Electrophile-induced bromocyclization of γ,δ-unsaturated ketimines to intermediate 1-pyrrolinium salts and their selective conversion into novel 5-alkoxymethyl-2-aryl-3-chloropyrroles and 2-aroylpyrroles†

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Received 8th August 2008, Accepted 8th August 2008
First published as an Advance Article on the web 4th September 2008
DOI: 10.1039/b813890g

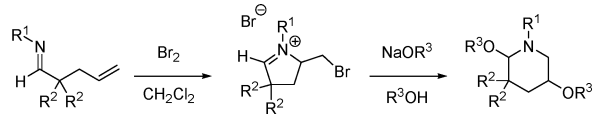
***N*-(1-Aryl-2,2-dichloropent-4-enylidene)amines were efficiently transformed into 5-bromomethyl-1-pyrrolinium bromides *via* electrophile-induced bromocyclization. The latter pyrrolinium salts were converted into novel 5-alkoxymethyl-2-aryl-3-chloropyrroles by reaction with alkoxides in the corresponding alcohol or in THF. This chemistry clearly deviates from the corresponding γ,δ-unsaturated α,α-dialkylaldimines under similar conditions. Furthermore, treatment of 5-bromomethyl-1-pyrrolinium bromides with sodium hydroxide in water afforded a new entry into 2-aroylpyrroles by an unexpected ring transformation of intermediate aziridine derivatives, which could be isolated as well.**

Halogenated pyrroles have received considerable attention in the literature since the isolation of a large variety of functionalized derivatives from natural sources, often associated with a range of biological activities. In particular, 3-halopyrroles have been shown to possess pronounced bioactivities in the fields of pharmacy and crop protection, although the 2-halopyrrole moiety is also often encountered as part of the molecule. A few examples of relevant 3-chloropyrroles comprise the antibacterial pyoluteorin, isolated from *Pseudomonas aeruginosa*,[1] the antileukemic roseophillin, isolated from *Streptomyces griseoviridis*,[2] and the antifungal pyrrolnitrin, isolated from the bacterium *Pseudomonas pyrociniae*.[3] Pyrrolnitrin has also served as a lead for the development of a number of novel fungicides,[4] insecticides,[5] nematicides[6] and molluscicides.[7] Besides halo atoms, the presence of oxymethyl groups is often observed in biologically relevant pyrroles. For example, 2-(hydroxymethyl)pyrroles have been described as a new class of inhibitors of α-chymotrypsin, a member of serine protease enzymes.[8]

Although chlorinated 2-(oxymethyl)pyrroles—in which both above-mentioned structural features are combined—might play a significant role in the discovery of novel bioactive compounds, little efforts have been devoted to the development of useful synthetic approaches towards this class of compounds. Known methods in that respect involve chlorination of pyrroles with sulfuryl chloride towards 3,4-dichloro-2-(hydroxymethyl)pyrroles,[9] domino reactions of 1-aminocarbonyl-1,2-diaza-1,3-butadienes with α,α-dichloroacetophenone towards 4-chloro-2-methoxymethyl-5-phenyl-1*H*-aminopyrrole-3-carboxylates,[10] and aromatization of 2-aryl-5-bromomethyl-3,3-dichloropyrrolines and reduction of 2-formyl- and 2-cyanopyrroles.[11]

In the present paper, the electrophile-induced cyclization of γ,δ-unsaturated α,α-dichlorinated arylketimines into 5-bromomethyl-1-pyrrolinium bromides and the reactivity of the latter with regard to alkoxides is evaluated as a new and efficient approach towards 5-alkoxymethyl-2-aryl-3-chloropyrroles. This chemistry deviates from the corresponding γ,δ-unsaturated α,α-dialkylaldimines which, under similar conditions, are convertible into 3-alkoxypiperidines. Furthermore, hydroxide is also used instead of alkoxide, providing a new entry into 2-aroylpyrroles *via* an unexpected rearrangement of intermediate aziridine derivatives.

