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Review

Hemetsberger–Knittel and Ketcham Synthesis of Heteropentalenes with Two (1:1), Three (1:2)/(2:1) and Four (2:2) Heteroatoms

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Abstract: The synthetic methods leading to furo[3,2-*b*]pyrroles and thiazolo [5,4-*d*]thiazoles are reviewed herein. Furo-, thieno- and seleno [3,2-*b*]pyrroles are related to heteropentalenes, containing two heteroatoms in the entire structure, one each per core. The synthetic approach follows the Hemetsberger–Knittel protocol covering three reaction steps—the nucleophilic substitution of halogen-containing aliphatic carboxylic acid esters, Knoevenagel condensation and, finally, thermolysis promoting the intramolecular cyclocondensation to O,N-heteropentalene. The Hemetsberger–Knittel reaction sequence is also known for the preparation of O,N-heteropentalenes with three heteroatoms (2:1) and their sulphur and selen heteroatoms containing structural analogues and *bis*pyrroles. The synthetic approach towards thiazolo [5,4-*d*] thiazoles represents a more straightforward route, according to the Ketcham cyclocondensation. Proceeding with the Ketcham process is more challenging since it occurs stepwise and the formation of by-products is obvious. Thiazolo [5,4-*d*]thiazole is a representative of the aromatic heteropentalene with four heteroatoms in the structure—twinned N and S, two for each of the five-membered rings. The synthetic approaches towards those particular heteropentalnes have been chosen as a consequence of our ongoing research dealing with the design, synthesis and applications of substituted furo [3,2-*b*]pyrroles and thiazolo [5,4-*d*]thiazole-based derivatives. While the furopyrroles are known for their pharmacological activity, thiazolothiazoles have become of interest to materials science. We are aware that from a "bank" of existing compounds/procedures not all are presented in this review, and we apologise to respective groups whose research have not been objectively included.

Keywords: heteropentalenes; furo [3,2-*b*]pyrroles; thiazolo [5,4-*d*]thiazole; Hemetsberger–Knittel; Ketcham cyclocondensation

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1. Introduction

Annelated [5+5] heterocyclic systems that consist of two-fused, five-membered rings represent a family of heteropentalenes (**HPs**) [1]. HPs are isoelectronic to pentalenyl dianion (**PnDa**, Figure 1) [2] with the preserved 10π-electron system since the electron pair/s of heteroatom/s are involved in the conjugation. In combination with the structural planarity and bicyclic motif, HP scaffolds are aromatic [3]. Since the first Ramsden's classification of HPs into four general types (**I**–**IV**, Figure 2) in 1977 [4,5], the number of identified 5-5 bicyclic regioisomers with two heteroatoms, one for each core (1:1), has increased dramatically [1,6]. The presence of four heteroatoms in a structure, two per core (2:2), has led to the rise of basic structural prototypes up to sixteen [7]. Undoubtedly, through the addition of more heteroatoms into the bicyclic system and by variations in modes of fusion altogether, including the non-classical heteropentalenes and betaines, the number of possible isoconjugates has reached an uncountable number. Generally, oxygen, sulphur, nitrogen, selenium and tellurium are the most commonly employed as heteroatoms [1–7],

but a few reports on HPs with phosphorus [8], boron [9] or silicon [10] in the position of heteroatom have recently been published.

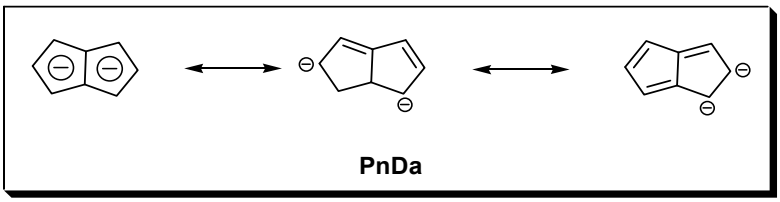


Figure 1. Resonance structures of the pentalenyl dianon (**PnDa**) as a leading structure for a class of heteropentalenes.

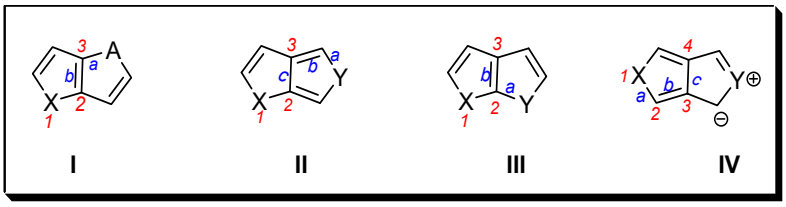


Figure 2. Structure of general types of HPs containing two heteroatoms, one per core, according to Ramsden's classification [4,11]: **I**—hetaryl [3,2-*b*]hetarene (1,4-diheteropentalene), **II**—hetaryl [2,3-*c*]hetarene = hetaryl [3,4-*b*]hetarene (1,5-diheteropentalene), **III**—hetaryl [2,3-*b*]hetarene (1,6-diheteropentalene), **IV**—hetaryl [3,4-*c*]hetarene (2,5-diheteropentalene). In combination with the Formula (1), the distinguishing strategy can be applied for a whole class of HPs. A,X,Y = heteroatoms (O,S,N, rarely Se, Te); a, b, c—condensed bond positioning.

For a structural description in combination with the HPs' nomenclature, the general Formula (1) can be applied for recognising the appropriate hetarene [11] according to:

$$\textbf{hetaryl[m,n-}p\textbf{]hetarene} \quad (1)$$

where m,n are numbers of carbon atoms shared by both rings, the *p*-junction mode reveals the shared bond, hetaryl is the name of a five-membered heterocycle in a prefix, and hetarene is the name of a superior five-membered heterocycle [1,4,6,7,11].

Although there is a plethora of HPs permutations, at the same time they represent a small-organic-type compounds with an advantage of being easily prepared. The ring closure reactions, cyclisations and cycloadditions are obviously performed to obtain a particular HP derivative [12–14]. With their synthetic availability, in combination with a variety of advantageous optoelectronic, physicochemical and pharmacological properties, HPs are of significant interest in the fields of both academic research and industry.

With respect to our research aims [15,16], together with taking into account the enormous number of existing derivatives, herein we have highlighted the synthesis of furo [3,2-*b*]pyrroles (**V**, Figure 3) using a three-step Hemetsberger–Knittel procedure, and thiazolo [5,4-*d*]thiazoles (**VI**, Figure 3) as representative products of the Ketcham reaction. While the furo [3,2-*b*]pyrroles come from a category of O,N-two heteroatoms containing HPs with applications in pharmaceuticals, the thiazolo [5,4-*d*]thiazole scaffold consists of two thiazole rings containing a combination of four heteroatoms, nitrogen and sulphur in each annelated core and are very important in applied science for the development of optoelectronic devices such as organic photovoltaic cells (OPV and organic field-effect transistors (OFETs).

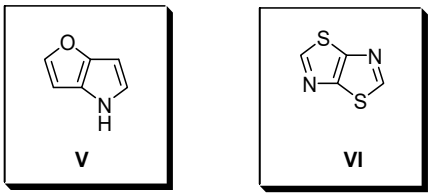


Figure 3. Structure of furo [3,2-*b*]pyrrole (**V**) as representative of two heteroatoms containing HPs (1:1, each core), achievable through the Hemetsberger–Knittel procedure, and thiazolo [5,4-*d*]thiazole (**VI**) from the category of four heteroatom-containing HPs (2:2, two per core) as a product of Ketcham's process, respectively.

