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Base-induced Cyclization of Trimethoxy-*o*-Aroyldiphenylphosphoryl methylbenzamide: a Formal Synthesis of (±) Cherylline and (±) Cherylline Dimethylether

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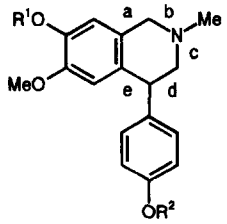
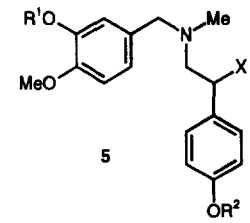
Abstract: The trimethoxy-*o*-aroyldiphenylphosphorylmethylbenzamide **9** can be cyclized by treatment with KHMDS; the procedure has been employed to synthesize (±)Cherylline **1** and its dimethylether **2**.

Synthetic studies on aryl-1,2,3,4-tetrahydroisoquinolines have attracted much attention from the synthetic community owing to the potential biological activities[1] of this class of compounds and their increasing medicinal interest.[2] Among these heterobicyclic compounds Cherylline **1**, a rare phenolic 4-phenyl tetrahydroisoquinoline alkaloid,[3] and its dimethylether **2** whose structures are unique for *Amaryllidaceae* alkaloids have long been fascinating targets for organic chemists as witnessed by a number of articles dealing with biogenesis,[3] isolation,[4] characterization[5] and synthesis.[6] Cherylline **1** isolated from *Crinum powellii* and other *Crinum* species[7] may be synthesized in different ways, the most common one involving cyclization under acidic conditions of appropriately substituted norbelladine derivatives **5**. These methods differ mainly by the nature of the leaving group X (hydroxy,[6a,8] alkoxy[6b,f] and halogeno[6a]) prone to generate the desired benzylic carbocation for the annulation step. A different route which mimics the general biogenetic pathway operative in the formation of *Amaryllidaceae* alkaloids relies upon the base-catalyzed cyclization of trihydroxy derivatives **5** (X = OH; R^1, R^2 = H)[6a] which proceeds *via* the *p*-quinone methide intermediate also involved in other sophisticated syntheses.[6c] However all these routes suffered from the need of several regioselective protection, deprotection and refunctionalization reactions on either parent models **5** or cyclized products such as **3** and **4**.



$R^1 = R^2 = H$ **1**
$R^1 = R^2 = Me$ **2**
$R^1 = R^2 = Bn$ **3**
$R^1 = Bn$ $R^2 = Me$ **4**



