Chemistry and applications of benzonaphthyridines

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Dedicated to Prof. Rudy Abramovich on the occasion of his 70th birthday
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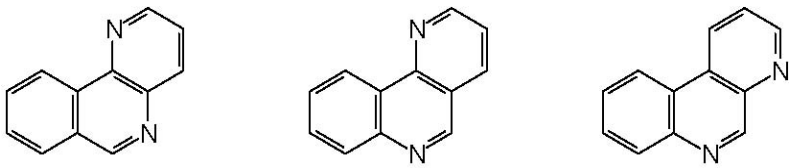
Abstract
Cycloadditions of benzonaphthyridines, their N-oxides and ylides from their quaternary salts are presented. Dimethylacetylenedicarboxylate, diethyl maleate, acrylonitrile and others were used as dipolarophiles. Cyclization of N-phenacylbenzonaphthyridinium bromides with ammonium acetate as well as vicarious substitution of hydrogen of benzonaphthyridine N-oxides are also reported and pathways to their formation are proposed.

Keywords: Benzonaphthyridines, benzonaphthyridiene N-oxides, benzonaphthyridine ylides cycloaddition reactions

Introduction

Isomeric benzo[c][1,5]-, benzo[h][1,6]- and benzo[f][1,7]naphthyridines **1** - **3**, the theme of our research, are interesting for their chemical reactivity, biological properties, and applications. They exhibit a wide spectrum of biological activity such as bactericidal, fungicidal, and cancerostatic.[1-3] They are also interesting ligands of the Werner-type σ-complexes with metal central atoms as well as EDA π-complexes.[4]



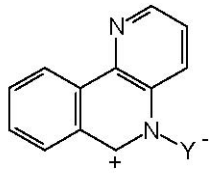
1 **2** **3**

This brief review covers our contribution to the knowledge of reactivity of benzonaphthyridines **1** - **3**. We present their N-oxidation, quaternization and cycloadditions of unsubstituted systems, as well as their ylides and N-oxides. We also report cyclization of a series

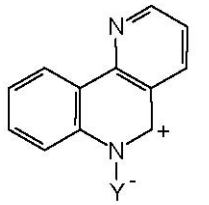
of the quaternary N-phenacylbenzonaphthyridinium bromides with ammonium acetate into tetracyclic benzoimidazonaphthyridines as well as vicarious nucleophilic substitution of hydrogen and formation of aziridine derivatives in reactions of benzonaphthyridines and their N-oxides with carbanions.

Formation of benzonaphthyridinium salts and cycloaddition reactions

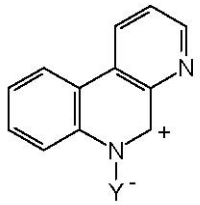
The 1,3-dipolar cycloaddition of ylides **4 - 6** derived from benzonaphthyridines **1 - 3**, i.e. to phenacylides, [5-7] ethoxycarbonylmethylides [8-11] and dichloromethylides [12] offer a convenient route to tetracyclic compounds.



4a Y = CHCOPh
4b Y = CHCOOEt
4c Y = CCl_2

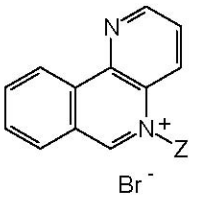


5a Y = CHCOPh
5b Y = CHCOOEt
5c Y = CCl_2

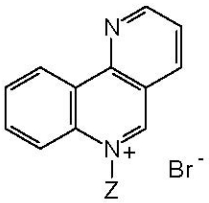


6a Y = CHCOPh
6b Y = CHCOOEt
6c Y = CCl_2

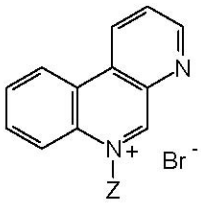
Quaternary bromides, **7a,b - 9a,b**, were precursors of ylides, **4a,b - 6a,b**.