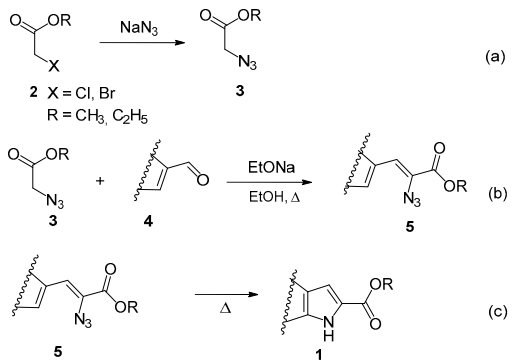
2. Furo-, Thieno- and Selenopheno [3,2-*b*]pyrroles

Furo [3,2-*b*]pyrroles (**V**, Figure 3) and their thieno- and selenopheno- analogues are isosteres of the indole ring system in which the benzene ring is replaced by the furan, thiophene or selenophene rings. Efficient synthetic routes to these heterocycles are of great interest [17–19] because of their significant biological activity. 4*H*-Furo [3,2-*b*]pyrrole derivatives have been screened for their analgesic and anti-inflammatory activity [20], or antituberculotic [21] activity. 4*H*-Furo [3,2-*b*]pyrrole-5-carboxylic acid showed inhibitory activity against D-amino acid (DAO) oxidase, which is important for the treatment of schizophrenia [22]. 2,3,5,7-Tetrabromobenzofuro [3,2-*b*]pyrrole, isolated from a marine *Pseudoalteromonas* sp., displayed significant antimicrobial activity against methicillin-resistant *Staphylococcus aureus* [23]. Furo [3,2-*b*]pyrrole derivatives are also used as fluorescent dyes [24]. Thieno [3,2-*b*]pyrroles has shown anti-tumorous [25] and antiviral [26] activity. Thieno [3,2-*b*]pyrrole dimers have promising semiconductive properties [27].

2.1. Hemetsberger–Knittel Synthesis of Furo [3,2-b]pyrroles and Related Compounds

The first preparation of various aromatic or heteroaromatic pyrrole-fused heterocycles was accomplished by H. Hemetsberger and D. Knittel in 1972 [28]. The Hemetsberger–Knittel reaction is a versatile method for the synthesis of functionalised indoles [29–31] or azaindoles [32]. The Hemetsberger process has been extended to include the synthesis of many heterocyclic compounds from 2-azido-3-heteroaromatic-acrylates, including nitrogen-containing heteropentalenes [33–35].

Hemetsberger–Knittel synthesis requires readily available starting materials with a wide variety of functional groups and often induces good overall yields. The overall process involves three steps: the initial synthesis of an alkyl azidoacetate **3**, followed by a base-promoted Knoevenagel condensation of alkyl azidoacetate **3** and an aromatic aldehyde **4** to form 2-azido-3-arylacrylate **5**, and finally the thermolysis of the 2-azido-3-arylacrylate **5** in an intramolecular cyclisation to form the fused pyrrole skeleton **1** (Scheme 1). The major limitation of the Hemetsberger–Knittel process emerged from the use of sodium azide and two potentially explosive intermediates, **3** and **5**, in sequence [36].



Scheme 1. Three steps of the Hemetsberger–Knittel reaction as following: (**a**) synthesis of alkylazidoacetate, (**b**) condensation towards azidoarylacrylate, (**c**) cyclization.

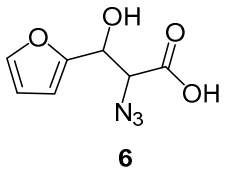
2.2. Behaviour of the Hemetsberger–Knittel Procedure

Alkyl azidoacetates **3** can be synthesised from an alkyl haloacetate **2** and sodium azide, usually by heating in DMF [35], aceton/H_2O [37] or methanol [38], producing high yields (85–87%).

The second step of the Hemetsberger–Knittel procedure involves the Knoevenagel condensation of aromatic aldehydes **4** with alkyl azidoacetate **3** to form 2-azido-3-arylacrylates **5** in relatively low yields. Typical yields of **5** have been reported to range from 12% to 65% when five-membered heteroaromatic aldehydes were used [28,39].

The low yields of **5** could be explained [36] due to two primary reasons. First, alkyl azidoacetates **3** decompose in the presence of base, and the decomposition competes with the desired condensation process.

The second reason lies in the hydrolysis of the ester functionality of the alkyl azidoacetate reagent **3**, the azido alcohol intermediate and the 2-azido-3-arylacrylate product **5**, which is promoted by the hydroxide by-product from the condensation. In the case of the Knoevenagel condensation of furan-2-carbaldehyde and ethyl azidoacetate, the undesired ester hydrolysis product of the azido alcohol intermediate (2-azido-3-hydroxy-3-(furan-2-yl)propanoic acid) **6** has been identified as a side product in yields as high as 40%. In this particular case, this acidic by-product did not undergo dehydration to afford 2-azido-3-(furan-2-yl)acrylic acid (Figure 4) [36].



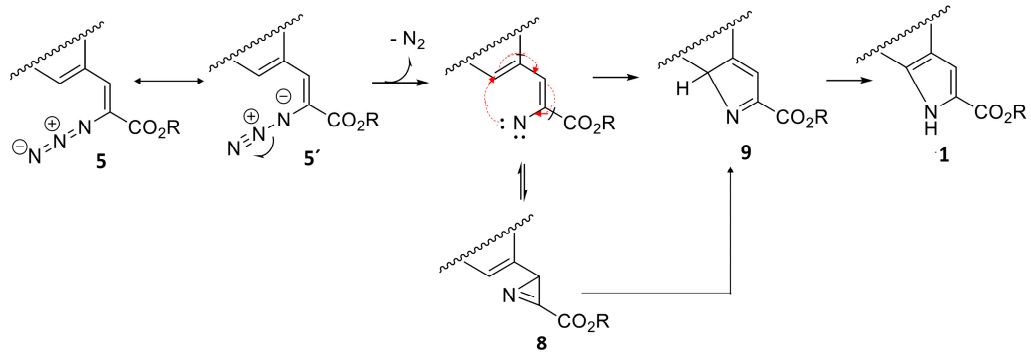
6

Figure 4. Chemical structure of the by-product of Knoevenagel condensation between furan-2-carbaldehyde and ethylazidoacetate [36].

The third step of the Hemetsberger–Knittel reaction is the thermolysis of the 2-azido-3-arylacrylate **5** in an intramolecular cyclisation to form a fused pyrrole skeleton (Scheme 1). The typical solvents that are used are toluene [18], xylenes [28] or mesitylene [38].

2.3. Mechanism of the Hemetsberger–Knittel Synthesis

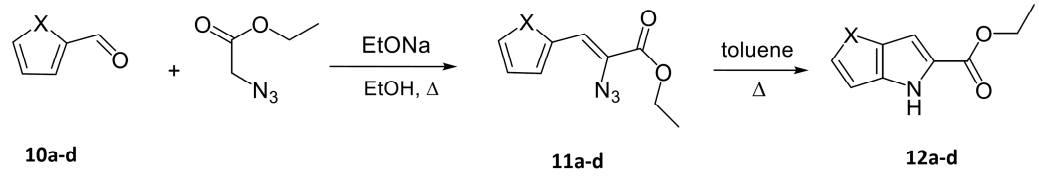
The mechanism [40] of the Hemetsberger–Knittel reaction proceeds via an azirene intermediate **8**. The first step is the thermal degradation of 2-azido-3-arylacrylate **5**, generating molecular nitrogen and nitrene **7**. Nitrene **7** is believed to be in equilibrium with the azirine intermediate **8**. The subsequent step is the insertion of the nitrene into the cyclic ring followed by a final [1,5] hydrogen shift that is accompanied by the final re-aromatisation, forming the pyrrole core of the fused aromatic system **1** (Scheme 2).



Scheme 2. Proposed mechanism of the Hemetsberger–Knittel synthesis of heteropentalenes.

2.4. Application of the Hemetsberger–Knittel Synthesis towards a Variety of [3,2-b]HPs

Hemetsberger and Knittel [28] also reported the synthesis of nitrogen-containing heteropentalenes (Hemetsberger). Furo- thieno- and 4-methyl-4*H*-pyrrolo [3,2-*b*]pyrrole-5-carboxylates **1** were synthesised in 85–97% yields by the condensation of appropriate aldehyde **10** with ethyl azidoacetate **3** and the subsequent thermal cyclisation of 2-azido-3-arylacrylate **5** in xylene (Scheme 3). The first synthesis of ethyl seleno [3,2-*b*]pyrrole-5-carboxylate **12c** was later accomplished with an 82% yield by Soth et al. [41].

