Dibenzo[*b*,*f*]oxepin-10(11*H*)-one and Dibenzo[*b*,*f*]thiepin-10(11*H*)-one as Useful Synthons in the Synthesis of Various Dibenzo[*e*,*h*]azulenes

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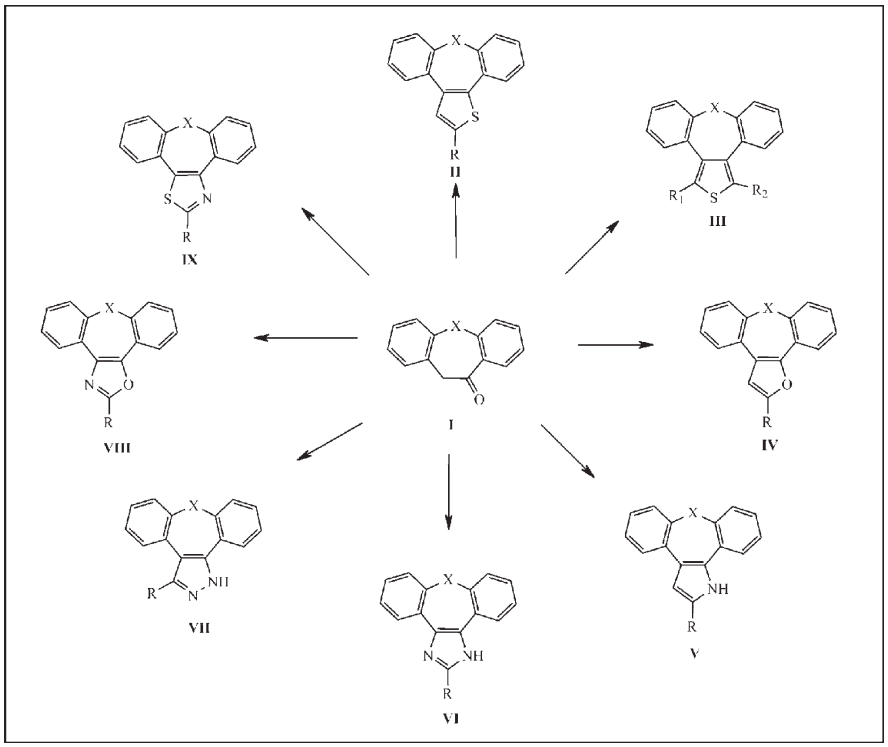

The present review focuses on dibenzo[*b*,*f*]oxepin-10(11*H*)-one (**I**, X = O) and dibenzo[*b*,*f*]thiepin-10(11*H*)-one (**I**, X = S) as common synthons in the efficient synthesis of various dibenzoxepino[4,5]- and dibenzothiepino[4,5]-fused five-membered heterocycles: [2,3] fused thiophene (**II**), [3,4] fused thiophene (**III**), furan (**IV**), pyrrole (**V**), imidazole (**VI**), pyrazole (**VII**), oxazole (**VIII**), and thiazole (**IX**). The potential of **I** to be converted into reactive intermediates that readily undergo heteroaromatic annulation reactions by cyclocondensation with proper binucleophiles allows formation of a range of enumerated functionalized dibenzo[*e*,*h*]azulene [4] structures (**II–IX**). Dibenzo[*e*,*h*]azulenes as heterotetracyclic scaffold can be exploited in further modifications to obtain compounds with altered physicochemical and biological profile.

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1. INTRODUCTION

A variety of compounds with dibenzo[*b,f*]oxepine or dibenzo[*b,f*]thiepine framework have attracted considerable attention due to their pharmacological applications as anti-inflammatory, psychotropic, cardiovascular, and analgesic drugs [5–9]. Broad biological activity prompted the use of dibenzo[*b,f*]oxepines and dibenzo[*b,f*]-thiepines as key building blocks in synthesis of various polycyclic compounds [10–12]. Recently, synthesis and biological activity of several novel heterocyclic dibenzo[*e,h*]azulene scaffolds have been reported [13–16]. Following literature findings that several different heterocycles can be synthesized from a single substrate [17,18], an extensive survey of the synthesis of various heterocyclic dibenzo[*e,h*]azulenes resulted in efficient and all-purpose strategy for the synthesis of dibenzoxepino[5,6]- and dibenzothiepino[5,6]-fused five-membered heterocycles originating from the common precursors, dibenzo[*b,f*]oxepine-10(11*H*)-one and its sulfur analogue. The key structures **1a**, **1b** are retrosynthetically related to a number of tetracyclic scaffolds as outlined in Figure 1. Various α-substituted derivatives of ketones **I** (**X–XVII**) are active intermediates suitable for further transformation into appropriate five-membered heterocycle and formation of dibenzo[*e,h*]azulene skeleton.

Herein, we review efficient synthetic approaches to an array of dibenzoxepino[5,6]- and dibenzothiepino[5,6]-fused five-membered heterocycles- [2,3] fused thiophene **II**, [3,5] fused thiophene **III**, furan **IV**, pyrrole **V**, imidazole **VI**, pyrazole **VII**, oxazole **VIII**, and thiazole **IX** that were afforded from common precursors: dibenzo[*b,f*]oxepin-10(11*H*)-one **1a** and its sulfur analogue **1b**, respectively. According to target molecules, those tetracyclic scaffolds can further be transformed by introducing substituents and subsequent functional group interconversions.

