Thienothiophenes: Synthesis and Applications

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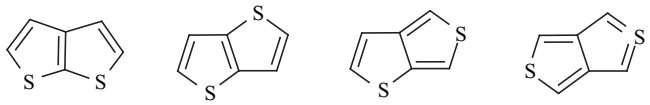
Abstract: The four isomers of thienothiophene have long been considered only for academic interest. Their usefulness in material science and biology has led to a renewal of their chemistry. The present paper reports the newest synthetic methods after the first review by Litvinov and Gol'dfarb in 1976.

Keywords: Cyclisation, sulphur, thiophene, material science and thienothiophene.

During the past fifty years, many research groups have been interested in the preparation of thienothiophenes for different purposes. All the methods described until 1976 have been extensively reviewed by Litvinov and Gol'dfarb [1]. Most of the papers since then consist in improvements of these methods. The inherent properties of thienothiophenes and their use as a building block for biological or medicinal applications are reflected in the increasing number of papers reporting new preparation methods.

When two five-membered rings are fused, four different annelation patterns are possible, giving [2,3-*b*] **I**, [3,2-*b*] **II**, [3,4-*b*] **III** and [3,4-*c*] **IV** fused systems (Scheme **1**).



I **II** **III** **IV**

Scheme 1.

We will see later that the last isomer requires a completely different approach for its preparation due to its particular structure. This point will be discussed separately at the end of the review.

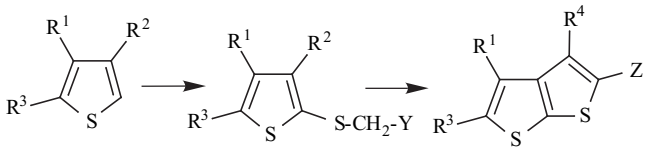
In this paper, we wish to present briefly the methods described for the preparation of the isomers of thienothiophene. We have classified them into 3 different groups, depending on the starting material. A last part will be dedicated to isomer **IV**. Our aim is to essentially summarise all the synthetic strategies used for their preparation, but obviously, not to establish a chronological list of the papers dealing with thienothiophenes.

SYNTHESIS OF ISOMERS I, II AND III

a) Starting from Thiophenes

Several synthetic ways were developed and reported in the review of Litvinov and Gol'dfarb [1] in 1976. The general strategy can be summarised as depicted in Scheme **2**.

The second sulphur atom is introduced and reacted with an active methylene halide. If R^2 is a ketone or a formyl group, a treatment in basic media allows obtaining the expected thienothiophene. If R^2 is H and Y is able to react with the thiophene group by aromatic electrophilic substitution, the cyclisation can occur and the second fused ring of the thienothiophene is formed.

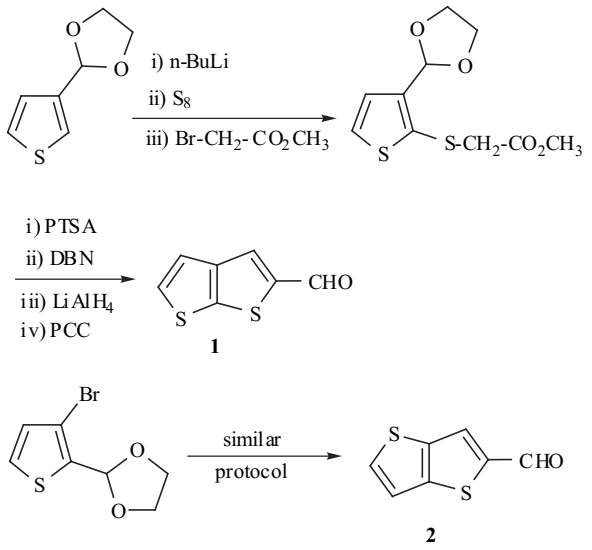


Z = Y when the methylene anion can react with R^2 (Dieckmann type reaction)

Z = H when R^2 = H and Y can react with the 3-position of the thiophene ring

Scheme 2.

This strategy is the only one that can lead to isomers **I**, **II** or **III**, depending on the starting thiophene and is largely documented in the literature. Many papers have been already listed in the review of Litvinov and Gol'dfarb [1]. We decided to focus on the most recent papers reporting the same synthetic way, but with improvements of the yields due to optimisation of crucial steps. One of the most cited references is the method developed by Prugh and Hartmann [2] published in 1991 and summarised in Scheme **3**.



