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Tetrahedron Letters 46 (2005) 5629–5632

Tetrahedron Letters

Halide trapping of the Nazarov intermediate in strained polycyclic systems: a new interrupted Nazarov reaction

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Received 6 June 2005; revised 20 June 2005; accepted 20 June 2005

Abstract—1,4-Dien-3-ones encased within bridged bicyclic frameworks undergo efficient Nazarov electrocyclization upon treatment with $TiCl_4$, but the resulting cyclopentenyl cations are trapped by chloride in preference to deprotonation. In contrast to the usual eliminative pathway, which destroys one of the stereocenters formed during electrocyclization, this process preserves both new centers and generates an additional one at the site of chloride trapping. Examples involving skeletal rearrangements and other Lewis acids are also discussed.

The Nazarov cyclization has enjoyed considerable recent attention as a result of the development of novel methods for diverting the intermediate 2-oxidocyclopentenyl cation from the usual eliminative termination pathway (the 'interrupted Nazarov reaction').[1] A second important focus has been on approaches for controlling the direction of conrotatory electrocyclization ('torquoselectivity'). In the latter area, recent progress has been realized in the relative control using the nearby auxiliary stereocenters,[2] and examples of the control of absolute configuration in simple Nazarov cyclization products using chiral Lewis acids have been reported.[3] We have recently examined the question of Nazarov torquoselectivity in the context of strained bicyclic dienone substrates.[4] The study employed β-silyl dienones, which cleanly cyclized with desilylative termination to give tricyclic products with high to complete diastereocontrol. For comparison, we examined several similar substrates lacking the silyl substituent, using titanium tetrachloride to initiate the electrocyclization, in order to examine the regioselectivity of the elimination step. Here, we report the results of these cases, in which a novel halide trapping process occurs in preference to, and often to the exclusion of, the usual elimination event.

Bicyclic dienones **3a–f** were prepared via addition of alkenyl anions **1a**,**b** (formed from Shapiro reaction[5] of the corresponding trisyl hydrazones[6]) to unsaturated aldehydes **2a–d** (Scheme 1). Subsequent oxidation of the resulting dienols was accomplished with $BaMnO_4$.[7]

Initial experiments using dienone **3a** employed $BF_3{\cdot}OEt_2$, which had served well in the related silyl-directed examples.[4] Unfortunately, these conditions led to complex mixtures. In contrast, low temperature treatment with $TiCl_4$, followed by stirring at 0 °C for several hours, led to a single new product (Scheme 2). Notably, the NMR data for this compound indicated the presence of no alkene protons or carbons. On the other hand, mass spectral analysis clearly implicated the incorporation of a chlorine atom. Based on these observations, we tentatively assigned the new product (formed in 88% yield) as either **4a** or **5a**, in which a chloride from Lewis acid trapped the 2-oxidocyclopentenyl cation formed after conrotatory electrocyclization. Incorporation of Lewis acid-derived halide during cationic rearrangements is known.[8–10] However, to the best of our knowledge, direct halide trapping of the Nazarov intermediate is unprecedented.[11,12]

^1H and ^{13}C NMR spectra along with COSY data clearly implicated the basic connectivity shown for **4a** and **5a**.

Keywords: Nazarov cyclization; Diastereoselective; Lewis acid; Carbocation; Halide.