2. SYNTHETIC PATHWAYS TO DIBENZO[*e,h*]AZULENES

2.1. 1-Thia-dibenzo[*e,h*]azulenes (II). The most common approach to the synthesis of 1-thia-dibenzo[*e,h*]azulenes **3a**,**b** (**II**, R = $CO_2CH_2CH_3$) comprises cyclization of α,β-unsaturated compounds **2a**,**b** with thioglycolic acid ester in the presence of a base (Fiesselmann reaction, Scheme 1) [10,19–21].

The most convenient α,β-unsaturated compounds are β-chlorovinylaldehydes **2a**,**b** that are easily accessible through Vilsmeier formylation of ketones **1a**,**b**. Activated methylene group in **1a**,**b** reacts with *in situ* formed Vilsmeier reagent forming **2a**,**b** in a high yield [10]. The cyclocondensation of **2a**,**b** with 1,2-binucleophile ethyl 2-mercaptoacetate in the presence of triethylamine provides [2,3] fused thiophene ring in the final 1-thia-dibenzo[*e,h*]azulene **3a**,**b** (**II**, R = $CO_2CH_2CH_3$). This reaction proceeds by nucleophilic attack of the thiolate anion at the β-carbon, followed by an internal condensation with the formation of C—C bond (Scheme 2) [19].

To obtain biologically valuable target molecules from this series, the ester group at C(2) position was further modified [22].

2.2. 2-Thia-dibenzo[*e,h*]azulenes (III). Synthetic pathway to 2-thia-dibenzo[*e,h*]azulene scaffold follows known synthesis of 3,4-diarylthiophenes (Scheme 3) [23–25]. Starting ketones **1a–c** are oxidized with selenium dioxide to corresponding 1,2-diketones **4a–c**, which are condensed with dimethyl 2,2′-thiodiacetate in the presence of potassium *tert*-butoxide in *tert*-butanol. This method, known as Hinsberg thiophene synthesis [24], provides tetracyclic, 1,3-disubstituted 2-thia-dibenzo[*e,h*]azulenes **5a–d** [15].

This base-induced cycloannulation is a Stobbe-type condensation proceeding *via* a δ-lactone intermediate **6**, and the ring synthesis follows the course presented at Scheme 4 [26], furnishing the half-acid, half-ester thiophene derivatives **5a**,**b**.

When symmetrical α-diketones **4a**,**b** were submitted to reaction, half-esters of thiophene dicarboxylic acids **5a**,**b** were obtained in good yields [15]. However, the use of unsymmetrically substituted α-diketone **1c** is complicated by the formation of approximately 50:50 isomeric mixture of **5c** and **5d** as a result of chemical equivalence of the two carbonyl groups (Scheme 3) [15]. α,α′-Dicarboxyl-substituted thiophenes **5** are promising platform for further derivatization toward anticipated target molecules [27].

2.3. 1-Oxa-dibenzo[*e,h*]azulenes (IV). One of the most important methods for the preparation of furans is acid-catalyzed Paal–Knorr cyclization of 1,4-dicarbonyl compounds. Annulation of furan to the tricyclic system of ketones **1a**,**b** by this method was limited by the availability of suitably substituted starting diones [28]. Using modified procedure for 1,4-dicarbonyl benzoine derivatives, 1,4-dicarbonyl compound **7a** was prepared (Scheme 5) [13,29,30]. However, analogous reaction of the sulfur derivative **1b** did not provide the corresponding thia-derivative.

The required 1,4-dicarbonyl derivative was prepared by reacting the pair of ketones **1a**,**b** with chloroacetone in the presence of sodium hydride in dimethylsulfoxide. The reaction results in formation of *C*- and *O*-alkylation products **7a** and **7b**, respectively, with their ratio depending on the heteroatom in the seven-membered ring. Oxa-analogue **1a** reacts prevalently to form *C*-alkylated product **7a** (up to 10% of *O*-alkylated product was