1 **2**

Scheme 3.

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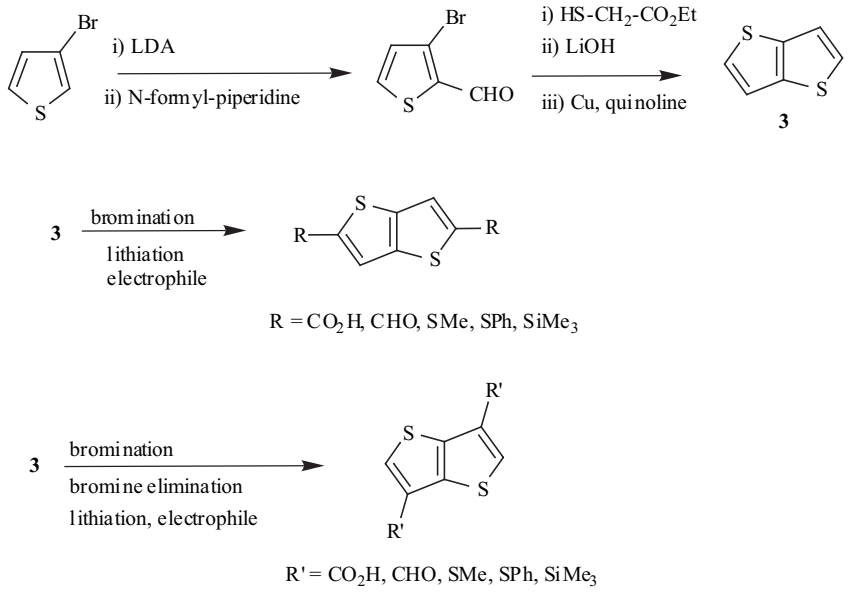


Scheme 4.

Many other studies [3] on thienothiophene derivatives for medicinal applications follow the protocol described in this paper. The protection-deprotection sequence is one of the modifications provided by the authors, most probably for better yields or easier work-up but is not always required if the formyl group is introduced by formylation of the thiophene just prior to Dieckman type cyclisation [4].

A similar approach [5] has been recently reported and used by other authors [6-9]. Sulphur is introduced directly by the use of thioglycolate reacting with 3-bromothiophene-2-carbaldehyde (aromatic nucleophilic substitution). The same 2-formylthieno[3,2-*b*]-thiophene previously described could be synthesised. Nevertheless, the authors described the preparation of unsubstituted thieno[3,2-*b*]thiophene **3** after two more steps as well as brominated products in order to investigate bromine-lithium exchange reactions (Scheme **4**).

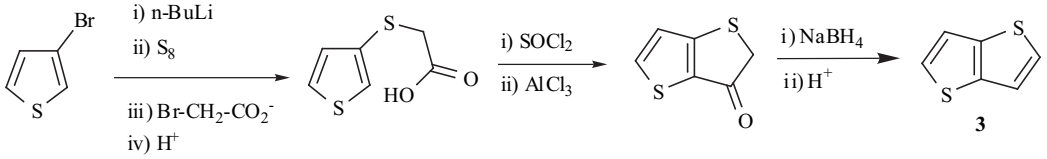
Some authors proposed alternative ways to avoid the decarboxylation step, what seems to be a drawback of the two preceding methods. In this case, the second thiophene ring is obtained by an aromatic electrophilic substitution. Leriche *et al.* [7] described a route starting from the lithiation of 3-bromo-thiophene which allows to introduce the sulphur, in a similar way than previously described [2] (Scheme **5**).

Reaction with bromoacetate and activation of the carboxylic group led to the formation of the second fused ring. Thieno[3,2-*b*]thiophene **3** was obtained after reduction of the ketone and a subsequent dehydration in acidic medium.

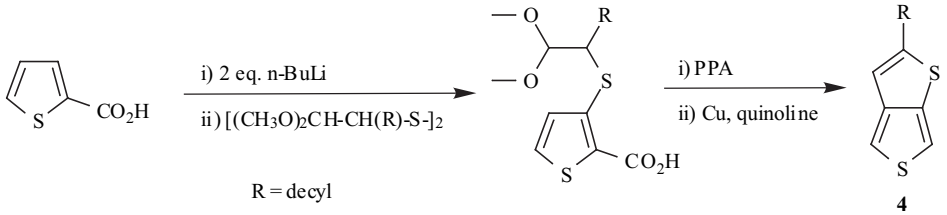
The same strategy has been applied to the formation of 2-decylthieno[3,4-*b*]thiophene **4** [10] where the thiophene ring is formed directly by cyclisation of the aldehyde (Scheme **6**).

