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Synthesis of 2-aryl-4-chloropyrroles via ring expansion of 2-aryl-1-chlorocyclopropanecarbaldehydes

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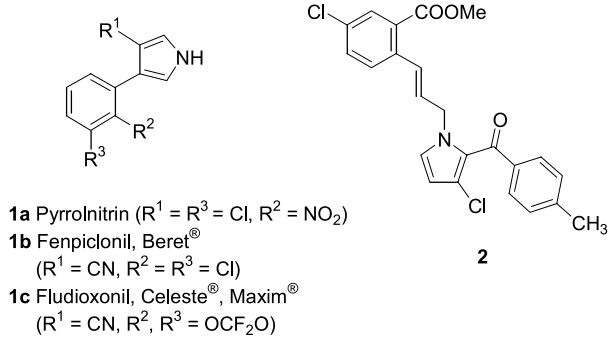
Abstract—An efficient electrophile-induced ring opening of 2-aryl-1-chlorocyclopropanecarbaldehydes is described towards halogenated butanals, which were converted to the corresponding imines. These α,α,γ-trichloroimines proved to be good substrates for a nucleophile-induced ring closure towards 2-pyrrolines as versatile synthons for the synthesis of pyrroles bearing physiologically interesting substitution patterns.

1. Introduction

In the unabated search for new physiologically active compounds, the study of substituted pyrroles still remains a subject of considerable importance. Halogenated pyrroles isolated from Nature, associated with diverse physiological activities, have served as lead structures to synthesize pyrroles with current use in agrochemistry (e.g., the antifungal pyrrolnitrin (**1a**) derivatives **1b**,**c**)[1] and medicine (e.g., 3-chloropyrrole **2**, a fibrosis inhibitor) (Fig. 1).[2]

Pentabromopseudilin **3** was first isolated from the marine bacterium *Alteromonas luteoviolaceus* and shows antitumor, antibacterial and antifungal activities. This polybrominated pyrrole (**3**) also inhibits various enzyme systems and the cholesterol biosynthesis.[3] Manzacidins A (**4a**) and B (**4b**) are alkaloids isolated from the Okinawan sponge *Hymeniacidon species*.[4] Roseophilin **5** is a 3-chloropyrrole found in *Streptomyces griseoviridis* and displays antibiotic and antileukemic properties.[5] More than 20 compounds of the 'oroidin' (**6**) family of β-brominated pyrroles (i.e., 4-bromo- and 4,5-dibromopyrrole-2-carboxamides) have been isolated from Nature and tested for physiological activities.[6] For instance, clathramides, isolated from *Agelas clathrodes*, possess antifungal properties,[7] while other oroidins show antiserotoninergic (keramadine), cytotoxic (agelastatin), antiviral (sceptrin), antihistaminergic (dispacamide) or antifouling (mauritiamine) activities.[6,8,9] With respect to this diversity of activities related to halogenated pyrroles, various synthetic methods to access these compounds have been developed, where each method displays its own advantages to access pyrroles with specific substitution patterns.[10] Of current interest for agrochemistry is the synthesis of 3-halogenated pyrroles bearing electron withdrawing groups (e.g., COOR, CN or CF_3) (Fig. 2).[11]



1a Pyrrolnitrin ($R^1 = R^3 = Cl$, $R^2 = NO_2$)
1b Fenpiclonil, Beret®
($R^1 = CN$, $R^2 = R^3 = Cl$)
1c Fludioxonil, Celeste®, Maxim®
($R^1 = CN$, R^2, $R^3 = OCF_2O$)

Figure 1.

Structure–activity relationship studies revealed that the presence of an aryl moiety at one pyrrole α-carbon is often responsible for specific biological activities, for example, 2-arylpyrrole **7** and derivatives are insecticidal compounds (100% mortality for *Spodoptera eridania* treated with **7** at 10 mg/L).[12] Related pyrroles **8** were recently patented for the protection of wood from termites.[13] In addition, substituted pyrroles with cyano- or carboxylic acid moieties at the α-carbon are important intermediates in the synthesis of porphyrins and other 'pigments of life'.[14]

Keywords: Ring expansion; Pyrroles; Cyclopropanes.
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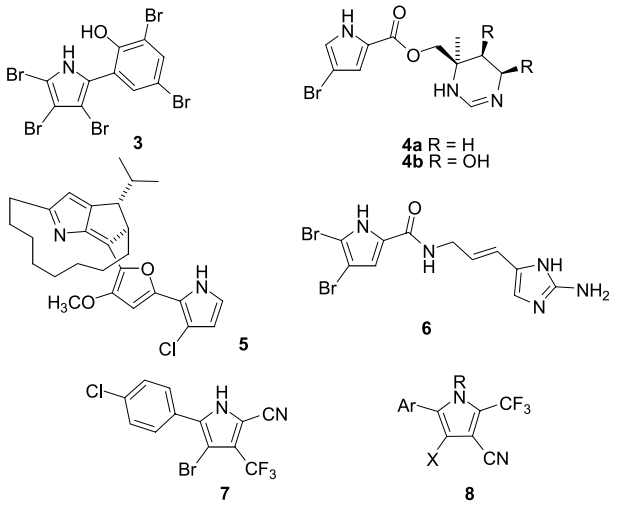


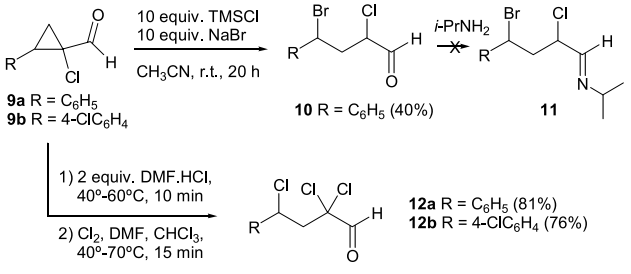
Figure 2.