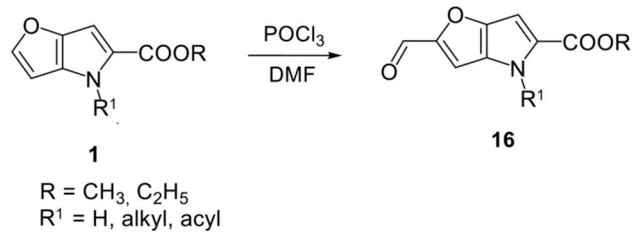


For: **10a**,**11a**,**12a**: X = O; **10b**,**11b**,**12b**: X = S; **10c**,**11c**,**12c**: X = NMe; **10d**,**11d**,**12d**: X = Se.

Scheme 3. Synthesis of [3,2-*b*]-fused heteropentalenes **12** with O, S, Se and NH/N-CH_3 heteroatoms.

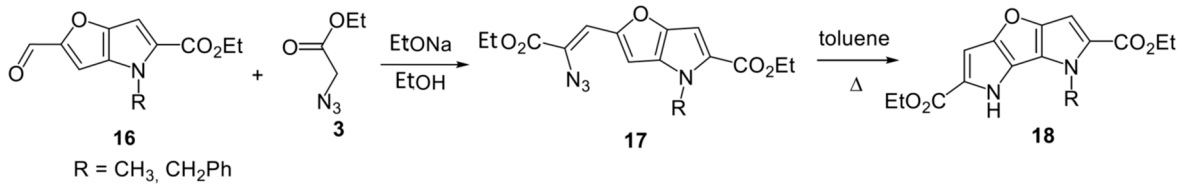
2.5. Structural Modifications to [3,2-b]HPs through Subsequent Treatment

The synthesis of various substituted furo [3,2-*b*]pyrrole derivatives was developed by Krutošíková [42,43]. Formylation, nitration, the Mannich reaction and copulation were accomplished. Vilsmeier formylation should preferably take place at the C-2 position of furo- or thieno [3,2-*b*]pyrrole-5-carboxylate **1**, affording aldehydes **16** at an ambient or moderately elevated temperature (Scheme 4).



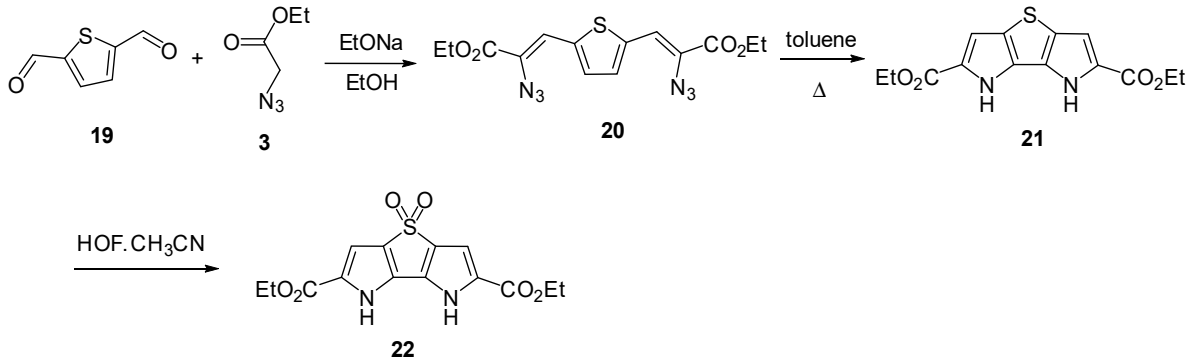
Scheme 4. Vilsmeier–Haack formylation of furo [3,2-*b*]pyrroles.

The reaction of the aldehydes **16** with azidoacetate **3** in the presence of sodium methoxide was found to proceed smoothly to give azide **17,** which upon thermolysis in boiling toluene gave diethyl 1,7-dihydrofuro [3,2-*b*:4,5-b′]dipyrrole-2,6-dicarboxylates **18** in 43 and 45% yields, respectively [44] (Scheme 5).



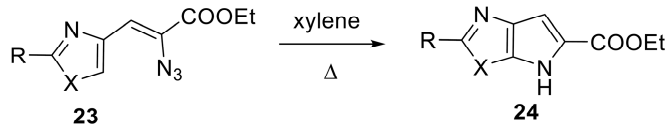
Scheme 5. Synthesis of diethyl 1-alkyl-1,7-dihydrofuro [3,2-*b*:4,5-*b*′]dipyrrole-2,6-dicarboxylates **18**.

The condensation reaction of thiophene-2,5-dicarbaldehyde **19** with ethyl azidoacetate **3** generated compound **20**, which was further subjected to cyclisation by heating in toluene to form the thienodipyrrole derivative **21** in an 85% yield (Scheme 6). Compound **21** was used as the starting material for the synthesis of thiophene polymers [45]. Compound **21** can be oxidised with an HOF.CH_3CN complex to give sulphone **22** with a 95% yield (Scheme 6) [46].



Scheme 6. Synthesis of diethyl 1,7-dihydrothieno [3,2-*b*:4,5-*b*′]dipyrrole-2,6-dicarboxylate **21** and -4,4-dioxide **22**.

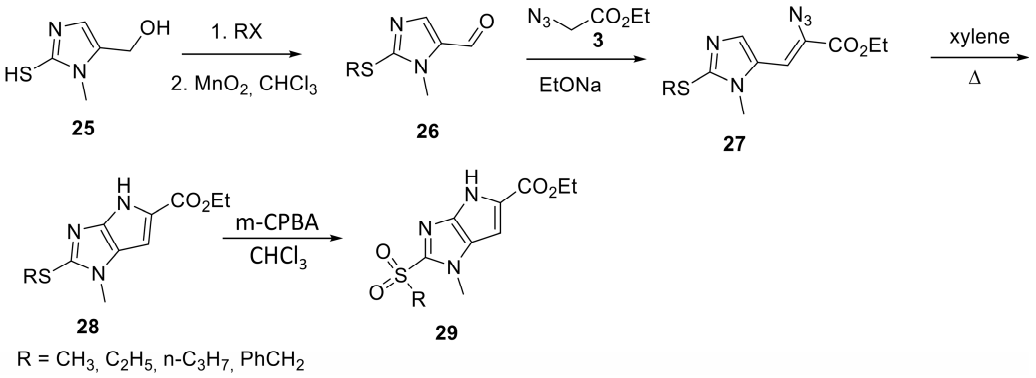
Further applications of the Hemetsberger reaction were also reported in the 1990s [47,48]. The intermediate nitrene I was inserted into a π-deficient heterocycle. The versatility of this approach is shown in the synthesis of pyrrolo [3,2-*d*]thiazoles or selenazoles **24** (Scheme 7). The thermolysis of the 3-thiazolyl- or 3-selenazolyl-2-azidoacrylates **23** produces these bicyclic heterocycles in high yields (85–90%).



X = S, Se
R = H, Me, Ph, 4-YC_6H_4 (Y = Br, Cl, OMe)
3-MeC_6H_4, 2-thienyl

Scheme 7. Synthesis of fused azoles **24**.

A series of substituted pyrrolo [3,2-*d*]imidazoles **28** were synthesised by Shaffiee and Hadizadeh [49]. The starting imidazole **25** was converted into the appropriate aldehydes **26** in two steps—the alkylation of the thiol group, and the subsequent oxidation of alcohol with manganese dioxide. The Knoevenagel condensation of aldehydes **26** with ethyl azidoacetate **3** produced acrylates **27**, which then underwent thermal cyclisation in boiling xylene to give pyrrolo [3,2-*d*]imidazoles **28**. Compounds **28** were oxidised with m-chloroperbenzoic acid (m-CPBA) to the desired sulphones **29** (Scheme 8).

