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Synthesis of di(imidazolium) and di(pyrazolium) salts as precursors for N-heterocyclic dicarbene complexes

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Abstract

Alpha,omega-bis(pyrazol-1-yl)alkanes and alpha,omega-bis(imidazol-1-yl)alkanes with spacers consisting of four to ten methylene groups have been prepared from pyrazole, 3,5-dimethylpyrazole or imidazole and corresponding dibromoalkanes in a superbasic medium KOH-DMSO. The proposed method of synthesis allowed the preparation of new flexible bidentate ligands without the need to use toxic solvents and tedious workup procedures. Bis(pyrazol-1-yl)alkanes were further functionalized for their use as precursors for “non-classical” mesoionic N-heterocyclic carbene ligands. One the first step, iodine atoms were introduced to positions 4 of pyrazole rings by oxidative iodination using I₂-HIO₃ system. On the next step, nitrogen atoms in positions 2 of pyrazole rings were alkylated using several agents. Reaction with methyl iodide unexpectedly led to the formation of only mono-alkylated products even after 7 days of refluxing in a neat alkyl iodide. Methylation by trimethyloxonium tetrafluoroborate or methyltriflate led to dimethylated products in high yields. Bis(imidazol-1-yl)alkanes were easily alkylated by methyl iodide to give di(imidazolium) salts – precursors to “classic” N-heterocyclic dicarbenes.

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Keywords: Pyrazole, imidazole, N-heterocyclic carbenes, imidazolium salts, pyrazolium salts;

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1. Introduction

Chemistry of stable N-heterocyclic carbenes (NHCs) is a rapidly developing area of organic and organometallic chemistry. Metal complexes of N-heterocyclic carbenes often demonstrate high catalytic activity¹. NHCs based on imidazole derivatives are widely known, one of the most important example of their complexes is Grubbs olefin metathesis catalyst². Carbenes based on other azoles, namely pyrazole and triazole are much less studied³, especially those containing two or more carbene centers⁴.

Bis(pyrazol-1-yl)alkanes are organic compounds comprising two pyrazolic cycles linked by spacers of various structures. They are effective chelating ligands forming complexes with more than 70 elements – most transition metals and some main group elements⁵. Nevertheless, studies of their properties and application areas are somewhat hindered by complex procedures for their preparation. Therefore, it is of interest to seek for new facile methods for the preparation of bis(pyrazol-1-yl)alkanes and related compounds, that would make them readily available. In literature, most data corresponds to pyrazole derivatives with one or two methylene groups in the linker, while for compounds with four and more methylene groups only isolated examples of synthesis are described.

Previously, we have developed a new procedure for the preparation of bis(pyrazol-1-yl)alkanes by double alkylation of pyrazoles by aliphatic dihalogenoderivatives in a superbasic medium^{6,7}. Here we report the synthesis of di(pyrazolium) and di(imidazolium) salts with long aliphatic spacers as precursors for the generation of pyrazole- and imidazole-derived dicarbenes.

2. Results and discussion

Bis(pyrazol-1-yl)alkanes with long spacers were prepared from pyrazoles or imidazoles and α,ω -dibromoalkanes (from 1,4-dibromobutane to 1,12-dibromododecane) in a superbasic KOH-DMSO medium (figure 1).

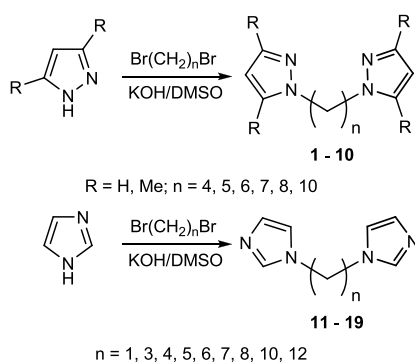


Fig. 1. Synthesis of bis(azoly)alkanes

Double alkylation proceeded smoothly with high yields of target products (>75%, table 1), which were isolated by quenching the reaction mixture with water and filtration of extraction with chloroform. The yields of imidazole derivatives were lower because of their higher solubility in water, which prevents their full extraction into the organic phase.

Prepared pyrazole derivatives were functionalized by iodine atoms, since they are rather reactive in oxidative addition to palladium center leading to the formation of carbenes⁸. Oxidative iodination was carried out using iodine and iodic acid in acetic acid, as shown in figure 2. Electron-donating methyl groups enhance the reactivity of pyrazole rings and iodination was complete in 20-30 minutes even at room temperature leading to previously unknown diiododerivatives in nearly quantitative yields (table 2).

The prepared bis(pyrazol-1-yl)alkanes and bis(imidazol-1-yl)alkanes were alkylated by different methylating agents – methyl iodide, methyl triflate, trimethyloxoniumtetrafluoroborate. Bis(imidazol-1-yl)alkanes are methylated smoothly by all of these agents to give di(imidazolium) salts (figure 3). It should be noted that most of these salts are liquid at room temperature and can be considered for application as dicationic ionic liquids^{9,10}.