Electrophile-induced cyclizations constitute a powerful methodology for the synthesis of a large variety of functionalized azaheterocyclic compounds.[12] In that respect, γ,δ-unsaturated imines comprise suitable substrates for seleno- and halocyclization towards highly electrophilic 1-pyrrolinium salts, thus affording useful approaches towards aziridines,[13] pyrrolidines and piperidines.[14,15] Previously, the synthesis of 5-bromomethyl-1-pyrrolinium bromides **2** through electrophile-induced bromocyclization of γ,δ-unsaturated aldimines **1** upon treatment with bromine and subsequent rearrangement of these 1-pyrrolinium salts **2** to oxygenated piperidines **3** by reaction with sodium alkoxides in the corresponding alcohol has been described (Scheme 1).[16] The latter transformation proceeded *via* addition of the alkoxide across the iminium moiety, followed by cyclization towards intermediate 1-azoniabicyclo[3.1.0]hexanes upon expulsion of bromide and subsequent ring opening of the latter aziridinium salts by alkoxide towards piperidines **3**.



Scheme 1 (Ref. 16).

In the present work, the deviating behaviour of *N*-(1-aryl-2,2-dichloropent-4-enylidene)amines **7** towards five-membered instead of six-membered azaheterocycles is highlighted.

N-(1-Aryl-2,2-dichloropent-4-enylidene)amines **7** were prepared *via* a three-step procedure starting from the required acetophenone derivatives **4**. Imination of the latter ketones **4** using 5 equivalents of a primary amine in diethyl ether in the presence of 0.7 equivalents of titanium(IV) chloride afforded the corresponding imines **5** after two hours, which were subsequently

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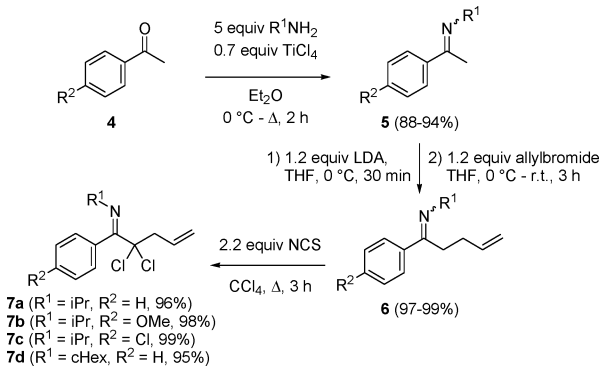
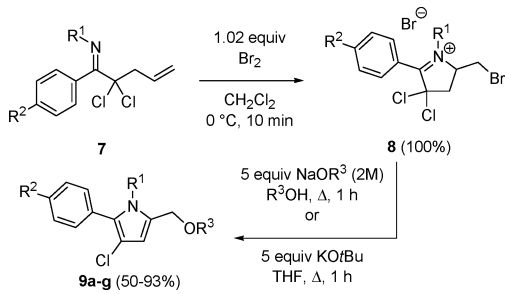
† Electronic supplementary information (ESI) available: Experimental data. See DOI: 10.1039/b813890g

α-allylated towards imines **6** utilizing 1.2 equivalents of lithium diisopropylamide (LDA) and 1.2 equivalents of allylbromide in THF (Scheme 2). A final α,α-dichlorination by means of 2.2 equivalents of *N*-chlorosuccinimide (NCS) in tetrachloromethane upon reflux for 3 hours afforded γ,δ-unsaturated α,α-dichlorinated arylketimines **7** in high yields (Scheme 2). This method comprises a slightly modified and improved alternative for a previously reported approach,[17] in which acetophenone was first α,α-dichlorinated, followed by imination and α-allylation.



Scheme 2

Treatment of γ,δ-unsaturated imines **7** with 1.02 equivalents of bromine in dichloromethane at 0 °C for 10 minutes afforded 5-bromomethyl-3,3-dichloro-1-pyrrolinium bromides **8** quantitatively, which were used immediately and as such for further elaboration due to their instability. Reaction of pyrrolinium salts **8** with 5 equivalents of sodium alkoxide (methoxide or isopropoxide) in the corresponding alcohol (2 M) or with 5 equivalents of potassium *tert*-butoxide in THF resulted in the formation of 5-alkoxymethyl-2-aryl-3-chloropyrroles **9** after reflux for one hour (Table 1, Scheme 3). When sodium ethoxide was used, rather complex reaction mixtures were obtained in which only 10% of the desired pyrroles were present, together with unidentified side products.