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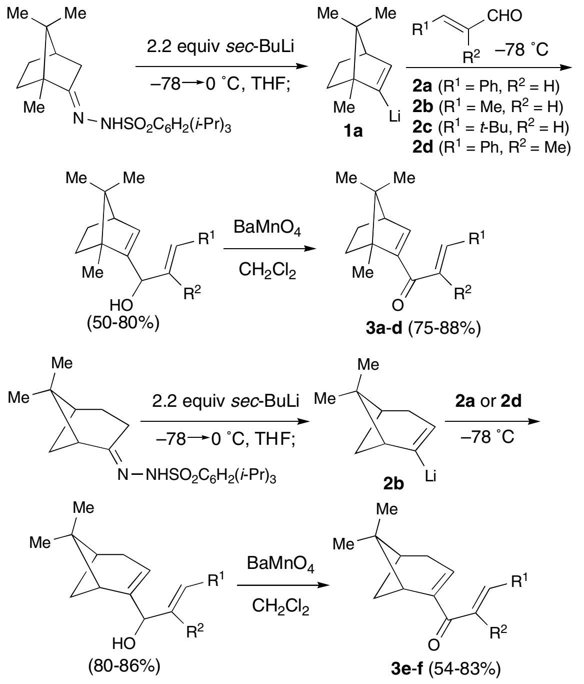
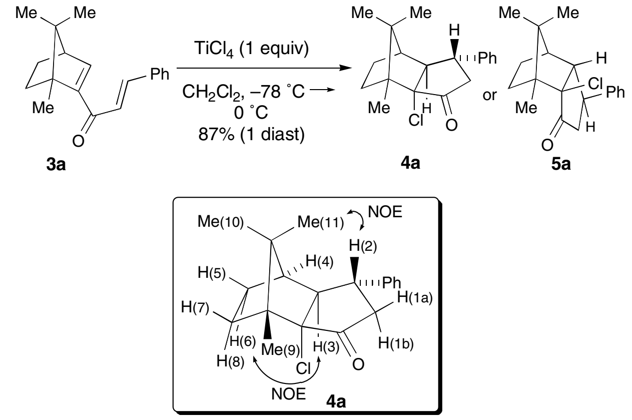
doi:10.1016/j.tetlet.2005.06.101



Scheme 1.



Scheme 2.

Importantly, benzylic proton H(2) displayed vicinal coupling to the neighboring diastereotopic methylene protons H(1a) and H(1b), as well as bridgehead proton proton H(3). However no other couplings to H(3) were observed, providing good evidence for the presence of a chlorine atom at the adjacent bridgehead position. The absence of any H(3)/H(4) coupling strongly suggested structure **4a**, with the newly formed cyclopentane ring *exo* to the preexisting bridged bicyclic skeleton, and H(3) and H(4) in an orthogonal orientation.[13] 2D NOESY data provided further support for this assignment, with H-2/Me-11 and H-3/H-6 interactions particularly diagnostic. High or complete selectivity in favor of *exo* cyclization is also consistent with what was seen in silicon-directed examples.[4]

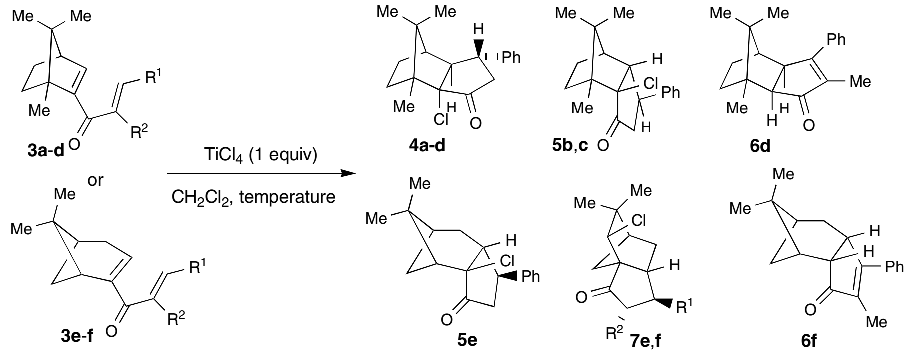
Given this surprising result, the additional bicyclic dienones **3b**–**f** were also subjected to the $TiCl_4$ conditions (Table 1). Camphor-derived dienones **3b**–**d** all displayed the same *exo* cyclization preference as **3a**, although with reduced selectivity. Notably, the more heavily substituted dienone **3d** furnished a mixture of chlorine-trapping product **4d** and simple elimination product **6d**. Finally, nopinone-derived substrates **3e**,**f** underwent efficient cyclization,[14] but in each case furnished a mixture of two skeletally distinct products. Dienone **3e** provided relatively minor amounts of **5e**, resulting from *endo* cyclization and chloride trapping. The major product **7e** apparently results from a 1,2-alkyl migration by the intermediate cyclopentenyl cation, with chloride trapping of the resulting secondary carbocation. Likewise, **3f** gave secondary chloride **7f** as the major product, and slightly less of enone **6f** (formed from elimination of the initially formed cyclopentenyl cation, in analogy to **6d**).

