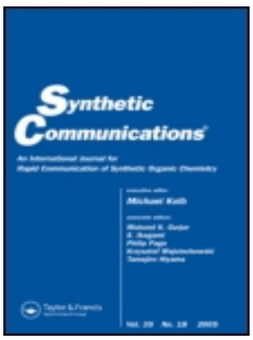

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LOW-VALENT TITANIUM MEDIATED REDUCTIVE CLEAVAGE OF BENZYLIDENE ACETALS: A MODIFIED McMURRY REACTION

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Abstract: Reductive cleavage of benzylidene acetals using low-valent titanium reagent results in the formation of aryl alkanes and stilbenes. Aliphatic acetals, however, remain unaffected. This cleavage offers an attractive, alternate stereoselective route to stilbenes in a modified McMurry reaction.

Cleavage of acetals is an important domain of research in protective chemistry[1a,b] and asymmetric synthesis[2a,b]. In continuation of our work on low-valent titanium (LVT) mediated synthetic transformations[3], we have explored the scope of this reagent for the cleavage of different carbon-heteroatom bonds[4a-d]. Towards this end, efficient protocols for the selective cleavage of C-O bonds in allyl, benzyl and propargyl ethers of alcohols and phenols, in the preference to dialkyl ethers were

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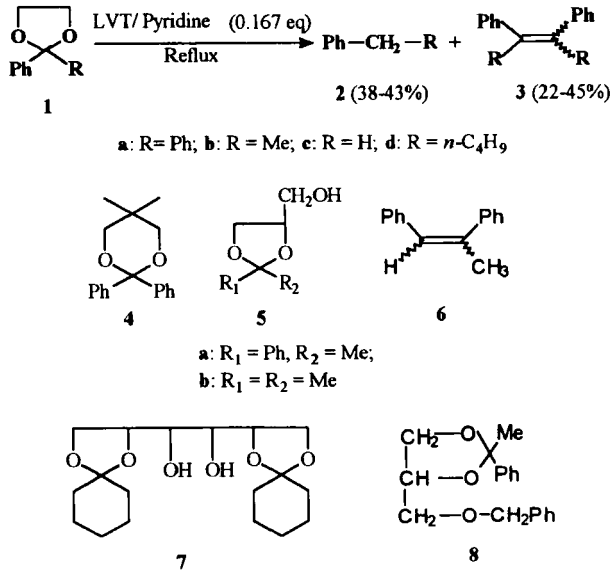
reported[4c,d]. It was argued that the relative stability of allyl and benzyl complexes of titanium is responsible for the selective cleavage of O-allyl/benzyl bonds over O-alkyl counterparts. Since acetals are extensively used in the protection of carbonyl functions, it was of interest to investigate the effects of LVT on these compounds. Amongst different acetals, benzylidene acetals which have two O-benzyl bonds are attractive substrates for this study. We envisaged that due to steric and electronic consequences, benzylidene acetals should undergo facile and stepwise cleavage with LVT. The benzylic radicals formed as a result of cleavage should provide, after quenching, the deoxygenated product/s. Therefore the cleavage of benzylidene acetals might provide unique opportunity for deoxygenation of the respective carbonyls. Hence, a detailed study on the reductive cleavage of C-O bonds in benzylidene acetals with LVT was undertaken and is presented here. A probable mechanism has also been postulated.

Although a variety of LVT-based reagents have been extensively utilized for the reductive dimerization of carbonyls to olefins[5a,b], their high oxophilicity and redox potentials have not been explored so far for the removal of oxygens from acetals (shielded carbonyls) which offers rich chemistry and holds considerable potential for the development of novel reactions and strategies. Although a number of methods[6a-c] have been developed for the reductive cleavage of acetals such as LAH-Lewis acids, Me_3SiH-Me_3SiOTf, Et_3SiH-acids, B_2H_6, $NaBH_3CN$-HCl, $NaBH_4$-CF_3COOH, Li/NH_3, $Zn(BH_4)_2$ along with Me_3SiCl including zirconium, herein we disclose our results on the LVT mediated deoxygenation of acetals.