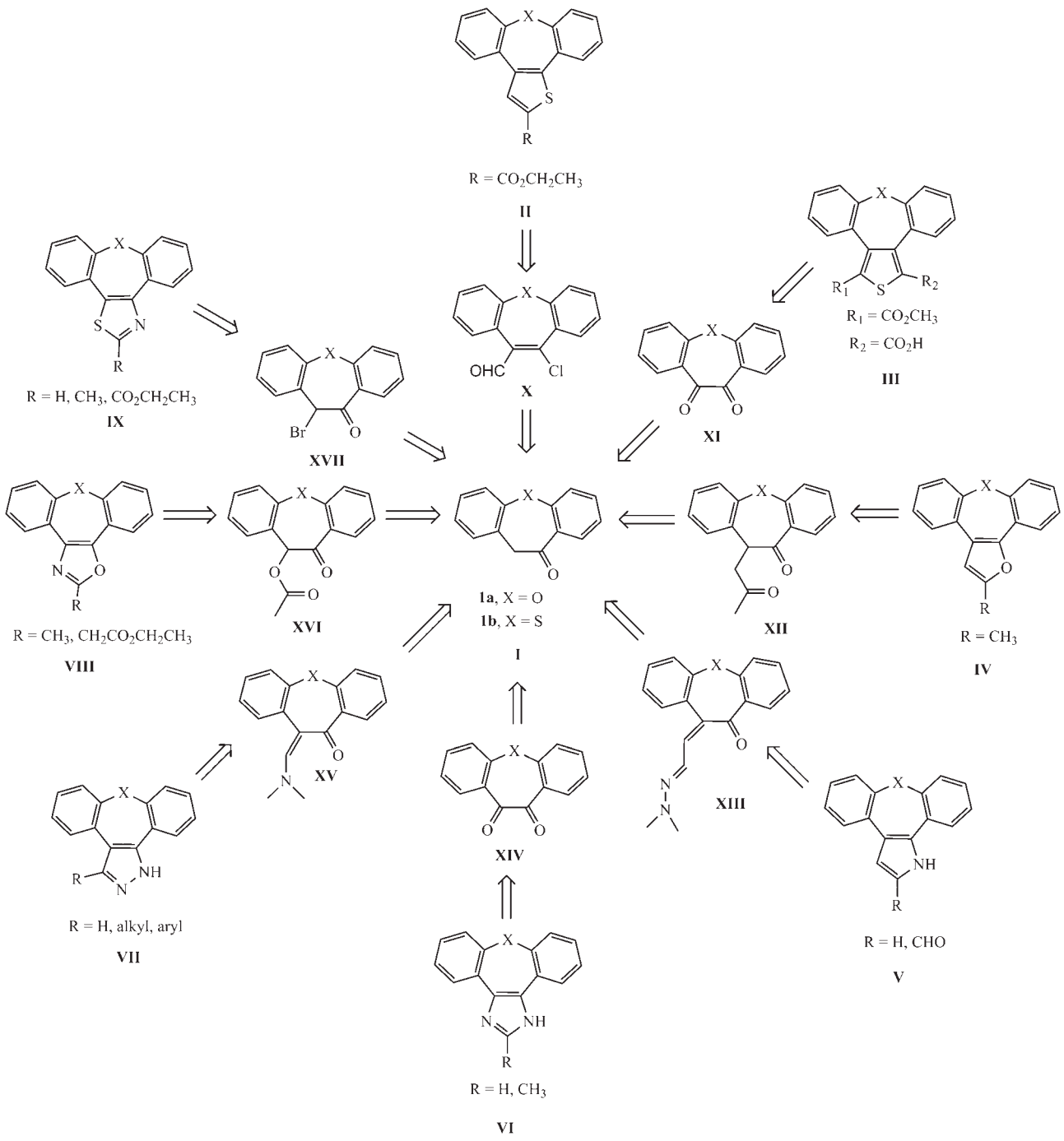
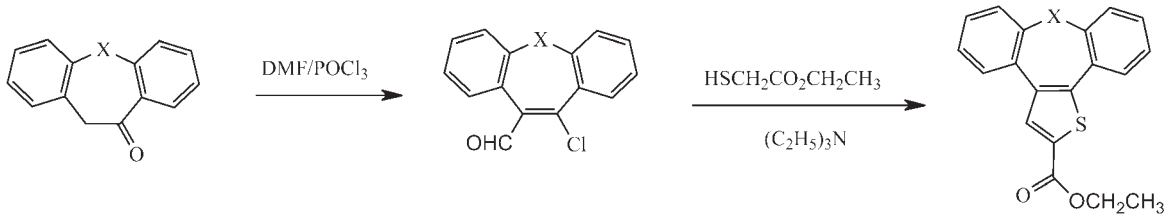


Figure 1. Dibenzo[*b*,*f*]oxepin-10(11*H*)-one (**1a**) and dibenzo[*b*,*f*]thiepin-10(11*H*)-one (**1b**) as common precursors for heterocyclic dibenzo[*e*,*h*]azulene scaffolds **II–IX**.

isolated) in contrast to nearly complete *O*-alkylation of thia-analogue **1b** and formation of **7b**. The difference and the unexpected selectivity in the *C*/*O* alkylation for oxa- versus thia- analogues may be explained by invoking HOMO–LUMO interactions (HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital) and the hard-soft acid base (HSAB) description of nucleophilicity [13].

Dehydration of **7a** with *p*-toluenesulfonic acid in benzene finally leads to the formation of 1,8-dioxa-dibenzo[*e*, *h*]azulene **8** (**IV**, R = CH_3) substituted at the C(2) position with a methyl group prone to possible derivatization [30].

Scheme 1



1a, X=O
1b, X=S

2a, X=O
2b, X=S

3a, X=O
3b, X=S

2.4. 1-Aza-dibenzo[*e,h*]azulenes (V). Several strategies for the synthesis of 2,3-diarylpyrroles, applicable for the annulation of pyrrole ring and preparation of tetracyclic system **V**, are described in the literature [31–33]. However, an original approach to the synthesis of 1-aza-dibenzo[*e,h*]azulenes, according to the Scheme 6, has been recently reported [14,34].

It is known that ketones with an active α-methylene group condense easily with monohydrazones of glyoxal [31]. When subjected to this reaction, ketones **1a**,**b** give the intermediate hydrazonoethylidene derivatives **9a**,**b** as a mixture of double bond isomers (Scheme 6) [14]. Sodium dithionite reduction of **9a**,**b** in aqueous ethanol results with pyrrole ring fusion and thus affords the target tetracyclic structure **11a**,**b**. The conversion mechanism presumably comprises reductive cleavage of hydrazones **9a**,**b** to intermediary γ-amino ketones **10a**,**b**, which on cyclization form pyrrole ring fused to tricyclic moiety in **11a**,**b**. Molecules functionalized at C(2) position of the pyrrole ring can be obtained by regiospecific formylation with Vilsmeier reagent (Scheme 7) [14,35] and subsequent modifications of the carbonyl group.

