An Alternative and Efficient Route to Chlorophacinone

René Csuk, Alexander Barthel, and Dieter Ströhl

Martin-Luther-Universität Halle-Wittenberg, Bereich Organische Chemie, Kurt-Mothes-Str. 2, 06120 Halle (Saale), Germany

Reprint requests to Prof. Dr. René Csuk. Fax: +49 345 5527030.
E-mail: rene.csuk@chemie.uni-halle.de

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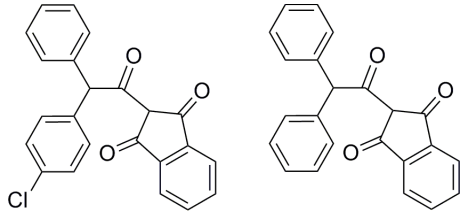
A straightforward synthesis for the anticoagulant rodenticide chlorophacinone is described. The short synthesis uses commercially available mandelic acid and 1,3-indanedione as staring materials.

Key words: Chlorophacinone, Anticoagulant, Friedel-Crafts Reaction

Introduction

A rodenticide is any product able to kill rodents, mice, gophers, squirrels and other small animals. They represent a diverse group of chemicals bearing little or no relationship to one another – apart from their current or historic use as rodenticides. Anticoagulant rodenticides [1] of the indanedione type (Fig. 1) are commonly used for the control of mice, rats and other rodents. The most important one, chlorophacinone (**1**), is widely used in Europe, the Americas and Asia as a rodenticide pest control substance to control *Rattus norvegicus* (Norway rat, brown rat) and *Mus musculus* (house mouse). It is a first-generation anticoagulant rodenticide which disrupts the normal blood clotting mechanisms resulting in increased bleeding tendency and, eventually, profuses hemorrhage and interfers with vitamin K [2] in the 'clotting cascade' that involves many clotting factors. These anticoagulants are toxic [3] with LD_{50} values of a few mg kg^{-1} for rodents but also [1] for cats and dogs. Because of a significant difference in their water solubility the synthesis of chlorophacinone free of other phacinones especially of diphacinone (**2**) is important for its use in bait formulations.

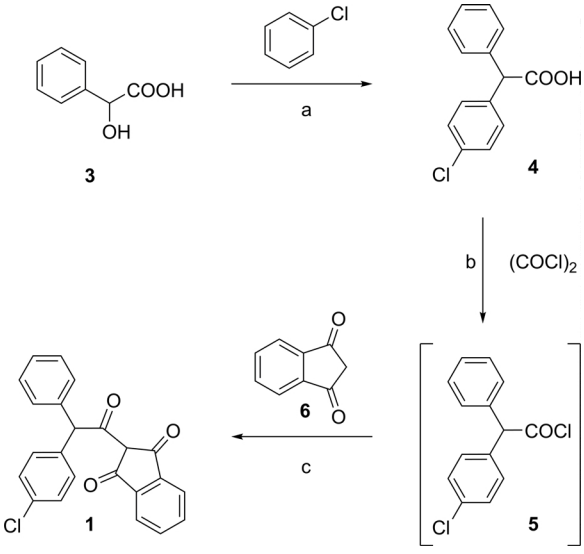


1 **2**

Fig. 1. Chlorophacinone (**1**) and diphacinone (**2**).

Results and Discussion

Chlorophacinone (**1**) is usually prepared in a multistep synthesis [4 – 9] starting from phenylacetone by a reaction sequence of bromination followed by a Friedel-Crafts reaction with chlorobenzene and finally a reaction with dimethyl phthalate in benzene in the presence of sodium methoxide to yield **1** in an overall yield of approx. 20 %. The material obtained by this sequence [10] may contain up to 5 – 10 % of **2** as an impurity.



3 **4** **5** **1**

Scheme 1. a) $SnCl_4$, 70 °C, 8 h, 85 %; b) 25 °C, 12 h, quant.; c) $AlCl_3$, 25 °C, 12 h, 60 %.

