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Reduction of imidazolium salts – An approach to diazocines and diazocanes

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ABSTRACT

A convenient approach to diazocine derivatives **8,9** starting from 1,2-polymethyle-neimidazolium salts **4** was developed. The polymethylenimidazolium salts **4** are partially reduced with sodium borohydride in DMF to give 5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-*a*]imidazoles **5** or under more forcing conditions – (sodium triacetoxyborohydride in acetic acid) with cleavage of the endocyclic C–N bond affording diamines **6**. Tertiary salts **7** readily prepared from compounds **5** react with $NaBH_4$ and KCN nucleophiles with cleavage of the endocyclic N–C bond to form diazocine derivatives **8,9**.

1. Introduction

The reduction of heteroaromatic compounds is a reliable method for the construction of partially and fully saturated heterocycles, of which synthesis is often difficult to imagine in other ways. Among nitrogen-containing heterocycles, the imidazole nucleus is one of the most inert with respect to reducing reagents. Thus, in the case of catalytic hydrogenation of condensed imidazoles, the carbocyclic moiety of the molecule, or the heterocyclic one annelated to the imidazole, is reduced first.[1–7] Nevertheless, quaternary imidazole and especially benzimidazole salts are easily reduced with complex metal hydrides to dihydro derivatives featuring a labile aminal fragment.[8–13] First of all, these compounds draw attention as electron-transfer reducing agents and are widely used in reduction reactions.[14–18] On the other hand, further reductive cleavage of cyclic aminals with complex metal hydrides makes it possible to quickly generate both highly substituted diamino derivatives and various functionalized heterocycles, including macrocyclic ones. The readily available fused imidazole derivatives are useful starting materials for the preparation of medium and large diazacycles.[19–27]

Previously we reported on the reduction of 1,2-polymethylenebenzimidazoles **I** (n = 1–4) with DIBAL-H which is markedly dependent on the size of the saturated cycle. In particular, when n = 1, 2 a mixture of the two products – fused 1,4-diazacycloalkanes **II** and anilines **III** were observed to form, whereas for n = 3, 4 fused 1,4-diazacycloalkanes **II** formed exclusively (Fig. 1).[28] In continuation of our research focused on macrocyclic diamines, we expected that analogous 1,2-polymethylenimidazoles **IV** (n = 1–4) would also serve as starting materials for the synthesis of macrocyclic diamines.

2. Results and discussion

Our previous study revealed that, unlike the related polymethylenebenzimidazoles **I**, 1,2-polymethylenimidazoles **IV** are highly resistant to reducing agents, and do not react with $LiAlH_4$ and DIBAL-H. At the same time, their salts **V** are susceptible to reduction and can be used for the preparation of medium cycles. The starting imidazolium salts **4** featuring an aryl substituent at the nitrogen atom were prepared analogously with the known procedure for the closely related 1,3-diaryl-5,6-dihydro-8H-imidazo-[2,1-c]-1,4-oxazinium bromides.[29] Treatment of the corresponding cyclic amidines **1** with α-phenacyl bromides **2** in acetonitrile led to

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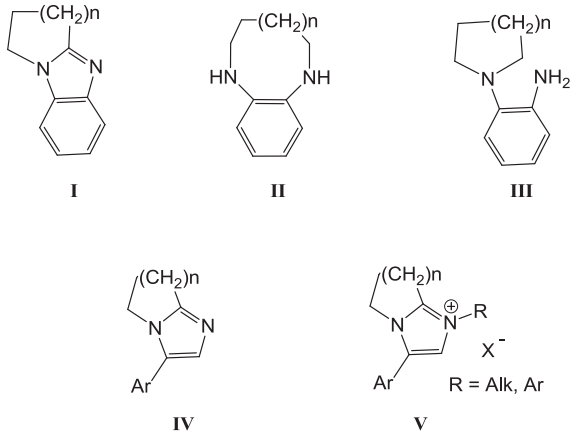


Fig. 1. Starting imidazole derivatives and reduction products.

Table 1
Designation of substituents of compounds **4**–**11** and their yields.

	n	R^1	R^2	X	Compounds#, yield, %							
					4	**5**	**6**	**7**	**8**	**9**	**10**	**11**
a	1	Ph	4-$CH_3C_6H_4$	Br	64	51	69	89	79	74	50	57
b	1	Ph	4-C_6H_4F	Br	66	62	79	85	77	77	52	58
c	1	4-BrC_6H_4	4-$CH_3C_6H_4$	Br	68	79	93	96	92	85	56	64
d	1	4-FC_6H_4	4-$CH_3C_6H_4$	Br	64	47	47	77	84	81	74	74
e	1	4-$MeOC_6H_4$	4-BrC_6H_4	Br	63	66	82	99	89	93	86	88
f	2	4-BrC_6H_4	Ph	Br	61		60					
g	2	4-BrC_6H_4	4-$CH_3C_6H_4$	Br	77		44					
h	3	4-BrC_6H_4	Ph	Br	87	47	57					
i	3	4-BrC_6H_4	4-$CH_3C_6H_4$	Br	69		58					
j	4	4-BrC_6H_4	Ph	Br	76	51	65					
k	4	4-BrC_6H_4	4-$CH_3C_6H_4$	Br	50		66					
l	1	Me	Ph	I	93		80					
m	3	Me	Ph	I	97		78					

