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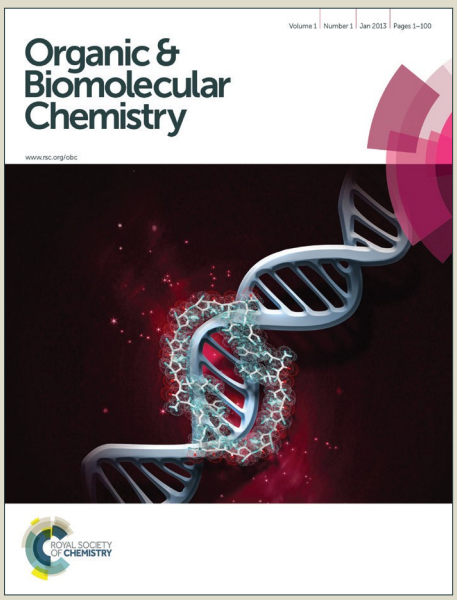

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Metal-free Brønsted acid mediated synthesis of fully substituted thiophenes via chemo- and regioselective intramolecular cyclization of α,α'-bis(β-oxodithioesters) at room temperature

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x
www.rsc.org/

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Metal-free *para*-toluenesulfonic acid mediated straightforward synthesis of hitherto unreported tetrasubstituted thiophenes has been achieved in quantitative yields by chemo- and regioselective dehydrative cyclization of α,α'-bis(β-oxodithioesters) at room temperature. Notably, the dithioester group at 4-position of thiophene ring has been further transformed to thiazoline group.

The extraordinary significance of thiophene derivatives comes not only from their widespread application in cutting edge research of biological and material science,[1] but also their irreplaceable application as potential building blocks in organic synthesis.[2] Among the numerous sulfur heterocyclic scaffolds, thiophenes and their derivatives are versatile and privileged structural motifs found in numerous natural products,[3] pharmaceuticals,[4] and functional materials.[5] Many thiophene derivatives display a broad spectrum of biological properties such as antibacterial,[6a] antifungal,[6b] antiamoebic,[7] antioxidant,[8] antithrombotic[9] antitumor,[10a,b] anti-inflammatory[10c] and plaque imaging[10d] activities. Amongst several pharmacologically active thiophene-containing products, tri- and tetrasubstituted thiophene derivatives are extremely important (Fig 1).

Owing to their privileged status and great importance in biological and other relevant fields, they have drawn tremendous attention of synthetic, medicinal, and material chemists. Therefore, exploring the more economical and eco-efficient strategies, and improvement in the existing methods of thiophene synthesis has been recognised as a strategic issue. The most prevalent and classical methods for the synthesis of thiophene scaffolds include the Gewald,[11] Paal–Knorr[12] and Fiesselmann[13] syntheses. Literature survey shows that two general approaches for the synthesis of thiophene derivatives are the direct functionalization of the thiophene ring[14] and thienannulation of suitable acyclic precursors.[15] Besides above methods, numerous synthetic routes to thiophene derivatives have also been developed.[16] Li and co-workers[17a] reported a regioselective synthesis of tetrasubstituted thiophenes by annulation of β-ketothioamides with arylglyoxals and 5,5-dimethyl-1,3-cyclohexanedione in CF_3CH_2OH. Very recently, Nishikata *et al*.[17b] synthesized tetrasubstituted thiophenes catalyzed by copper, which involves multiple steps under harsh reaction conditions. One-pot Ag-catalyzed synthesis of tetrasubstituted thiophenes was reported by Wang and co-workers.[17c] The main problem of these metal-catalyzed syntheses lies in the frequent presence of trace metal contaminant, which critically prevents from practical application especially in the field of biologically relevant investigations.

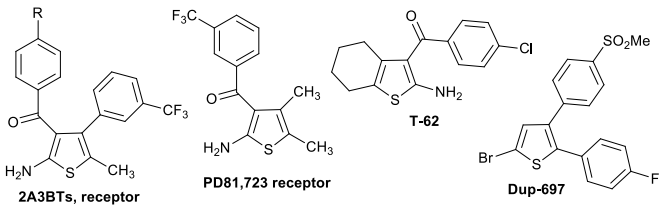

Fig. 1. Some biologically active products containing thiophene framework.