5

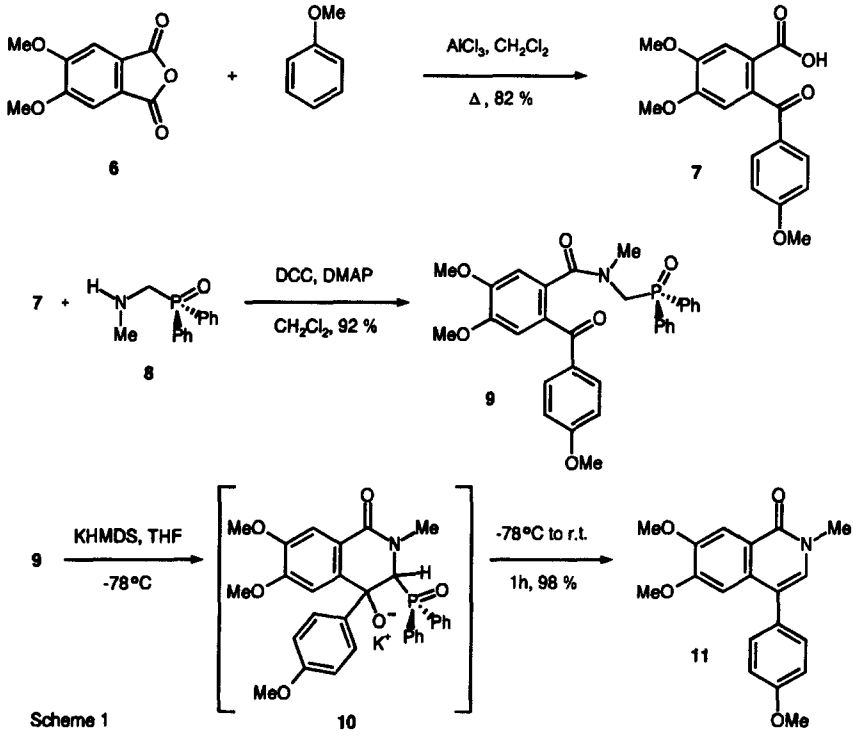
R^1 = H, Me, Bn
X = OH, OR^3, Br

Other methods have also been described based upon (i) the Polonovski reaction of properly substituted dibenzazocine *N*-oxides,[9] (ii) the Bischler-Napieralski cyclization of polyalkoxyaromatic formamide[7b] and isocyanide[6d] derivatives followed by several regioselective deprotection, demethylation and *N*-methylation reactions and (iii) the photochemically induced ring closure of *ortho*-halogenated *N*-acylbenzylamines.[10] Noteworthy, the cyclization is invariably achieved through formation of the benzylic bonds *a* and *e* of **1-4** by these methodologies. Paradoxically Cherylline dimethylether **2** has rarely been prepared by adapting the

preceding methodologies.[11] Some specific syntheses have been developed taking into account that the regioselective protection of phenol groups in the parent models is not a prerequisite to their annulation. These new routes include (i) ring opening of suitably substituted 3-arylphtalide with methylamine followed by metallation, trapping with DMF and subsequent treatment of the primary annulated product,[12] (ii) reaction of *p*-methoxyphenylmagnesium bromide on an appropriate dimethoxy-4-(*2H*)-isoquinolone derivative[3] and (iii) nickel assisted intramolecular Barbier reaction of *N*-(2-iodobenzyl) phenacylamines.[13]

We wish to report in this paper a conceptually new and simple approach to the Cherylline skeleton which allows for the access to Cherylline **1** and its dimethylether **2** indifferently. Our strategy hinges upon the remarkable nucleophilicity of phosphorylated α-aminocarbanions[14] and their ability to generate inter[14c,15] and intramolecularly[16] the easily reducible N-C=C unit in a variety of open chain or annulated adducts.

Initially the dimethoxyphthalic anhydride **6** readily accessible by oxidation of *m*-meconine[17] was opened by Friedel-Crafts reaction with anisole to afford the *o*-aroyldimethoxybenzoic acid derivative **7**[18,19] (scheme 1). The acid **7** was subsequently coupled with *N*-diphenylphosphorylmethyl-*N*-methylamine **8** prepared by a



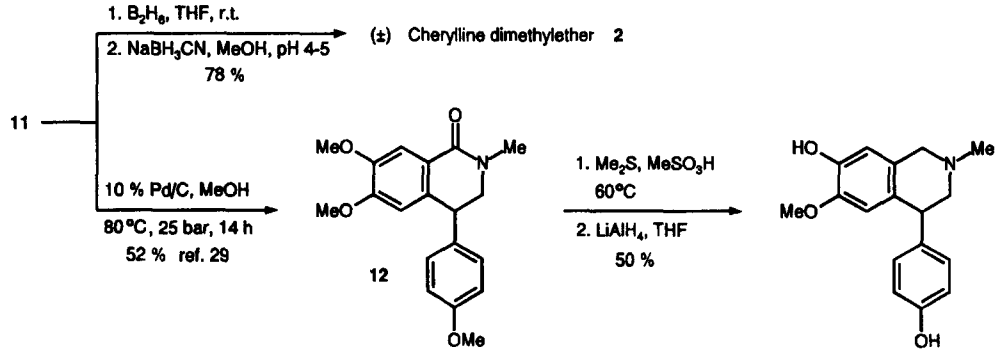
Scheme 1

procedure recently developed in our laboratory.[14a,20] Initial attempts to prepare the phosphorylated carboxamide **9** by Schotten-Baumann reaction between **8** and the carboxylic acid chloride deriving from **7** were unrewarding due to the difficulty associated with the acid chloride function. Indeed, despite the investigation of an extensive range of reagents and conditions, treatment of **7** with a number of chlorinating agents led invariably to the 3-chloro-3-arylphthalide derivative.[21] On the other hand the choice of the diphenylphosphoryl group in the aminophosphorylated counterpart was dictated by the properties of diphenylphosphane oxides incontestably superior in many respects to phosphonium salts and phosphonates.[22]