2.5. 1,3-Diaza-dibenzo[*e,h*]azulenes (VI). First synthesis of polycondensed compounds presented by formula **VI** was reported by Lombardino [11] and was based on the general imidazole synthesis using cyclocondensation of the 1,2-dicarbonyl compound with aldehydes and ammonia (Radziszewski imidazole synthesis) [36,37].

As in the synthesis of **III**, activated α-methylene group of starting ketones **1a**,**b** is oxidized with selenium dioxide to give 1,2-diketones **4a–d** [11,38–42], which on condensation with paraformaldehyde, and ammonium acetate in acetic acid form imidazole ring in the target compounds **13a–d** (Scheme 8) [36]. The use of substituted aldehyde and/or amine enables synthesis of 1,2-substituted 1,3-diaza-dibenzo[*e,h*]azulenes. Moreover, compounds **13** themselves can be exploited as a useful framework for further modifications into numerous derivatives [16,43].

Although there is no general mechanism for the synthesis of **13a–d** in the literature, it is plausible that ammonia (or primary amine) reacts with α-dicarbonyl compounds **4a–d** to form α-diimine, which then condenses with an aldehyde, as displayed at Scheme 9.

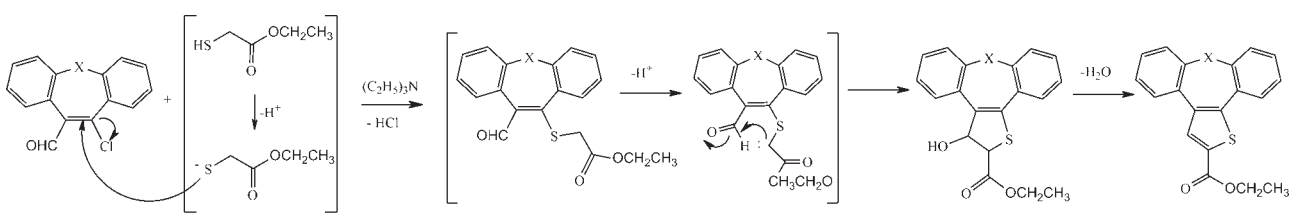
Symmetric imidazole derivatives **13a**,**b** (Y = H) exist in two equivalent tautomeric forms and subsequent alkylation results in single isomers **14a**,**b** (Scheme 10).

However, when nonsymmetrically substituted imidazole derivatives **13c**,**d** were used as the starting compounds, *N*(1)-alkylation afforded structural isomers **15c**,**d** and **16c**,**d** (Scheme 11) [16].

2.6. 1,2-Diaza-dibenzo[*e,h*]azulenes (VII). Starting from the ketones **1a**,**b**, tetracyclic compounds comprising fused pyrazole ring can be effectively prepared by following the procedure depicted in Scheme 12. This method is reported as convenient for the synthesis of 4,5-diaryl pyrazoles [44–47], and it is applicable also on dibenzo[*b,f*]oxepine and dibenzo[*b,f*]thiepine framework [48].

Active methylene ketones **1a**,**b** condense readily with *N*,*N*-dimethylformamide dimethyl acetal to yield enaminones **17a**,**b** [49–51], which are further converted to the corresponding tetracyclic pyrazoles **18a**,**b** by amine-

