Pergamon

Tetrahedron Letters 42 (2001) 7393–7396

TETRAHEDRON LETTERS

Hypervalent iodine(III)-mediated oxidative acetoxylation of 2-methoxyphenols for regiocontrolled nitrogen benzannulation

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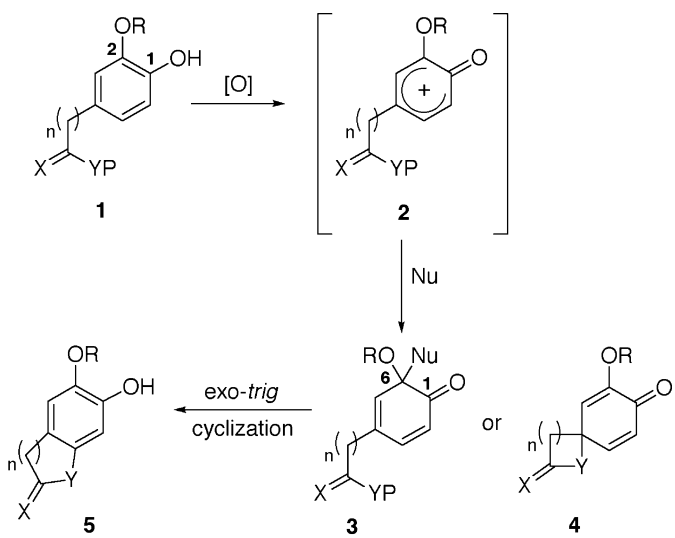
Received 4 July 2001; accepted 17 August 2001

Abstract—Nitrogen-tethered 2-methoxyphenols are conveniently dearomatized into synthetically useful orthoquinol acetates by treatment with phenyliodine(III) diacetate in methylene chloride at low temperature. Subsequent fluoride- or base-induced intramolecular nucleophilic addition reactions furnish indole and quinoline derivatives. The potential of this methodology for the synthesis of a functionalized lycorine-type alkaloid skeleton is introduced here. © 2001 Elsevier Science Ltd. All rights reserved.

The oxidative activation of hydroxylated aromatic rings or arenols is a valuable tactic for the synthesis of polyoxygenated carbo- and heterocyclic motifs of natural products.[1] This activation can easily find expression in the displacement of two ring electrons through the phenol unit to furnish a phenoxenium ion-type species with concomitant loss of the phenolic hydrogen (e.g. **1**→**2**, Scheme 1).[2] In the presence of a nucleophile, this electrophilic species is trapped either in a concerted or a stepwise fashion to give rise to cyclohexadienone derivatives. Various metallic reagents have traditionally been used to mediate these oxidative nucleophilic substitutions,[2,3] but hypervalent iodine(III) derivatives have today become the reagents of choice because their utilization is easy to implement, economic and non-toxic.[4–7]

Our interest in the chemistry of hypervalent iodine(III) reagents resides in their remarkable and versatile utility in the transformation of functionalized 2-alkoxyarenols **1** into 6-alkoxycyclohexa-2,4-dienones **3** and 6-alkoxycyclohexa-2,5-dienones **4** (Scheme 1). Reaction outcomes can be controlled by the choice of the iodine(III) ligands whose chemical reactivity can vary. The two kinds of hypervalent iodine(III) reagents that we commonly use to oxidatively activate arenols are commercially available phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA).

The first reagent bears nucleophilic acetate ligands that can participate in the oxidative nucleophilic substitution reaction whereas the second one can release a strong organic acid, trifluoroacetic acid (TFA, $pK_a = 0.23$) into the reaction medium; this acidity can be exploited for facilitating special bond cleavage in nucleophilic addition cascades.[8] With both iodine(III) species, iodobenzene and residual organic acids are conve-



R = alkyl group; X = H,H or O; Y = N- or O-nucleophile
P = H or protecting group; Nu = any nucleophiles

Scheme 1.

Keywords: hypervalent iodine; arene chemistry; oxidative activation; orthoquinol acetate; heterocyclization.

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PII: S0040-4039(01)01514-3

niently removed by simple drying under vacuum. No toxic metallic salts are generated in contrast to the alternative use of lead- or thallium-based reagents in Wessely or McKillop oxidation.[9–11]

