ORGANIC LETTERS

2006
Vol. 8, No. 23
5191−5194

Silylative Dieckmann-Like Cyclizations of Ester-Imides (and Diesters)

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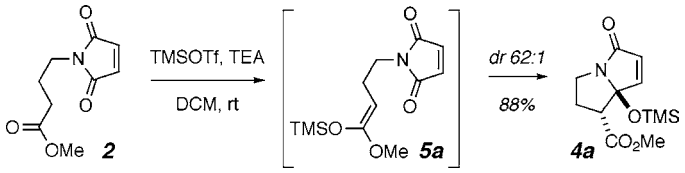
Received August 10, 2006

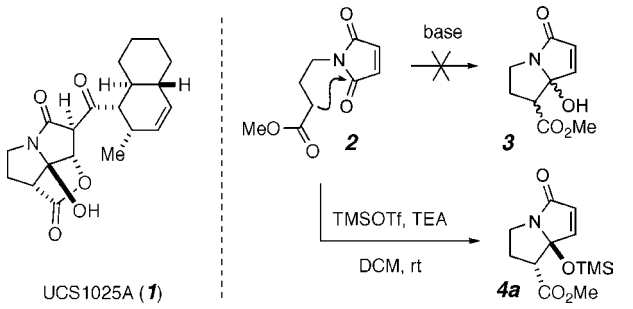
ABSTRACT



Trialkylsilyl triflates effect cyclization of ester-imides such as 2 to produce adducts such as 4a. Trapping of the in situ generated, nucleophilic ketene acetal (cf. 5a) is a key aspect of the transformation. A range of substrates amenable to this operationally simple reaction is reported. In many instances the levels of diastereoselectivity are very high. Mechanistic points are inferred from spectroscopic observations.

Upon contemplating modes of construction of the heterocyclic core of the telomerase inhibitor UCS1025A (**1**), we considered the cyclization of an ester enolate equivalent with an imide carbonyl group as in **2**. The base sensitivity of **2** quickly revealed itself; no trace of an adduct such as **3** (Scheme 1) was ever observed under basic reaction conditions. This turned our attention to a cationic process involving a silyl ketene acetal (SKA) derived from the enolizable ester in **2**. SKAs serve as nucleophiles in various addition reactions to C=X containing electrophiles, including aldehydes/ketones, imines, enones, and acid halides to provide β-hydroxyesters, β-aminoesters, δ-ketoesters, and β-ketoesters, respectively.[1] We are not aware of an imide functional group serving the role of acceptor. This approach proved to be very effective for generating species such as **4**,[2] and this tactic was successfully implemented in two syntheses of **1**.[3]

Scheme 1



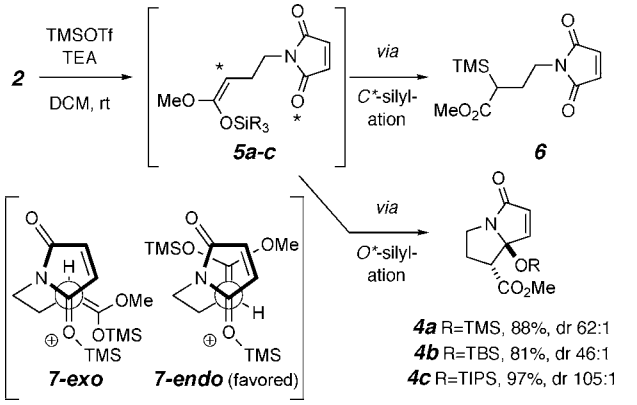
Silyl ketene acetals are typically generated by silylation of an ester enolate with a silyl chloride. Attempts to prepare them by reaction with silyl triflates in the presence of weak bases [e.g., Et_3N (TEA)], by analogy with silyl enol ether formation, are usually thwarted by overconversion to the α-silylated esters. However, in appropriate settings one can imagine simultaneous silylative generation of both a SKA and an activated electrophile, which would co-react faster than conversion of the SKA to its isomeric α-silylated ester.

