Unprecedented Reductive Dealkoxylation of Aryl Alkyl Ethers and Intramolecular C–C Coupling of 2,2′-Dialkoxystilbenes with Low Valent Titanium: One-pot Synthesis of Phenanthrenes

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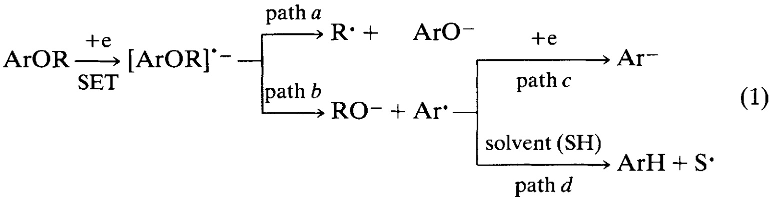
Facile dealkoxylation of aryl alkyl ethers has been carried out using $TiCl_3$–Li–THF (tetrahydrofuran); a novel one-pot synthesis of phenanthrenes from *ortho*-alkoxyaromatic aldehydes/ketones is described.

In continuation of our work[1–3] on the use of low valent titanium in organic synthesis, we report for the first time an unusual reductive dealkoxylation of aryl alkyl ethers and intramolecular C–C coupling of 2,2′-dialkoxystilbenes leading to a one-pot synthesis of phenanthrenes from *ortho* alkoxy aromatic aldehydes/ketones by Ti^0.

2,3-Bis(4-methoxyphenyl)but-2-ene **2c** was obtained by the reductive deoxygenation of 4′-methoxyacetophenone **1b** with Ti^0 species prepared from $TiCl_3$–Li–dimethoxyethane (DME) (Table 1, entry 1). Our recent findings on the profound influence of solvents (THF *vs.* DME) on the reactivity and stereochemistry ($E:Z$) of reductive dimerisation of aromatic carbonyl compounds,[1] prompted us to undertake the present investigation. This communication deals with results obtained by the change of solvent from DME to THF. Thus, Ti^0 induced coupling of **1b** in THF produced 2,3-diphenylbut-2-ene **2g** (Table 1, entry 10) exclusively without any detectable amount of **2c**. Thus, it was inferred that under the above reaction conditions, reductive dealkoxylation also took place in tandem with reductive deoxygenation of the carbonyl function. The fact that dealkoxylation by Ti^0 in THF is an independent step was further substantiated by the dealkoxylation of 4-methoxybiphenyl and 6-methoxytetralin to biphenyl and tetralin in 40 and 43% yields, respectively. This observation is in contrast with the reported compatibility of ether functionalities in Ti^0-induced carbonyl coupling reactions.[4c]

Though elegant methods of deoxygenation of alcohols have been reported recently,[5] relatively few good methods are available for the deoxygenation of phenols.[6,7] A selective indirect deoxygenation of phenols *via* phosphates with Ti^0 ($TiCl_3$–K–THF) in preference to alkyl ethers has been reported earlier by Welch *et al.*[8] Therefore, use of Li as the reducing metal *i.e.* $TiCl_3$–Li–THF system, in the present investigation turned out to be a critical factor for the dealkoxylation of aryl alkyl ethers.

Ti^0 induced dealkoxylation of aryl alkyl ethers presumably follows a mechanism similar to the one proposed for the ether cleavage by alkali metals.[9] Eqn. (1) shows the possible steps



$$\mathrm{ArOR} \xrightarrow[\text{SET}]{+e} [\mathrm{ArOR}]^{\cdot -} \begin{cases} \xrightarrow{\text{path } a} \mathrm{R}^{\cdot} + \mathrm{ArO}^{-} \\ \xrightarrow{\text{path } b} \mathrm{RO}^{-} + \mathrm{Ar}^{\cdot} \begin{cases} \xrightarrow[\text{path } c]{+e} \mathrm{Ar}^{-} \\ \xrightarrow[\text{path } d]{\text{solvent (SH)}} \mathrm{ArH} + \mathrm{S}^{\cdot} \end{cases} \end{cases} \qquad (1)$$

Table 1 Reductive deoxygenation–reductive dealkoxylation of alkoxy aromatic aldehydes–ketones by low valent titanium