7a Z = CH_2COPh
7b Z = CH_2COOEt



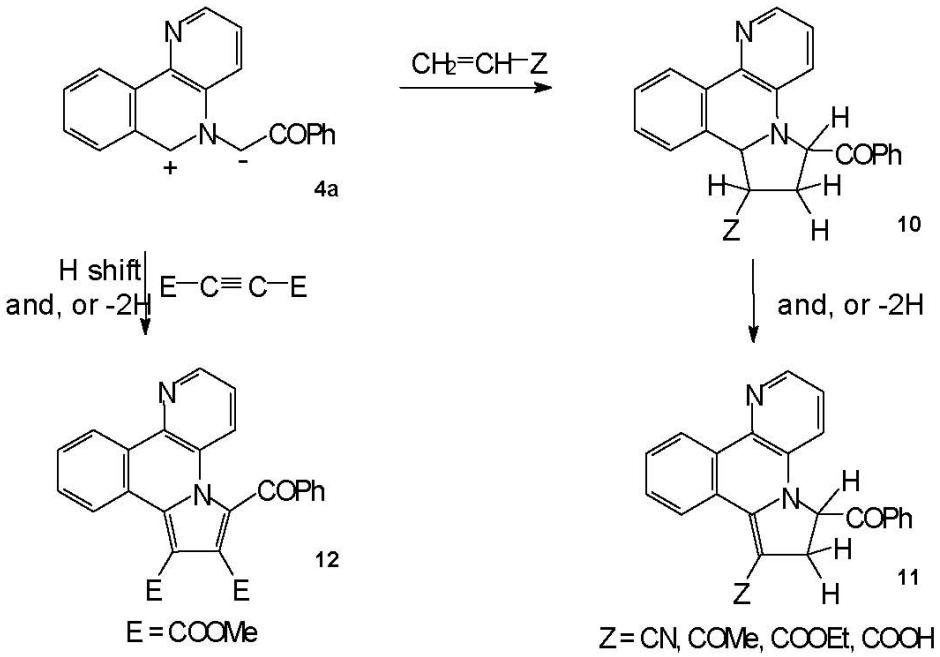
8a Z = CH_2COPh
8b Z = CH_2COOEt



9a Z = CH_2COPh
9b Z = CH_2COOE

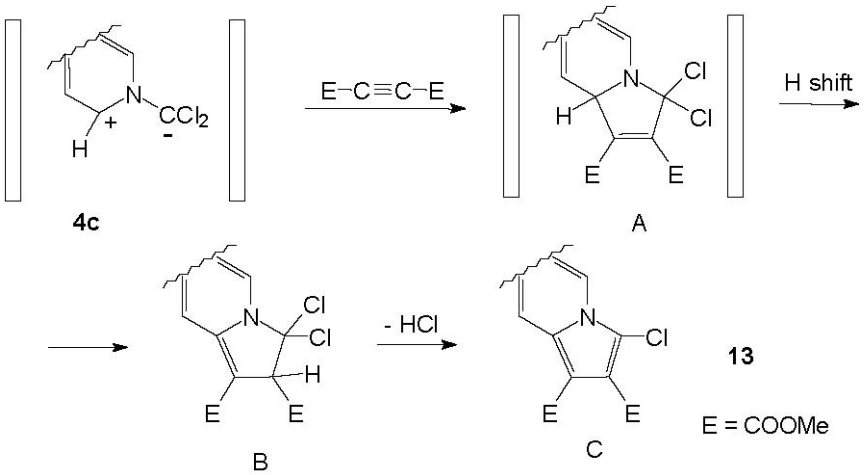
The benzonaphthyridinium salts **7a,b - 9a,b** were obtained by quaternization of **1 - 3** with phenacyl bromide or ethyl bromoacetate. The quaternary salts reacted with Et_3N into corresponding ylides **4a,b - 6a,b**. The latter reacted *in situ* with one of the following dipolarophiles: acrylonitrile, ethyl acrylate, dimethylacetylenedicarboxylate, maleic anhydride, diethyl maleate, methyl vinyl ketone, acrylic and methacrylic acid. In this manner tetracyclic substituted cycloadducts benzopyrrolo-, benzopyrroline- or benzopyrrolidine-naphthyridines were obtained (Scheme 1).

