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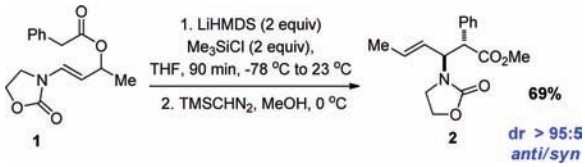
silylketene acetals in high geometrical purity suggests a significant gap in the synthetic repertoire, which would benefit from the devlopment of a new protocol to answer this issue.

Our own experience with silylketene acetals in an Ireland−Claisen rearrangement context[10,11] has prompted us to re-examine this issue of *E*/*Z* control during the formation of silylketene acetals derived from phenylacetates. We were keen to closely model the expected silylketene acetal formation from enamide−phenylacetate **1** as this rearrangement had been observed to proceed with particularly high diastereoselectivity (Scheme 1).

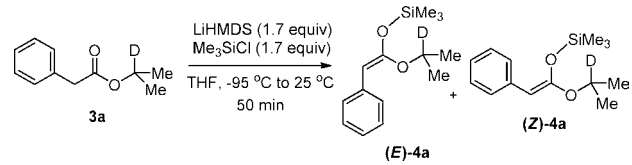
**Scheme 1.** Ireland−Claisen Rearrangement of an Enamide




Accordingly, isopropyl phenylacetate was initially chosen as a model substrate, mirroring the secondary ester motif seen in **1**. An internal quench was utilized with the addition of an isopropyl phenylacetate solution to a mixture of $Me_3SiCl$ and LiHMDS in a dry NMR tube at −95 °C under a stream of $N_2$. The NMR tube was then rapidly transferred to the precooled spectrometer prior to NMR experimentation. Standard THF has been used without recourse to $^2H_8$ THF, for NMR spectroscopy, more closely mimicing the developed synthetic conditions even though locking and shimming operations at cryogenic temperatures become more challenging.[12]

We were delighted to observe the formation of the expected silylketene acetal at −95 °C, on warming to −50 °C and finally at 25 °C.[13] However, these initial experiments were complicated by the overlap of the isopropyl methine signal with the minor *Z*-silylketene acetal signals, leading to an inability to detect *E*/*Z* silylketene acetal ratios. To overcome this, $^2H_1$-isopropyl phenylacetate **3a** was instead examined (Scheme 2).

**Scheme 2.** Silylketene Acetal Formation of Phenylacetate **3a**




The data obtained from this initial experiment were informative with only a single *E*-silylketene acetal isomer observed at −95 °C. However, on warming to −50 °C and to 25 °C a change in *E*/*Z* purity was observed (*E*/*Z* = 61:1 and 30:1, Figure 1).

The time dependence of starting material consumption and *E*/*Z* ratio has been followed at the intermediate temperature of −50 °C (Figures 2 and 3). This monitoring clearly demonstrates an initial fast yet partial consumption (ca. 30%) of ester **3a**, which was unexpected at the loading level of LiHMDS used (1.7 equiv, Figure 2). After 3 h the reaction mixture is warmed to 25 °C (final data point) with an ensuing jump in the consumption of **3a**.

A similar scenario is observed when monitoring the *E*/*Z* ratio of the forming silylketene acetal (Figure 3). Initially high levels of *E*/*Z* control are observed. A plateau in the level of silylketene acetal *E*/*Z* geometry is observed while the conversion remains low. However, on warming to room temperature a striking worsening of the observed silylketene acetal *E*/*Z* ratio is seen to occur (final data point, Figure 3).

The observation presented in Figure 1, i.e. high levels of *E*/*Z* control, requires consideration in the context of the previously reported studies concerning the formation of phenylacetate derived silylketene acetals with poor *E*/*Z* control. The conditions used by Fuji[8a] and Solladié-Cavallo[8c] involve the use of LDA (1.2 equiv) and an external $Me_3SiCl$ quench (4 equiv) 30 min after initiation of enolate formation at −78 °C. However, the most interesting comparison is with the study of Corset,[8b] which most closely mirrors the protocol presented in this communication where both LiHMDS (1.2 equiv at −70 °C) and an internal $Me_3SiCl$ quench (6 equiv) are used. However, an isolated *E*/*Z* ratio of 4:1 in the Corset study contrasts markedly with the level of *E*/*Z* selectivity