Earlier, we have reported[4c] that Tyrlik's LVT reagent ($TiCl_3$-Mg-THF, Reagent A) selectively cleaves O-allyl bonds in preference to O-benzyl bonds, while

McMurry's reagent ($TiCl_3$-Li-THF, Reagent B) efficiently cleaves both O-allyl and O-benzyl bonds. Keeping this in mind, for the cleavage of O-benzyl bonds in the benzylidene acetals, a model reaction on 2,2-diphenyl-1,3-dioxolane (**1a**) was carried out using Reagent B. However, use of Reagent B proved to be capricious where no definite information could be generated. Though all the starting compound was consumed (monitored by TLC), the above reaction yielded a complex, non-tractable mixture of products. This could be due to the high activity of the Reagent B. Recently, in connection with our work on the rational design of reagents[7a-d], it was demonstrated that the activity of THF solvated LVT can be reduced by the addition of π-acceptor ligands such as pyridine[7c] or fullerenes[7d]. We, therefore, anticipated that use of pyridine might modulate the reaction. In fact, the use of pyridine (0.167 eq. of LVT) proved ameliorative. Thus, when the reaction on **1a** was repeated with a modified LVT species [$TiCl_3$/Li/THF/pyridine (0.167 eq.)] (Reagent C) under refluxing conditions, deoxygenative cleavage liberated a mixture of two products (Scheme 1) which were characterized as diphenylmethane (**2a**, 43%) and tetraphenylethylene (**3a**, 26%) (Table 1, entry 1). Reagent C has therefore been used for further investigations. The formation of **2a** and **3a** suggests that two independent reaction pathways are in operation. A working mechanism is proposed to explain the formation of these products.

Similar to McMurry reaction[5a,b] which involves initial formation of ketyl radical by electron transfer; the reductive cleavage of acetals proceeds *via* partial fragmentation of one of the two O-benzyl bonds through single electron transfer (SET) mechanism to furnish the "intermediate radical I" (Scheme 2). However, unlike McMurry reaction where the ketyl radical undergoes only dimerization to form a pinacolate; in the present case, the radical **I** follows two possible pathways *viz.*, (i) dimerization to pinacol **II** (path a) and/or (ii) quenching of the radical **I** by

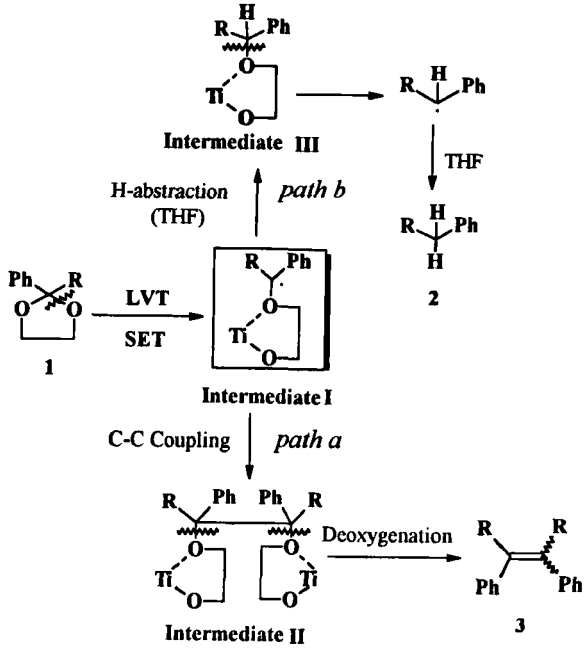


Scheme 1

Table 1. Reductive Cleavage of Benzylidene Acetals.

Entry	Substrate/s	Time[a](h)	Product/s (% yield[b])
1	**1a**	16	**2a** (43) + **3a** (26)
2	**1b**	18	**3b** (45)[c]
3	**1c**	16	**3c** (42)[c]
4	**1d**	16	**2d** (38) + **3d** (32)
5	**4**	2.5	**2a** (42) + **3a** (28)
6	**5a**	16	**3b** (32)
7	**1b + 1c**	16	**3b**[d] (26) + **3c**[d] (28) + **6**[d](22)
8	**5b**	16	no reaction
9	**7**	16	no reaction
10	**1a + 5b**	16	**2a** (40) + **3a** (22) + **5b** (98)

[a]All reactions were carried out under reflux. [b]Yields refer to pure isolated product. [c]Other products *i.e.*, aryl alkanes **2** were not isolated. [d]These stilbenes were characterized by GC and GC-MS and the yields refer to GC yields.



