Iodine transfer cyclization mediated by DIBAL-H/THF

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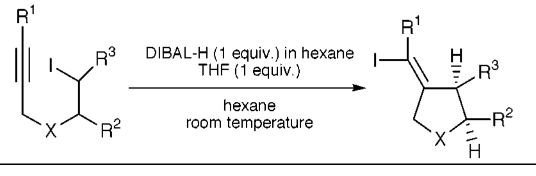
The combination of DIBAL-H/THF in a 1 : 1 ratio offers a unique and useful protocol for iodine transfer cyclization *via* a radical pathway; different iodo acetals are employed to obtain the corresonding tetrahydrofuran derivatives in good to excellent yield.

The trialkyltin hydride mediated cyclization of hex-5-enyl and hex-5-ynyl halides (and related radical precursors) is one of the most powerful tools at the disposal of the synthetic chemist for the formation of carbocycles and heterocycles.[1] However, one of the inherent limitations of these tin hydride reagents is the formation of a carbon–hydrogen bond at the end of the sequence. Reagents that mediate the *non-reductive*[2] cyclization have been the focus of recent research and in this endeavour the photolytic ditin method has emerged as a remarkable general procedure due to its unique ability to promote atom transfer cyclizations[3] (or isomerizations)[4] in a *non-reductive* manner. Herein, we report our preliminary results in this area and specifically the use of DIBAL-H–THF (in a 1 : 1 ratio) as a reagent for iodine transfer cyclization.

During the course of a study aimed at the hydrometallation and carbometallation reactions of functionalized substrates,[5] we wanted to prepare a vinylaluminium derivative[6] in the presence of a sensitive acetal moiety and an sp[3] carbon–iodine bond. Earlier studies of Yamamoto *et al.*[7] revealed that DIBAL-H cleaves acetals regio- and stereo-selectively to the corresponding alcohols due to the complexation of one of the oxygen atoms of the acetal with the oxyphilic organoaluminium compound.[8] In order to overcome this cleavage it was necessary to decrease the Lewis acidity of the aluminium reagent. Accordingly, we felt that addition of 1 equiv. of THF per equiv. of DIBAL-H, as used by Zweifel for the hydroalumination reaction of propargylic THP ethers,[9] should prevent acetal cleavage. However, when we performed the reaction as per our plan, the chemical outcome was totally different and instead of the hydroalumination reaction, we observed an unexpected iodine transfer cyclization under mild conditions and in good overall yield, as described in Table 1.

Although radical processes are known in aluminium chemistry,[10] this type of iodine transfer cyclization[11] mediated by DIBAL-H has no precedent.[12] As expected for such isomerizations, we obtained two isomers for the vinyl iodides **1**, **2**, **3** and **5** in a 1 : 1 ratio; no trace of the β-fragmentation of the starting material into the propargylic alcohol or enol ether was observed. This behavior is characteristic of the generation of a radical since an organometallic is known to β-eliminate[13] faster than the carbocyclization reaction across a triple bond.[14] Moreover, when the reaction is performed in the presence of 40 mol% of Galvinoxyl or TEMPO, no iodine transfer is observed and only the starting material is recovered. The vinyl iodide **1** was also obtained in the same ratio and yield by isomerization following the photolytic ditin procedure.[3] It is interesting to note that variation of the concentration decreases the yield of **1**, and more specifically by changing the amount of THF with respect to DIBAL-H as described in Table 2.

Table 1 Iodine transfer cyclization



Entries	R[1]	X	R[2]	R[3]	Product	Yield (%)[n]
1	H	O	OBu	H	**1**	80
2	Me	O	OBu	H	**2**	60
3	Et	O	OBu	H	**3**	60
4	H	O	$OCH_2CH_2CH_2$		**4**	90
5	H	CH_2	H	H	**5**	60

[a] Isolated yields after hydrolysis.

The best result for cyclization was obtained using a stoichiometric ratio of DIBAL-H/THF (entries 1 and 5). In all examined cases, very little radical attack on the solvent is observed (less than 3%). Several other aluminium reagents were tested and we found that the dialkylaluminium hydrides was the best reagents for this isomerization (DIBAL-H, 80%), followed by trialkylaluminium derivatives (Me_3Al, 65%), alanate derivatives[15] [sodium bis(2-methoxyethoxy)aluminium hydride, known as Red-Al, 40%], dialkylaluminium halides (Et_2AlCl, 16%), and methylaluminoxane $[Al(CH_3)O]_n$ in only 7% yield; no isomerization was observed with activated aluminium oxide. Although the combination DIBAL-H/THF can be replaced by DIBAL-H/THP without any change in this overall isomerization, Et_3N as co-additive (instead of THF) did not lead to a good yield (26%).

Disubstituted alkynes (Table 1, entries 2 and 3) do undergo similar isomerization to provide both vinylic isomers of **2** and **3** in 1 : 1 ratio,whereas a secondary alkyl iodide (entry 4) gives the cyclic product as the *cis* isomer with a *Z* : *E* ratio of 13 : 1 in excellent yield.

Although it is tempting to speculate that the aluminium complex behaves in a similar fashion to BEt_3 in the presence of oxygen,[16] when we repeated the reaction in entry 1 (Table 1) either in a totally degassed THF and hexane solution or in the dark, we did not observe any change in the chemical outcome of this cyclization. Interestingly, during the formation of **4**, addition of benzaldehyde after the completion of the reaction yielded benzyl alcohol quantitatively, which emphasized the presence of the hydride in the reaction mixture even after the normal course of reaction.

To substantiate the generality of this newly found strategy, we examined the similar treatment of a substrate which did not have an acetal moiety. We were pleased to find that 1-iodohex-5-yne (entry 5, Table 1) produced the cyclic isomer as expected. When the alkyne is slightly activated as 6-iodo-1-trimethyl-

Table 2 Variation of the DIBAL-H : THF ratio for the formation of **1**

Entries	DIBAL-H : THF	Yield (%)[a]
1	1 : 1	80
2	1 : 2	50
3	1 : 5	42
4	2 : 1	0
5	3 : 3	94

[a] Isolated yields after hydrolysis.

silylhex-1-yne, the classical hydroalumination reaction occurs to give the vinyl silane after hydrolysis.

In conclusion, the use of the combination DIBAL-H/THF provides a new and efficient method for iodine transfer cyclization for the formation of five-membered rings.[17] Synthetic applications of the present methodology[18] and investigations to understand the mechanistic rationale of the reaction are now in progress in our laboratory.

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17 *Experimental procedure* for **4** (it is important to follow the order of addition of substrates for these experiments): Into a dry, argon-flushed flask kept under a static pressure of argon is placed a 1.0 molar solution of DIBAL-H (1.76 ml, 1.76 mmol) in hexane. To the cooled solution (0 °C) is added sequentially THF (127 mg, 1.76 mmol) and the iodide (467 mg, 1.76 mmol) in hexane (1 ml). The solution is stirred at 0 °C for 15 min and then allowed to attain room temperature and stirred overnight. The reaction mixture was then quenched with 1 M HCl, extracted with Et_2O and washed several times with water, dried ($MgSO_4$) and then the solvent was evaporated to provide the crude product. After purification by chromatography on silica gel (10% EtOAc in hexanes), 421 mg (90%) of the title compound was obtained.

18 All our attempts to form the six-membered ring as well as to promote the isomerization across a double bond failed.

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