Although the reported approaches are useful tools and represent important advances toward the objective of a general and efficient method for the construction of thiophene frameworks, most of them suffer from many drawbacks with respect to their practical execution in the laboratory. Efficient and practical metal-free protocols to access tetrasubstituted thiophenes are still scarce and full of challenge. Therefore, development of efficient and viable routes for the synthesis of tetrasubstituted thiophenes is highly desirable.

In continuation of our research interests regarding the development of operationally simple and efficient methods for the synthesis of functionalized thiophenes,[18] recently, we

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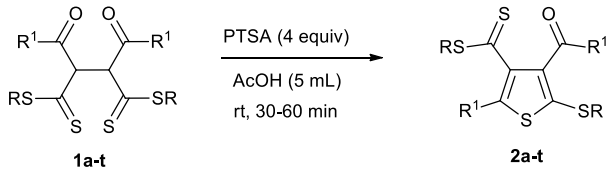
† Electronic Supplementary Information (ESI) available: [Elaborate reaction procedure, characterization data, scanned spectra of all the products]. See DOI: 10.1039/b000000x/

reported a one-pot synthesis of symmetrical thiophenes from α-enolic dithioesters promoted by *N*-chlorosuccinimide (NCS).[18d] Meanwhile, α-enolic dithioesters undergo NCS-mediated oxidative C–C coupling to give α,α'-bis(β-oxodithioesters), which possess multiple reactive sites and unique reactivity. We envisioned that they could be further explored as versatile intermediates for the construction of sulfur and oxygen-heterocycles.

With the aim to improve the efficiency and generality of our previous method for the synthesis of thiophenes,[18d] this time we thought to treat α,α'-bis(β-oxodithioesters) at room temperature under metal-free conditions. In this context, we herein disclose a straightforward, selective, and metal-free method to access tetrasubstituted thiophenes in quantitative yields via *para*-toluenesulfonic acid (PTSA) mediated intramolecular ring closure of α,α'-bis(β-oxodithioesters) at room temperature (Scheme 1).

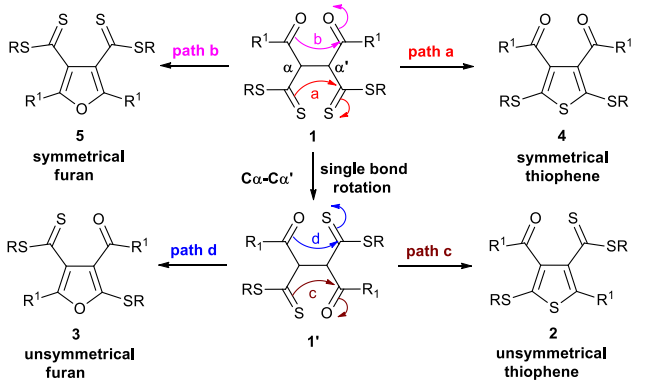


1a-t **2a-t**

1a: R=Me, R^1=C_6H_5; **1b**: R=Et, R^1=C_6H_5; **1c**: R=CH_2Ph, R^1=C_6H_5;
1d: R=Et, R^1=3-MeC_6H_4; **1e**: R=Et, R^1=3-MeOC_6H_4;
1f: R=Et, R^1=4-MeOC_6H_4; **1g**: R=Et, R^1=3,4-$OCH_2OC_6H_3$;
1h: R=Et, R^1=4-FC_6H_4; **1i**: R=Et, R^1=4-ClC_6H_4; **1j**: R=*n*-Pr, R^1=3-BrC_6H_4;
1k: R=Et, R^1=biphenyl; **1l**: R=Et, R^1=1-naphthyl; **1m**: R=Et, R^1=2-naphthyl;
1n: R=*n*-Bu, R^1=2-naphthyl; **1o**: R=Et, R^1=2-thienyl; **1p**: R=Et, R^1=2-furyl;
1q: R=*n*-Pent, R^1=2-furyl; **1r**: R=Et, R^1=cyclopropyl;
1s: R=1-butenyl, R^1=3-BrC_6H_4; **1t**: R=1-pentenyl, R^1=2-naphthyl

Scheme 1. Synthesis of structurally diverse thiophenes **2**.