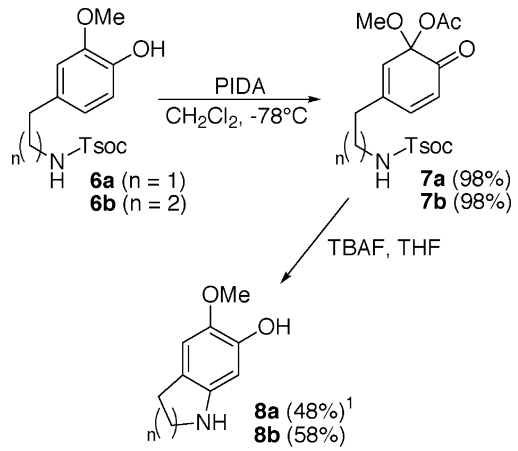
PIDA is used to generate 6-acetoxy-6-alkoxycylohexa-2,4-dienones **3** (Scheme 1, Nu = OAc from PIDA), commonly referred to as orthoquinol acetates, from 2-alkoxyarenols **1**. Arenols are usually 2-methoxylated because they are easily derived from commercially available materials, and because the 2-methoxy group has proved its efficacy at directing the attack of the entering nucleophile on its carrier carbon rather than on the other *ortho* and *para* electrophilic centers.[2,12] Starting 2-methoxyarenols can be appended with oxygen- or nitrogen-bearing tethers.[1] Protecting groups are placed on these centers when their nucleophilic power otherwise permits intramolecular reactions to compete with the desired acetoxylation. Such competitions usually lead to oxo- or azaspirocyclohexa-2,5-dienone derivatives **4** (Scheme 1).[13,14]

Adequately protected orthoquinol acetates of type **3** can then be further transformed into benzannulated heterocycles **5** via *exo-trig* cyclization (Scheme 1). Differently sized benzannulated ether rings have been prepared by this methodology.[15] Nitrogen versions of these oxygen heterocyclizations have now been implemented for the construction of benzannulated nitrogen-containing five- and six-membered rings. Triisopropylsilyloxycarbonyl (Tsoc)-protected[16] amino-tethered 2-methoxyphenols **6a**/**b** were submitted to PIDA-mediated oxidative acetoxylation to furnish the orthoquinol acetates **7a**/**b** in excellent yields. Treatment with TBAF as a source of fluoride ions for desilylation in THF induced cyclizations to furnish the indoline **8a**[1] and the tetrahydroquinoline **8b** as the only isolated regioisomers in good yields, both resulting from *exo-trig* cyclizations (Scheme 2). The carbamate **9** directly furnished the corresponding orthoquinol acetate **10** in good yield, although a certain instability of this ketal species was noticed in $CDCl_3$ solution during the NMR analysis. Nevertheless, the acetate **10** was cyclized upon treatment with LiHMDS in THF to give the indoline **11** in 32% yield (Scheme 3). At this point, it is difficult to attribute this rather moderate cyclization yield to the instability of the orthoquinol acetate intermediate or to the lower nucleophilic force of the carbamate nitrogen when compared to that of the transient amino anion released upon cleavage of the Tsoc group in **7a**/**b** (Scheme 2).

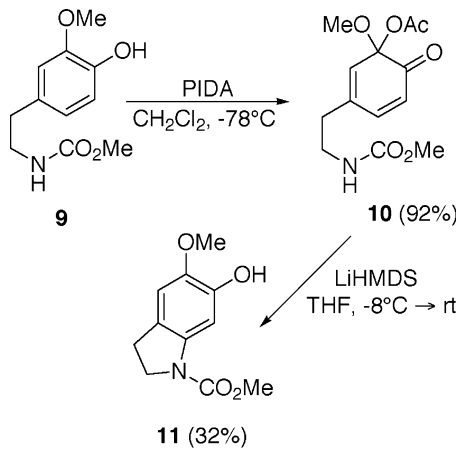
Amide nitrogen benzannulation was next investigated with the aim of preparing functionalized 2-oxindoles and 2-oxoquinolines, which can potentially constitute interesting pharmacophores. Benzylated amido 2-methoxyphenols **12a**/**b** were thus transformed into orthoquinol acetates **13a**/**b**. Notwithstanding a certain instability of these monoketal intermediates that was here also noticed in $CDCl_3$ and acetone-d_6 solutions over prolonged periods of time (ca. 5–10 h), base-induced cyclizations were carried out. Potassium *tertio*-butoxide in refluxing THF was identified as the best base system to induce the desired benzannulation. The 2-oxindole **14a** and the 3,4-dehydro-2-oxoquinoline **14b** were obtained in unoptimized yields of 17% and 38%, respectively (Scheme 4).

This work is reminiscent of investigations by Kita,[17] Wipf,[18] Jacquesy[19] and Ciufolini[14] on the preparation of hydroindolenones and hydroquinolenones using PIDA or PIFA to transform various starting *N*-acyl and *N*-alkylamino phenols into cyclohexa-2,5-dienone intermediates that are adequately functionalized for intramolecular Michael-type nitrogen additions. In our work, Tsoc-protected amine, benzylated amide and carbamate nitrogens are induced to benzannulate from cyclohexa-2,4-dienone intermediates.

