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THALLIUM IN ORGANIC SYNTHESIS. 68. A CONVENIENT SYNTHESIS OF 2-PHENYLINDOLES FROM ANILIDES[1,2]

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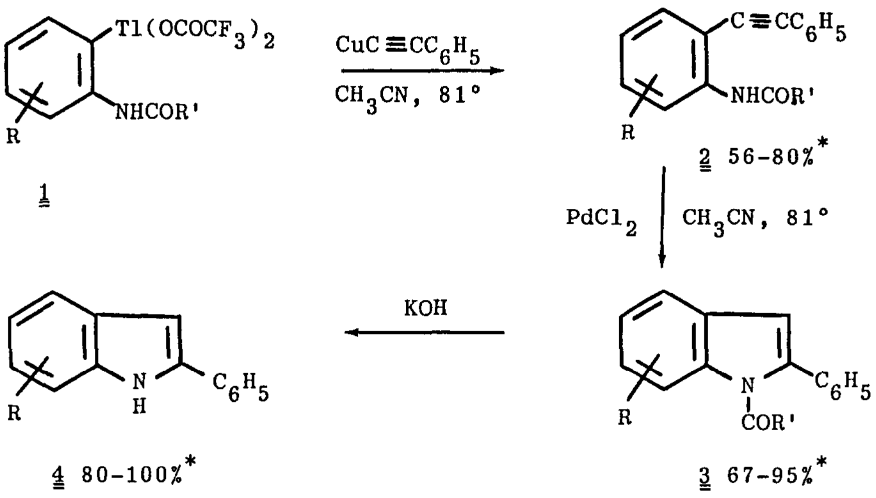
Abstract: Thallation of anilides with TTFA in a mixture of TFA and ether gives ortho-thallated derivatives, which yield 2-acetamidotolanes upon reaction with copper(I) phenylacetylide in acetonitrile. Treatment of the latter compounds with palladium(II) chloride results in ring closure to give 1-acyl-2-phenylindoles, from which 2-phenylindoles are obtained by alkaline hydrolysis.

Only a few procedures have been described for the conversion of ortho-unsubstituted anilines to indoles. These include intramolecular electrophilic cyclization of methanesulfonamides of N-(2,2-diethoxyethyl)anilines,[3] the classical Fischer indole synthesis,[4] the Bischler reaction involving the reaction of anilines with α-haloketones,[5] and the Sommelet rearrangement of anilinosulfonium ions, exploited extensively by Gassman.[6] Related sigmatropic rearrangements of arylhydroxylamine derivatives, which yield ortho-alkylated anilines suitable for further cyclization to indoles, utilize nitroarenes (which are reduced to the precursor hydroxylamines) as starting materials rather than anilines.[7-9]

Electrophilic thallation of arenes bearing substituents such as COOH, COOR, and CH_2OH, which are capable of forming Lewis acid/Lewis base complexes with thallium(III) tris(trifluoroacetate) (TTFA), undergo exclusive ortho-substitution as a consequence of *intra*molecular delivery of the Tl^{3+} electrophile.[10] Both we[11] and Larock[12] have extended this observation to anilides, which likewise give only ortho-thallation products upon treatment with TTFA/TFA or with TTFA/TFA/ether.[13] Larock[12] has described the conversion of ortho-thallated acetanilide to 1-acetyl-2-methylindole and to 1-acetylindole by palladium-promoted olefination with allyl chloride or with bromoethylene respectively. We describe in this paper a complementary procedure for the conversion of these ortho-thallated anilides to 2-phenylindoles.

Thus, treatment of a variety of anilides with TTFA in a mixture of TFA and ether leads to regiospecific ortho-thallation. Reaction of these ortho-thallated anilides (1) with the copper(I) salt of phenylacetylene in acetonitrile results in smooth formation of 2-acetamidotolanes (2) (Scheme 1).

Scheme 1



* For yields of individual compounds see refs 19, 20 and 21

This coupling reaction probably proceeds via a one-electron transfer process similar to that previously proposed for the reaction of arylthallium(III) bis(trifluoroacetates) to aromatic nitriles with CuCN in acetonitrile.[14] The ease of these transformations contrasts sharply with the strenuous conditions required for the Rosenmund-von Braun[15] and for the Castro[16] reactions, which involve aryliodides rather than arylthallium(III) intermediates, and is almost certainly a consequence of the higher oxidation potential of Tl(III). However, attempts to form simple tolanes from substrates such as phenylthallium(III) bis(trifluoroacetate) or *p*-tolylthallium(III) bis(trifluoroacetate) by reaction with copper(I) phenylacetylide resulted primarily in oxidation of the latter to 1,4-diphenyl-1,3-butadiyne. It thus appears that the success of the coupling reaction with ortho-thallated anilides is due to some moderation of this high oxidation potential by the anilide substituent.

