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First synthesis of 3-aryl-5-dichloromethyl-2-pyrazolines. The electrochemical generation of 2,2-dichlorovinylacetophenones as a key step

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Abstract—An efficient synthetic route to the title compounds has been established. Chloralacetophenones **2** were prepared by treatment of acetophenones **1** with anhydrous chloral. Dehydration of intermediates **2** under acidic conditions yielded 2,2,2-trichloroethylideneacetophenones **3**, which were transformed to 2,2-dichlorovinylacetophenones **5** in nearly quantitative yields by selective electrochemical monodechlorination at either mercury or graphite electrodes. Finally, 3-aryl-5-dichloromethyl-2-pyrazolines **7** were efficiently obtained on treatment of compounds **5** with either hydrazine or methylhydrazine.

1. Introduction

Pyrazolines[1] are compounds with noteworthy applications. One special interest lies in the use as synthetic intermediates for preparing cyclopropane[2] and pyrazole[1b,2f,3] derivatives. Certain compounds containing the 2-pyrazoline moiety have been demonstrated to have an important therapeutic potential, mainly as anti-inflammatory,[4] antidepressant,[5] antipyretic,[6] antibacterial,[7] antifungal,[7a,d,8] and antitumor[9] agents.

Over the years, the synthesis of 2-pyrazolines has received considerable attention. The most extended methodologies to generate this ring system involve the use of either diazoalkanes[1b,2a,b,10a–c] or α,β-unsaturated carbonyl compounds[1b,2c,d,10d,e,11] as immediate precursors. As a part of our research project on the synthesis of heterocyclic compounds based on the chemistry and electrochemistry of chloral derivatives,[12] we herein report an efficient approach to the synthesis of dichloromethylated pyrazolines. Chloral is an inexpensive multipurpose starting material for organic synthesis.[13] Reaction of chloral with acetophenones **1** provides chloralacetophenones **2** in high yields.[14] As is shown in Scheme 1, we recognized this reaction as the starting point for preparing 3-aryl-5-dichloromethyl-2-pyrazolines **7**, which pertain to a hitherto unknown family of pyrazolines.

Given the above, the preparation of compounds **7** itself shows remarkable interest and highly attractive also is a promising value arising from the synthetic utility of geminal dihalide groups. Notwithstanding, the synthesis of compounds of type **7** has not yet been reported. This seems to be attributable to incompatibility of pyrazolines with the reagents mostly used to generate dichloromethyl groups.[15] However, the aim of this approach is to circumvent the indiscriminate action of these reagents by utilization of a pre-chlorinated synthon derived from chloral with the advantageous result of the development of a general, facile and highly efficient synthesis of products **7** (Table 1). As far as we know, this is the first time that chloral has been used as starting material for preparing pyrazolines.

2. Results and discussion

In an attempt to prepare the key intermediates **5** chloralacetophenones **2** were treated with zinc in warm acetic acid. These reactions showed erratic induction periods and were found to be of little synthetic utility. The main reaction products were formed along with

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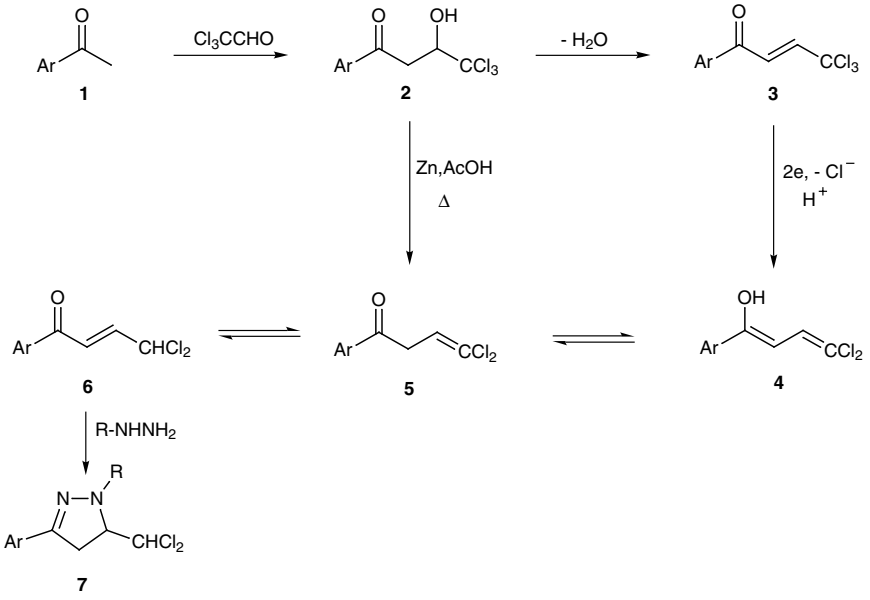

Scheme 1.