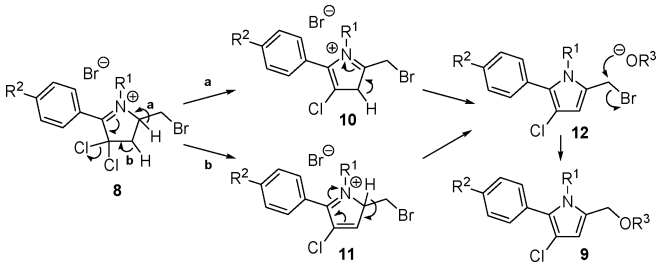


Scheme 3

Table 1 Synthesis of 5-alkoxymethyl-2-aryl-3-chloropyrroles **9**

Entry	R^1	R^2	R^3	Compound (yield)
1	iPr	H	Me	**9a** (86%)
2	iPr	OMe	Me	**9b** (83%)
3	cHex	H	Me	**9c** (50%)
4	iPr	H	tBu	**9d** (93%)
5	iPr	Cl	tBu	**9e** (81%)
6	iPr	Cl	iPr	**9f** (85%)
7	iPr	Cl	Me	**9g** (91%)

From a mechanistic point of view, two different pathways can be considered in order to explain the transformation of pyrrolinium salts **8** into pyrroles **9** (Scheme 4). Dehydrochlorination of 3,3-dichloropyrrolinium bromides **8** can occur in either a 1,4-fashion (pathway a) or a 1,2-fashion (pathway b), giving rise to intermediates **10** or **11**, respectively, followed by aromatization towards 5-(bromomethyl)pyrroles **12** *via* a second deprotonation. In a final step, nucleophilic displacement of bromide by alkoxide in pyrroles **12** furnished the corresponding 5-(alkoxymethyl)pyrroles **9**. The intermediacy of 5-(bromomethyl)pyrroles **12** in this transformation was further supported by the presence of small quantities in the crude reaction mixtures (based on ^{1}H NMR analysis).

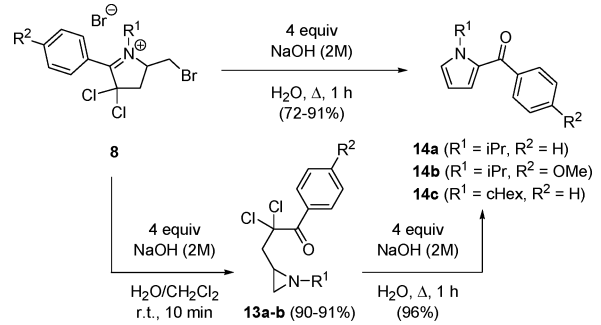


Scheme 4

It should be noted that ring expansion of 2-aryl-5-bromomethyl-3,3-dichloropyrrolidinium bromides **8** into oxygenated piperidines upon treatment with alkoxides was never observed, in contrast with the reactivity of 3,3-dialkyl-5-(bromomethyl)pyrrolidinium bromides **2**, which completely underwent ring expansion to piperidines **3** (*cf.* Scheme 1).[16] These observations point to a distinct difference in reactivity between aldiminium bromides **2** and ketiminium bromides **8** upon treatment with alkoxides, as aldiminium salts **2** easily undergo nucleophilic addition across the C=N bond, followed by further transformation towards oxygenated piperidines, whereas ketiminium salts **8** suffer from dehydrohalogenation leading to pyrroles instead of nucleophilic addition.

The methodology described above enables the regioselective preparation of substituted 3-chloropyrroles in a convenient way. From a synthetic point of view, the access to halopyrroles in a regiospecific way is limited due to problems associated with the halogenation of pyrroles, *i.e.* the problem of overhalogenation, the instability of reaction products, the formation of oxidation products and the solvent dependency.[18] Thus, the preparation of 3-chloropyrroles *via* intermediate 3,3-dichloro-1-pyrrolinium salts is of synthetic importance, in analogy with the previously reported transformation of 2-aryl-3,3-dichloropyrrolines upon treatment with sodium methoxide in methanol.[19]