Table 1. Melting points and product yields of bis(azolyl)alkanes

| Comp. No. | R | n | Yield, | m.p., °C (recryst. solvent) |
|-----------|-----------------|----|--------|--------------------------------|
| 1 | H | 4 | 88 | 40-42 (benzene) |
| 2 | CH ₃ | 4 | 93 | 113-114 (benzene) |
| 3 | H | 5 | 97 | oil |
| 4 | CH ₃ | 5 | 67 | 64-65 (hexane-benzene, 1:1) |
| 5 | H | 6 | 98 | 47-48 (toluene) |
| 6 | CH ₃ | 6 | 73 | 52-53 (hexane) |
| 7 | H | 8 | 94 | 42-43 (hexane) |
| 8 | CH ₃ | 8 | 78 | 37-38 (hexane) |
| 9 | H | 10 | 93 | 54-55 (benzene) |
| 10 | CH ₃ | 10 | 85 | oil |
| 11 | – | 1 | 53 | 167-169 (EtOAc) |
| 12 | – | 3 | 31 | oil |
| 13 | – | 4 | 25 | 80-82 (i-PrOH) |
| 14 | – | 5 | 41 | oil |
| 15 | – | 6 | 65 | oil |
| 16 | – | 8 | 56 | oil |
| 17 | – | 9 | 70 | oil |
| 18 | – | 10 | 41 | oil |
| 19 | – | 12 | 99 | oil |

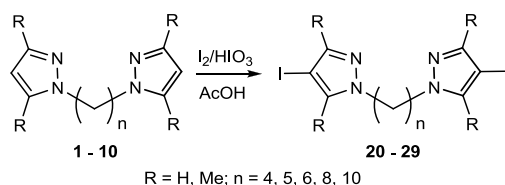


Fig. 2. Iodination of bis(pyrazol-1-yl)alkanes

In contrast to imidazole derivatives, reaction of bis(pyrazol-1-yl)alkanes with iodomethane gave almost no di(pyrazolium) salts and mono(pyrazolium) derivatives were isolated instead (figure 4). The yields of di(pyrazolium) derivatives increased with the elongation of polymethylene spacer and only dialkylated product was obtained in case of twelve CH₂ groups in the spacer.

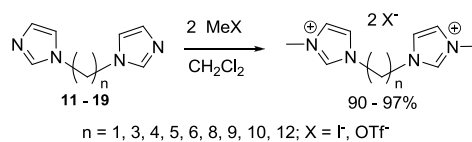


Fig. 3. Synthesis of di(imidazolium) salts

Table 2. Melting points and product yields of bis(4-iodopyrazol-1-yl)alkanes

| Comp. No. | R | n | Yield, | m.p., °C (recryst. solvent) |
|-----------|-----------------|----|--------|---------------------------------|
| 20 | H | 4 | 86 | 92-93 (benzene) |
| 21 | CH ₃ | 4 | 86 | 142-143 (i-PrOH) |
| 22 | H | 5 | 95 | oil |
| 23 | CH ₃ | 5 | 96 | 82-83 (benzene) |
| 24 | H | 6 | 90 | 72-73 (benzene) |
| 25 | CH ₃ | 6 | 94 | 142-143 (i-PrOH) |
| 26 | H | 8 | 87 | 64-65.5 (benzene) |
| 27 | CH ₃ | 8 | 93 | 54-55 (hexane- benzene, 1:1) |
| 28 | H | 10 | 92 | 72-74 (benzene) |
| 29 | CH ₃ | 10 | 90 | 98-100 (benzene) |

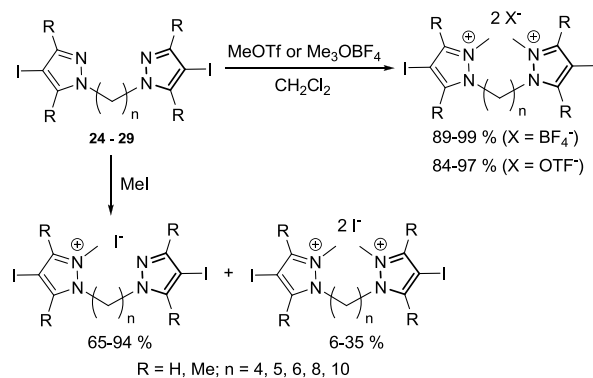


Fig. 4. Synthesis of di(pyrazolium) salts

Lower yields of dialkylated products are probably explained by low solubility of mono(pyrazolium) salts in reaction medium. Longer and more flexible aliphatic spacers increase the solubility of monocationic salts, leading to increased yields of di(pyrazolium) products.

The solubility of pyrazolium salts also increased when iodide counter-ions were changed to tetrafluoroborates or trifluoromethanesulfonates (triflates). When trimethyloxonium tetrafluoroborate or methyl triflate were used for alkylation, only dimethyl-derivatives were formed.

3. Conclusion

In summary, new pyrazolium and imidazolium salts were prepared by various methods. Alkylation using iodomethane does not require expensive or unstable alkylating agents and in case of bis(imidazol-1-yl)alkanes and unsubstituted bis(pyrazol-1-yl)alkanes leads to diazolium salts, which can be further used as precursors to classic and mesoionic N-heterocyclic dicarbenes. Although dipyrazolium salts could not be prepared in case of 3,5-dimethylpyrazole derivatives, alkylation by iodomethane allows to prepare monopyrazolium salts, unavailable by other routes.

Di(pyrazolium) salts with substituents in pyrazole rings could be prepared using other alkylating agents, which also allow to vary the counter-ion.

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