The synthesis of tetrasubstituted thiophenes is known to be a challenge owing to steric hindrance from substituents. The tandem process involves *in situ* C–C single bond rotation followed by selective intramolecular cyclization of α,α'-bis(β-oxodithioesters) **1** at room temperature. This protocol represents an efficient and straightforward method for the construction of structurally diverse tetrasubstituted thiophenes under mild reaction conditions. Given the multiple reactive sites of α,α'-bis(β-oxodithioesters) **1** and their propensity to engage in various ways of reactions, it was of interest to determine if the **1** could be utilized to access furan/thiophene derivatives. In this context, four directions of the reaction could occur, which are outlined in Scheme 2. The bifunctional molecule **1** could probably undergo chemo- and regioselective intramolecular S-cyclization or O-cyclization employing thiocarbonyl and carbonyl moiety *via* path a or path b to give symmetrical thiophenes **4** or symmetrical furans **5**, respectively. Our previous studies suggested that **1** may undergo C_α–$C_{\alpha'}$ single bond rotation to give rotamer **1'**, which could further undergo chemo- and regioselective intramolecular S-cyclization or O-cyclization via path c or path d to give unsymmetrical thiophenes **2** or unsymmetrical furans **3**, respectively.



Scheme 2. Plausible reaction scenario of α,α'-bis(β-oxodithioester) **1**.

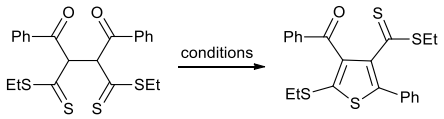
To test the above assumption, we stirred the solution of dithioester **1b** (1.0 mmol) in 5 mL of glacial acetic acid at room temperature. No cyclization occurred and the substrate **1b** remained completely unconsumed even after 24 h of stirring (Table 1, entry 1). Then, we increased the temperature of the reaction. At 50 °C after 24 h only a trace of the desired thiophene was observed and at 80 °C the substrate **1b** was consumed completely within 5 h affording the product **2b** in 30% yield (Table 1, entries 2 and 3). The product **2b** was characterised as tetrasubstituted unsymmetrical thiophene by satisfactory spectral (^{1}H and ^{13}C NMR, and HRMS) studies. Surprisingly, under the reaction conditions the formation of other expected furan derivatives **3** and **5** were not observed even in a trace demonstrating the high chemo- and site-selectivity of the protocol.

Encouraged by the above result, we focused on exploring the optimal reaction conditions for the synthesis of tetrasubstituted unsymmetrical thiophene **2b**. To improve the efficiency of this protocol, the reaction was optimized under varying conditions using dithioester **1b** as a model substrate and the results are listed in Table 1. From our previous experiences, we assumed that use of Brønsted acid may promote the intramolecular cyclization. Next, we performed the above model reaction in the presence of cheap and readily available *para*-toluenesulfonic acid (PTSA, 1.0 equiv) at room temperature. To our great pleasure, the desired product **2b** was obtained in 90% yield in 15 h (Table 1, entry 4). Further, to reduce the reaction time and to make the process more practical higher percentage loadings of PTSA were investigated (Table 1, entries 5-7). To our great satisfaction, increasing the amount of PTSA from 1.0 equiv to 4.0 equiv not only reduced the time of completion of the reaction significantly from 15 h to 30 min, but also improved the yield from 90 to 98% (Table 1, entry 7).

Next, in order to ascertain the effectiveness and practicability of other solvents on the reaction, solvents like EtOH, DMSO, THF, DCM and toluene were investigated (Table 1, entries 8-12). It was observed that all the above solvents led to lower yields and prolonged reaction times. Obviously, AcOH turned out to be a solvent of choice as it not only provided quantitative yield, but also reduced the reaction time significantly. The use of water as a solvent shut down the

reaction and starting substrate **1b** was recovered as such because of its poor ability to dissolve the substrate (Table 1, entry 13). Since the reaction is nicely promoted by Brønsted acids such as PTSA and CSA (Table 1, entry 14), we intended to employ Lewis acids in the reaction to make it more general. Lewis acids such as $FeCl_3$, $InCl_3$ and $AlCl_3$ promoted the reaction well and the starting substrate **1b** was consumed completely within 1 h at room temperature. But workup of the reaction furnished symmetrical thiophene **4**[18d] as major product, while our desired unsymmetrical thiophene **2b** was obtained in poor yield (Table 1, entries 15-17). Consequently, the optimum reaction condition for the synthesis of **2b** was achieved by employing **1b** (1.0 mmol), PTSA (4.0 equiv) in 5 mL of glacial acetic acid at room temperature in an open flask (Table 1, entry 7).