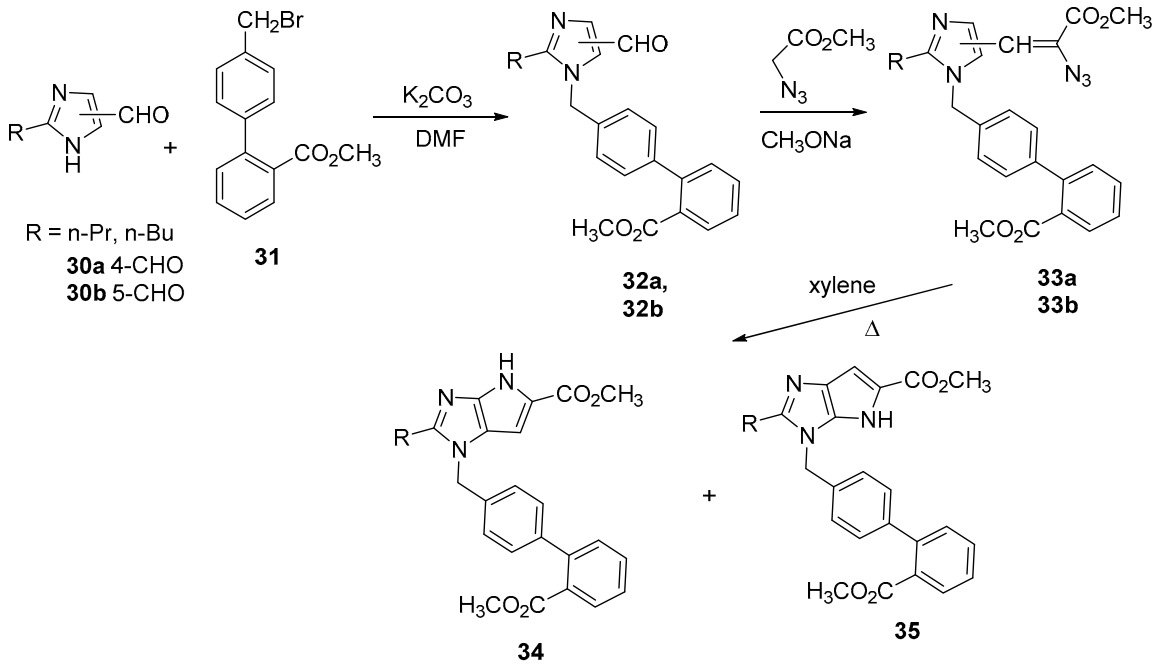


R = CH_3, C_2H_5, n-C_3H_7, $PhCH_2$

Scheme 8. Synthesis of pyrrolo [3,2-*d*]imidazoles **28** and **29**.

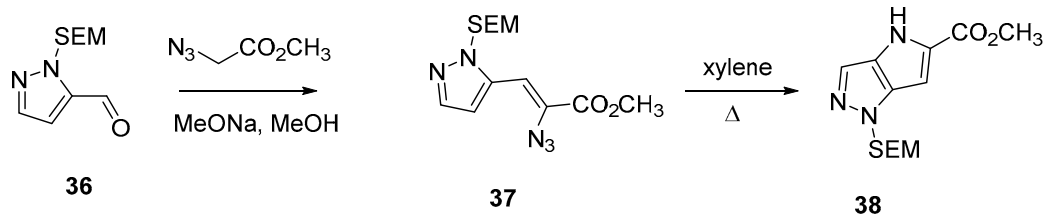
Schaffie et al. [50] later synthesised substituted pyrrolo [2,3-*d*]imidazole-5-carboxylates **34** and isomeric pyrrolo [3,2-*d*]imidazole-5-carboxylates **35** (Scheme 9). The alkylation of 2-alkylimidazole-4-carbaldehyde **30a** (or 5-carbaldehyde **30b**) with methyl 4′-bromomethylbiphenyl-2-carboxylate

31 gave a 30:70 mixture of aldehydes **32a** and **32b**, respectively. Both aldehydes **32a** and **32b** were separated by column chromatography. Further condensation of compounds **32a** and **32b** with methyl azidoacetate **3** produced acrylates **33a** and **33b**, and their subsequent cyclisation into the desired compounds **34** and **35** was accomplished through heating in xylene in 32–39% yields (Scheme 9).



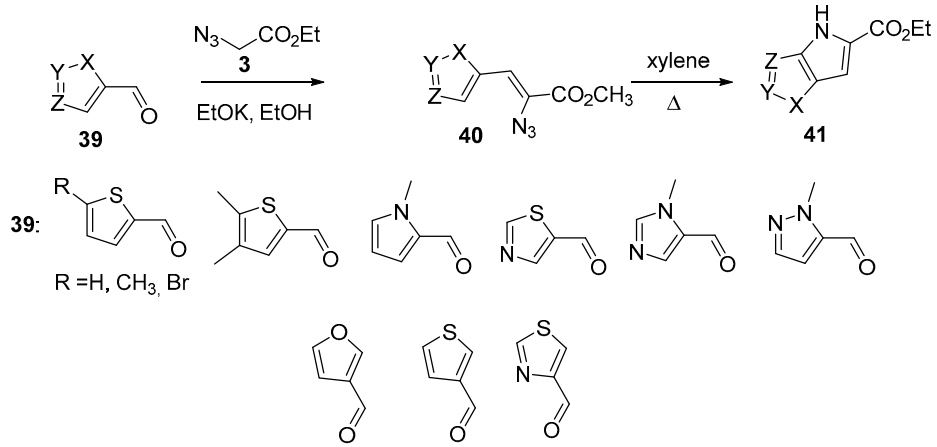
Scheme 9. Synthesis of pyrrolo [2,3-*d*]imidazole-5-carboxylates **34** and pyrrolo [3,2-*d*]imidazole-5-carboxylates **35**.

2-(Trimethylsilyl)ethoxymethyl- (SEM)-protected pyrazole-2-carbaldehyde **36** was used for the preparation of pyrrolo [3,2-*c*]pyrazole **38** under Hemetsberger–Knittel conditions. Knoevenagel condensation, followed by the thermal cyclisation of azidoacrylate **37**, produced **38** [22] (Scheme 10).



Scheme 10. Synthesis of methyl 1-SEM-protected 1,4-dihydropyrrolo [3,2-*c*]pyrazole-5-carboxylate **38**.

Recently, Sartori et al. [51] described the Hemetsberger–Knittel synthesis of various heteropentalenes. (Scheme 11). The appropriate heterocyclic aldehydes **39** were converted into azido derivatives **40** through the reaction with ethyl azidoacetate **3** and potassium ethoxide in ethanol. The subsequent cyclisation of **40** occurred by refluxing in xylene. The yields of all products **41** were reported to range from 91% to 99%, except for ethyl 1-methyl-4*H*-pyrrolo [3,2-*b*]pyrrole-5-carboxylate (54%) and ethyl 1-methyl-6*H*-pyrrolo [2,3-*c*]pyrazole-5-carboxylate (18%).



Scheme 11. Application of Hemetsberger–Knittel synthesis in order to produce three- and four-heteroatom-containing heteropentalenes.

2.6. Application Potential of Seleno-, Thieno- and Pyrrolo [3,2-b]pyrroles as HP Related to Furo[3,2-b]pyrroles

Generally, furo [3,2-*b*]pyrrole (**V**, Figure 3), as representative for the category of (1:1), (1:2)/(2:1) heteropentalenes and their derivatives, are known as effective antimicrobial [23], anti-inflammatory [20] and antituberculotic agents [21]. Their thieno-and seleno [3,2-*b*]pyrrole-type analogues have gained interest due to possessing antivirotic activity [52–54], and in the field of proteomics [55,56]. In particular, the derivatives 6-[2-(*N*,*N*-dimethylamino)ethyl]-4*H*-thieno [3,2-*b*]pyrrole (**42**, Figure 5) are bioisosteric analogues of the hallucinogen and the serotonine agonists and have become leading derivatives in such fields of medicinal research since their discovery [57].

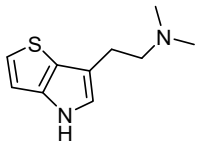


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Figure 5. 6-[2-(*N*,*N*-dimethylamino)ethyl]-4*H*-thieno [3,2-*b*]pyrrole (**42**) as the representative compound from the category of S,N-heteroatom containing (1:1) HPs [57].