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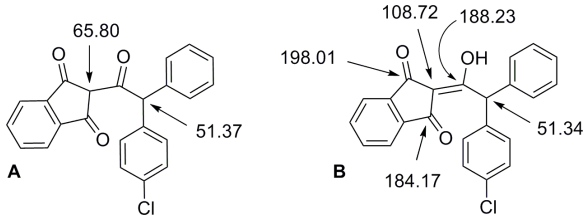

Fig. 2. Selected ^{13}C NMR spectroscopic data of **1**; **A** in $[D_6]$DMSO (shortly after dissolving); **B** in $CDCl_3$ solution.

Recently, we became interested in the synthesis [11] of radiolabelled [12] **1** which is free of any significant amounts of **2** and other impurities difficult [13] to remove. Therefore, an alternative synthesis for **1** was called for.

Retrosynthetic planning revealed mandelic acid (**3**) as an appealing starting material; it is commercially available and cheap. Thus, **3** was reacted with chlorobenzene (Scheme 1) in the presence of $SnCl_4$ [14] to afford 85 % of the phenylacetic acid **4**. Alternative routes to **4** have been devised [15 – 19] but yields dropped significantly upon scaling up. Treatment of **4** with oxalyl chloride [20] at room temperature gave the chloride **5** which could be used in the next step without any purification. Friedel-Crafts reaction of **5** with 1,3-indanedione (**6**) provided chlorophacinone (**1**). HPLC analysis [21] of this material gave no indication for the presence of significant amounts of diphacinone.

As previously [22] shown, **1** adopts in the solid state the keto form **A** (Fig. 2). Contrary to this finding, on dissolving **1** in $CDCl_3$ and leaving the solution stand for an hour at room temperature, the ^{13}C NMR spectrum revealed the presence of 19 signals, among them three signals (δ = 198.01, 188.23 and 184.17 ppm) which are typical for a C=C unit carrying an oxygen-containing substituent. Guided by symmetry considerations, therefore in $CDCl_3$ the presence of an enol form **B** is most likely. A similar behavior is observed in $[D_6]$DMSO although the enolization needs more time to take place.

In summary, our approach allows the synthesis of chlorophacinone in a straightforward manner from commercially available starting materials.

Experimental Section

General methods

Melting points are uncorrected (Leica hot stage microscope). The solvents were dried according to usual procedures.

*rac-2-(4-Chlorophenyl)phenyl acetic acid (**4**)*

To a mixture of racemic mandelic acid (**3**) (19.0 g, 0.12 mol) and chlorobenzene (70 mL) at 70 °C $SnCl_4$ (48.8 g, 0.19 mol) was slowly added and the mixture heated under reflux for 8 h. After cooling to 25 °C, the reaction mixture was poured onto crushed ice and extracted with dichloromethane (4 × 200 mL). The extracts were washed (10 % aq. HCl, 25 mL; water 2 × 25 mL) and dried (Na_2SO_4), and the solvent was removed. Recrystallization from ethanol yielded **4** (25.2 g, 85 %) as a colorless solid. M. p. 116 – 118 °C (lit.: 117 – 118 °C [23]; 115 – 117 °C [16]).

*rac-2-(Phenyl-4-chlorophenylacetyl)indane-1,3-dione (chlorophacinone) (**1**)*

At 0 °C to a solution of **4** (3.4 g, 13.7 mmol) in dry dichloromethane (30 mL), oxalyl chloride (3.5 g, 27.4 mmol) was added, and the mixture was stirred at 25 °C for 12 h. The solvents were removed under reduced pressure, and the residue was dissolved in dry dichloromethane (20 mL). This solution was slowly added to a mixture of 1,3-indanedione (**6**) (2.0 g, 13.7 mmol) and $AlCl_3$ (3.2 g, 24.0 mmol) in dry dichloromethane (20 mL). Stirring was continued for 12 h. The mixture was poured onto crushed ice (containing 10 % aq. HCl) and extracted with ethyl acetate (4 × 200 mL). The extracts were dried (Na_2SO_4), washed (10 % aq. HCl, 25 mL; then water, 2 × 25 mL) and dried again (Na_2SO_4), and the solvents were removed. Flash chromatography (silica gel, hexane/ethyl acetate, 8 : 2) yielded **1** (3.0 g, 60 %) as a pale-yellowish solid. M. p. 137 – 140 °C (lit.: 140 °C [6]).

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