Scheme 1 shows a pathway of 1,3-dipolar cycloaddition of benzo[c][1,5]-naphthyridinium N-phenacylide to a series of dipolarophiles. Similar pathways were proposed for cyclizations with benzo[h][1,6]naphthyridinium phenacylide,[5,6] as well as benzo[c][1,5]-, benzo[h][1,6]- and benzo[f][1,7]naphthyridinium carboethoxymethylides. [8-11]



Scheme 1

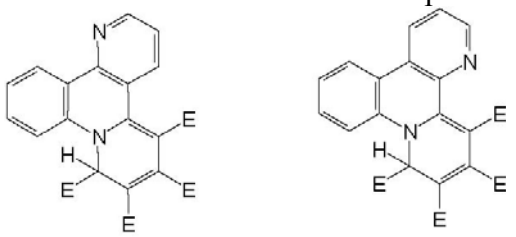
N-dichloromethylides **4c** - **6c** were formed *in situ* from benzonaphthyridines **1** - **3** and dichlorocarbene thermally generated from sodium trichloroacetate in chloroform in the presence of benzyltriethylammonium chloride (TEBA). The 1,3-dipolar cycloaddition of N-dichloromethylides **4c** - **6c** with dimethyl acetylenedicarboxylate (DMAD) as dipolarophile produced compounds of the type C (Scheme 2) [12] .



Scheme 2

Compounds **14** and **15**, which were formed as minor products of the above reactions[12] present examples of cycloadducts of unsubstituted benzonaphthiridine systems to acetylenedicarboxylate. Cycloadduct **15** constituted a main product in the cycloaddition of

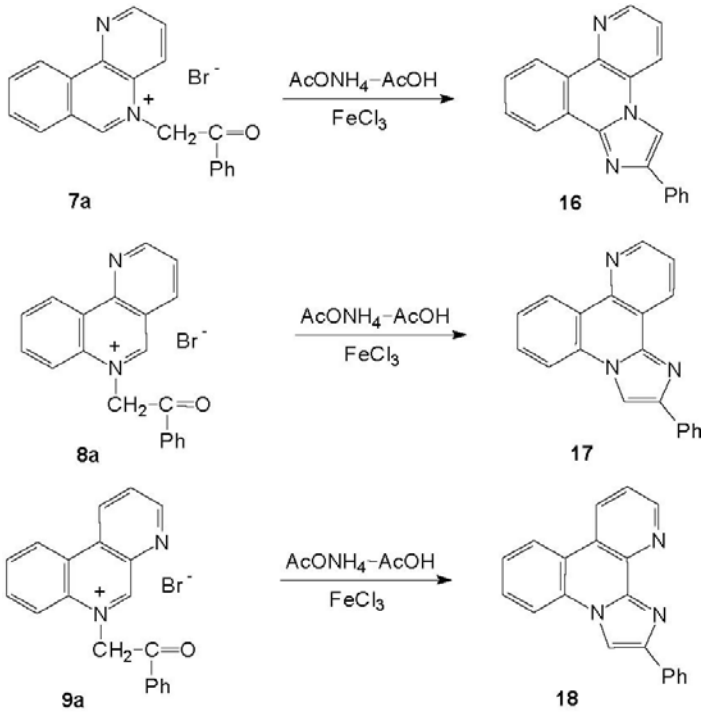
benzo[f][1,7]naphthyridine to DMAD carried out at room temperature in benzene solution. [11]



^{1}H NMR as well as mass spectra of cycloadducts of benzo[c][1,5]-, benzo[h][1,6]-naphthyridinium phenacylides and benzo[c][1,5]-, benzo[h][1,6]-naphthyridinium ethoxycarbonylmethylides with a series of dipolarophiles were determined and discussed in separate papers.[13-16] ^{1}H NMR spectra of cycloadducts were compared with those of parent benzonaphthyridines; all observed shifts were explained by electronic and steric features.