			Products[a]	
Entry	Substrates	Reagents	Stilbenes yield (%)	Phenanthrenes yield (%)
1	**1b**	$TiCl_3$–Li–DME	**2c** (78)[13]	—
2	**3a**	$TiCl_3$–Li–DME	**2a** (79)[14,f]	—
3	**3a**	$TiCl_3$–Li–THF[b]	—	**4a** (36)[15]
4	**3b**	$TiCl_3$–Li–THF	—	**4b** (25)[15]
5	**3c**	$TiCl_3$–Li–THF	—	**4c** (35)[16,f]
6	**3d**	$TiCl_3$–Li–THF	—	**4d** (36)[15,f]
7	**3e**	$TiCl_3$–Li–THF	—	**4e** (38)[g]
8	**3f**	$TiCl_3$–Li–THF	—	**4a** (38)
9	**3g**	$TiCl_3$–Li–THF	—	**4a** (32)
10	**1b**	$TiCl_3$–Li–THF	**2g** (42)[4a]	—
11	**1a**	$TiCl_3$–Li–THF	**2b** (53)[17]	—
			2e (18)[g]	—
			2g (10)	—
12	**3a**	$TiCl_3$–Mg–THF[c]	**2a** (85)	—
13	**3a**	$TiCl_4$–Zn–THF[d]	**2a** (89)	—
14	**3a**	$TiCl_4$–Mg–THF[e]	**2a** (90)	—

[a] All the products showed the expected IR, MS and ^{1}H NMR spectra. Yields are based on the product purified by preparative thin layer or column chromatography. [b] Followed the same procedure as in ref. 4*a* except THF was used in place of DME. [c] Followed the same procedure as in ref. 4*d*. $TiCl_3$: Mg : ketone was 1 : 1.7 : 0.25. [d] Followed the same procedure as in ref. 4*b*. $TiCl_4$: Zn : ketone was 1 : 2 : 0.25. [e] Followed the same procedure as in ref. 4*e*. $TiCl_4$: Mg : ketone was 1 : 1 : 0.25. [f] *Selected physical and spectral data* for **2a**, **4c** and **4d**.

2a: Mixture of *cis*- and *trans*-isomers; m.p. 82–83 °C (lit.[14] m.p. 86–88 °C); IR (KBr) ν_{max}/cm^{-1}: 1600, 1500, 1440, 1030 and 760; ^{1}H NMR (CCl_4) δ: 1.7 and 2.03 (2s, 6H, 2 × –Me), 3.77 and 3.83 (2s, 6H, 2 × –OMe), 6.47–7.42 (m, 8H, ArH); MS(*m/z*): 269 (M^+ + 1), 268 (M^+), 135.

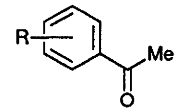
4c: M. p. 102–103 °C (lit.[16] m.p. 103–105 °C); IR (KBr) ν_{max}/cm^{-1}: 1580, 750 and 720; ^{1}H NMR (CCl_4) δ: 1.37 (t, 6H, 2 × $-CH_2-\mathit{CH}_3$, J = 7 Hz), 3.2 (q, 4H, 2 × $-\mathit{CH}_2-CH_3$, J = 7 Hz), 7.43–8.8 (m, 8H, ArH); MS (*m/z*): 234 (M^+), 219.

4d: M.p. 239–240 °C (lit.[15] m.p. 240 °C); IR (KBr) ν_{max}/cm^{-1}: 1490, 1070, 760, 700 and 620; ^{1}H NMR (CCl_4) δ: 7.49–8.84 (m, ArH); MS (*m/z*): 330 (M^+), 253.

[g] Satisfactory spectroscopic and analytical data were obtained for the new compounds **2e** and **4e**.

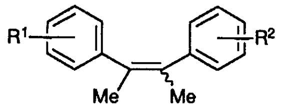
for the above dealkoxylation. Cleavage according to path *a*, would cause only *o*-dealkylation. However, since 2,3-bis(4-hydroxyphenyl)but-2-ene **2d** was not obtained from the reaction of **1b** with Ti^0, the other type of cleavage (see path *b*) must be operative under the present reaction conditions.