Thieno [3,2-*b*]pyrroles, beyond their biological activities, have been investigated as the donor-moieties in a variety of organic semiconductors. Recently, the importance of seleno [3,2-*b*]pyrrole-type compounds in materials chemistry has been highlighted. In some studies, it has been proposed that through the replacement of the thieno [3,2-*b*]pyrrole segment by selenophene [3,2-*b*]pyrrole in a particular compounds such as **43** and **44** (Figure 6), there could be an improvement in the performance of organic field effect transistors (OFETs) [58]. However, the results are not clearly understood since some studies explain the converse trend [59]. Contrary to this, S,N and Se,N-heteroatoms containing HPs, and their N,N-azanalogues, have been always investigated and applied as electron-acceptor units and chromophores in organic photovoltaic devices [59–61]. In a novel study, the deep red emission for B/N-doped, ladder-type pyrrolo [3,2-*b*]pyrroles **45a/45b** (Figure 7) has been developed [62]. Such a novel type of dye underwent a fully reversible first oxidation, located on the diphenylpyrrolo [3,2-*b*]pyrrole core, directly to the di(radical cation) stage.

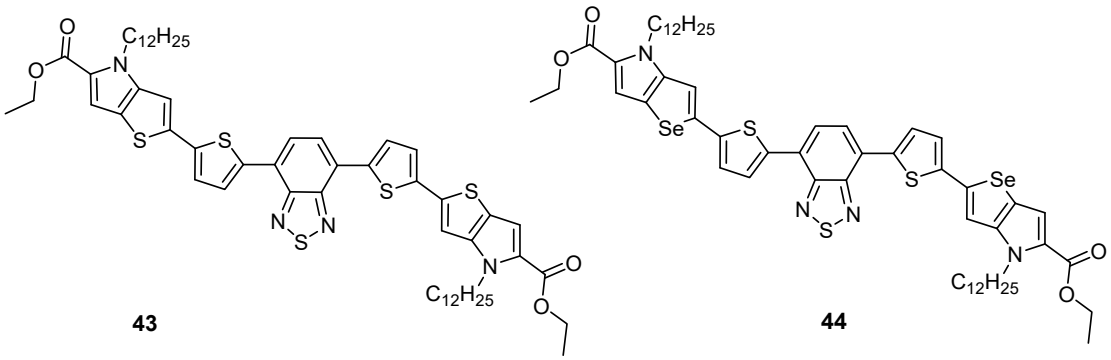
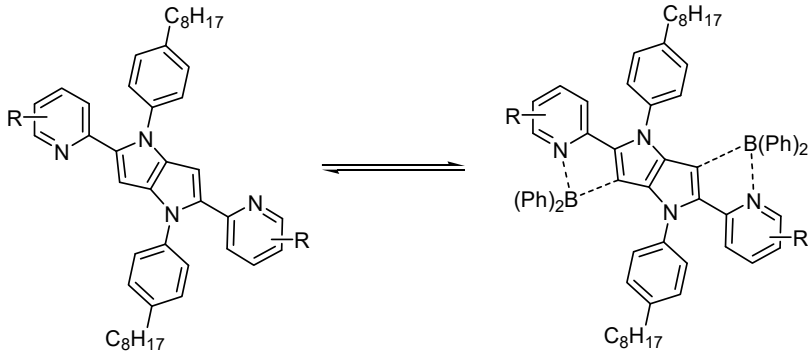


Figure 6. Derivatives of thieno [3,2-*b*]pyrrole **43** and seleno [3,2-*b*]pyrrole **44** as representatives of the S,N and Se,N (1:1) HPs for interests in organic semiconducting materials [58].



R = H, *o*-CH_3, *m*-Br, *p*-Br, *m*-F, 1,2-C_4H_4, 2,3-C_4H_4

Figure 7. Pyrrolo [3,2-*b*]pyrrole-based dyes/emitters **45a**/**45b** possessing deep red emission [62].

3. Thiazolo [5,4-*d*]thiazoles

Thiazolo [5,4-*d*]thiazole (TzTz) is a conjugated (π)-heterocyclic scaffold containing two fused thiazole rings presenting a rigid planar structure (**46**, Figure 8) [63]. Unsubstituted TzTz is a white powder containing two nitrogen, two sulphur and four carbon atoms, and without a wide range of utilisation, but its derivatives have attracted enormous attention.

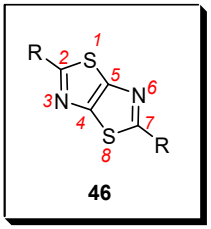


Figure 8. Structure of a thiazolo [5,4-*d*]thiazole scaffold with atom numbering.

According to ScienceDirect® 490 and Scopus®, 289 peer-reviewed papers/articles on TzTz compounds were published between 1959 and 2021 (Figure 9). The first papers published by Johnson and Ketcham presented only the preparation of TzTz and provided some other general information, such as UV–Vis spectra, mass spectra and IR characterisation [64]. The number of papers showed a slight increase until 2004, when the first TzTz based donor–acceptor–donor molecules were presented [65,66]. Since 2008, the trend has been for a rapid increase in research works focusing on intensive studies of applications

of TzTz in organic electronics. In particular, since the first n-type thiazolo [5,4-*d*]thiazole-based organic field-effect transistor (OFET) was presented [67], reports on TzTz-containing materials have increased almost exponentially [68]. Although the applications of TzTz-type materials in the development of OFETs [69], organic-light emitting diodes (OLEDs) [70], optical sensors [71] and organic redox flow batteries [72] have already been described, TzTz-based organic photovoltaics (OPVs) [73], including dye-sensitised solar cells (DSSCs) [74], bulk heterojunction solar cells (BHJ) [75], perovskite solar cells [76], hybrid solar cells [77] and polymer solar cells [78] with high values of power conversion efficiency (PCE), ranging from 3% up to a maximum of 17%, have been presented in a vast number of research works. Concerning the structure of the heterocyclic core, the functionalisation of thiazolo [5,4-*d*]thiazole-based derivatives towards materials with efficient charge transfer, [79] intense absorption and strong fluorescence, [80] as well as higher solubility, is due to the lack of free positions handled mainly through the substituents at C2 and C7 (**46**, Figure 8) [81].

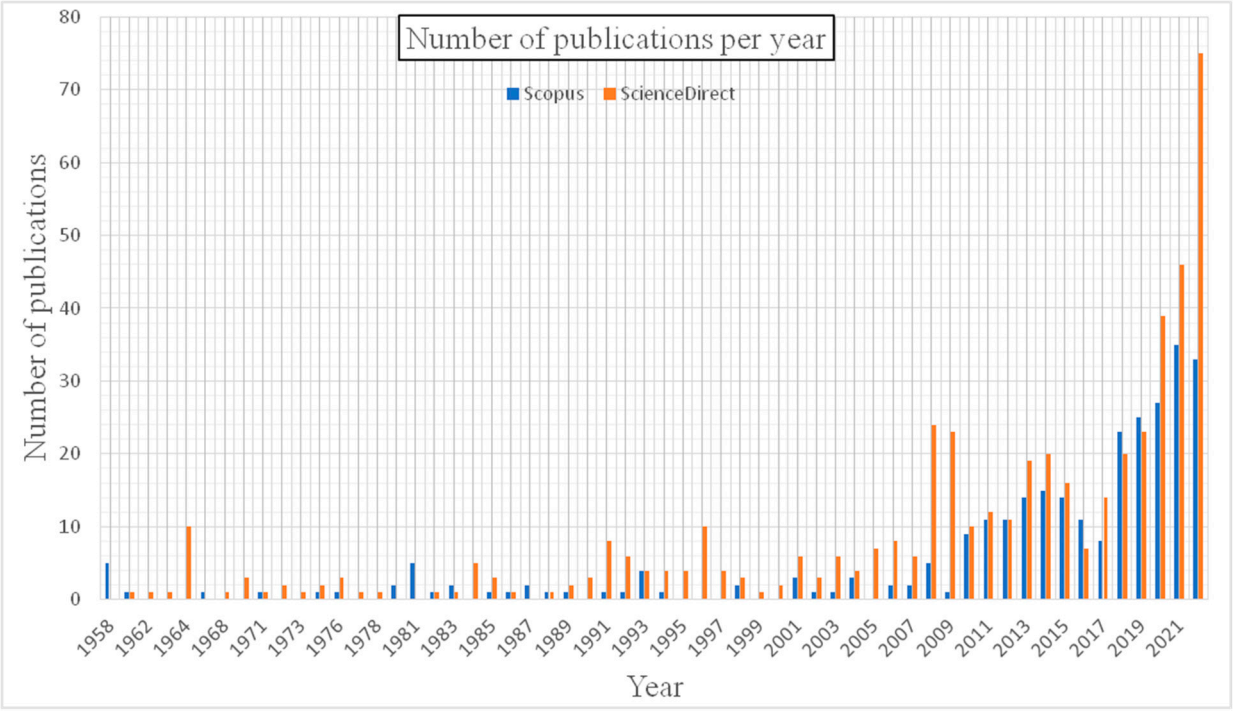
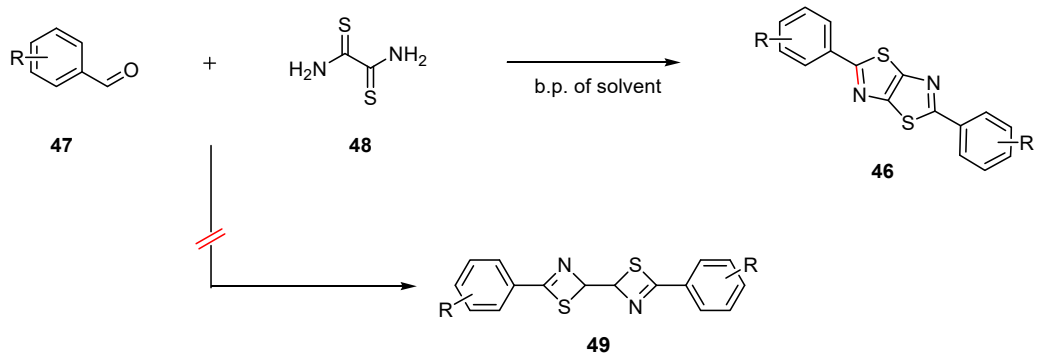