Treatment of the 2-acetamidotolanes with palladium(II) chloride in acetonitrile results in smooth cyclization to 1-acyl-2-phenylindoles (3). This cyclization is analogous to the reported conversion of 1-amino-3-alkyn-2-ols to pyrroles with Pd(II) chloride,[17] and presumably involves initial formation of a π-complex between the acetylenic triple bond and Pd(II), which rearranges to a σ-complex with concomitant intramolecular nucleophilic attack by the ortho-situated amide grouping. Proton transfer with loss of Pd(II) then gives the 1-acyl-2-phenylindole, from which the indole (4) is readily prepared by deacylation with alcoholic potassium hydroxide.

Since both the carbon-carbon bond forming reaction [treatment of the 2-acetamidoarylthallium(III) bis(trifluoroacetate) with the copper(I) acetylide] and the subsequent Pd(II)-catalyzed cyclization are carried out in acetonitrile, it is not necessary to isolate the intermediate 2-acetamidotolane; addition of Pd(II) chloride to the reaction mixture results in direct formation of the 1-acyl-2-phenylindole.

General Procedure for the Preparation of 2-Acetamidotolanes[18,19]: A mixture of 2-acetamidoarylthallium(III) bis(trifluoroacetate) (10 mmol) and copper(I) phenylacetylide (10 mmol) in 50 mL of acetonitrile was heated under reflux, in a stream of nitrogen, for 3-5 hours. The reaction mixture was then concentrated under reduced pressure, a mixture of 80 mL of ethyl acetate and 80 mL of saturated sodium chloride added, and the resulting amber suspension was filtered through Celite and the organic layer separated, washed with saturated sodium chloride (1 x 20 mL) and water (2 x 20 mL), dried over anhydrous magnesium sulfate, and evaporated. The product was washed with hexane to remove a small amount of 1,4-diphenyl-1,3-butadiyne and recyrstallized from ethanol.

General Procedure for the Preparation of N-Acyl-2-phenylindoles[18,20]: The 2-acetamidotolane (1-2 mmol) and a catalytic amount of palladium(II) chloride (ca. 20 mg) in 10-20 mL of acetonitrile was heated under reflux under a stream of nitrogen for 1-3 hours. The reaction mixture gradually turned dark brown. Solvent was removed under reduced pressure, and a mixture of 20 mL of ethyl acetate and 20 mL of saturated sodium chloride was added. The mixture was filtered through Celite and the organic layer separated, washed with saturated NaCl (1 x 10 mL) and water (2 x 20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residual oil was filtered through a short column of florisil, with a 1:1 mixture of hexane:benzene as eluant, to give the pure N-acyl-2-phenylindole.

General Procedure for the Preparation of 2-Phenylindoles[18,21]: The N-acylindole (0.3-0.7 mmol) was dissolved in 3 mL of ethanol, and 10 mL of 2 N alcoholic potassium hydroxide and one drop of water were added. The mixture was heated at 70°C for 1 hour, and the ethanol was then removed under reduced pressure. The residue was dissolved in 20 mL of ether and the ether layer was washed with saturated sodium chloride (1 x 10 mL) and water (1 x 10 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to give the 2-phenylindole.

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18. Microanalytical and/or spectroscopic data were consistent with the structures assigned to all new products.
19. (a) R = H, R' = C_6H_5, 56%; (b) R = 4-CH_3, R' = CH_3, 72%; (c) R = 5-CH_3, R' = CH_3, 74%; (d) R = 4,5-$(CH_3)_2$, R' = CH_3, 80%; (e) R = 4-Cl, R' = CH_3, 74%.
20. (a) R = H, R' = C_6H_5, 78%; (b) R = 6-CH_3, R' = CH_3, 95%; (c) R = 5-CH_3, R' = CH_3, 80%; (d) R = 5,6-$(CH_3)_2$, R' = CH_3, 90%; (e) R = 6-Cl, R' = CH_3, 67%.
21. (a) R = H, 100%; (b) R = 6-CH_3, 80%; (c) R = 5-CH_3, 100%; (d) R = 5,6-$(CH_3)_2$, 95%; (e) R = 6-Cl, 90%.

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