In particular, when ester-imide **2** was treated with TMSOTf and TEA in chlorocarbon solvents (CH_2Cl_2 or $CDCl_3$), the bicyclic lactam **4a** was produced in high yield and diastereomeric ratio (dr) (Scheme 2). The *endo* orientation of the carbomethoxy group in the predominant product, a fortunate outcome vis-à-vis synthesis of **1**, was established on the basis of a single-crystal X-ray analysis (Figure 1a) and eventual elaboration into UCS1025A.[3] The sense of diastereoselectivity of this reaction is consistent with C−C bond formation through an open transition state geometry for the addition

(1) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120.
(2) Dvornikovs, V.; Hoye, T. R. *Abstr. Pap. Am. Chem. Soc.* **2005**, *229*, 665-ORGN.
(3) (a) Lambert, T. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 426−427. (b) Hoye, T. R.; Dvornikovs, V. *J. Am. Chem. Soc.* **2006**, *128*, 2550−2551.

10.1021/ol061988q CCC: $33.50
Published on Web 10/11/2006

Scheme 2



of the SKA to an O-silylated imide carbonyl as suggested in **7-endo** (as opposed to the *synclinal* geometry of **7-exo**). This reaction could be extended to higher trialkylsilyl triflates. TBSOTf and TIPSOTf gave products **4b** and **4c**, respectively, with comparable outcomes; the only difference was a progressively slower overall reaction rate ($t_{1/2} \approx 6$ min, **4a**; 15 min, **4b**; and 7 h, **4c** at [**2**] = 0.3 M in $CDCl_3$ and 1.5 equiv of R_3SiOTf). In addition, we observed a low, steady-state level of each of the intermediate SKAs **5b** and **5c** by ^1H NMR spectroscopy.[4]

When the reaction mixture was undercharged with TMSOTf, major product **4a** was accompanied by a small amount of α-silylated ester **6** (Scheme 2). This suggested that the SKA **5** was competitively and, perhaps, reversibly silylated at the C* vs O* atoms in **5**. Indeed, resubjection of isolated **6** to TMSOTf/Et_3N in $CDCl_3$ resulted in its clean conversion to lactam **4a**. Simple esters are known to be silylated with R_3SiOTf in diethyl ether.[5] As a model we examined the silylation of methyl propionate (**8**), but under conditions more similar to those used for the cyclization of **2** (Scheme 3). Namely, in $CDCl_3$ solution we could easily monitor (^1H NMR) the extent of conversion to a mixture of SKA **9** and the α-silylated ester **10**. Starting with 2 equiv each of TMSOTf and TEA, the system equilibrated to a steady-state mixture of **8**:**9**:**10** in a ratio of ~5:trace:1.

This observation implies that the success of the cyclizations to form **4** derives from the in situ O-silylative activation

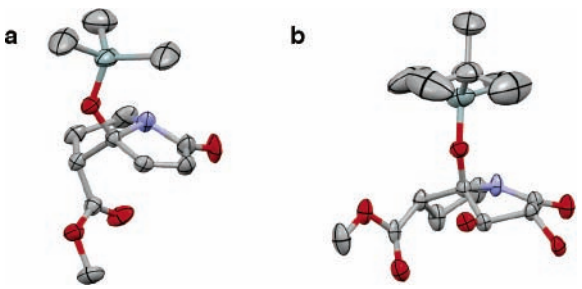
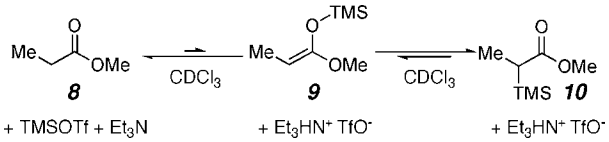


Figure 1. ORTEP representation of **4a** (panel a) and **24** (panel b).

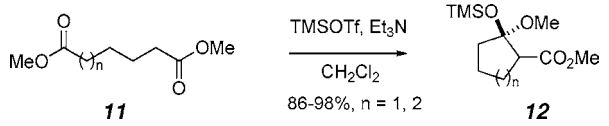
Scheme 3



of an imide carbonyl group in **5**, which allows the low steady-state population of SKA to be dragged to the desired products.