Synthesis of benzoimidazonaphthyridines

Cyclization of a series of the quaternary N-phenacylbenzonaphthyridinium bromides **7a - 9a** with ammonium acetate in the presence of ferric chloride in acetic acid provided tetracyclic fused imidazole derivatives such as 2-phenylbenzo[c]-imidazo[1,2-a][1,5]naphthyridine **16**, 2-phenylbenzo[h]imidazo[2,1-f][1,6]naphthyridine **17**, and 2-phenylbenzo[f]imidazo[1,2-h][1,7]naphthyridine **18** (Scheme 3). [17]

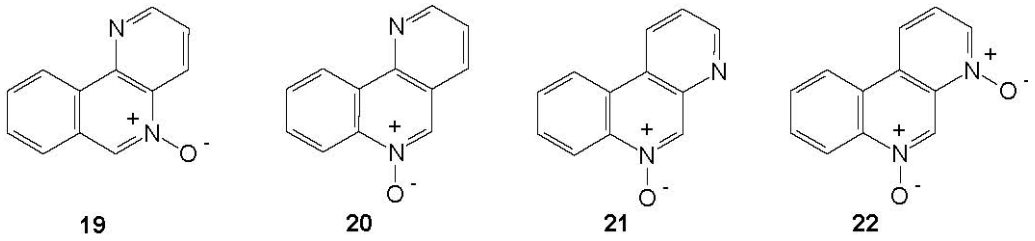


Scheme 3

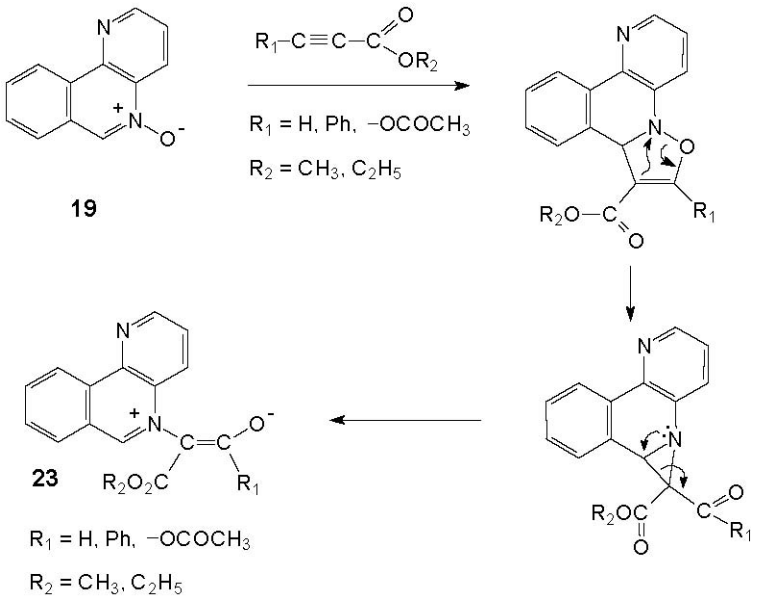
It should be mentioned that analogous arylimidazo[2,1-a]isoquinolines were shown to exhibit

pregnancy terminating activity in both hamsters and rats.[18] We anticipate similar interesting applications for above imidazole derivatives.