Figure 9. Dramatic increase in publications presenting the synthesis and application of TzTz derivatives between 1958 and 2022, according to Scopus® and ScienceDirect®.

3.1. Ketcham's Cyclocondensation Reaction

Pioneering synthesis of TzTz-based compounds was performed by John Johnson and Roger Ketcham, who published their work in 1960. The goal of the authors was to monitor the condensation of dithiooxamide (**48**) with different aromatic carbaldehydes (**47**) [64]. A condensation experiment (Scheme 12) was carried out in different solvents (benzyl chloride, phenol, benzene and chloroform) at boiling point temperature. The most commonly used solvents were *N*,*N*-dmiethylformamide (DMF), nitrobenzene, chlorbenzene and phenol, or a solvent-free method was applied. The presented TzTz derivatives were formed in moderate to good yields (7–78%). A curiosity concerning the synthesis was that the first condensation between the aromatic aldehyde with rubeanic acid was performed by Ephraim in 1891 [82], but in that period the structure of the products was primarily misstated as 2,2′-diaryl-4,4′-bisthiazetine (**49**, Scheme 12) [83]. Later, the correct structure of TzTz-based derivatives was confirmed.



Scheme 12. Representative synthesis of symmetrical thiazolo [5,4-*d*]thiazoles (**46**) by Ketcham/Johnson [64], also showing the misstated structure of Ephraim (**49**) [82].

Ketcham cyclocondensation is the most widely utilised process for the synthesis of TzTz-based derivatives, mainly symmetrically substituted by aromatic and heteroaromatic rings (Scheme 12). On the one hand, the reaction represents a very available process since it represents a single step, one-pot method which does not require an inert atmosphere or cooling [84] and can be performed under solvent-free conditions using microwave irradiation [85]. Moreover, dithiooxamide and a broad range of aldehydes are widely affordable at good prices. Still, such an elegant synthetic approach is accompanied by a few drawbacks, such as long reaction times, high reaction temperatures and the formation of products in poor to average yields [86–90]. The formation of by-products, as a consequence of the stepwise process, probably contributes the most to lowering the yield of the desired products.

3.2. Mechanism of the Ketcham Reaction

In our previous work [16], we presented the completed mechanism of the Ketcham stepwise process. The proposal was based on our experimental observation, and the structural characterisation of the main products and by-products [16]. Our proposal was supported by data from the literature [91,92], where the authors proposed a shortened version of the mechanism or highlighted the formation of by-products **51** and **54** (Figure 10) resulting from the process' behaviour. In detail, according to Scheme 13 the condensation of two equivalents of substituted furan-2-carbaldehyde (**50**) produced the stable imine-type derivative **51**. Such iminie-type derivatives are formed during the early stage of the reaction that is followed by a ring-closing reaction, producing the non-isolable dihydro intermediate **52**. The process is completed by double intramolecular rearrangement of the dihydro intermediates **52**, **53**, ending up with oxidative cyclisation to furan-substituted TzTz **55**. Some improvements to the oxidation step were presented by the use of SeO_2 as an oxidising agent [93]. This approach shows oxidation from the cyclised 2,3-dihydrothiazolo [5,4-*d*]thiazole (Scheme 13, Pathway B). The free amino group of the initially formed single thiazole ring allows condensation with another amount of aldehyde. The intermediate bearing the -SH moiety, possibly dimerize, forms the bisthiol-type compound **54** in which the S-S bond is subsequently cleaved. The unsaturated TzTz core is oxidised further. In spite of that, the presented proceeding could be taken as being hypothetical, according to two independent research works previously published in [16,93]. It has to be mentioned that the formation, isolation and identification of intermediate bis-thiol type derivative **54** (Figure 10) was possible only if the presence of the oxygen atom of the substituent stabilised the nitrogen of the imine bond by intramolecular effects. Such a phenomenon, nevertheless, has not been discussed as of yet.

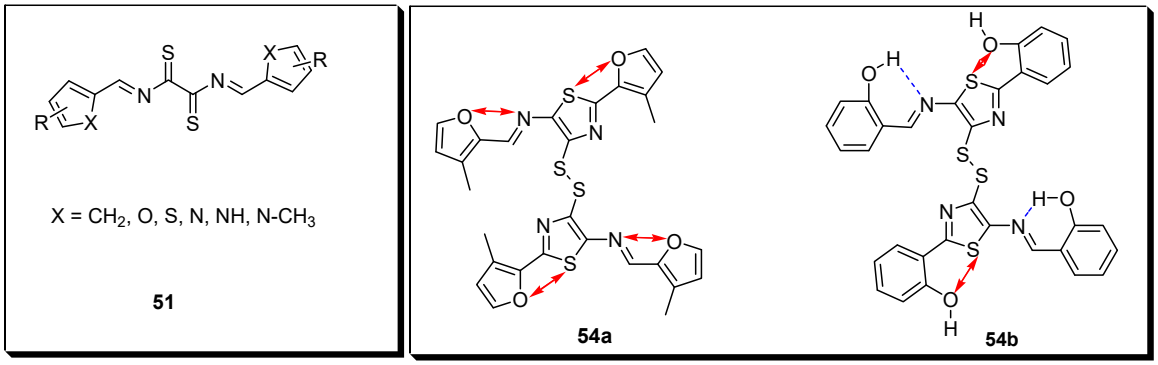
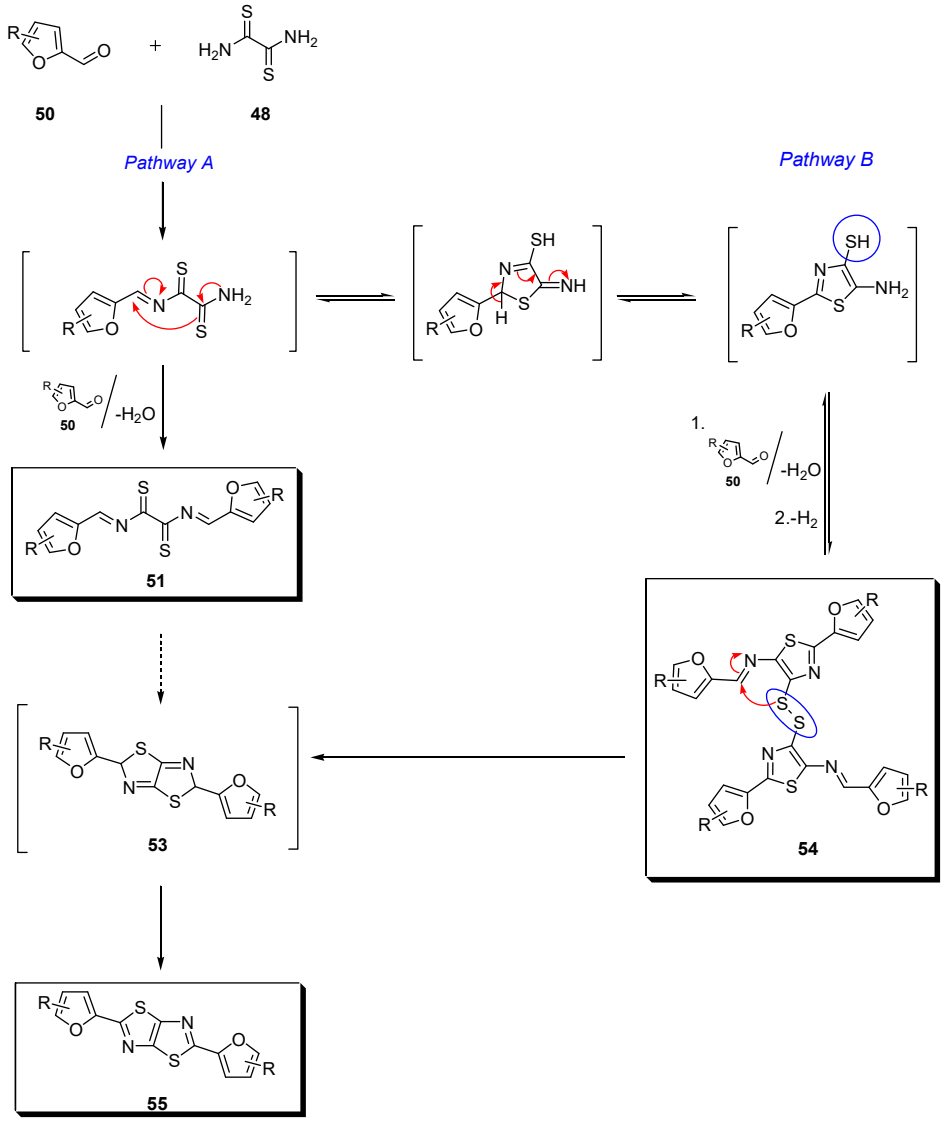