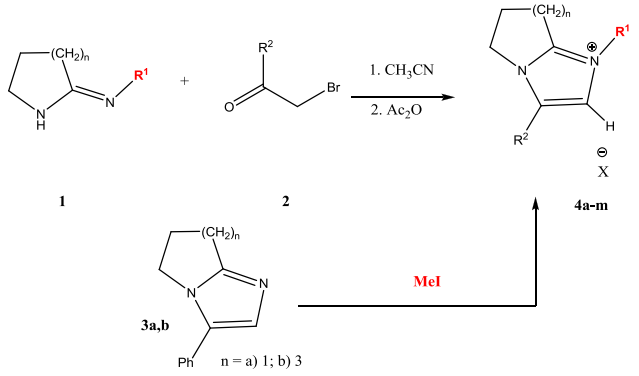
the precipitation of intermediate salts as a result of quaternization at the exocyclic nitrogen atom. To the reaction mixture acetic anhydride was added and refluxed for a few hours to effect imidazole ring formation affording target imidazolium salts **4a-k** (Scheme 1) (see Table 1). The analogous imidazolium salts **4l,m** featuring an alkyl substituent were prepared by alkylation of fused imidazoles **3** with excess CH_3I at rt according to the known literature procedure.[30]

In the ^{1}H NMR spectra of salts **4** the proton of the imidazole ring exhibits a singlet in the downfield region 7.8–8.5 ppm. The distinguishing features of salts **4** fused with five-membered cycle (n = 1) are the markedly downfield shifted imidazolium protons in the range 8.44–8.51 ppm, and in the ^{13}C NMR spectra, carbon atoms at 153.1–153.4 ppm.

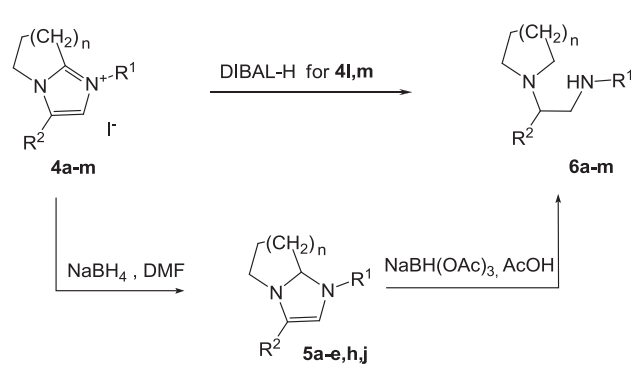
In the literature there is no information on the reduction of fused imidazolium salts **4**, but the reduction of imidazolium salts themselves with sodium borohydride was studied in detail. As a result, we decided to use sodium borohydride as a reducing agent. Reduction of both *N*-alkyl and *N*-aryl-substituted quaternary salts **4** was studied. Salts **4** featuring an aryl substituent at the nitrogen atom were found to undergo partial reduction to give tetrahydro-1H-pyrrolo[1,2-*a*]imidazoles **5** (Scheme 2). The reduction of imidazolium salts **4** with sodium borohydride in DMF proceeds readily, affording neutral partially reduced compounds **5** in a moderate yield. In the majority of cases partially reduced compounds **5** are highly unstable, thus they decompose upon crystallization or chromatographic separation. We managed to prepare analytically pure samples for tetrahydro-1H-pyrrolo[1,2-*a*]imidazoles **5a-e** by rinsing them with isopropanol or acetonitrile. In the solid state they can be stored for a few weeks at 0–4°C. They readily decompose in the presence of acidic traces, for example on taking NMR spectra in $CDCl_3$. Other fused dihydroimidazoles **5** featuring a larger saturated cycle (n = 2–4) are less stable, so that we were able to separate and characterize only two compounds **5h,j**. Under similar conditions, imidazolium salts **4f,g,i,k** gave products that, judging by ^{1}H NMR spectroscopy, are the corresponding dihydroimidazoles **5**. We failed to separate them because neither crystallization nor chromatography could be applied for their purification as it led to their complete destruction. All obtained dihydroimidazoles **5** are bright yellow or light green substances exhibiting significant fluorescence in solution. Upon storage on open air they gradually decomposed. ^{1}H NMR spectra of compounds **5a-e** are characterized by a double doublet in the region 4.9–5.3 ppm corresponding to the proton at the chiral center.

At the same time, fused imidazolium salts **4l,m** remain inert towards sodium borohydride. Like *N*-methyl benzannelated analogs of **I,** *N*-methyl quaternary salts **4l,m** were readily reduced with DIBAL-H with cleavage of the C=N double bond affording diamines **6l,m** (Scheme 2).[28]

To prepare the target diazocine derivatives we applied a stronger reducing agent, namely sodium triacetoxyborohydride in acetic acid for imidazolines **5.** It turned out that, regardless of the size of the saturated ring, selective cleavage of the C–N bond leading to the formation of tertiary amines **6a-e,h,j** occurred in a good yield. We also found that under these conditions imidazolium salts **4f,g,i,k** can also be reduced to the corresponding diamines **6f,g,i,k**. Alternatively, salts **4a-k** can be reduced by a one-pot procedure using sodium borohydride in DMF. Judging by NMR spectroscopy, this led to the corresponding partially reduced compounds **5** which gave diamines **6**, albeit in low yield, after addition of acetic acid.



Scheme 1. Synthesis of starting imidazolium salts **4**.



Scheme 2. Reduction of imidazolium salts **4**.