As noted above, the generally high *exo* selectivity displayed by camphor-derived substrates **3a**–**d** parallels that seen in silyl-directed cases.[4] Although a pericyclic process such as the Nazarov 4π cyclization differs fundamentally from ionic addition reactions, certain analogies can be drawn to the well-known *exo* selectivity seen in electrophilic additions to norbornene systems. Many of the arguments used to explain this facial preference, such as torsional strain,[15] nonequivalent orbital extension,[16] alkene pyramidalization,[17] or transition state allylic bond staggering,[18] may also be applicable to the present work.

Nopinone-based examples **3e**,**f** display a propensity for skeletal reorganization after the initial electrocyclization. An *endo*-selective cyclization furnishes intermediate **8** (Scheme 3), which can either undergo chloride trapping to give **5e**, elimination to **6f**, or Wagner–Meerwein shift via carbocation **9**, which is then trapped by chloride to give **7e**,**f**. The indicated NOE contacts from the 2D NOESY spectrum of **7f** clearly implicated this regio- and stereochemistry, and **7e** was assigned by analogy. Skeletal rearrangements in the course of Nazarov reactions have been described, but those involving a migration to the 2-oxidocyclopentenyl cation intermediate are rare.[19] Attack by chloride from the *endo* face of the rearranged bridged polycyclic system suggests the possible involvement of a bridged norbornyl cation.[20] This stereochemical outcome also precludes intramolecular delivery from the titanium enolate, which had been considered a possible pathway to **4a**–**d** and **5b**,**c**,**e**. Selective electrocyclization of **3e**,**f** via the *endo* mode is consistent with selectivity seen in the silyl-directed Nazarov cyclization of a related substrate.[21] Formation of a tetrasubstituted alkene in the case of **6f** apparently allows the elimination pathway to compete with chloride trapping, as was seen with **6d**. Notably, none of the alternative elimination product resulting in the ring-fusing alkene was seen in any of these examples.[22]

Further experiments were then undertaken to probe the generality of the halide trapping process. Silyl-substituted dienone **3g**[4] was subjected to $TiCl_4$ under the standard conditions, and furnished 43% of the known

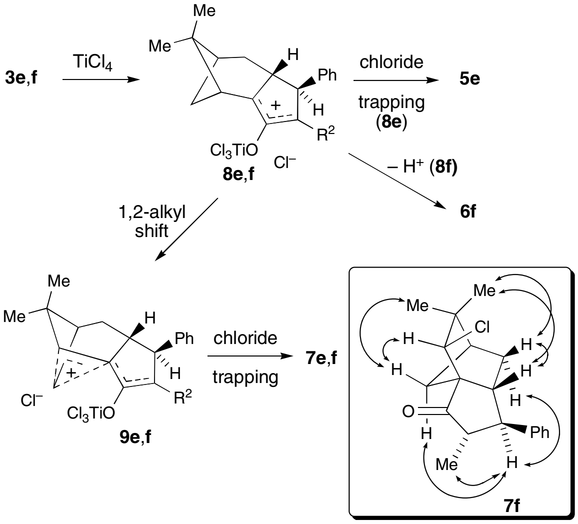
Table 1. Nazarov cyclization/chloride trapping of dienones **3a–f**[a]