In view of the presence of phenanthrene moieties in several natural products, often with valuable chemotherapeutic properties,[10] considerable efforts have been directed to their syntheses.[11] Our recent work[1] has shown that the use of $TiCl_3$–Li–THF in the reductive coupling of aromatic carbonyl compounds leads to preferential formation of (*Z*)-stilbenes, an essential attribute for the synthesis of phenanthrenes. This, along with the present methodology for dealkoxylation of aryl alkyl ethers, could be useful for the synthesis of phenanthrenes. From a retrosynthetic perspective (Scheme 1), *ortho* alkoxy aromatic aldehydes/ketones **3** seemed to be appropriate substrates as the incipient dealkoxylated (*Z*)-alkene can undergo intramolecular coupling in preference to other reactions (paths *c* and *d*) leaving the dealkoxylated *E*-isomer **2g**. Thus, when a reaction was carried out with 2′-methoxyacetophenone **3a** with Ti^0 ($TiCl_3$–Li–THF), 9,10-dimethylphenanthrene **4a** was obtained as the sole product (Table 1, entry 3). Surprisingly however, no dealkoxylated (*E*)-alkene **2g** was isolated. Use of other reagent systems such as $TiCl_3$–Li–DME, $TiCl_3$–Mg–THF, $TiCl_4$–Zn–THF and $TiCl_4$–Mg–THF furnished **2a** as the sole product (Table 1, entries 2, 12, 13 and 14) without any dealkoxylation. This demonstrates the uniqueness of our reagent system ($TiCl_3$–Li–THF) for reductive dealkoxylation of aryl alkyl ethers. Intermediary of **2a** in the formation of **4a** from **3a** was demonstrated by the direct conversion of **2a** to **4a** in moderate yield (51%). However, in contrast to **3a**, 2′-hydroxyacetophenone **1c** under the above reaction conditions did not yield **4a**, but a mixture of 2,3-bis(2-hydroxyphenyl)but-2-ene **2f** and 2,3-bis(2-hydroxyphenyl)butane[3] was obtained.



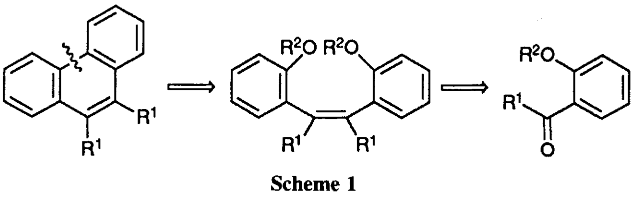
1

a; R = 3′–OMe
b; R = 4′–OMe
c; R = 2′–OH

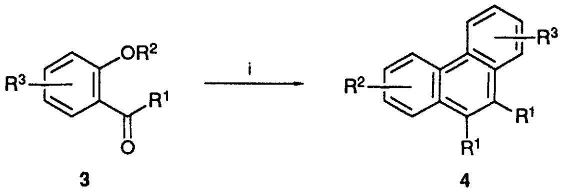


2 (*E* and *Z*)

a; R^1 = 2–OMe, R^2 = 2′–OMe
b; R^1 = 3–OMe, R^2 = 3′–OMe
c; R^1 = 4–OMe, R^2 = 4′–OMe
d; R^1 = 4–OH, R^2 = 4′–OH
e; R^1 = 3–OMe, R^2 = H
f; R^1 = 2–OH, R^2 = 2′–OH
g; R^1 = R^2 = H



Scheme 1



3

a; R^1 = R^2 = Me, R^3 = H
b; R^1 = R^3 = H, R^2 = Me
c; R^1 = Et, R^2 = Me, R^3 = H
d; R^1 = Ph, R^2 = Me, R^3 = H
e; R^1 = R^2 = Me, R^3 = 5′–Me
f; R^1 = Me, R^2 = Et, R^3 = H
g; R^1 = R^2 = Me, R^3 = 4′–OMe

4

a; R^1 = Me, R^2 = R^3 = H
b; R^1 = R^2 = R^3 = H
c; R^1 = Et, R^2 = R^3 = H
d; R^1 = Ph, R^2 = R^3 = H
e; R^1 = Me, R^2 = 2–Me, R^3 = 7–Me

Scheme 2 *Reagents and conditions*: i, $TiCl_3$–Li–THF, heat

Application of this methodology with other *ortho* alkoxyaromatic aldehydes and ketones **3b–f** as substrates (Scheme 2) expectedly furnished the corresponding phenanthrenes **4a–e** (Table 1, entries 4–8), thereby demonstrating the generality of the reaction. Use of 2′,4′-dimethoxyacetophenone **3g** as substrate yielded a completely demethoxylated product **4a** (Table 1, entry 9), suggesting ready demethoxylation of the *para* methoxy group. However, dealkoxylation of 3′-methoxyacetophenone **1a** was partial as evidenced by the formation of a mixture of **2b**, **2e** and **2g** (Table 1, entry 11) under the same reaction conditions.

Thus, the uniqueness of Ti^0 generated by using Li as the reducing metal in a THF medium for the dealkoxylation of aryl alkyl ethers has been established. Based on the above findings in conjunction with our previously described method for (*Z*)-selective reductive deoxygenation of aromatic carbonyls, a general one-pot synthesis of phenanthrenes from readily accessible *ortho* alkoxy aromatic aldehydes/ketones has been formulated which otherwise needs lengthy routes.[12] Mechanistic investigation and optimization of the yields are currently under progress.

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