In this article, an efficient synthesis of halogenated 2-arylpyrroles from 3-aryl-2,2-dichlorocyclobutanones via the intermediacy of 1-chlorocyclopropanecarbaldehydes is disclosed. Only a few publications report the use of cyclopropanecarbaldehydes as building blocks for pyrrole syntheses by thermal rearrangement of the corresponding imines.[15] In contrast, our approach deals with an initial ring opening of appropriate 1-chlorocyclopropane-1-carbaldehydes. Subsequent imination of the resulting γ-haloaldehydes followed by treatment with cyanide to induce a ring closure provides a new entry towards synthetically useful azaheterocyclic compounds.

2. Results and discussion

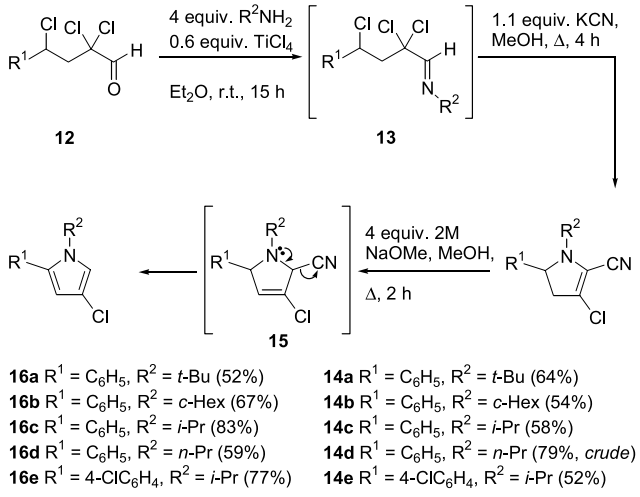
In continuation of the previously reported ring contraction of 2,2-dihalocyclobutanones towards 1-chlorocyclopropanecarbaldehydes **9**, [16] attempts were made to validate the latter compounds as useful synthons for the application in azaheterocyclic synthesis.

Analogous to earlier reported electrophile-induced ring opening reactions of cyclopropylketones under mild conditions,[17] α-chlorocyclopropanecarbaldehyde **9a** was treated with trimethylsilylchloride and sodium bromide to yield a diastereomeric mixture of γ-bromobutanals **10** (ratio 1:1) (Scheme 1). Compounds of this kind could be used to construct five-membered azaheterocycles after imination. Unfortunately, treatment of the aldehyde **10** with isopropylamine in the presence of $MgSO_4$ or $TiCl_4$ under various



Scheme 1.

reaction conditions did not result in the corresponding imines **11**. When an inverse imination procedure was applied, a mixture of cyclopropanecarbaldehyde **9a** and the corresponding imine was obtained due to α-deprotonation of **10** by isopropylamine. In order to eliminate the latter reaction, γ-bromo-α-chlorobutanal **10** was treated with chlorine gas to synthesize the α,α-dichlorinated analogue, which could be used as imine precursor. After chlorination, an inseparable mixture of reaction products was obtained. To overcome this problem an efficient synthesis of 4-aryl-2,2,4-trichlorobutanals **12** was developed by a HCl-induced ring opening and in situ chlorination of the obtained intermediate α-chloroaldehydes.[18] This procedure yielded compounds **12** in almost quantitative yield, which could be purified by distillation. Imination of compound **12** by the use of various amines in the presence of titanium(IV) chloride and subsequent treatment with potassium cyanide in methanol yielded 5-aryl-3-chloro-2-cyano-2-pyrrolines **14** in good yield (Scheme 2). The obtained intermediate imines **13** were not stable enough to purify by distillation or chromatography and were used directly after isolation from the reaction mixture. 2-Pyrrolines **14** proved to be stable at low temperatures (−20 °C) for several days.



Scheme 2.

The treatment of 2-pyrrolines **14** with 4 equiv of 2 M sodium methoxide in methanol at reflux temperature for 2 h resulted in the formation of 3-chloropyrroles **16**.

The mechanism can be rationalized by an initial base induced isomerization towards 3-pyrrolines **15** and subsequent expulsion of cyanide. Further isomerization results in 2-aryl-4-chloropyrroles **16** in good yield (Scheme 2). With this procedure β-chloropyrroles can be synthesized on a multi-gram scale using cheap reagents and facile chemistry.

When handling pyrrolines **14** in wet solvents, often some hydrolysis product was formed. These products (**19**) were formed by electrophilic addition of a proton and subsequent attack of water, as shown in Scheme 3. In a more controlled manner, *cis*-substituted pyrrolidinones **19** could be obtained quantitatively by treatment of pyrrolines **14** with aqueous 2 M HCl in acetic acid at room temperature. When higher