To probe if in situ activation of an ester electrophile might also serve to induce a net, silylative Dieckmann cyclization, we investigated simple dimethyl α,ω-dicarboxylates (Scheme 4). The reaction proved to be successul for five- and six-

Scheme 4



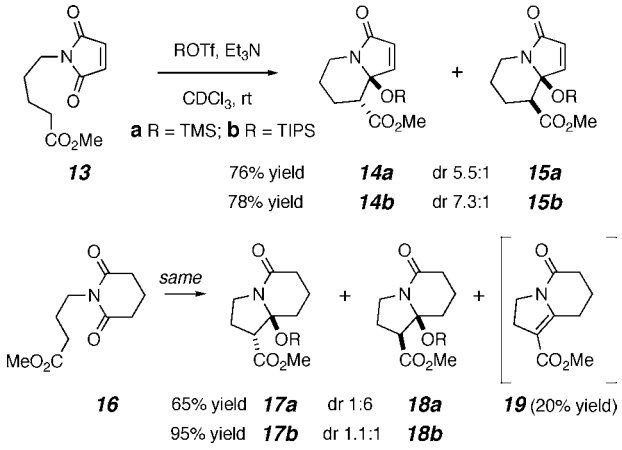
membered ring formation, giving excellent yields of the ketals **12** (dr 2:1) from dimethyl adipate and dimethyl pimelate (**11**, $n = 1$ and 2). No cyclization was observed (^1H NMR analysis) for substrates that would have given rise to four-, seven-, and eight-membered rings (**11**, $n = 0$, 3, and 4).

We have also defined some of the scope of the imide cyclization reaction, particularly with respect to ring size. Substrate **13** (the one-carbon-longer homolog of **2**) smoothly cyclized to the 6/5-bicyclic lactams **14** and **15** with slightly lower levels of dr (Scheme 5) compared with **2**. The glutarimide substrate **16** also cyclized in high yield, but the stereochemical outcome was quite different. TMSOTf gave rise, predominantly, to the *exo* adduct **18a**, suggesting that the saturated (and puckered) glutarimide ring deterred an anti-addition analogous to that indicated in **7-endo** (the assignment of relative configuration for **17** vs **18** is based on convincing differences in NOE effects and coupling constant data). On the other hand, the bulkier TIPSOTf reagent gave a nearly 1:1 mixture of adducts **17b** and **18b**, reflective of a competitive interaction with the silyl moiety in a *synclinal* mode of addition similar to that in **7-exo**. The less hindered (and more reactive) TMSOTf induced competitive elimination of TMS_2O from **17a** and/or **18a** under the reacion conditions to give the pyrroline byproduct, **19**. Fortunately (again), in the UCS1025A-relevant cyclization of **2** (and **20**, see below), this type of elimination event is thwarted by virtue of destabilization of the carbocationic intermediate.

The behavior of chiral imide substrates was also of interest, so we studied the cyclization of various ether-protected

(4) *Z-O*-Silylketene acetals are more stable than their *E*-isomers: Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451−1453.
(5) Emde, H.; Simchen, G. *Liebigs Ann. Chem.* **1983**, 816−834.

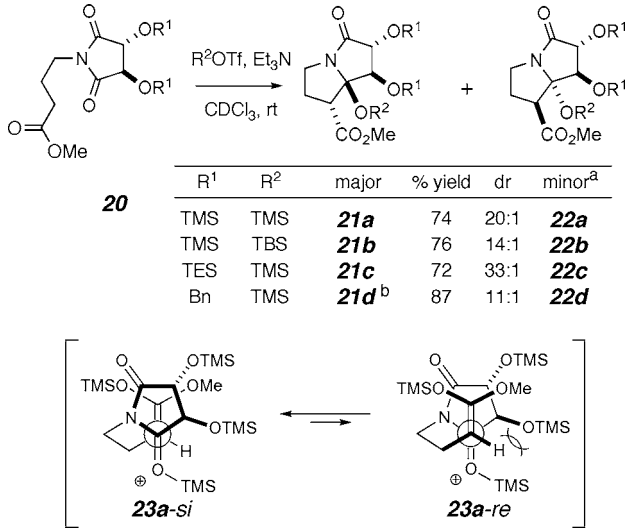
Scheme 5



tartarimides **20** (Scheme 6). When chiral imide **20a**,[2,3a] derived from l-tartaric acid, was subjected to TMSOTf/Et_3N, lactam **21a** was obtained with excellent diastereoselectivity (dr 20:1:0:0). In the *endo* transition states (**23a-*si*** vs **23a-*re***), approach from the *re* face of either of the homotopic imide carbonyl groups is disfavored by repulsion between OTMS and the SKA α-H. Each of the products **21a**−**d** was obtained in good to excellent yield and diastereoselectivity.