Table 1. Optimization of reaction conditions for the synthesis of **2b**[a]



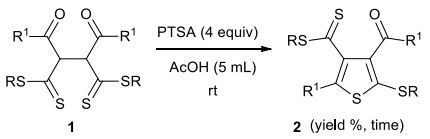
1b **2b**

entry	acid (equiv)	solvent (5 mL)	temp (^oC)	time (h)	yield[b] **2b** (%)
1	none	AcOH	25	24	-[c]
2	none	AcOH	50	24	trace
3	none	AcOH	80	5	30
4	PTSA (1)	AcOH	25	15	90
5	PTSA (2)	AcOH	25	5	95
6	PTSA (3)	AcOH	25	2	95
7	PTSA (4)	AcOH	25	0.5	98
8	PTSA (4)	EtOH	25	24	22
9	PTSA (4)	DMSO	25	24	20
10	PTSA (4)	THF	25	24	23
11	PTSA (4)	DCM	25	12	76
12	PTSA (4)	toluene	25	24	25
13	PTSA (4)	H_2O	25	24	-[c]
14	CSA (4)	AcOH	25	8	88
15	$FeCl_3$ (4)	AcOH	25	1	20[d]
16	$InCl_3$ (4)	AcOH	25	1	20[d]
17	$AlCl_3$ (4)	AcOH	25	1	14[d]

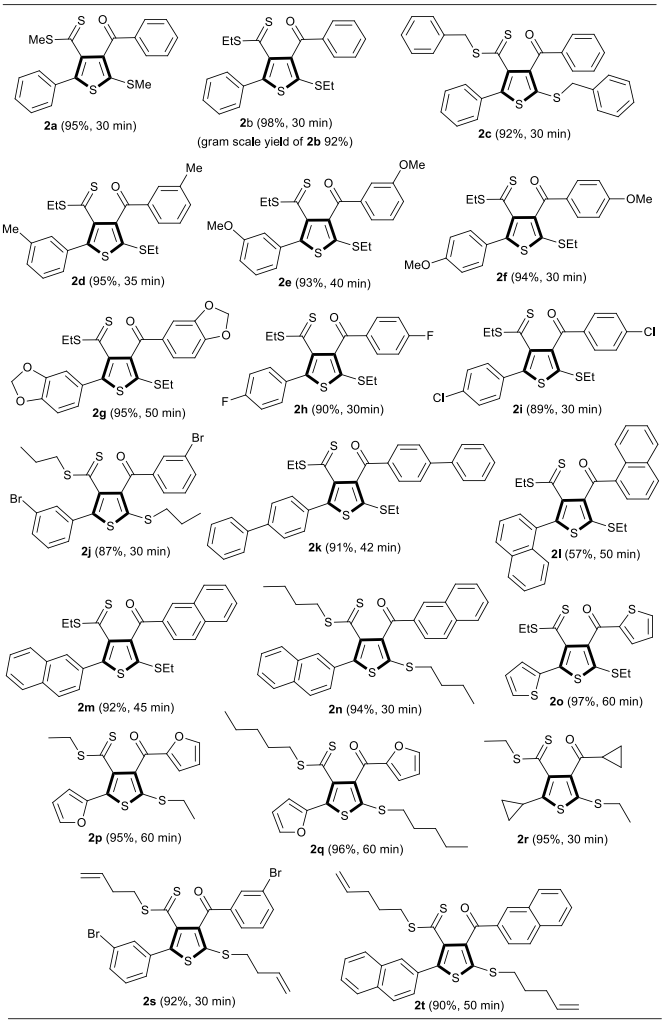
[a]All reactions were performed using 1.0 mmol of **1b**. [b]Isolated yield. [c]No reaction and **1b** was recovered as such. [d]Formation of symmetrical thiophene **4** as major product.