The latter was polymerised and its performance as conducting polymer evaluated.

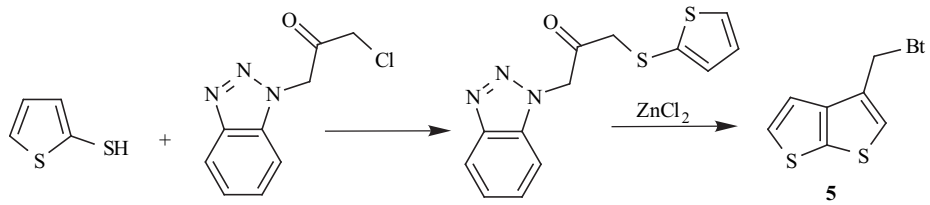
Benzotriazole derivatives reactivity permitted Katritzky's group [11] to propose a similar way from 2-thienylthiol. Reaction with 1-(1*H*-[1,2,3]benzotriazol-1-yl)-3-chloroacetone and treatment of the β-ketosulphide obtained with zinc chloride led to the formation of the second fused ring of compound **5** (Scheme **7**).



Scheme 5.



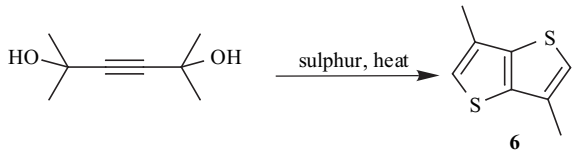
Scheme 6.



Scheme 7.

b) Starting from Acetylenic Derivatives

Nakayama *et al.* [12] have developed a convenient way to obtain 3,6-dimethyl-thieno[3,2-*b*]thiophene **6** directly from commercially available 2,5-dimethyl-3-hexyne-2,5-diol in one step by heating with sulphur over 170°C (Scheme **8**). Although the yields are modest, around 30%, this one step procedure remains attractive compared to other multi-steps methods and its reproducibility has been demonstrated.

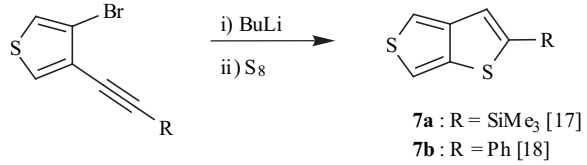


Scheme 8.

Although this method is limited to the preparation of only one thienothiophene, this compound has been used and studied in the field of materials science [13] for the preparation of electroconductive polymers. Due to the fact that the 2- and 5-positions of this compound are free, the latter can be electropolymerised and used for its physical properties or functionalised and transformed into a conducting spacer for different applications [8,14].

Another approach has been reported by Brandsma *et al.* [15], starting from a diyne and carbon disulphide as a source of sulphur, in a basic medium (Scheme **9**). This way has been applied for the preparation of a dimer of thieno[2,3-*b*]thiophene, isostere of perylene [16].

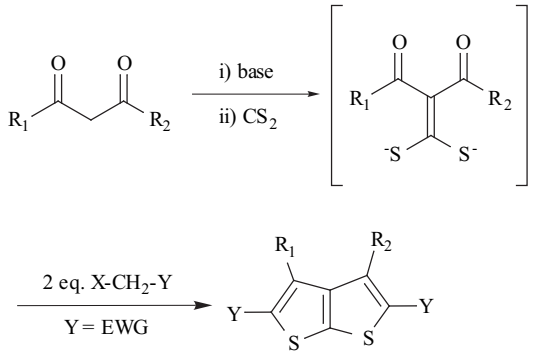
Another closely related approach for the preparation of thieno[3,4-*b*]thiophenes has been recently reported by two different groups [17,18] involved in material science. They observed that the cyclisation of 3-bromo-4-(substituted) ethynylthiophene occurred when treated by butyllithium followed by addition of elemental sulphur and led to compounds **7** (Scheme **10**).



Scheme 10.