Figure 10. Chemical structure of Ketcham's reaction by-products—the common imine-type derivative **51** and unusual bis-thiol type **54**, evidenced only twice according to [16,93]. The possible intramolecular effects are proposed—the dipole–dipole interactions (red arrow) and hydrogen bonds (red dashed line) as a probable interpretation of the stabilisation of this unusual by-product.

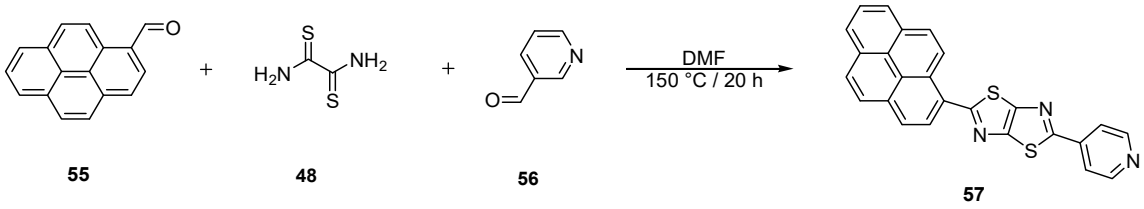


Scheme 13. Proposed mechanism of the Ketcham reaction according to [16,91–93], including the formation of imines **51** as isolable and stable types of by-products (*Pathway A*) and the possible formation of an unstable and unique intermediate of bis-thiol type **54** (*Pathway B*).

3.3. Synthesis of Asymmetrical Thiazolo [5,4-d]thiazoles by Ketcham's Reaction

It is quite surprising to achieve an asymmetrically substituted TzTz-based compound through simple cyclocondensation. To the best of our knowledge, there have only been two examples of such phenomenon in the literature presented until now.

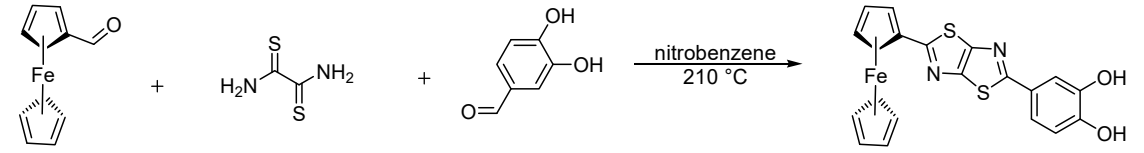
The first example was presented in the literature very recently, in 2022, and it shows the use of two different carbaldehydes, pyrene-1-carbaldehyde **55** and 4-pyridinecarboxaldehyde **56**, in a ratio of 1:1 in cyclocondensation with dithiooxamide (**48**) towards C2-pyrene and C7 p-pyridine-substituted thiazolo [5,4-*d*]thiazole **57** (Scheme 14) [94]. Interestingly, the authors report only the sole asymmetric product; however, the character of this reaction would possibly enable the formation of symmetrical products as well.



55 **48** **56** **57**

Scheme 14. Example of the synthesis of unsymmetrically substituted thiazolo [5,4-*d*]thiazole **53** by the use of a mixture of two different aldehydes **55** and **56** with dithioxamiede [94].

Another example of the achievement of asymmetrical TzTz derivative **56** using a direct Ketcham procedure was presented recently [95]. The reaction of ferrocenyl aldehyde (**58**) with protochatecuic aldehyde (**59**) produced thiazolo [5,4-*d*]thiazole **60** (Scheme 15).



58 **48** **59** **60**

Scheme 15. Synthesis of monoferrocenyl-substituted TzTz-derivative **60** [95].

3.4. Cyclopolymerisations Following Ketcham's Reaction Protocol

Recently, a very promising way to achieve a TzTz-based oligomer or polymer directly was offered by the simple Ketcham's synthetic protocol. Instead of a small-molecule thiazolo [5,4-*d*]thiazole-type derivative, the compound had approximately two to seven repeating TzTz units in the final oligo- or polymer. Such types of reactions are rather rare, but this seems to be very promising for the construction of organic materials with enhanced π-conjugation and the required electronic properties. Reports on Ketcham-type polycondensation have recently garnered interest. At the moment, there are on average only ten reports [96–105] presenting the direct Ketcham reaction approach towards TzTz-based oligomers and polymers.

1. The first report, published in 2016 [96], presented the synthesis of a 9-hexyl-9H-carbazole-unit bearing a TzTz-based oligomer **61** with seven repeating units (Figure 11a). A similar product geared towards the same oligomer was presented in 2021 [97].
2. The polycondensation reaction of the Ketcham-type of dithiooxamide with triethylamine and carbazole-based aldehydes was published by Dabuliene at al. in 2022 [98]. GPC analysis showed the average molecular weights of triphenylamine-based compounds (**62**) (Figure 11b) between 2980 and 3080, while in the case of carbazole containing derivatives (**63**) it was from 1640 to 3290. The published GPC results indicated that the molecules contained approximately three to seven repeating units.
3. Zhu et al. (2014) [99] demonstrated the preparation of a porous cross-linked polymer **64** (Figure 11c) containing TzTz and phenyl units. Similar phenyl-based monomers

with three carbaldehyde groups, such as tris(4-formylphenyl)-benzene and tetra(4-formylphenyl)-benzene, can be also condensed with dithiooxamide to give a cross-linked copolymer with a porous structure [100].

4. The polycondensation of 1,3,5−triformylfloroglucinol with 4,4′-(thiazolo [5,4-*d*] thiazole-2,5-diyl)dianiline gave a crosslinked copolymer **65** with a porous structure (Figure 11d) [101,102].
5. Cross-linked copolymer **66** was synthesised by the condensation of dithiooxamide with (1,3,5- tris(4-formylphenyl)-benzene) or with (2,4,6-tris(4-formylphenyl)-1,3,5-triazine (Figure 11e) [103].
6. Finally, the structure of cross-linked polymers **67** as products of Ketcham's type polycondensation of dithiooxamide with different monomers containing multiple carbaldehyde groups was described according to [104] (Figure 11f).
7. The polycondensation approach following the Ketcham procedure was successfully used to achieve porous, cross-linked copolymer containing porphyrin-residues **68** (Scheme 16) [105].