Scheme 2

solvent (THF) to **III** (path b). Analogous to the McMurry reaction the intermediate **II** is deoxygenated to yield alkene **3**. On the other hand, **III** undergoes further O-benzyl bond cleavage followed by radical quenching by solvent (THF) to yield aryl alkanes **2**. Exothermicity of the strong Ti/O bonds in TiO_2 may be the driving forces for these reactions.

To substantiate the postulated mechanism and to explore the generality of C-O bond cleavage, several benzylidene acetals were used as depicted in Table 1. Thus, the reaction on 2-methyl-2-phenyl-1,3-dioxolane (**1b**) yielded the corresponding 2,3-diphenyl-2-butene (**3b**) as sole product in 45% yield (entry 2). Similarly, the

reaction on 2-phenyl-1,3-dioxolane (**1c**) yielded stilbene (**3c**) in 42% yield (entry 3). However, the deoxygenated aryl alkanes, **2** *viz.*, ethylbenzene (**2b**) and toluene (**2c**) from **1b** and **1c** respectively could not be isolated due to their volatility under the experimental conditions. But, the reaction on 2-*n*-butyl-2-phenyl-1,3-dioxolane (**1d**) yielded the aryl alkane (**2d**) in addition to stilbene (**3d**) (entry 4). Reductive cleavage was also carried out on six membered acetal *i.e.*, benzylidene acetal of 1,3-dioxane. In fact, both **2a** (42%) and **3a** (28%) were isolated when reaction was performed on 5,5-dimethyl-2,2-diphenyl-1,3-dioxane (**4**) (entry 5). Moreover, cleavage of **4** was much faster (2.5 h) when compared (16 h) with that of the corresponding 1,3-dioxolane (**1a**). In a similar reaction on 2-methyl-2-phenyl-4-hydroxymethyl-1,3-dioxolane (**5a**), the expected stilbene **3b** was obtained in 32% yield (entry 6). Efforts to isolate the alcohols *viz.*, ethylene glycol, 2,2-dimethyl-propane-1,3-diol and glycerol were unsuccessful probably because of their ready deoxygenations[5a,b,8].

The intermediacy of radical **I** during the reductive cleavage of aromatic acetals was substantiated by crossover experiments. Thus, when a 1:1 mixture of **1b** and **1c** were exposed to Reagent C, in addition to the expected symmetrical stilbenes (**3b** and **3c** respectively), the crossover product *i.e.*, 1,2-diphenyl-1-propene (**6**) (entry 7) was also isolated. This could be possible only if the reaction passes through the intermediacy of radical **I**.

Effects of Reagent C on the cleavage of aliphatic acetals were also investigated. In fact, when 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane (**5b**) or 1,2:5,6-di-*O*-cyclohexylidene-*D*-mannitol (**7**) were exposed to this reagent, no cleavage took place and starting compounds were recovered (entries 8, 9). The compatibility of aliphatic acetals could be further established by a competitive reaction with a

mixture of **1a** and aliphatic acetal **5b**. Thus, when a 1:1 mixture of **1a** and **5b** was subjected to Reagent C, **2a** (40%) and **3a** (22%) were isolated, along with the almost quantitative recovery of **5b** (entry 10). The selective cleavage of C-O bonds in benzylidene acetals in preference to their aliphatic counterparts could be attributed to the stability gained through resonance in aryl alkyl radical.