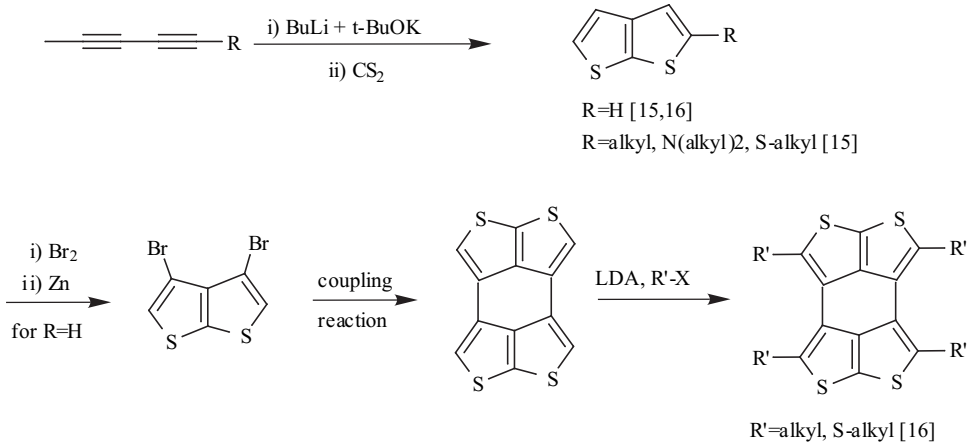
c) Synthesis Using Carbon Disulfide

Since the early 60's and the papers of Gompper *et al.* [19], it is well known that active methylene compounds can react readily with carbon disulphide in basic media to afford ketene dithioacetals. Generally, these intermediates are good nucleophiles and their reaction with active methylene halides affords symmetrical thieno[2,3-*b*]thiophenes (Scheme **11**).

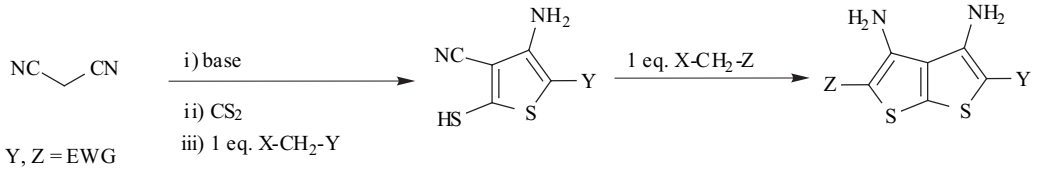


Scheme 11.

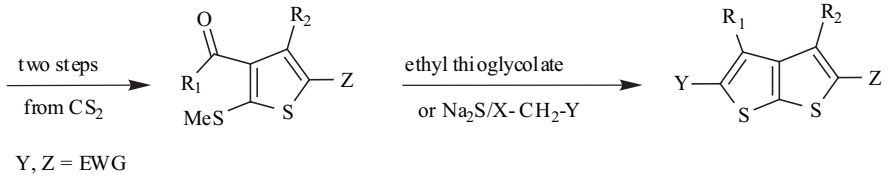
The low yields in the first experiments have been improved, making the method as a strategy of choice for the



Scheme 9.



Scheme 12.



Scheme 13.

preparation of thieno[2,3-*b*]thiophenes [20]. Moreover, the ketene dithioacetals do not require isolation. The thienothiophenes can, therefore, be prepared in a one-pot procedure, which adds to the attractivity of the method. Obviously, this is restricted to the formation of only one isomer of thienothiophene but it is the most documented preparative method [21].

The preparation of unsymmetrical thieno[2,3-*b*]thiophenes using this way is scarcely described in the literature. Briel [22] claimed that the addition of only one equivalent of active methylene halide followed by hydrolysis led to the formation of 2-mercapto-thiophene which reacted further with an other equivalent of halide in order to obtain eventually the expected unsymmetrical thienothiophene (Scheme **12**).

Another alternative has been recently described by Kirsch *et al.* [23] starting from 2-methylsulfanyl-thiophene and ethyl thioglycolate or a mixture of sodium sulphide and active methylene halide. The ability of the methylsulfanyl group to act as a leaving group by aromatic nucleophilic substitution plays a key role in this versatile synthetic way (Scheme **13**).