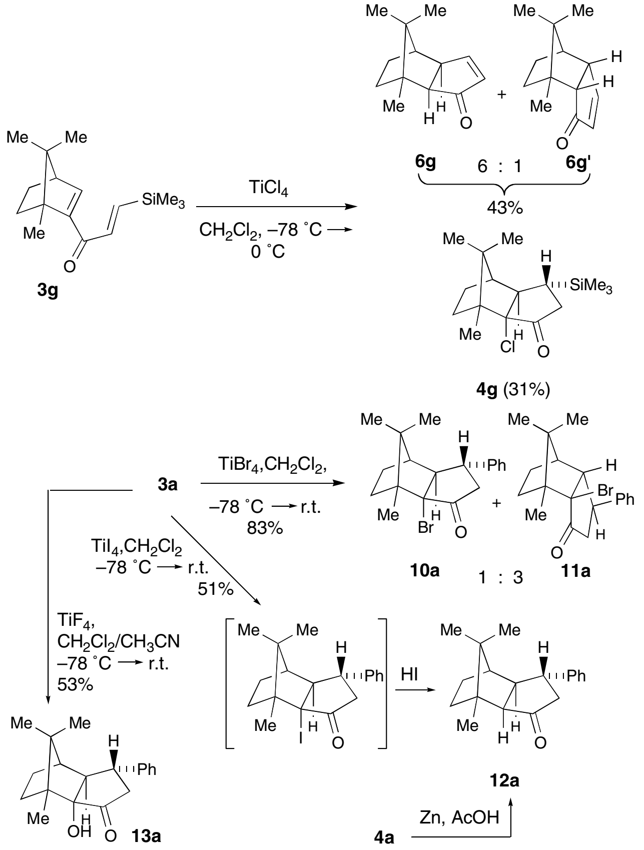
Dienone	R^1	R^2	Temperature	Time	Yield **4**[b] (%)	Yield **5**[b] (%)	Yield **6**[b] (%)	Yield **7**[b] (%)	Combined yield[b] (%)
3a	Ph	H	−78 → 0 °C	5 h	87	—	—	—	87
3b	Me	H	−78 → 0 °C	2 h	59	7	—	—	66
3c	*t*-Bu	H	−78 → 0 °C	2 h	50	16	—	—	66
3d	Ph	Me	−78 °C	10 min	25	—	25	—	50
3e	Ph	H	−78 → −20 °C	14 d	—	12	—	48	60
3f	Ph	Me	−78 °C	10 min	—	—	29	33	62

[a] Representative procedure: dienone **3** was dissolved in CH_2Cl_2 (0.01 M) and the solution was cooled to −78 °C. A CH_2Cl_2 solution of $TiCl_4$ (3.7 M; 1 equiv) was added dropwise, and the reaction was allowed to warm to the appropriate temperature and was stirred until TLC analysis showed complete consumption of **3**. The reaction was quenched (H_2O), the aqueous phase was extracted (Et_2O), and the combined organic layers were dried ($MgSO_4$) and concentrated. The resulting crude product was purified by flash chromatography, radial chromatography, or MPLC.

[b] All yields reflect isolated material after chromatographic purification.



Scheme 3.



Scheme 4.

enones **6g** and **6g′** in a 6:1 ratio (Scheme 4). These products were accompanied by an additional 31% of chloride adduct **4g**. The surprising extent of chloride capture along with the generally very facile desilylation pathway provides good evidence that this process is quite efficient. Substrate **3a** was also subjected to other titanium halide Lewis acids with interesting results. Treatment with $TiBr_4$ furnished bromide adducts **10a** and **11a**, analogous to **4a** and **5a**, in good yield as a 1:3 ratio. Interestingly, the major product in this case was the *endo* isomer **11a**. The reasons for this reversal in electrocyclization diastereoselectivity remain obscure. Titanium tetraiodide also effected the cyclization of **3a**, but the resulting product clearly lacked either an alkene C=C bond or an iodide. The presence of one extra proton in both ^1H NMR and HRMS data suggested reduced material, and the structure was tentatively assigned as **12a**. This assignment, including the *exo* orientation of the new cyclopentanone ring, was confirmed by correlation to the product resulting from Zn/AcOH reduction of **4a**. Product **12a** presumably results from deiodination of the initially formed α-iodo ketone by additional iodide.[23] Finally, cyclization with TiF_4 was attempted. However, the major product in this case was hydroxy-ketone **13a** rather than the expected fluoride. This result was attributed to the presence of adventitious water in the highly hygroscopic TiF_4.

This work highlights a new example of the interrupted Nazarov reaction. Bridged bicyclic dienone substrates constrained from ready elimination of the 2-oxidocyclopentenyl intermediate undergo efficient chloride trapping when subjected to stoichiometric $TiCl_4$. The resulting polycyclic products are formed with mostly high diastereoselectivity. Dienones appended to bicyclo[4.2.1]heptene ring systems undergo competitive skeletal rearrangement following the Nazarov electrocyclization. Further applications of this novel process will be published in due course.

Acknowledgements

We thank NIGMS and NSF (CHE 0078974) for their generous support of this work.

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