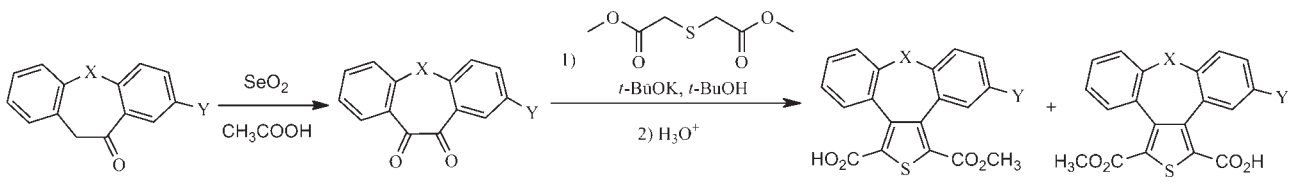
Scheme 2



2a, X=O
2b, X=S

3a, X=O
3b, X=S

Scheme 3



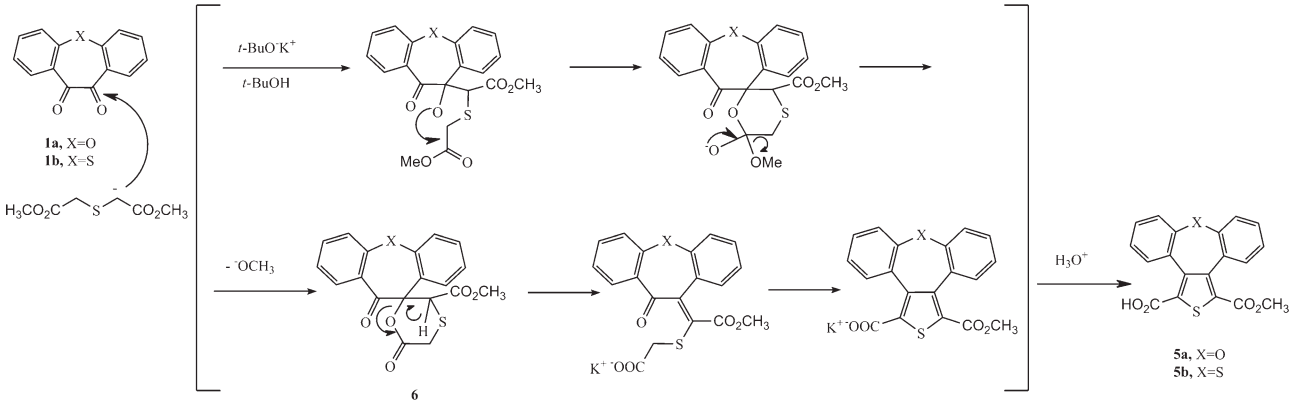
1a, X=O, Y=H
1b, X=S, Y=H
1c, X=O, Y=Cl

4a, X=O, Y=H
4b, X=S, Y=H
4c, X=O, Y=Cl

5a, X=O, Y=H
5b, X=S, Y=H
5c, X=O, Y=Cl

5d, X=O, Y=Cl

Scheme 4



1a, X=O
1b, X=S

6

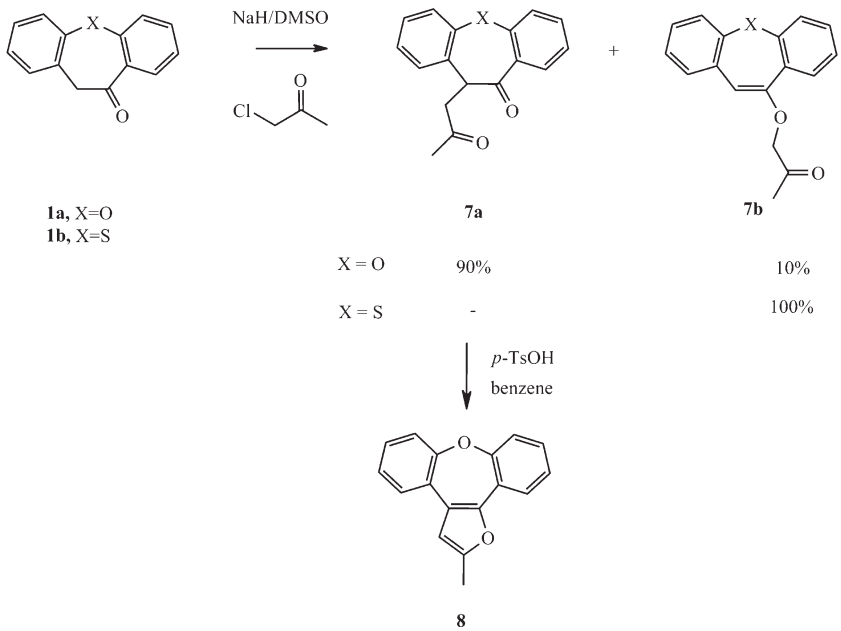
5a, X=O
5b, X=S

exchange/heterocyclization with appropriate hydrazine in aqueous ethanol.

To prepare functionalized derivatives pyrazole ring in **18** was further modified [48].

2.7. 1-Oxa-3-aza-dibenzo[*e*,*h*]azulenes (VIII). According to the synthesis of 4,5-diaryl-substituted oxazole derivatives reported in the literature [5,52–54], synthesis of 1-oxa-3-aza-dibenzo[*e*,*h*]azulenes **VIII** can be accomplished

Scheme 5



1a, X=O
1b, X=S

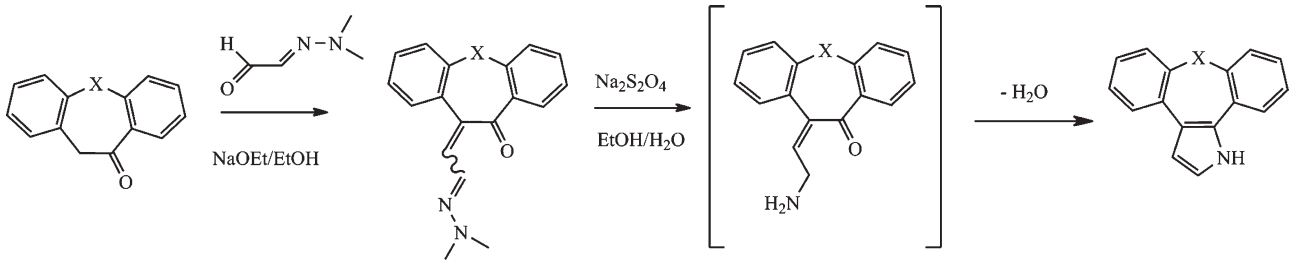
7a

7b

X = O	90%	10%
X = S	-	100%

8

Scheme 6



1a, X=O
1b, X=S

9a, X = O E : Z = 80% : 20%
9b, X = S E : Z = 80% : 15%

10a
10b

11a, X=O
11b, X=S

Scheme 7

11a, X=O
11b, X=S

12a, X=O
12b, X=S

by the routes depicted in Scheme 13 [55]. Either the route A, cyclization of appropriate α-acyloxyketones **19a**,**b**, or the route B, cyclodehydration of α-acylaminoketones **23a**,**b**, in the presence of dehydrating agents (Robinson-Gabriel synthesis) leads to tetracyclic system **VIII**. Routes A and B are distinct by the oxazole regioisomer formed, and this is important when using starting ketones with asymmetrically substituted aromatic rings (Y ≠ H).