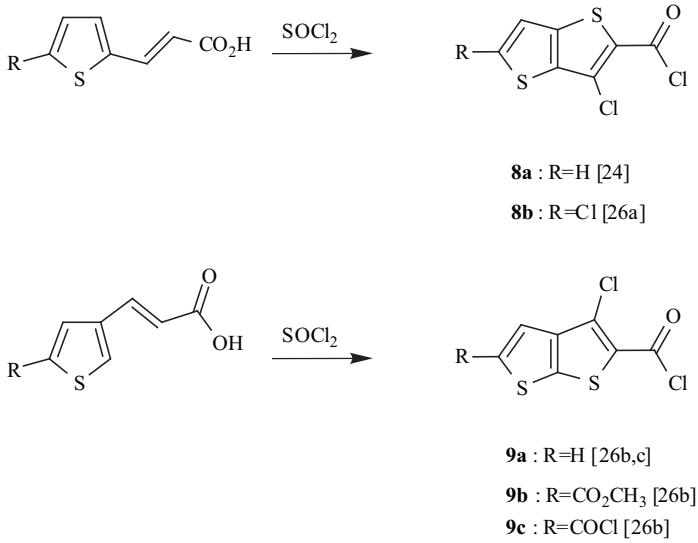
d) Sulphur Insertion Allowing the Second Ring Formation

Wright [24] described in 1972 the formation of 3-chlorothieno[3,2-*b*]thiophene by heating 3-(2-thienyl)acrylic acid with thionyl chloride. Shortly after, Gronowitz *et al.* [25] published an extension of this method. This strategy has been used recently by some authors for medicinal applications for the synthesis of thieno[3,2-*b*]thiophenes **8** and thieno[2,3-*b*]thiophenes **9** [26] (Scheme **14**).

Another route is based on the reactivity of dilithiated species with strongly reactive sulphide [27]. Although this method seems to be not really easy to handle, it offers the advantage to lead to isomers **I**, **II** and **III** of thienothiophene and, moreover, is appropriate for the formation of other bicyclic systems (thienofused five-membered rings containing selenium, tellurium, phosphorus, arsenic and antimony) as described in Scheme **15**.

The bicyclic compounds formed **10**-**12** were free of substituents, which, obviously, greatly facilitated their synthesis.

Lawesson's reagent has been used by Yang and Fang [28] for the synthesis of 6-aryl-thieno[3,4-*b*]thiophene **13** as well, by cyclisation of a 1,4-ketol (Scheme **16**).



8a : R=H [24]

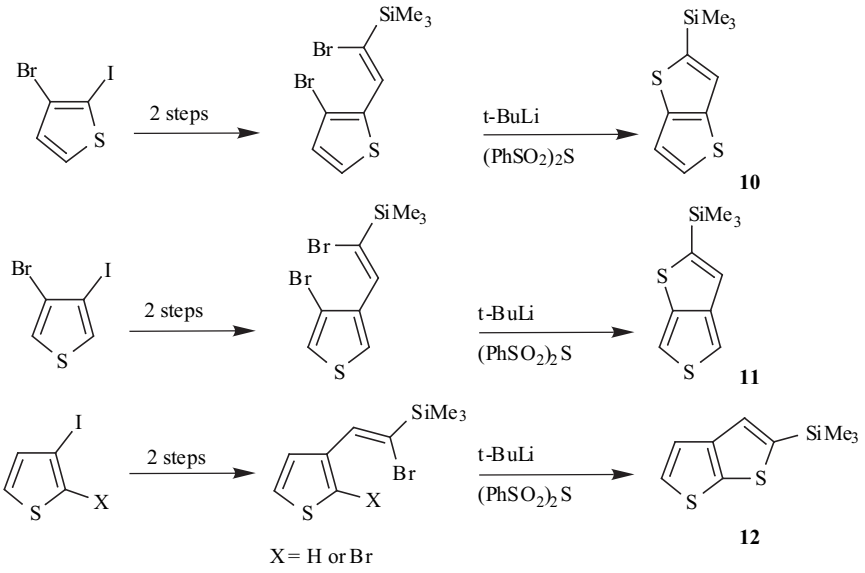
8b : R=Cl [26a]

9a : R=H [26b,c]

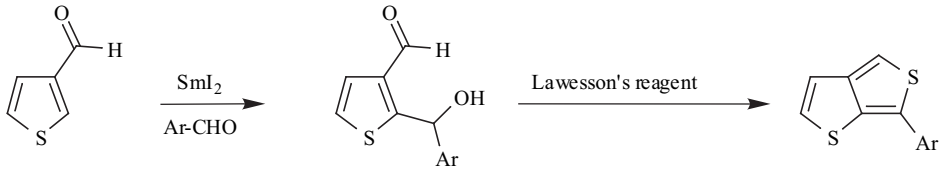
9b : R=CO_2CH_3 [26b]

9c : R=COCl [26b]

Scheme 14.