(5) (a) Su, S.; Porco, J. A. *Org. Lett.* **2007**, *9*, 4983. (b) Ollevier, T.; Nadeau, E. *Org. Biomol. Chem.* **2007**, *5*, 3126. (c) Ollevier, T.; Nadeau, E. *Synlett* **2006**, 219. (d) Itoh, J.; Fuchibe, K.; Akiyama, T. *Synthesis* **2006**, 4075. (e) Akiyama, T.; Matsuda, K.; Fuchibe, K. *Synthesis* **2005**, 2606. (f) Akiyama, T.; Itoh, J.; Fuchibe, K. *Synlett* **2002**, 1269. (g) Akiyama, T.; Takaya, J.; Kagoshima, H. *Adv. Synth. Catal.* **2002**, *344*, 338.

(6) Mioskowski and co-workers have reported the preparation of three para-substituted aryl substituted silylketene acetals with the *p*-methoxy system reported as a 13:1 *E*/*Z* mixture; see: Heurtaux, B.; Lion, C.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2005**, *70*, 1474.

(7) The use of highly *Z*-enriched phenyl acetate derived silylketene acetals in Rh(II)-catalyzed aminations has been described. However, the method of silylketene acetal formation is not discussed, see :Tanaka, M.; Kurosaki, Y.; Washio, T.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2007**, *48*, 8799.

(8) (a) Tanaka, F.; Fuji, K. *Tetrahedron Lett.* **1992**, *33*, 7885. (b) Corset, J.; Froment, F.; Lautie, M. F.; Ratovelomanana, N.; Seyden-Penne, J.; Strzalko, T.; Roux-Schmitt, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 1684. (c) Solladie-Cavallo, A.; Csaky, A. G. *J. Org. Chem.* **1994**, *59*, 2585.

(9) For a study of the sensitivity of enolization conditions in the aldol reaction of phenylacetate esters, see: Pinheiro, S.; Lima, M. B.; Gonçalves, C. B. S. S.; Pedraza, S. F.; de Farias, F. M. C. *Tetrahedron Lett.* **2000**, *41*, 4033.

(10) Ylioja, P. M.; Mosley, A. D.; Charlot, C. E.; Carbery, D. R. *Tetrahedron Lett.* **2008**, *49*, 1111.

(11) Tellam, J. P.; Kociok-Köhn, G.; Carbery, D. R. *Org. Lett.* **2008**, *10*, 5199.

(12) The use of a sealed tube insert to assist NMR locking was considered. However, drying the sealed insert carefully becomes impractical, leading to potential synthetic complications. Solvent suppression techniques were not required as THF and silylketene acetal signals were not coincident.

(13) The intermediate temperature of −50 °C was chosen as quenching studies have shown that rearrangement of **1** proceeds smoothly at −50 °C.

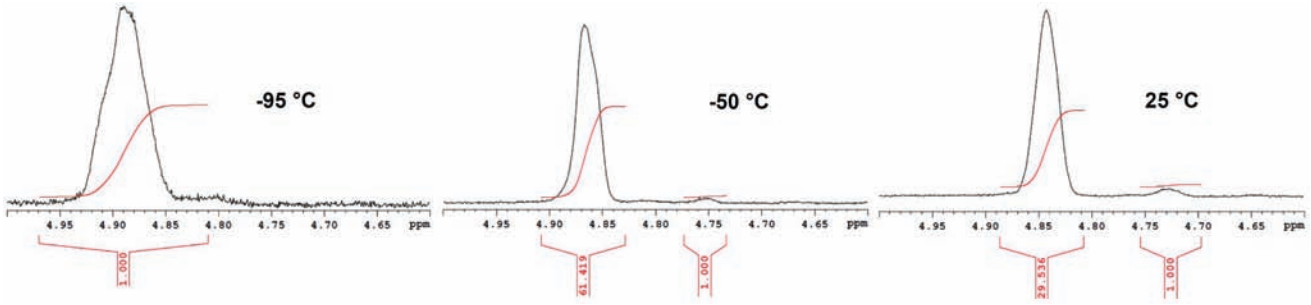



**Figure 1.** Variable temperature $^1$H NMR study of silylketene acetal formation of phenylacetate **3a** in THF. Line broadening due to poor shimming at low temperature.