The stereochemistry of the stilbene **3** formed as a result of such reductive processes is of special significance. Radical **I** offers additional steric constraints for the dimerization (C-C coupling) towards pinacolate **II** as compared to those obtained directly from carbonyls (McMurry reaction[5a,b]). The deoxygenation of pinacolate **II** is likely to result the *trans* stilbene preferentially possibly due to the higher bulk offered by the residual diol moiety in **II** unlike in McMurry reaction. A comparative study of the stereoselectivity of stilbenes formed through deoxygenation of carbonyls (normal McMurry reaction) or through deoxygenation of the corresponding benzylidene acetals of the carbonyls are presented in Table 2. In fact, McMurry reaction on acetophenone (selected as model substrate) using $TiCl_3$-Li-THF (Reagent B) afforded 89% of the corresponding stilbene **3b** (entry 1) with the predominant formation of the *trans* isomer[9]. Addition of 0.167 equivalent of pyridine to the LVT *i.e.*, use of Reagent C reduces the yield of **3b** to 80% without affecting the stereoselectivity (entry 2). However when the carbonyl in acetophenone is masked in the form of 1,3-dioxolane as in **1b**, the reaction with Reagent C enhances the *trans* stereoselectivity in **3b**, but the yield of stilbene decreases to 45% (entry 3). It was anticipated that with the increase in steric bulk in the diol, the stereoselectivity in the stilbene would increase further. In fact, use of bulkier alcohol for the protection of carbonyl function in acetophenone as in **5a** resulted in the substantial improvement of stereoselectivity (91% *trans*, entry 4).

Table 2. Stereoselectivity in 2,3-diphenyl-2-butene (3b)

Entry	Substrate	LVT	Time[a] (h)	Yield (%)	$E : Z$[b]
1	Acetophenone	Reagent B	16	89	75 : 25
2	Acetophenone	Reagent C	16	80[c]	75 : 25
3	**1b**	Reagent C	18	45	81 :19
4	**5a**	Reagent C	16	32	91: 9
5	**8**	Reagent C	20	38	99 : 1

[a]All reactions were carried out under reflux. [b]Isomeric ratio was established from NMR data[9]. [c]Considering 9% unreacted starting material along with 5% of the corresponding pinacol.

Similarly, in a more crowded environment as in benzylidene acetal **8**, high stereoselectivity (E/Z = 99:1) could be achieved though at the cost of low yield (entry 5). Hence the reductive cleavage of benzylidene acetals offers an indirect protocol for olefination with improved stereoselectivity using LVT reagents in a modified McMurry pathway.

Thus, it has been shown that the benzylidene acetals undergo stepwise C-O bond cleavages leading to the formation of both corresponding symmetrical stilbenes and alkanes as a result of deoxygenation. Aliphatic acetals were unaffected under similar reaction conditions. Thus, it should be possible to deoxygenate aromatic carbonyls in presence of aliphatic ones *via* formation of their benzylidene acetals. The preferential cleavage of C-O bonds in benzylidene acetals is aided by the resonance stability in the intermediate benzylic radical which is absent from those generated from the aliphatic ones. The reductive opening of acetals is subjected to steric factors which probably influences the stereochemical courses of the

reaction. This is the first report of detailed study of the reactivity of acetals towards LVT reagents. In addition, the reductive cleavage of benzylidene acetals is likely to be useful for the stereoselective synthesis of stilbenes in a modified McMurry reaction. Further, detail information on C-heteroatom bond cleavages in different electronic and steric environments finds use in developing new chemical reactions. Studies in this direction involving cleavage of *N,N*-, *N,O*-, and *O,S*-acetals are currently under investigation in our laboratory.

Experimental

General Details. General information regarding instruments, techniques and sources of chemicals used are the same as mentioned in our previous publication[7a].

1,3-Dioxolanes and 1,3-dioxanes were prepared according to literature procedure[10].

General Procedure for the Reductive Cleavage of Acetals. A mixture of $TiCl_3$ (2.31 g, 15 mmol) and lithium (346 mg, 49.5 mmol) in freshly dried THF (70 ml) was refluxed (argon, 3 h). To the LVT reagent thus prepared, pyridine (2.5 mmol, 0.2 ml) was added at 25 °C and stirred (10 min.). To this modified reagent, a benzylidene or an aliphatic acetal (5 mmol, 5 ml THF) was added and then refluxed for certain periods (Tables 1 and 2) for respective substrates. After completion (monitored by TLC), the reaction mixture was cooled followed by slow, careful addition of saturated solution of ammonium chloride (25 ml.) and stirred (10 min.). It was then diluted with petroleum ether-ethyl acetate mixture (80:20) and passed through celite; the organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent gave the crude product which was

purified by preparative thin layer chromatography (SiO_2) to furnish aryl alkane **2** and stilbene **3**. The yields are reported in the Tables 1 and 2.

Products were characterized by comparison with authentic samples (IR, ^1H NMR, TLC and m.p.).

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