With the optimal reaction conditions in hand, we commenced exploring the generality and substrate scope of the protocol. The results are summarized in Table 2. A wide range of α,α'-bis(β-oxodithioesters) **1a**-**t** with various substitution patterns at R (different alkyl groups) and R^1 (aromatic, extended aromatic, heteroaromatic and aliphatic groups) were well-tolerated, and in all cases the reactions proceeded smoothly affording the corresponding thiophenes in almost quantitative yields (Table 2, **2a**-**t**). Substituents at both *meta*- and *para*-positions of the phenyl ring were well tolerated, leading to the formation of the corresponding thiophenes in excellent yields (Table 2, **2d**-**j**). Halide substituents such as F, Cl, and Br on the aromatic rings were well-accepted in the reaction providing the possibility of further functionalization of the thiophenes (Table 2, **2h-j**, **2s**). α,α'-Bis(β-oxodithioesters) incorporating extended aromatics like biphenyl and naphthyl substituents were also suitable for the reaction and furnished the corresponding thiophenes in excellent yields (Table 2, **2k**, **2m**, **2n**, **2t**). However, in case of 1-naphthyl as R^1 substituent, the desired product (Table 2, **2l**) was obtained in 57% yield that may be due to steric crowding. Further, α,α'-bis(β-oxodithioesters) **1** bearing heterocyclic substituents such as 2-thienyl and 2-furyl groups at R^1 were used to explore the scope of this reaction. Notably, heteroaryl-based α,α'-bis(β-oxodithioesters) **1o**-**q** reacted smoothly leading to the formation of corresponding thiophenes in 95-97% yields (Table 2, **2o-q**). Moreover, the method is also amenable to α,α'-bis(β-oxodithioesters) **1r** with a aliphatic cyclopropyl group at R^1 and afforded the corresponding unsymmetrical thiophene **2r** in quantitative yield (95%).

Table 2. Substrate scope for the synthesis of tetrasubstituted thiophenes **2**.

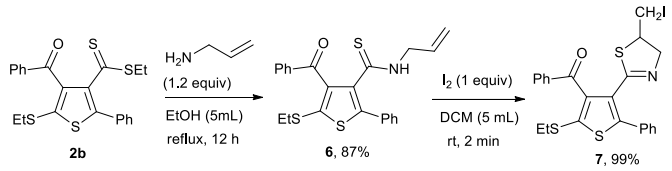


1 **2** (yield %, time)



To illustrate the broad synthetic utility and generality of our cascade protocol, we further extended the scope of the reaction with respect to substituent R of α,α'-bis(β-oxodithioesters) **1**. Various homologous alkyl groups such as methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, and benzyl groups were employed well under the optimal reaction conditions to afford the corresponding thiophenes in excellent yields (Table 2, **2a**-**r**). Next we sought to extend the generality of this protocol employing α,α'-bis(β-oxodithioesters) bearing R substituent as terminal alkene groups. Nowadays, terminal alkene groups are very much attractive in organic synthesis to perform various modifications through C–H activation *via* Heck and Fujiwara-Moritani couplings.[19] Notably, α,α'-bis(β-oxodithioesters) bearing R as long chain terminal alkene groups such as butenyl **1s** and pentenyl **1t** were also compatible with the optimal reaction conditions and afforded the corresponding thiophenes in 90-92% yields (Table 2, **2s**, **2t**).

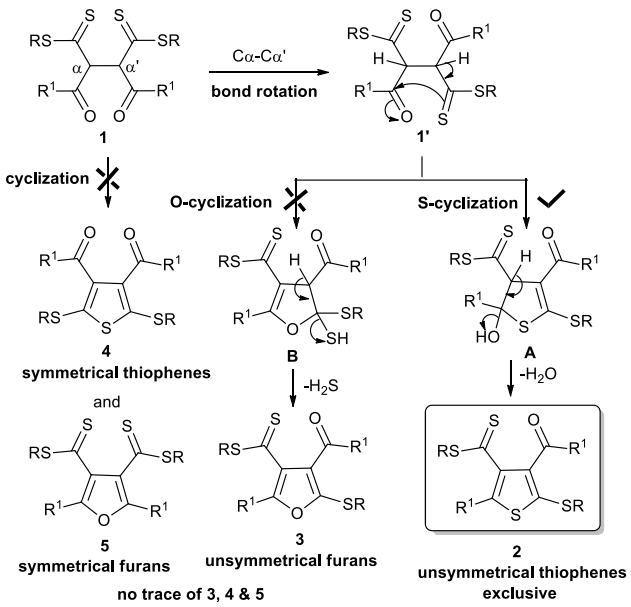
In order to improve the molecular diversity of our system, we thought to investigate the possibility of additional functionalization of the substituent present on the thiophene ring. Thiazoles and thiazolines are widely present as core skeleton in various natural products and show a wide range of potential medicinal applications.[21] The dithioester group (CS_2R) at 4-position of thiophene **2b** was transformed to thiazoline ring in quantitative yield. Inspired by the challenging molecular architecture of thiophene **2**, we treated **2b** with allyl amine (1.2 equiv) in 5 mL of EtOH at 80 °C. Workup of the reaction afforded the corresponding *N*-allylthioamide derivative **6** in 87% yield. Subsequently, compound **6** was treated with I_2 in DCM at room temperature, which undergoes iodoelectrophilic cyclization to form thiophene derivative **7** in 99% yield within 2 min (Scheme 3). Thiophene **7** having iodomethyl substituted thiazoline group could be further functionalised by standard coupling techniques to useful molecules.