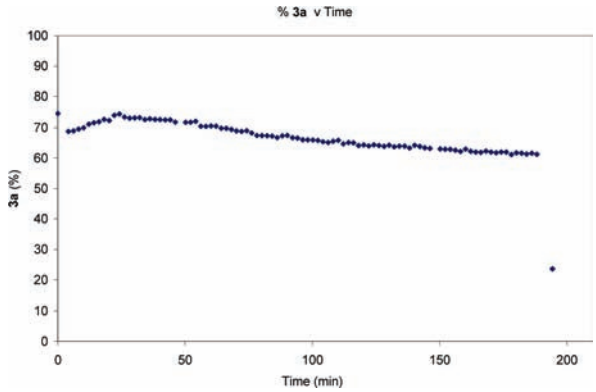



**Figure 2.** Time dependence of percent **3a** present in the formation of silylketene acetal **4a** at −50 °C. Initial data point ($t = 0$) observed at −95 °C prior to warming to −50 °C. Final data point measured at 25 °C.

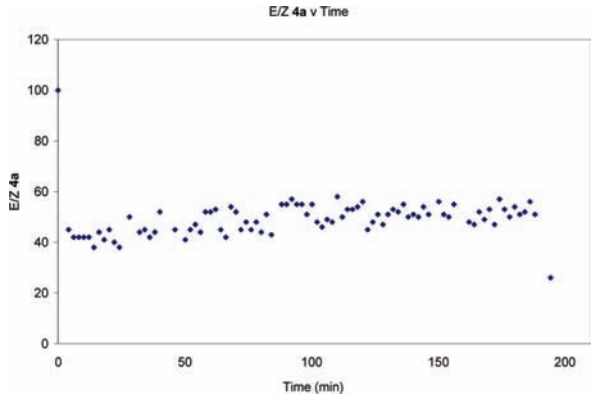
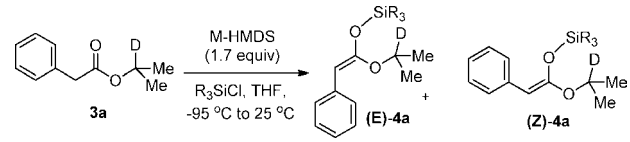



**Figure 3.** Time dependence of *E*/*Z* control in the formation of **4a** at −50 °C. Initial data point ($t = 0$) observed at −95 °C prior to warming to −50 °C. Final data point measured at 25 °C.

obtained with the presented protocol. In an attempt to clarify these differences we have performed a number of control experiments aimed at identifying the key features controlling the high levels of *E*-silylketene acetal purity seen in this protocol (Table 1).

**Table 1.** Control Experiments




| entry | M | R (equiv) | **4** (*E*/*Z*)[a] (−95 °C) | **4** (*E*/*Z*)[a] (−50 °C) | **4** (*E*/*Z*)[a] (25 °C) |
|---|---|---|---|---|---|
| 1 | Li | Me (1.7) | >100:1 | 61:1 | 30:1 |
| 2[b] | Li | Me (1.7) | 71:1 | 42:1 | 16:1 |
| 3 | Li | Me (6) | >100:1 | >100:1 | 64:1 |
| 4[c] | Li | Me (6) | >100:1 | >100:1[d] | 56:1 |
| 5 | Li | Me (1.7)[e] | >100:1 | 8:1 | 5:1 |
| 6 | Li | Me (1.1) | >100:1 | >100:1 | 33:1 |
| 7 | Na | Me (6) | - | 8:1 | 6:1 |
| 8 | Li | $^i$Pr (6) | >100:1 | 10:1 | 4:1 |
| 9 | Li | Et (6) | >100:1 | >100:1 | 22:1 |
| 10 | –[f] | Me (6) | 4:1 | 4:1 | 4:1 |

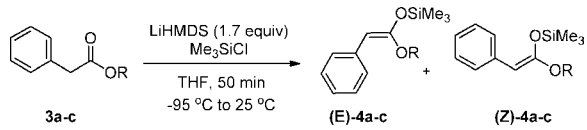
[a] E/Z ratio measured by $^1$H NMR integration of appropriate silylketene acetal signals. [b] Initiated at −78 °C. [c] Observed at −65 °C for 60 min. [d] Observed at −25 °C. [e] External quench: $Me_3SiCl$ added to reaction mixture 30 min after initiation of enolate generation. [f] LDA used as base.