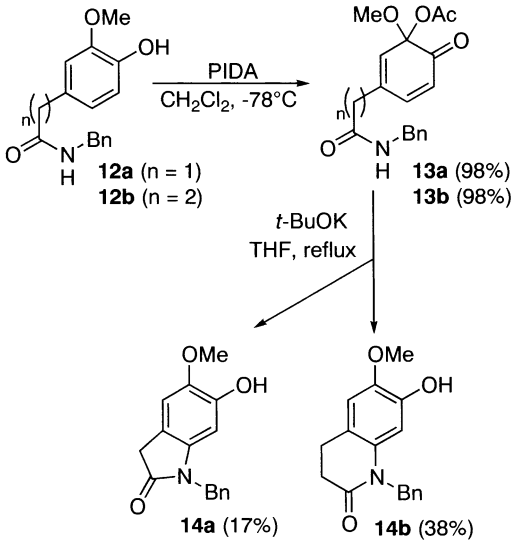
Application of this methodology to natural products synthesis is being explored for the construction of the lycoran-type polycyclic skeleton of *Amaryllidaceae* alkaloids such as lycorine (**18**) (Scheme 5).[20,21] Thus, the bis(orthoquinol acetate) Tsoc-protected secondary amine **16** was derived in three steps from the known secondary amine **15**[22] as indicated in Scheme 5. It was then subjected to the fluoride ion-mediated deprotec-



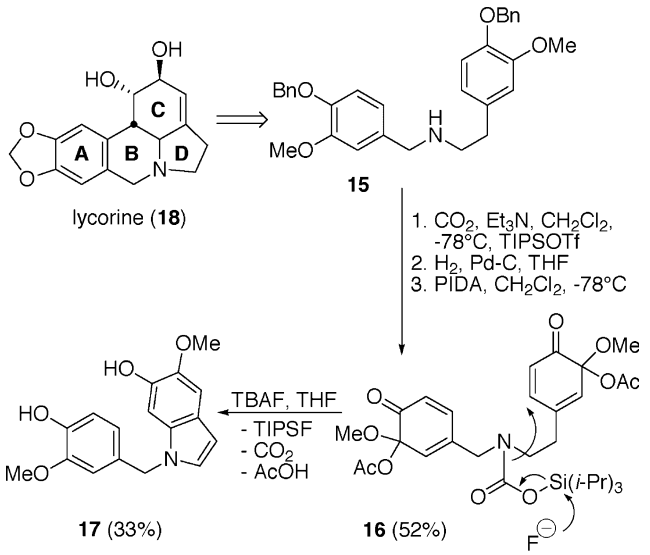
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

tion–cyclization conditions described here. Heterocyclization occurred in a moderate yield of 33% leading to the indole product **17**,[23] but not to a dehydroindole like in the case of the conversion of **7a** into **8a** (Scheme 2).[1] This oxidation of an initially formed dehydroindole product is concomitant with the reduction of the second orthoquinol acetate moiety of **16**.

We are now working on elucidating this apparent intramolecular oxido-reduction process for identifying reaction conditions that will enable a domino formation of the nitrogen–carbon and carbon–carbon bonds of the lycorine-type ABCD tetracyclic system prior to any rearomatization.

Acknowledgements

We wish to thank the Délégation Régionale à la Recherche et à la Technologie pour l'Aquitaine (FEDER Grant Z0131) and the Conseil Régional d'Aquitaine (Grant 990209003) for financially supporting this research. We are also grateful to the Centre de Recherche en Chimie Moléculaire (CNRS, Fédération d'Unités FR1981) for its contribution to the postgraduate fellowships to Daniel K. Whelligan (Cambridge University, UK) and Matthew A. Looney (Texas Tech University, USA).

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23. *Experimental procedure and characterization data for indole* ***17***: To a stirring ice-cold solution of orthoquinol acetate **16** (150 mg, 0.24 mmol) in dry THF (5 mL) was added dropwise a commercial solution of TBAF (1 M in THF, 1.1 equiv). The reaction mixture immediately became darker. After 20 min, the ice bath was removed, and the reaction was stirred at room temperature for an additional 20 min period. Progression of the reaction was monitored by the disappearance of the orthoquinol acetate, as indicated by TLC [hexanes–Et_2O (1:4)]. The mixture was diluted with EtOAc (50 mL), washed with brine (2×10 mL), dried over Na_2SO_4, filtered and evaporated at room temperature. The resulting brown residue was purified by column chromatography, eluting with hexanes–Et_2O (1:4), to afford the indole derivative **17** as a dark oil (23.9 mg, 33%); IR (NaCl) 3535, 3456, 1588 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz): δ 3.79 (s, 3H), 3.87 (s, 3H), 5.21 (s, 2H), 6.34 (dd, $J=0.7$, 3.2 Hz, 1H), 6.67 (dd, $J=2.0$, 8.1 Hz, 1H), 6.78 (d, $J=8.1$ Hz, 1H), 6.89 (d, $J=0.7$ Hz, 1H), 6.92 (d, $J=2.0$ Hz, 1H), 7.09 (s, 1H), 7.16 (d, $J=3.2$ Hz, 1H); ^{13}C NMR (acetone-d_6, 62.9 MHz): δ 148.3, 146.8, 144.5, 144.2, 132.2, 130.5, 127.3, 122.1, 120.7, 115.7, 111.7, 103.0, 101.4, 96.6, 56.6, 56.1, 50.4; EIMS m/z (relative intensity) 301 (1), 300 (MH^+, 11), 299 (M^+, 60), 163 (93), 137 (100); HRMS (EI) calcd for $C_{17}H_{17}NO_4$ 299.1157, found 299.1156.