Scheme 15.



Scheme 16.

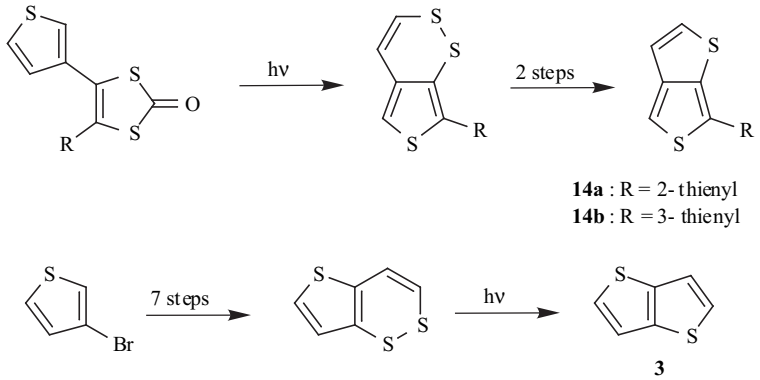
e) Miscellaneous Methods

Some authors [29] claimed that the established routes [1,2] to 2-formyl-thieno[3,2-b]thiophene suffered the limitations of low overall yield and/or delicate synthetic operations and proposed an original way, in 4 steps, starting from previously described 3-hydroxy-5,6-dihydrothieno[3,2-b]thiophene-2-carboxylate (Scheme **17**), itself obtained in a two-step procedure from the corresponding β-keto carboxylate [30].

Scheme 17.

An alternative way for the preparation of 6-hetarylthieno[3,4-*b*]thiophene described by Yang and Fang [28] has been recently published. Photochemical irradiation of 4-thiophen-3-yl-5-thiophen-2(or 3)-yl[1,3]dithiol-2-one led to the formation of a thieno[3,4-*c*]dithiin, precursor of the expected 6-thiophen-2(or 3)-yl-thienothiophene **14** formed after reduction by sodium borohydride and further treatment with methyl iodide and sodium carbonate (Scheme **18**). The versatility of the method is currently investigated by the authors [31].

A recently described related method, starting from a thieno[3,2-*c*]dithiin, led to thieno[3,2-*b*]thiophene **3** by irradiation in dimethylsulphoxide [32] (Scheme **18**). Although the preparation of the thienodithiin from 3-bromo-thiophene requires 7 steps, this method is obviously not the



Scheme 18.

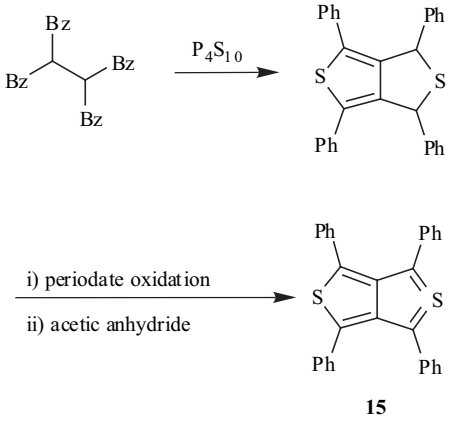
method of choice for the preparation of compound **3** but can be interesting for further applications.

Inspite of all these recent references in the literature, some authors [33, 34, 9] still referred respectively to the key article published more than 30 years ago by Bugge [35] for the preparation of functionalised thieno[3,2-*b*]- and thieno[2,3-*b*]thiophenes or other papers edited at that time [36,37]. On the other hand, Kobayashi's group [38] published during the last 15 years at least a dozen of papers on the physical properties of several thieno[3,2-*b*]- and thieno[2,3-*b*]thiophenes. All the products reported were fully described and, for some of them, the way to obtain them from the unsubstituted thieno[3,2-*b*]- or thieno[2,3-*b*]thiophenes was reported [39], but the origin of the starting thienothiophenes remains unclear. Nevertheless, a preparation of 3-bromothieno[3,2-*b*]thiophene, similar to the one described by Rutherford [4], was disclosed in one of their first papers [40] dealing with conducting polymers. However, it was never clearly specified that this was the method used in the following papers.