These control experiments have been informative and clearly point to temperature control and enolate lifetime as key parameters in accessing high *E*/*Z* purity. Accordingly, initiation at higher temperatures (entry 2), the use of an external quench (entry 5), and lower loadings of silyl chloride (entry 6) all lead to diminished *E*/*Z* purity. In contrast higher loadings of trimethylsilyl chloride lead to a more rapid silylation and reduced *E*/*Z* interconversion (entries 3 and 4). Indeed, complete silylation is now observed at −50 °C after approximately 20 min; in all other instances a similar pattern of subtrate conversion is oberved to that originally displayed in Figure 2. The nature of the amide base counterion is crucial with NaHMDS leading to reduced *E*/*Z* control (entry 7). Bulkier silyl chlorides also lead to lowered *E*/*Z* control (entries 8 and 9). Finally, the necessity of a disilazide base is apparent when compared with the poor *E*/*Z* control observed with LDA, in agreement with the prior studies (entry 10).[8]

In the instance of silylketene acetal **4a**, we have observed that an NMR sample in THF retained a significant excess of

the *E*-geometrical isomer after extended periods of time at room temperature. Accordingly, after 48 h, the *E*/*Z* ratio was observed as 10:1. This ratio remains significantly in excess of the ratios described in the literature and points toward this simple protocol for silylketene acetal formation being valuable in organic synthesis. For this study to offer synthetic utility we have looked to isolate these silylketene acetals with high levels of *E*/*Z* purity. Excellent yields of isolated silylketene acetals derived from phenylacetates are obtained with good to excellent *E*/*Z* control (Table 2).

**Table 2.** Isolation of Phenylacetate-Derived Silylketene Acetals




| entry | ester | method[a] | R | (*E*/*Z*)[b] | yield[c] |
|---|---|---|---|---|---|
| 1 | **3a** | A | $CDMe_2$ | 68:1 | 81 |
| 2 | **3a** | B | $CDMe_2$ | 17:1 | 88 |
| 3 | **3a** | C | $CDMe_2$ | >100:1 | 82 |
| 4 | **3b** | C | Me | 67:1 | 80 |
| 5 | **3c** | C | $C(Me)_3$ | 25:1 | 76 |

[a] Methods: (A) ester added to base via syringe pump and $Me_3SiCl$ (1.7 equiv) before warming to room temperature; (B) ester added to base by hand and $Me_3SiCl$ (1.7 equiv) before warming to room temperature; and (C) ester added to base via syringe pump and $Me_3SiCl$ (6 equiv), holding at −95 °C for 30 min before warming to room temperature. [b] *E*/*Z* ratio measured by $^1H$ NMR integration of appropriate silylketene acetal signals. [c] Isolated yield.

By employing an excess of silyl chloride, adding the substrate slowly by syringe pump, and holding the reaction before warming to room temperature, excellent *E*/*Z* ratios of the $^i$Pr-silylketene acetal can be obtained (entry 3). The sensitivity of *E*/*Z* control should also be noted, with higher *E*/*Z* control obtained relative to the use of the Me ester **3b** (entry 4) or $^t$Bu ester **3c** (entry 5).

In conclusion, *E*/*Z* control during the formation of phenylacetate derived silylketene acetals is reported and is observed to be highly *E*-selective for the first time with this reported protocol, in contrast to current literature understanding. The precise level of *E*-purity and the rate of *E*/*Z* isomerization is not only dependent on the nature of the ester alkoxy moiety, but in fact is highly influenced by initiation temperatures and the rate of silylation. We are currently examining the nature and rate of enolate interconversion relative to silylation and will report in due course.

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**Supporting Information Available:** Experimental procedures, compound characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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