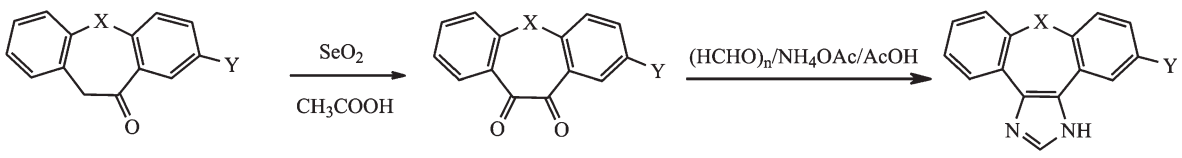
Lead(**IV**) acetate in hot acetic acid is known as a convenient reagent for acetoxylation of ketones **1a**,**b** [55,56] to produce α-acyloxyketones **19a**,**b**. Subsequent cyclization of **19a**,**b** was achieved with ammonium acetate in acetic acid to form targeted 2-methyl-substituted oxazole derivatives **20a**,**b** (Scheme 13, route A).

On the other hand, reaction of ketones **1a**,**b** with sodium nitrite in ethanolic hydrochloric acid results in the formation of oximes **21a**,**b** that were transformed into α-amino ketones **22a**,**b** by the reduction with zinc in acetic acid (Scheme 13, route B). Amidation of **22a**,**b** with formic acid or acyl halides provides the amides **23a**,**b** that on treatment with phosphorus(**III**) oxychloride undergoes cyclization and dehydration to form the other regioisomer of the target (C2-substituted) tetracyclic structures **24a**,**b**. The experiments with ^{18}O labeling revealed the mechanism of this reaction and confirmed that oxygen atom of the oxazole ring is derived from acyl group (Scheme 14) [57].

2.8. 1-Thia-3-aza-dibenzo[*e*,*h*]azulenes (IX). To prepare tetracyclic thiazole derivatives **IX**, two partially distinct synthetic routes were followed [58] differing in possibility for subsequently introducing a suitable substituent at C(2) position (Scheme 15). Bromination of activated α-methylene group of ketones **1a**,**b** under acidic conditions affords α-bromoketones **25a**,**b** as key intermediates for the cyclization step in both approaches [58,59].

Thiazoles **26a**,**b** are prepared by reaction of corresponding α-bromoketones **25a**,**b** with substituted thioamides. Tetracyclic ring system substituted at C(2) position with methyl or ethoxycarbonyl moiety is, thus, formed in moderate yields, when ethanethioamide or ethyl 2-amino-2-thioxoacetate were used, respectively (route A, Scheme 15) [60]. Alternatively, using a mixture of formamide and phosphorus pentasulfide in toluene to generate thioformamide *in situ*, C(2) substituent free thiazoles **27a**,**b** were prepared according to route B (Scheme 15) [61,62].

Scheme 8

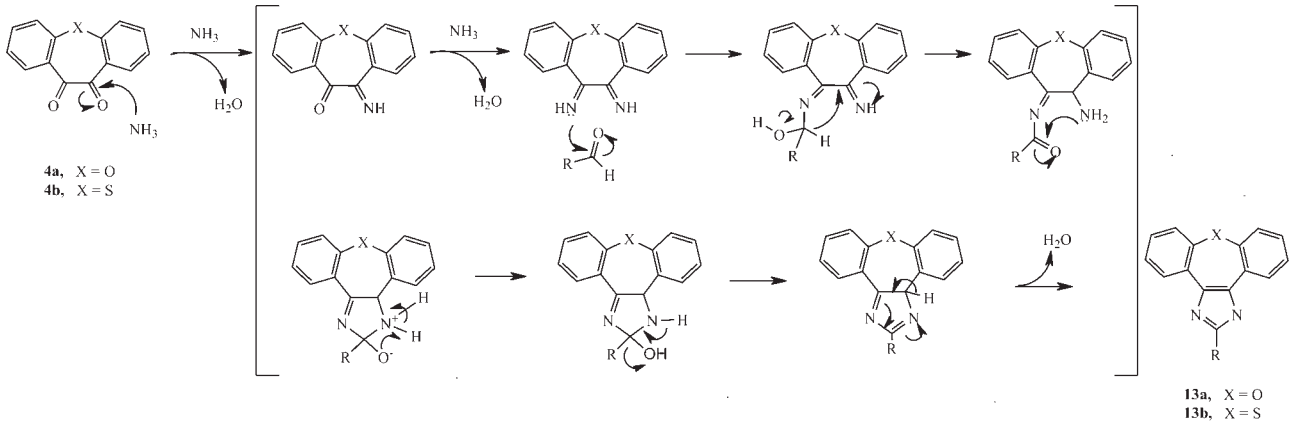


1a, X = O, Y = H
1b, X = S, Y = H
1c, X = O, Y = Cl
1d, X = S, Y = Cl

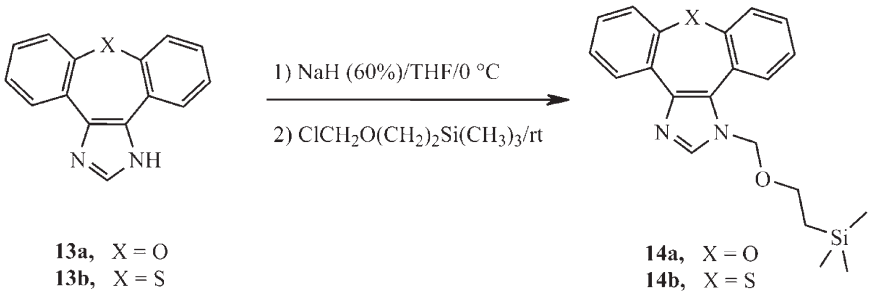
4a, X = O, Y = H
4b, X = S, Y = H
4c, X = O, Y = Cl
4d, X = S, Y = Cl