SYNTHESIS OF ISOMER 4, THIENO[3,4-*C*]THIOPHENES

Thieno[3,4-*c*]thiophene is unique among the isomeric thienothiophenes in that it cannot be represented by a classical *Kekule* structure without invoking the presence of a tetravalent sulphur. A few stable derivatives have been prepared in the last thirty years.

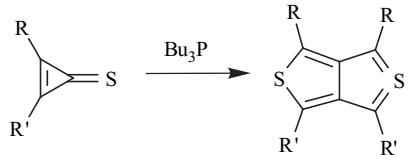
Although some unstable thieno[3,4-*c*]thiophenes were prepared and immediately trapped as cycloaddition products, the first isolable and remarkably stable tetraphenyl substituted derivative **15** was described by Cava *et al.* [41] (Scheme **19**). Similar access to other thieno[3,4-*c*]thiophenes were further described by Nakayama *et al.* [42].



15

Scheme 19.

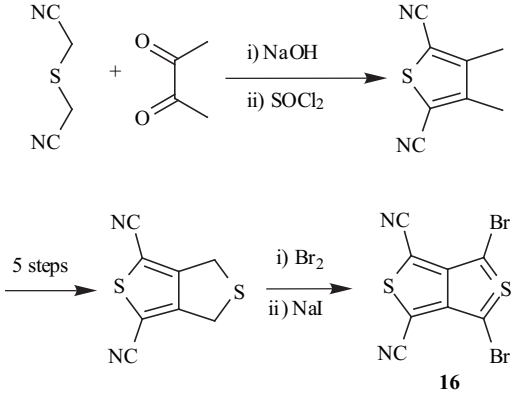
An alternative synthetic pathway, based on auto-condensation of cyclopropenethiones in the presence of tributyl phosphine, was reported sixteen years later by Yoneda *et al.* [43]. Matsumura's group [44] further extended this method to the preparation of many other derivatives and investigated the reactivity of these bicyclic compounds (Scheme **20**). It is important to notice that the stability of all these compounds is strongly related to the size of their four substituents as clearly shown by Yoneda [43].



R, R' = S- alkyl [43] or S- alkyl, aryl, hetaryl [44]

Scheme 20.

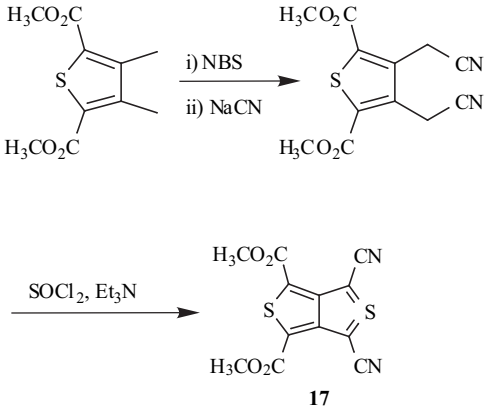
Twenty-five years after the synthesis of the first stable thieno[3,4-*c*]thiophene, Cava *et al.* reported the preparation and characterisation of the new, stable 1,3-dibromo-4,6-dicyano-thieno[3,4-*c*]thiophene **16**, which is stabilised only by electronic effects [45] (Scheme **21**).



16

Scheme 21.

The same group developed and optimised in a last and recent paper [46] a new synthetic way, also based on a final elimination step in order to aromatise the second fused ring (Scheme **22**). They reported the formation of several new thieno[3,4-*c*]thiophenes, such as compound **17**, described a few years earlier by the same authors [47]. They therefore proved that bulky substituents are not necessary to obtain isolable derivatives if electronic withdrawing groups are used instead.



17

Scheme 22.

CONCLUSION

All the thienothiophene isomers are at present well-known compounds [48] but their classical preparation methods suffered from drawbacks such as poor overall yields and multi-step procedures that limited during many years their use by material designers. According to the numerous

recent, easy to handle preparation methods and interesting properties clearly evidenced in material science, the attractivity of these bicyclic systems should increase in the near future. Their development is likely related to their use as synthetic blocks in other fields owing to their physical, chemical or biological properties.

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found that thienothiophenes merit their own updated review. Theses two references are given below.

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