The stereochemical assignment of the major product was made on the basis of several lines of reasoning. The conversion of **21b** into the natural enantiomer of **1** proved both the relative and absolute configurations of **21b**.[3a] In our studies, the ^{1}H NMR characteristics of **21a** and **22a** indicated that each of these diastereomers was an *endo* adduct (cf. **4a**).

Scheme 6



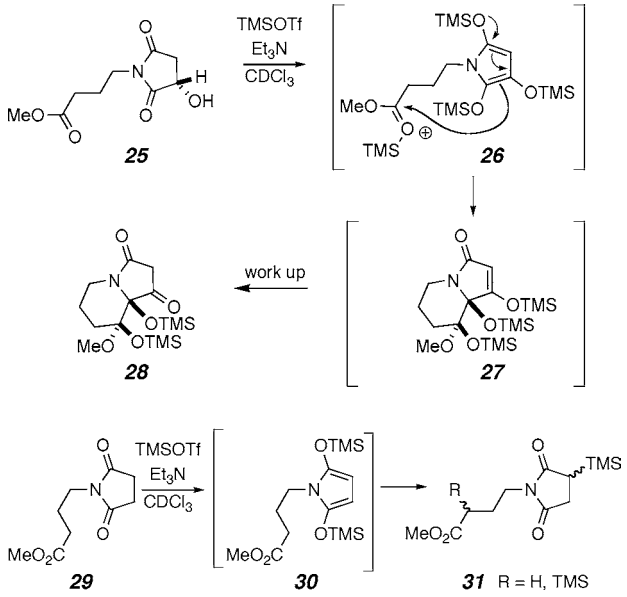
R^1	R^2	major	% yield	dr	minor[a]
TMS	TMS	**21a**	74	20:1	**22a**
TMS	TBS	**21b**	76	14:1	**22b**
TES	TMS	**21c**	72	33:1	**22c**
Bn	TMS	**21d**[b]	87	11:1	**22d**

[a] Each of the minor isomers was identified by GC−MS; **22a** was isolated and fully characterized; **22b** and **22d** were observed by ^{1}H NMR analysis of the crude product mixture and had characteristics similar to those of **22a**. [b] Hünig's base (DIPEA) was used instead of TEA, because use of the latter resulted in competitive elimination of the β-OBn group.

Further, selective removal of the two TMS groups in **21b** gave the crystalline, mono-TBS ether **24**, which was subjected to single-crystal X-ray structure determination (cf. Figure 1b).

Another chiral substrate, hydroxysuccinimide **25**, derived from L-malic acid, was subjected to TMSOTf and Et_3N (Scheme 7). However, an entirely different reaction course

Scheme 7



ensued. Following an initial, essentially instantaneous O-silylation step, a rapid cyclization reaction occurred to give a labile product, to which we have assigned the structure of β-ketolactam **28**. The skeleton of this indolizidinedione is different from that of all of the previous products. We surmise that rapid silylketeneaminal formation now diverts the imide functionality to an electron-rich pyrrole; silylative activation of the ester would then produce **26**. This species is apparently sufficiently reactive to cyclize to form the new six-membered ring present, initially, as **27**. GC−MS analysis of an aliquot taken directly from the reaction mixture gave evidence for an intermediate containing three trimethylsilyl groups ($M^+ = 431$). Workup following addition of aqueous sodium bicarbonate solution gave **28**. This alternative reaction course arises from a reversal of the roles of the imide and ester carbonyl carbons (here the nucleophile and electrophile, respectively) and represents a silylative umpolung. In retrospect, the tartarimides (Scheme 6) are apparently resistant to this alternative mode of cyclization because of a steric barrier toward silylative enolization of the imide. More specifically, loss of an α-proton, which is required for initial silylketenaminal formation, is disfavored. Finally and in contrast, the unsubstituted, parent succinimide substrate **29** quickly formed the 2,5-bis(trimethylsilyloxy)pyrrole **30** (in situ ^{1}H NMR analysis),[6] which was apparently resistant to

(6) Barrett, A. G. M.; Broughton, H. B.; Attwood, S. V.; Gunatilaka, A. A. L. *J. Org. Chem.* **1986,** *51,* 495−503.

