Reductive Dicarbonyl Coupling with Low-valent Titanium Reagents: a New Entry to Phenanthrene Alkaloids

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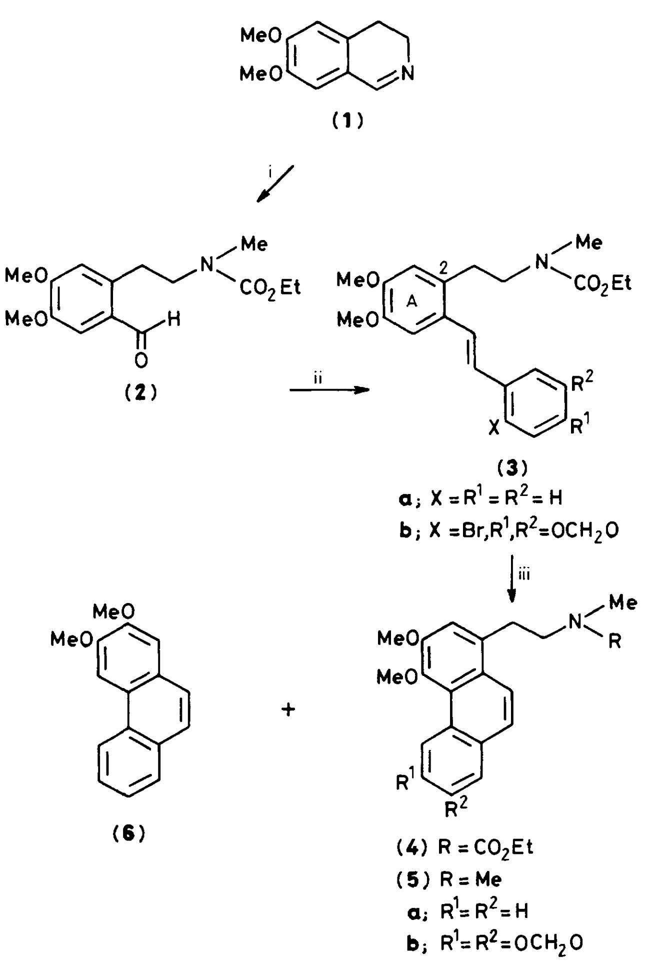
A new and direct synthesis of phenanthrene alkaloids using a low-valent titanium reagent is described which is compatible with ethoxycarbonyl as the *N*-protecting group.

We are currently studying the use of low-valent titanium reagents,[1] the chemistry of which has been investigated extensively recently and has been applied to the synthesis of natural products.[2] However, these natural products have not contained nitrogen groups, the reactivity of which with low-valent titanium has been little studied.[3]

We have recently applied reductive dicarbonyl coupling with low-valent titanium to the synthesis of the phenanthrene skeleton,[2b] and we felt that this approach could also be extended to the total synthesis of the phenanthrene alkaloids, a class of aporphinoid compounds only obtained, to date, by degradation of the corresponding aporphines.[4] Our synthetic



Scheme 1. *Reagents:* i, MeI, then HO^-, $ClCO_2Et$; ii, ArCHO, $TiCl_3$, Li, 1,2-dimethoxyethane; iii, *hν*.

plan is based upon cyclization of a stilbene precursor obtained by mixed dicarbonyl coupling[5] of two suitable aldehydes, one of which incorporates the ethanamide side chain present in the phenanthrene alkaloids, with the nitrogen protected as the ethoxycarbonyl derivative.

We first studied the preparation (Scheme 1) of atherosperminine (**5a**), a typical phenanthrene alkaloid with known psychopharmacological properties.[6] The methiodide of the isoquinoline (**1**) was thus treated with ethyl chloroformate and 45% KOH to give compound (**2**) in 87% yield.[7] Mixed reductive coupling of (**2**) and benzaldehyde with titanium(III) chloride (Li, 1,2-dimethoxyethane, reflux) afforded the stilbene (**3a**) in 55% yield. The compatibility of the urethane group with low-valent titanium species is to be noted, since this can be potentially applied to the synthesis of other nitrogen-containing compounds. Photocyclization of (**3a**) was attempted under various conditions, the best yield of the phenanthrene (**4a**) (35%) being achieved by using a 450 W Hanovia medium-pressure mercury lamp equipped with a Pyrex filter in Et_2O as solvent and I_2–O_2 as oxidant. This relatively low yield in (**4a**) is due, in part, to the formation of 2,3-dimethoxyphenanthrene (**6**) (35% yield) which we assume is formed from (**3a**) *via* alternative cyclization at position 2 of ring A and subsequent elimination of the side chain with re-aromatization. It is known that 2,2′,4,4′-tetramethyl-5,5′-dimethoxystilbene cyclizes at positions 6 and 2′ with loss of methane.[8]

Reduction of (**4a**) with $LiAlH_4$ afforded, in 82% yield, atherosperminine (**5a**), whose physical and spectroscopic data agree with those reported for the alkaloid.[9]

In order to improve the photocyclization step by avoiding formation of (**6**), we attempted to introduce a halogen atom at position 2′ of (**3**). However, coupling of (**2**) and 2-bromobenzaldehyde afforded the same stilbene (**3a**). When the reaction was applied to 2-bromo-4,5-methylenedioxybenzaldehyde the stilbene (**3b**) was obtained in 67% yield, suggesting that the homolytic fission of the Ar–Br bond with low-valent titanium species is less favoured. Photocyclization[10] of (**3b**) gave (**4b**) in 50% yield, reduction of which afforded thalictuberine (**5b**) in 87% yield, with spectral data agreeing with literature data.[11]

This route thus constitutes an easy method for the preparation of phenanthrene alkaloids without having to resort to the corresponding aporphines.

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