13a, X = O, Y = H
13b, X = S, Y = H
13c, X = O, Y = Cl
13d, X = S, Y = Cl

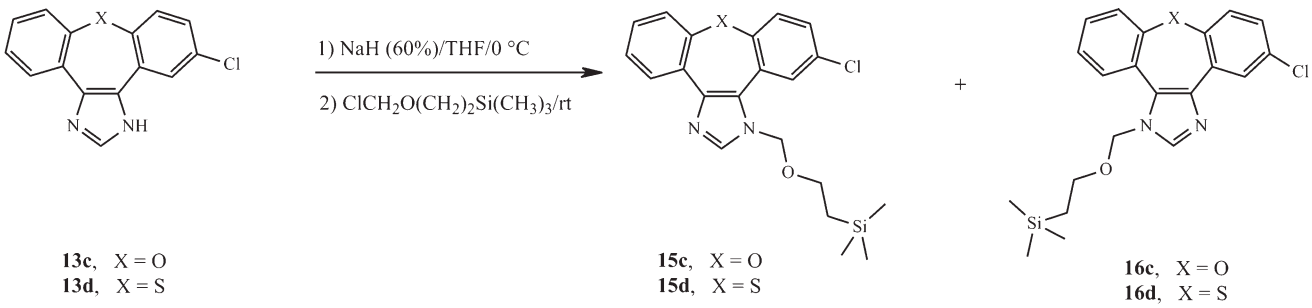
Scheme 9



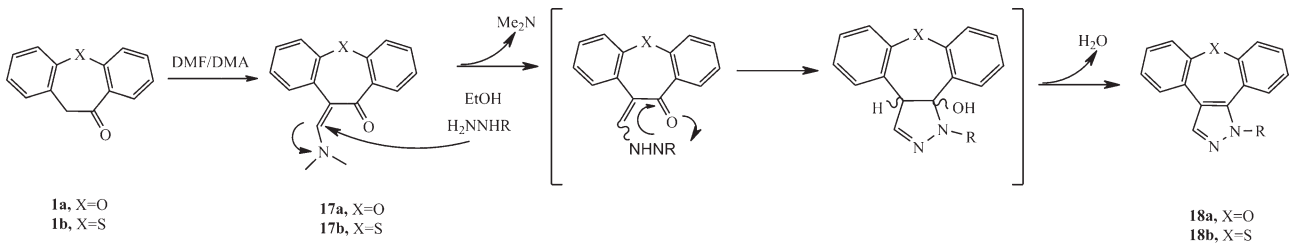
Scheme 10



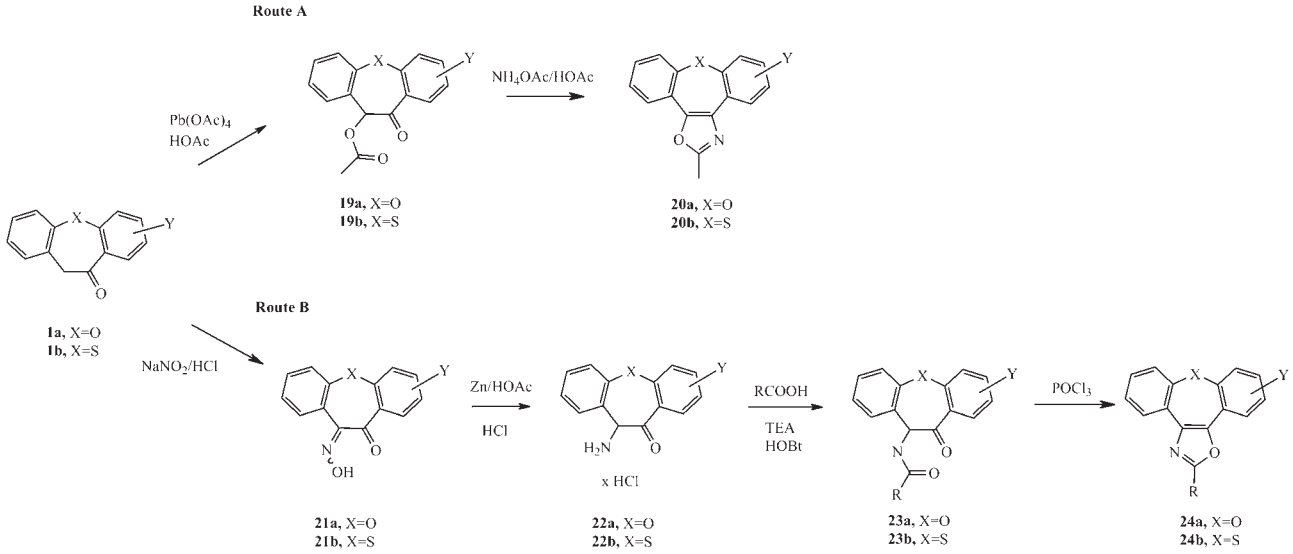
Scheme 11



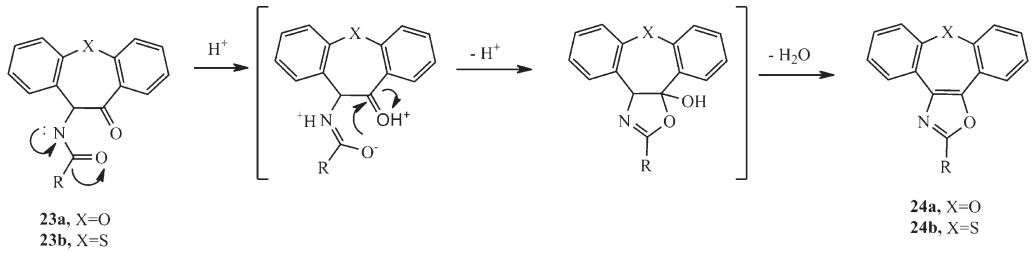
Scheme 12



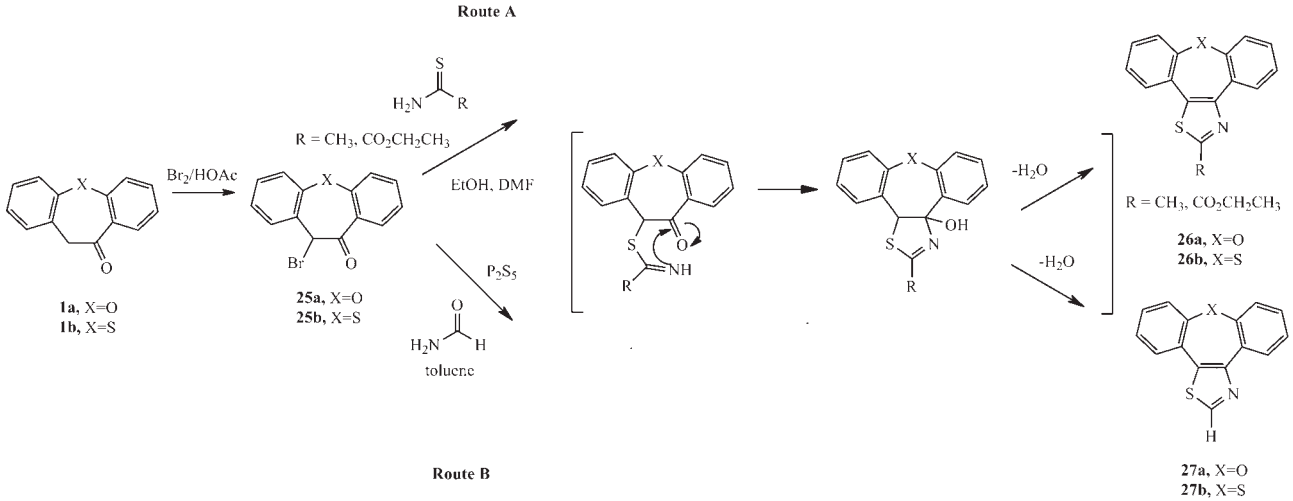
Scheme 13



Scheme 14



Scheme 15



Proposed mechanism for thiazole ring closure is depicted in Scheme 15 and comprises nucleophilic attack of thioamide sulfur and nitrogen atoms on α-halo carbonyl compounds **25a**,**b** and formation of C—S and C—N bonds, followed by the elimination and formation of tetracyclic compounds **26a**,**b** or **27a**,**b** [63].

Tetracyclic scaffolds **26** as well as **27** are expected useful frameworks for further modifications toward required target molecules [64].

3. CONCLUSION

This synthetic overview demonstrates the versatility of synthesis of various heterocyclic dibenzo[*e*,*h*]azulenes **II–IX** starting from dibenzo[*b*,*f*]oxepin-10(11*H*)-one (**I**, X = O) and dibenzo[*b*,*f*]thiepin-10(11*H*)-one (**I**, X = S). Activated methylene group in **I** reacts with various reagents to provide α-substituted ketones **X–XVII** suitable for transformations into tetracyclic scaffolds encompassing annulated five-membered heterocycles (**II–IX**). The formation of heterocycles proceeds *via* mechanisms of nucleophilic substitution and elimination.

