

Investigación

A Novel Diaryl Ether Ullmann-Type Synthesis using Thallium Derivatives as Both Aryl Components[&]

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Recibido el 11 de Agosto del 2003; aceptado el 29 de septiembre del 2003

Abstract. An Ullmann type diaryl ether synthesis using thallium derivatives as both aryl components (Thallous phenolate and aryl *bis*-trifluoroacetyl Thallium (III) derivatives) is described. A salient feature of this procedure is that it allows 4-nitrophenolate to participate as the nucleophilic reagent in the Ullmann ether synthesis.

Keywords: Ullmann reaction, thallium, 4-nitrophenolate, ether synthesis.

Resumen. Se describe una síntesis de Ullmann de diaryl éteres empleando derivados de talio como reactantes (fenolato o *p*-nitrofenolato de talio y derivados de ariltalio *bis*-trifluoroacetato). Una característica sobresaliente de este procedimiento es que permite la participación de *p*-nitrofenolato como reactivo nucleofílico en la síntesis.

Palabras clave: Reacción de Ullmann, talio, 4-nitrofenolato, síntesis de éteres.

The year 2005 will mark the 100 anniversary of the Ullmann reaction. In 1905 Ullmann and Stein discovered that copper catalyzes the reaction between alkali phenoxides and aryl halides.

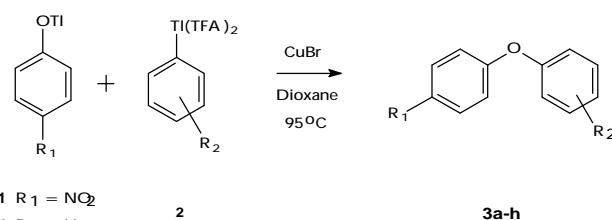
Diaryl ethers are useful compounds that have found wide application in biological systems [1]. They are traditionally prepared by the condensation of an aryl halide with an alkali metal salt (preferably the more reactive potassium salt) [2] of a phenol in the presence of copper salts such as cuprous bromide, and the process is termed the Ullmann diaryl ether synthesis [3]. The reaction is normally carried out at 100-220 °C, either in a refluxing inert solvent [4], or sometimes in the absence of solvent [5]. Yields are normally moderate, but are higher when electron-withdrawing groups are present in the aryl halide. Reactivity decreases in the order I > Br > Cl >> F [6] although there are examples where aryl fluorides showed outstanding reactivity when properly substituted with a nitro- or other electron-withdrawing substituent [7]. By contrast, nitrophenols participate only with difficulty, an understandable situation due to a reduced nucleophilicity. Interestingly, there have been recent advances in the catalysis of carbon-heteroatom coupling methodologies that have improved the Ullmann diaryl ether synthesis [8,9]. As early as 1925, Menzies [10] made the interesting observation that diphenyl ether was formed on refluxing a solution of thallous phenoxide and iodobenzene, in the absence of copper salts. No further reports on this reaction have appeared since that time. We now report an Ullmann-type diaryl synthesis applied to the preparation of mainly aryl 4-nitrophenyl ethers but applicable to the synthesis of other arylethers as well.

Results and discussion

This approach uses thallium derivatives as both reaction components, in the presence of copper salts, the outstanding feature being that a thallium (I) (hard center) nitrophenolate stands for the nucleophile, whereas the thallium (III) (soft center) moiety acts as the departing group. It would be fair to say that thallium (III) derivatives have shown a chemical behavior similar to iodine substituted compounds and indeed they can even be substituted with iodine [11].

The thallium(I) salt of 4-nitrophenol (**1**) (readily prepared from 4-nitrophenol and thallous ethoxide) [12] reacted with a variety of arylthallium(III) bis-trifluoroacetates (**2**) in the presence of cuprous bromide to give 4-nitrophenyl aryl ethers in good to excellent yields (see Table 1).

This reaction was very simple to perform in the laboratory. It proceeded smoothly even when the arylthallium(III) *bis*-trifluoroacetate component was insoluble in dioxane. Noteworthy is the high yield obtained with compound **2e** when compared with the moderate yields of ethers obtained with 4-haloanisoles [17]. In the case of diaryl ether **3f**, methyl benzoate, formed via protodethallation, was also detected as a side-product (reductive dehalogenation is occasionally



Scheme 1

[&] This work is dedicated to Professor Edward C. Taylor (Princeton University) for his outstanding contribution to Organic Chemistry.

Table 1. Diaryl ethers prepared according to Scheme 1.

3	R ₁	R ₂	Yield (%)	Mp (°C)	Lit mp (°C)
a	NO ₂	H	63	56-57	58 [13]
b	NO ₂	4-Me	70	49 [11]	49 [13]
c	NO ₂	3,4-di-Me	83	87-87.5	86-87.5 [14]
d	NO ₂	4-Cl	66	74-75	76 [15]
e	NO ₂	4-MeO	95	109-110	111 [16]
f	NO ₂	2-COOMe	65	75-76	76-78 [17]
g	H	H	75	Oil	26.8-27 [13]
h	H	Me	80	Oil	Oil [13]

observed in the classical Ullmann reaction) [3]. Thallous phenoxide itself (4) also reacted with arylthallium(III) *bis*-trifluoroacetates **2a** and **2b** under similar experimental conditions to give the diaryl ethers **3g** and **3h**, respectively, in excellent yields.

Although the mechanism of these reactions has not been investigated, it seems probable that it may involve a radical pathway with exchange of thallium(I) by copper as an initial step. Diaryl ethers have been prepared from aryl halides and copper phenoxides [19,20].

Experimental

All yields given in the table refer to isolated products after column chromatography purification. All products were characterized by conventional spectroscopy through IR and ¹H NMR spectral data. Thallium compounds are extremely toxic, their effects are cumulative and they can be absorbed through the skin.

General procedure for the preparation of diaryl ethers. Thallous 4-nitrophenoxide (2.8 g, 8.2 mmol) and cuprous bromide (1.2 g, 8.3 mmol) were stirred for 10 min in dry (Na) dioxane (30 mL) at room temperature and under nitrogen. To the resulting suspension, 3,4-dimethylphenylthallium(III) *bis*-trifluoroacetate (3.75 g, 7.0 mmol) dissolved in dioxane (8 mL) was gradually added via syringe. The mixture was heated to gentle reflux (95 °C) and maintained at this temperature for 5 h. Then the reaction mixture was cooled to room temperature and most of the solvent was removed under reduced pressure. Ethyl acetate (40 mL), 1 N HCl (5 mL) and brine were added, and the whole was stirred for 15 min at room temperature, filtered through Celite, and the organic layer successively washed with water (1 × 15 mL), aq. NH₄OH (3 × 10 mL), water (1 × 15 mL) and then dried (anh. MgSO₄). Removal of the solvent left a semisolid product that crystallized on standing to give 3,4-dimethylphenyl-4-nitrophenyl ether (1.44 g, 83 %), mp 87-87.5 °C (lit [14] mp 86.5-87.5 °C).

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