Table 1. Preparation of dichlorovinylacetophenones **5** and dichloromethylpyrazolines **7**

Entry	Ar	R	Prod. 5 mp °C (%)	Prod. 7 mp °C (%)
a	C_6H_5	CH_3	50–51 (95)	Oil (85)
b	4-$O_2NC_6H_4$	CH_3	104–105 (72)	117–118 dec (78)
c	2-$C_{10}H_7$	CH_3	81–82 (96)	156–157 (80)
d	4-$CH_3OC_6H_4$	H	72–74 (97)	107–109 dec (96)
e	4-ClC_6H_4	H	58–59 (96)	126–127 dec (93)

numerous unidentified compounds and were isolated in remarkably low yields and purified only with considerable difficulty. They were identified as dichlorovinylacetophenones **5**. The reduction applied to **2b**, which bears a nitro group, showed a total incapability to give product **5b**. In this case the generation of a very complex mixture of unidentified products was detected. All products **5**, however, were found to be directly convertible to the targeted products **7** in near quantitative yields by treatment with hydrazines.

Given the high synthetic interest evidenced by intermediates **5** we focused our attention on the search for an effective preparative procedure. As such, the compounds **2** could be easily transformed to 2,2,2-trichloroethylideneacetophenones **3** (85–94% yield) by dehydration with either sulfuric or *p*-toluenesulfonic acids.[16] A highly efficient generation of the key intermediates **5** was achieved by selective electrochemical reduction of products **3**. These electrolyses provided single products in near quantitatively yields (Table 1), which were identical to that inefficiently originated by zinc reduction of compounds **2**. Compound **5b** could also be synthesized in good yield in this manner. As far as we know it is the first time that 2,2-dichlorovinylacetophenones **5** have been prepared. However, some aliphatic analogues have been described.[17] The molecular structure of compound **5d** has been determined by X-ray crystallographic analysis.[18]

Products **5** reacted easily with hydrazine hydrate as well as methylhydrazine to give the corresponding 3-aryl-5-dichloromethyl-2-pyrazolines **7** in high yields (Table 1). The easy and efficient formation of these products can be explained by participation of intermediates **6**. This is the first time that the synthesis of 3-aryl-5-dichloromethyl-2-pyrazolines **7** has been reported. The structure of one of these compounds (**7c**) was determined by single crystal X-ray diffraction.[18]

To conclude, a convenient new method for the synthesis of 3-aryl-5-dichloromethyl-2-pyrazolines **7** is reported. Versatility, good yields, easy availability of starting materials, mildness, and simple experimental procedure are noteworthy advantages of this approach, which provides access to previously unattainable compounds of significant interest. It seems feasible that the intermediates involved in this synthetic route, particularly 2,2-dichlorovinylacetophenones **5**, would also be useful for preparing a variety of heterocyclic compounds.

3. Experimental

3.1. Electrogeneration of 2,2-dichlorovinylacetophenones (5)

Reductive electrolyses of 2,2,2-trichloroethylideneacetophenones **3** were carried out under a constant cathodic potential in a concentric cylindrical cell with two com-

partments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred. The temperature was kept at approximately 18 °C by external cooling. The reductions were performed in MeCN (60 mL)–AcOH (10 mL)–$LiClO_4$ (3.5 g); 55 and 15 mL were placed in the cathodic and the anodic compartments, respectively. Sodium acetate (1 g) was placed in the anodic compartment. Solutions of **3** (5 mmol) were electrolyzed under the following cathodic potentials, which were selected in order to provide operative current intensities (close to 220 mA at the beginning and 10 mA at the end): **3a** (−0.20); **3b** (−0.40); **3c** (−0.60); **3d** (−0.50); **3e** (−0.72) V versus SCE. The electricity consumption was 2 F/mol in all cases. Isolation of products **3** was carried out by removing the solvent in vacuo,[19] adding water (150 mL) and collecting the resulting solid by filtration. These were crystallized from petroleum ether or cyclohexane (**5b**).

These syntheses were found to be reproducible when using graphite instead of mercury as cathodic material. Thus, the electrolysis of **3e** (2.5 mmol) provided **5e** in 95% yield by a procedure as described above with an operating potential of −1.00 V versus SCE. The current intensity was 100 mA at the beginning, and 20 mA at the end. The electricity consumption was 2 F/mol.

3.2. Preparation of 3-aryl-5-dichloromethyl-2-pyrazolines (7)

To a suspension of compound **5** (7 mmol) in EtOH (15 mL) a solution of hydrazine (8.4 mmol) in EtOH (7 mL) was added dropwise. The mixture was refluxed for 10 min. Then the solution was concentrated under reduced pressure (half of volume) and was kept at −15 °C until the precipitation of a pale yellow solid, which was collected by filtration and crystallized from EtOH.

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18. Details of the structure determination will be reported in a future full paper.
19. Caution must be exercised when handling perchlorates in order to exclude risk of explosion. Evaporation of organic solutions containing perchlorates needs to be carried out in vacuo and at moderate temperature. Contact with strong acids must be avoided.