In spite of the presence in the parent model **9** of the base sensitive acyl group and several orthodirecting substituents for aromatic metallation, namely methoxy groups[23] associated to a tertiary carboxamide function,[24] the phosphorylated *o*-aroylaromatic carboxamide **9** underwent regioselective metallation by treatment with potassium hexamethyldisilylazide in tetrahydrofuran at low temperature. Warming the reaction

mixture to room temperature ensured completion of the reaction and classical work-up delivered the fused *N*-methyl-6,7-dimethoxy-4-(4-methoxyphenyl)-1-(*2H*)-isoquinolone **11**[25] in almost quantitative yield (scheme 1). The high degree of conjugation of this product, due notably to the marked olefinic character of the carboxamide moiety, associated with the simultaneous presence of the Ph_2PO group[22b] and of the weakly bound potassium counterion[22b] in the adduct **10** accounts for the high yields of the annulation step.

With this material in hand two different transformations could be envisioned (scheme 2). Preliminar diborane reduction of the carbonyl function of **11** and subsequent reduction of the enamine function of the intermediate 1,2-dihydroisoquinoline under slightly acidic conditions furnished the Cherylline dimethylether **2** with a satisfactory yield. On the other hand the catalytic hydrogenation of the diarylenamide C=C bond of **11** gave rise to *N*-methyl-3,4-dihydro-6,7-dimethoxy-4-(4-methoxyphenyl)-1-(*2H*)-isoquinolone **12**[26] which could be easily converted, albeit in moderate yield, into (±) Cherylline[27] by cleavage of aryl ether linkages,[6g,19,28] and subsequent reduction of the carboxamide function.



Scheme 2

(±) Cherylline 1

In conclusion the method presented here offers a new approach to the Cherylline skeleton (bond *d* formation). Furthermore the reported protocol which complements the existent methodologies could undoubtedly be broaden to include the synthesis of a variety of alkaloids containing the 4-aryl-isoquinoline unit.

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18. Selected data for compound **7**: mp 197-198°C; ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 3.81 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.77 (1H, s, H_{arom}), 6.87 (2H, d, *J* 9, H_{arom}), 7.52 (1H, s, H_{arom}), 7.68 (2H, d, *J* 9, H_{arom}).
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25. Selected data for compound **11**: mp 178-179°C; ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 3.65 (3H, s, NCH_3), 3.82 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 6.88 (1H, s, NCH=), 6.93 (1H, s, H_{arom}), 7.00 (2H, d, *J* 9, H_{arom}), 7.31 (2H, d, *J* 9, H_{arom}), 7.89 (1H, s, H_{arom}); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: C 161.4, 159.1, 153.0, 149.1, 125.3, 119.9, 118.7; CH 132.1, 130.8, 130.3, 129.0, 128.2, 114.1, 107.9, 105.0; CH_3 56.2, 55.9, 55.3, 37.0.
26. Selected data for compound **12**: mp 128-129°C; ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 3.05 (3H, s, NCH_3), 3.55 (1H, dd, *J* 12.5, 7.5, N-CH_2), 3.72 (3H, s, OCH_3), 3.76 (4H, s + m, OCH_3 + N-CH_2), 3.96 (3H, s, OCH_3), 4.15 (1H, dd, *J* 5.5, 7.5, CH), 6.39 (1H, s, H_{arom}), 6.85 (2H, d, *J* 8.5, H_{arom}), 7.07 (2H, d, *J* 8.5, H_{arom}), 7.67 (1H, s, H_{arom}); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: C 164.5, 158.7; 151.8, 151.0, 148.0, 134.0, 133.1; CH 129.3, 114.1, 110.2, 109.5, 55.2; CH_2 42.8; CH_3 55.7, 55.9, 56.1, 35.2.
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29. Commercial palladium on carbon (10%, Aldrich) was preliminarly activated by heating at 180°C for 12 h under vacuum (10^{-1} Torr).

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