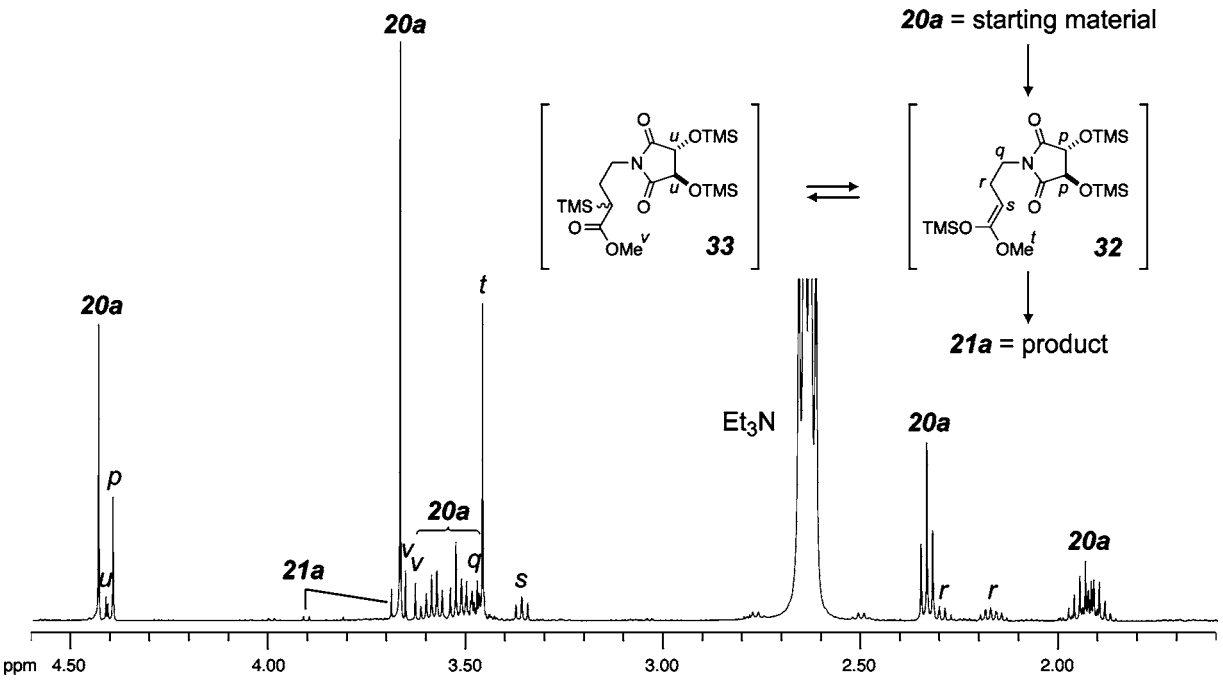


Figure 2. ^{1}H NMR (500 MHz, $CDCl_3$) snapshot (time = 35 min) of the reaction of starting imide **20a** to give product lactam **21a**. Resonances assigned to arise from intermediates **32** and **33** are labeled with lower case letters.

cyclization. In the presence of excess TMSOTf and over time, **30** gave rise instead to a mixture of mono- and bis-C-silylated succinimides **31**.

Finally, most of the reactions described above were monitored directly by proton NMR analysis (in $CDCl_3$) at one time or another. As an example of the insights gained from such studies, consider the spectrum shown in Figure 2. It is of the reaction mixture for the tartarimide **20a**, shown in Scheme 6. Starting material (**20a**), intermediate ketene acetal (**32**), isomeric C-silylated intermediates (**33**), and (a trace of) product **21a** are all identifiable in this snapshot taken after 35 min at room temperature. These assignments are based upon and consistent with observations of the ^{1}H NMR profile over the entire course of the reaction.

In conclusion, we have discovered a highly efficient and operationally simple method for silylative Dieckmann-like cylizations that is applicable to ester/imide- and diester-containing substrates. The reactions can be run at room temperature and at relatively high concentrations (0.3−0.5 M in substrate) and are easy to work up. Potential applications to other carbonyl-containing compounds as well as bimolecular versions are currently being investigated.

Acknowledgment. This project was supported by Grant GM-65597 from the National Institute of General Medical Sciences, National Institutes of Health. We thank William W. Brennessel, Victor G. Young, Jr., and the X-ray Crystallographic Laboratory, Department of Chemistry, University of Minnesota.

Supporting Information Available: Spectroscopic characterization data and procedures for preparation of all new compounds (**4**, **6**, **12**−**15**, **17**−**21**, **24**, **25**, **28**, and **31**) and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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