Benzonaphthyridine *N*-oxides as 1,3-dipoles



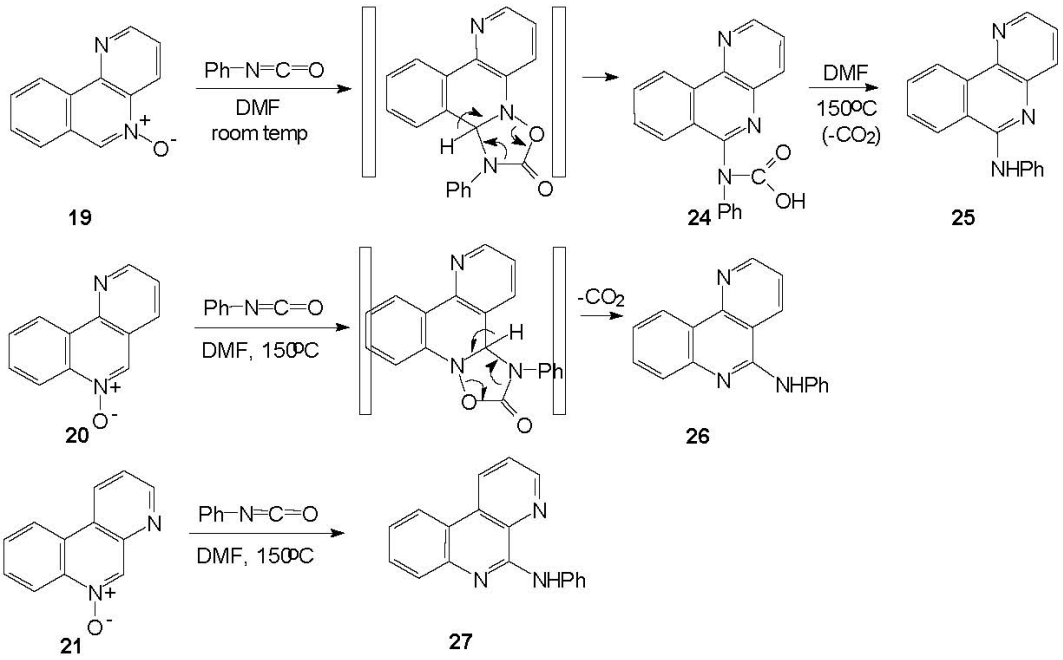
Benzo[c][1,5]naphthyridine-5-oxide **19**, benzo[h][1,6]naphthyridine-6-oxide **20**, benzo[f]-[1,7]naphthyridine-6-oxide **21,** and benzo[f][1,7]naphthyridine-4,6-dioxide **22** reacted with such dipolarophiles as dimethyl acetylenedicarboxylate, ethyl propiolate and ethyl phenylpropiolate to give the ylides [1 9,20](Scheme 4).



Scheme 4

Scheme 4 illustrates a pathway for the formation of ylides. Initial 1,3-dipolar cycloaddition was followed by the ring contraction to aziridine derivative and the ring opening.

Reaction of **19** with phenyl isocyanate, carried out at room temperature (DMF), led to carbamic acid derivative **24**. Decarboxylation of **24** induced by heating at 150°C in DMF resulted in the formation of 6-anilino-benzo[c][1,5]naphthyridine **25**. N-Oxides **20** and **21** reacted with phenyl isocyanate at 150°C in DMF into 5-anilino-benzo[h][1,6]naphthyridine **26** and 5-anilino-benzo[f][1,7]naphthyridine **27** respectively (Scheme 5). Dioxide **22** failed to react at room temperature as well as at 150°C, possibly for steric reasons. [21]

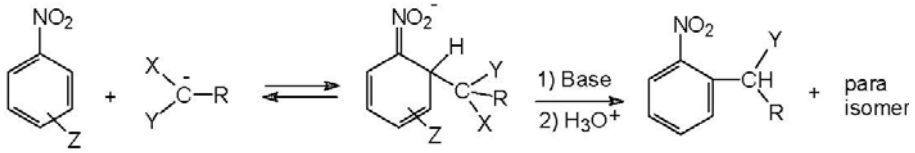


Scheme 5

Proposed pathway of these reactions comprises of initial 1,3-dipolar cycloaddition of phenyl isocyanate to benzonaphthyridine N-oxides followed by aromatization and decarboxylation. Our results and proposed mechanisms of the investigated reactions as shown in Schemes 4 and 5 are in accordance with literature data for similar 1,3-dipolar cycloaddition reactions of azaaromatic N-oxides with activated acetylenes and phenyl isocyanate. [22]

Vicarious nucleophilic substitution of hydrogen in the chemistry of benzonaphthyridines