Scheme 3. Functionalization of dithioester group at position-4 of thiophene **2b**.

The structures of all the synthesized thiophenes **2a-t** are confirmed by their satisfactory spectral (^{1}H and ^{13}C NMR, and HRMS) studies, and unequivocally confirmed by a single crystal X-ray diffraction analysis of one of the representative thiophene **2f** (see SI).[20] The chemistry is amenable to both small and gram-scale reactions. To demonstrate the usefulness of this protocol, a gram-scale experiment (**1b** 5 mol, 2.223 g) was carried out under the standard reaction conditions. The reaction proceeded smoothly providing 1.971 g (92%) of our desired thiophene **2b**, which is comparable to the small scale experiment shown in Table 2.

Based on literature report and our experimental observations, a tentative mechanism for the formation of tetrasubstituted unsymmetrical thiophenes **2** is outlined in Scheme 4. First, the α,α'-bis(β-oxodithioester) **1** undergoes C_α–$C_{\alpha'}$ single bond rotation to give rotamer **1'**. The intermediate **1'** in the presence of PTSA may undergo intramolecular thiacyclization and/or oxacyclization *via* intermediates **A** or **B** to furnish unsymmetrical thiophene **2** and/or unsymmetrical furan **3**, respectively. α,α'-Bis(β-oxodithioester) **1** may also undergo intramolecular S-cyclization and/or O-cyclization to give symmetrical thiophene **4** and/or symmetrical furan **5**, respectively. During our optimized reaction conditions, we did not observe a trace of **3**, **4** and **5**, and unsymmetrical thiophene **2** was obtained exclusively. Although the elimination of H_2S gas is thermodynamically more favourable than the release of H_2O, but under the acidic reaction conditions the release of H_2O is favoured process. It should be noted that S-cyclization of intermediate **1'** is more favourable than O-cyclization under the reaction conditions making the protocol chemoselective and regioselective.



Scheme 4. Tentative mechanism for the formation of thiophenes **2**.

In conclusion, we have developed a straightforward, operationally simple and efficient method for the synthesis of tetrasubstituted thiophenes in quantitative yields by intramolecular cyclization of α,α'-bis(β-oxodithioesters) at room temperature. The procedure can be considered as an ideal means to access tetrasubstituted thiophenes because of the following features: (1) the rapid production of thiophenes by intramolecular regio- and chemoselective cyclization mediated by cheap Brønsted acid PTSA; (2) no need of any metal catalyst or other additives; (3) high atom-economy since only one molecule of water is lost; (4) wide substrate scope and reliable scalability. These advantages make this process suitable for the synthesis of diverse tetrasubstituted thiophenes, which is known to be a challenge due to the steric crowding of the substituents.

We gratefully acknowledge the financial support from the Science and Engineering Research Board (SB/S1/OC-30/2013), New Delhi, India and the Council of Scientific and Industrial Research (02(0072)/12/EMR-II), New Delhi, India.

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Table of Content

Cα-Cα' rotation followed by cyclization at room temperature

20 examples
yield up to 98%

 # Metal-free mild conditions
 # Highly chemo- and regioselective
 # Excellent FGs tolerance # 100% Carbon-economy
 # H_2O only as by product # Scalable

Metal-Free Brønsted acid mediated synthesis of tetrasubstituted thiophenes via intramolecular cyclization of α,α'-bis(β-oxodithioesters) is devised at room temperature.