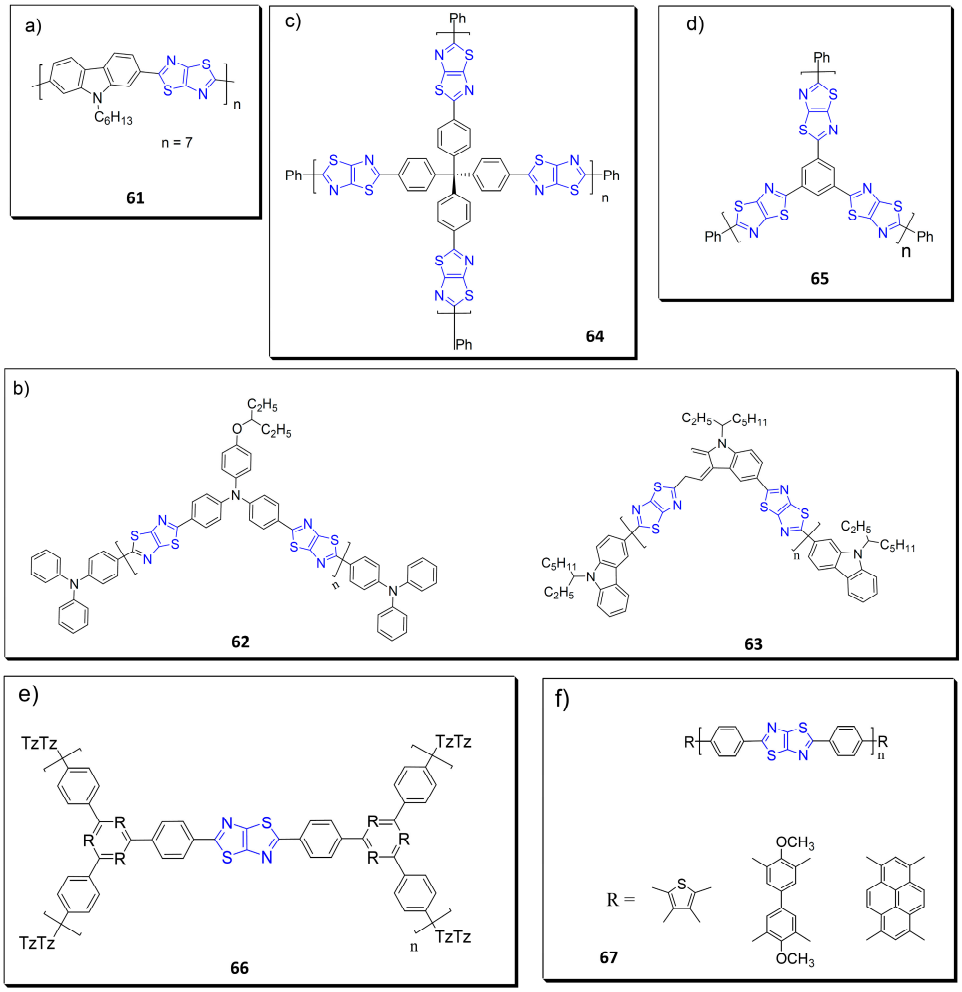
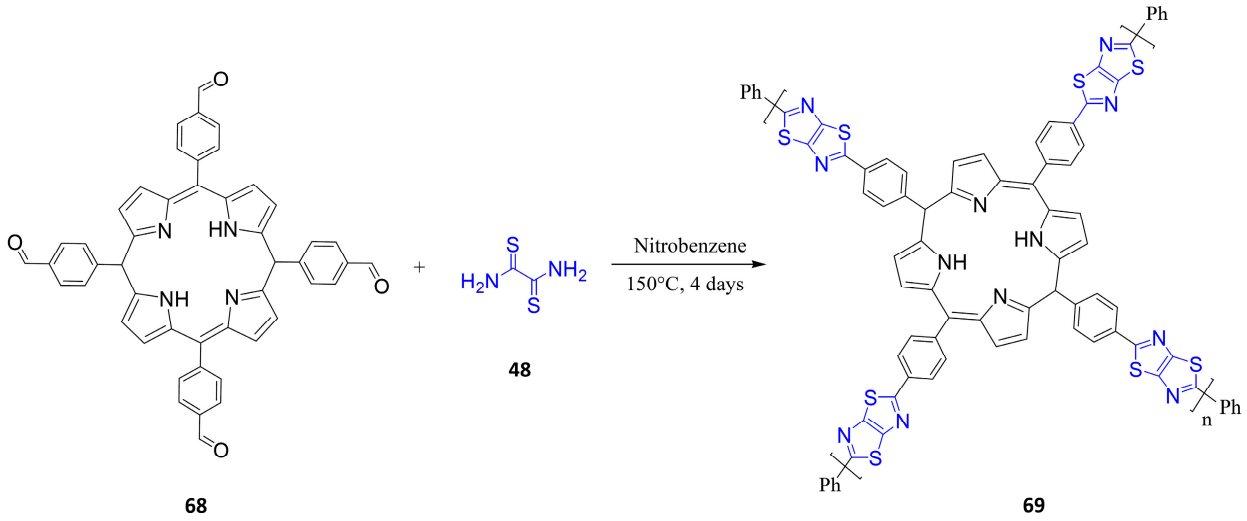


Figure 11. Chemical structure of oligo- and copolymers prepared by simple Ketcham's reaction protocol. (**a**) 9-hexyl-9H-carbazole-unit bearing a TzTz-based oligomer **61**; (**b**) triphenylamine-based TzTz-type oligomers **62**,**63**; (**c**) TzTz-based star-shaped oligomer **64**; (**d**) TzTz-based porous cross-linked polymer **65**; (**e**) trisbenzene and triazine cross-linked TzTz-based oligomers **66**; (**f**) aromatic and heteroaromatic polycondensed thiazolo[5,4-d]thiazoles **67**.



Scheme 16. Synthesis of porphyrin-centred TzTz-based copolymer achieved by simple Ketcham's synthetic protocol according to [105].

With the final example presented in Scheme 16, it can be concluded that the utilisation of Ketcham's ring-closure method significantly extends beyond its generally accepted potential. The polycyclocondensation approach is, moreover, a novel alternative way to achieve novel functional materials using a simple, one-step manner affecting significant cost-reduction and enhancement of the eco-friendliness of the entire process, from design through synthesis up to real-life application.

4. Conclusions

In combination with our several years of experience in the field of synthesis and applications of furo [3,2-*b*]pyrroles and thiazolo [5,4-*d*]thiazole-based derivatives with respect to published research work, the knowledge and current "state-of-the-art" of the Hemetsberger–Knittel synthesis regarding furopyrroles and their sulphur- and seleno- heteroatom containing derivatives and the Ketcham cyclocondensation methodology affording thiazolothiazoles is detailed herein. The primary interest is focused on the preparation processes, benefits and drawback of each method. The mechanism or the proposal of the mechanism is discussed. Both types of discussed heteropentalenes are very important in applied sciences. Furo [3,2-*b*]pyrroles exhibit a variety of pharmacological effects, and thiazolo [5,4-*d*]thiazole are targets of materials research, particularly in the field of optoelectronic materials. Both the Hemetsberger–Knittel approach and the Ketcham synthesis represent a versatile route towards a concrete type of heteropentalenes. Under current review are insights into both methodologies with the ambition of the further design and synthesis of a novel type of heteropentalenes with two (1:1); three (1:2)/(2:1) and four (2:2) mainly O, S,N heteroatoms. Both series of compounds are of prospective interest for pharmacological sciences (furopyrroles) and for materials research (thiazolothiazoles). Current applications of thieno-, selenopheno, pyrrolo [3,2-b]pyrroles are included as well, mainly focusing on fields of materials chemistry.

Author Contributions: Conceptualisation, Z.T.; methodology: Z.T. and R.G.; validation, M.G. and N.K.; investigation, Z.T. and R.G.; resources, Z.T. and R.G.; data curation, M.G. and N.K.; writing—original draft preparation, Z.T.; writing—review and editing, Z.T.; visualisation, N.K. and M.G.; supervision, Z.T.; project administration, Z.T.; funding acquisition, Z.T. and R.B. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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