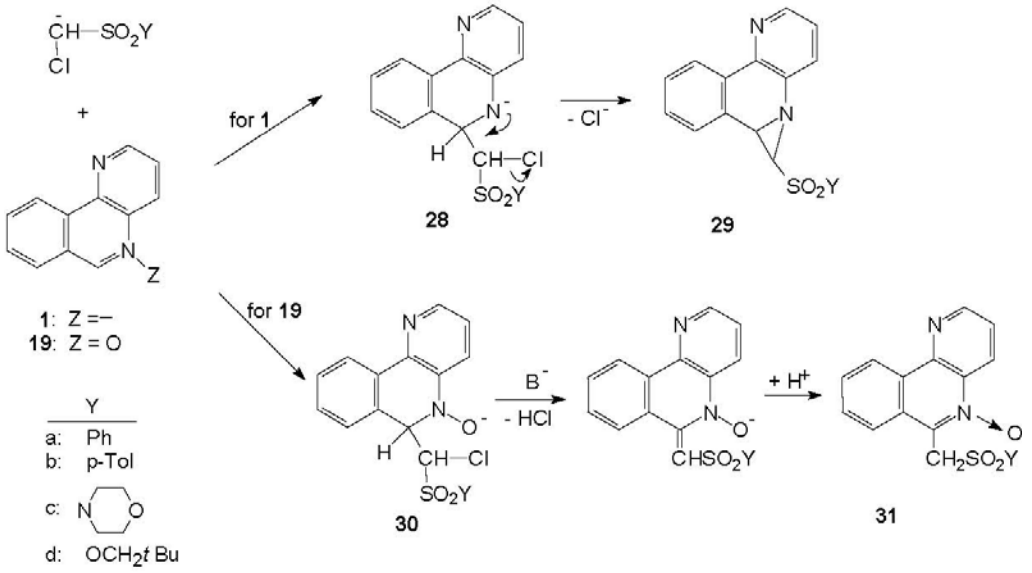
Vicarious nucleophilic substitution of hydrogen (VNS) offered a facile procedure for the introduction of substituents into electrophilic aromatic rings. The VNS is a general reaction between carbanions containing a leaving group X and a variety of electrophilic aromatic and heteroaromatic compounds. Examples of such carbanions precursors are $ClCH_2SO_2Ph$, $ClCH_2COR$, Cl_2CHCO_2R, $PhOCH_2CN$ and $CH_2(SPh)_2$. VNS proceeded *via* addition of the carbanions to the electrophilic aromatic compounds resulting in the formation of anionic σ-adducts. Base-induced β-elimination of HX followed by protonation gave products of the substitution [23] (Scheme 6).



Scheme 6

Application of these reactions to benzonaphthyridines and their N-oxides was proven. Reactions of benzo[c][1,5]-, benzo[h][1,6]- and benzo[f][1,7]naphthyridines **1** - **3** and of their N-

oxides **19** - **22** with chloromethyl phenyl sulfone as the carbanion precursor were carried out at room temperature using KOH suspended in DMSO as a base.[24] The proposed pathway for such kind reactions of benzo[c][1,5]naphthyridine **1** and benzo[c][1,5]naphthyridine-5-oxide **19** are presented in Scheme 7.



Scheme 7

Extensive charge delocalization in the anionic σ-adduct of the carbanion with benzonaphthyridine N-oxide **30** caused by the strong electron accepting oxygen atom, favoured base-induced β-elimination resulting in the formation of 6-benzenesulfonylmethyl-benzo[c][1,5]-naphthyridine-5-oxide **31a** as the VNS product. However, in the σ-adduct with benzonaphthyridine **28** the negative charge was localized chiefly on the vicinal nitrogen atom, which behaved as a strong nucleophilic center and underwent fast intramolecular substitution leading to the annelation product, the aziridine derivative, 6-benzenesulfonyl-aziridine[1,2-a]benzo[c]-[1,5]naphthyridine **29a**. The same reactions with benzo[h][1,6]-, benzo[f][1,7]-naphthyridines, their 6-oxides and with benzo[f][1,7]-naphthyridine-4,6-dioxide were also investigated. They proceeded in acordance with literature data for some electrophilic bicyclic azines such as quinoxalines [25] and quinoxaline-1-oxide. [26]

Satisfactory results were available also with chloromethyl *p*-tolyl sulfone, bromo- and chloromethanesulfomorpholide and neopentyl chloromethanesulfonate as carbanion precursors[27].

Acknowledgements

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