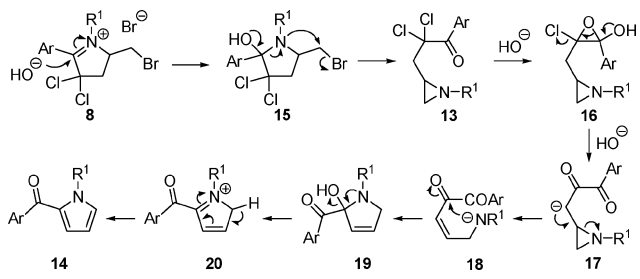
Surprisingly, different types of pyrroles, *i.e.* 2-aroylpyrroles **14**, were isolated when pyrrolinium bromides **8** were treated with 4 equivalents of sodium hydroxide (2 M in H_2O) under reflux for one hour (Scheme 5). On the other hand, functionalized aziridines **13a–b** were obtained in high yields upon treatment of pyrrolinium salts **8** with NaOH in a H_2O–CH_2Cl_2 (1 : 1) solvent mixture for 10 minutes at room temperature (Scheme 5). Previously, the transformation of 5-bromomethyl-3,3-dimethyl-1-pyrrolinium salts into 3-(aziridin-2-yl)-2,2-dimethylpropanals has been described as a new and efficient method for the intramolecular aziridination of olefins by transfer of alkylamine moieties (N–R) from a remote position



Scheme 5

in the molecule to the alkene.[13] The net result comprises the elegant conversion of an unactivated carbon–carbon double bond into an aziridine. Most likely, aziridines **13** participate in the transformation of pyrrolinium salts **8** into 2-aroylpyrroles **14**, as treatment of these aziridines **13** with 4 equivalents of sodium hydroxide (2 M in H_2O) under reflux for one hour furnished pyrroles **14** in excellent yield (Scheme 5). Aroylpyrroles are of biological interest, as for example aminoacyl substituted 2- and 4-aroylpyrroles have been reported as a new class of anticonvulsant agents.[20]

A plausible mechanistic rationale for the ring transformation of pyrrolinium salts **8** into 2-aroylpyrroles **14** is suggested in Scheme 6. Considering the electrophilic nature of 1-pyrrolinium salts **8**, nucleophilic addition of hydroxide across the C=N double bond results in hemi-aminals **15**, which rearrange into aziridines **13** *via* ring opening and subsequent cyclization upon expulsion of bromide. The presence of two chloro atoms in aziridines **13** enables further transformation of these substrates. α,α-Dichloroalkyl aryl ketones are known to be very poor substrates for direct α-substitution reactions (even intramoleculary),[21] as nucleophilic addition across the carbonyl moiety followed by epoxide formation and further transformation is usually observed.[22] Accordingly, the intermediate epoxides **16** can be formed through addition of hydroxide. The highly unstable epoxides **16** are then converted into 1-aryl-3-(aziridin-2-yl)propane-1,2-diones **17**, which undergo ring opening due to the abstraction of proton by hydroxide in α-position with respect to the carbonyl group and the aziridine moiety. Nucleophilic addition of the resulting nitrogen anion in acyclic diones **18** across the most reactive carbonyl group furnishes 3-pyrrolines **19**, which are smoothly aromatized towards pyrroles **14** *via* iminium salts **20**.



Scheme 6

In summary, a new and convenient approach towards novel 5-alkoxymethyl-2-aryl-3-chloropyrroles is disclosed based on the electrophile-induced bromocyclization of *N*-(1-aryl-2,2-dichloropent-4-enylidene)amines into 5-bromomethyl-1-pyrrolinium bromides and subsequent treatment with alkoxides in the corresponding alcohol or in THF. The deviating behaviour of *N*-(1-aryl-2,2-dichloropent-4-enylidene)amines towards five-membered instead of six-membered azaheterocycles was thus highlighted. Furthermore, reaction of the afore-mentioned pyrrolinium salts with sodium hydroxide in water afforded a new entry into 2-aroylpyrroles *via* unexpected ring transformation of 1-aryl-2,2-dichloro-3-(aziridin-2-yl)propan-1-ones, which could be isolated as well.

Acknowledgements

The authors are indebted to the "Fund for Scientific Research - Flanders (Belgium)" (FWO-Vlaanderen) and to Ghent University (GOA) for financial support.

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