Dibenzo[*e*,*h*]azulenes as heterotetracyclic scaffold can serve as a useful framework for further modifications toward required target molecules.

REFERENCES AND NOTES

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[4] (a) The substitutive nomenclature is used here for these classes of compounds, but correct IUPAC defined nomenclature is as follows: dibenzo[*b*,*f*]thieno[2,3-*d*]thiepine (**II**, X = S), dibenzo[*b*,*f*]-thieno[2,3-*d*]oxepine (**II**, X = O); dibenzo[*b*,*f*]thieno[3,4-*d*]thiepine (**III**, X = S), dibenzo[*b*,*f*]thieno[3,4-*d*]oxepine (**III**, X = O); dibenzo[*b*,*f*]furo[2,3-*d*]oxepine (**IV**, X = O), dibenzo[*b*,*f*]furo[2,3-*d*]thiepine (**IV**, X = S); 1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrole (**V**, X = O), 1*H*-dibenzo[2,3:6,7]thiepino[4,5-*b*]pyrrole (**V**, X = S); dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (**VI**, X = O), dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (**VI**, X = S); 1*H*-dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrazole (**VII**, X = O), 1*H*-dibenzo[2,3:6,7]thiepino[4,5-*c*]pyrazole (**VII**, X = S); dibenzo[2,3:6,7]oxepino[4,5-*d*]oxazole (**VIII**, X = O), dibenzo[2,3:6,7]thiepino[4,5-*d*]oxazole (**VIII**, X = S); dibenzo[2,3:6,7]oxepino[4,5-*d*]thiazole (**IX**, X = O), dibenzo[2,3:6,7]thiepino[4,5-*d*]thiazole (**IX**, X = S); (b) Olivera, R.; SanMartin, R.; Churruca, F.; Domínguez, E. J Org Chem 2002, 67, 7215.

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