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GENERAL SYNTHESIS OF 2,5-DIHYDROTHIOPHENES (3-THIOLENES) FROM DIKETO SULFIDES

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Abstract: The intramolecular reductive coupling reaction of easily accessible diketo sulfides by a low-valent titanium reagent [prepared from titanium(IV) chloride and zinc powder] provides an efficient general synthesis of 2,5-dihydrothiophenes.

2,5-Dihydrothiophenes are synthetically important compounds and many methods have been devised to prepare this heterocycle.[1] Diketo sulfides are easily accessible compounds in which three functional groups [carbonyl, active methylene (methyne), and sulfide moieties] are suitably arranged for various intra- and intermolecular chemical transformations. However, syntheses with these compounds have not been fully explored. As a part of our synthetic study with diketo sulfides, herein we report a general synthesis of 2,5-dihydrothiophenes from these compounds.

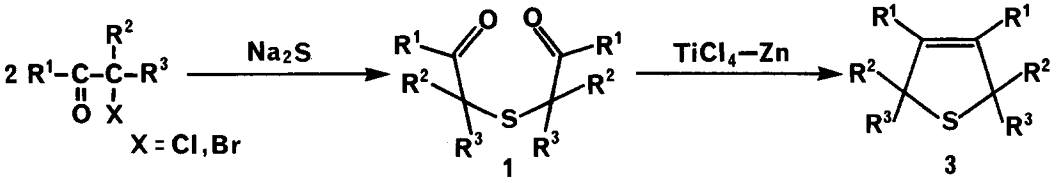


Table 1 Preparation of Symmetrically Substituted 2,5-Dihydrothiophenes (3)

run	R^1	R^2	R^3	conditions (solvent, temperature, time)	yield (%)
1	C_6H_5	H	H	dioxane, 18 h at r.t.	67[a)]
2	C_6H_5	H	H	dioxane, 4 h at r.t. and then 2 h at 50 °C	62
3	C_6H_5	H	H	THF, reflux, 5 h	77
4	2-naphthyl	H	H	as above	71
5	C_6H_5	CH_3	H	as above	73[a,b)]
6	C_6H_5	C_2H_5	H	as above	86[b)]
7	2-thienyl	H	H	dioxane, 4 h at r.t. and then 2 h at 50 °C	66
8	4-$CH_3C_6H_4$	H	H	as above	68[a)]
9	4-$CH_3OC_6H_4$	H	H	as above	70
10	4-BrC_6H_4	H	H	as above	68
11	C_6H_5	CH_3	CH_3	THF, reflux, 5 h	75

a) These dihydrothiophenes were converted to the corresponding thiophenes quantitatively by oxidation with DDQ in refluxing dioxane. b) The use of the pure meso-sulfides provides *cis*-2,5-dialkyl-3,4-diphenyl-2,5-dihydrothiophenes, exclusively.

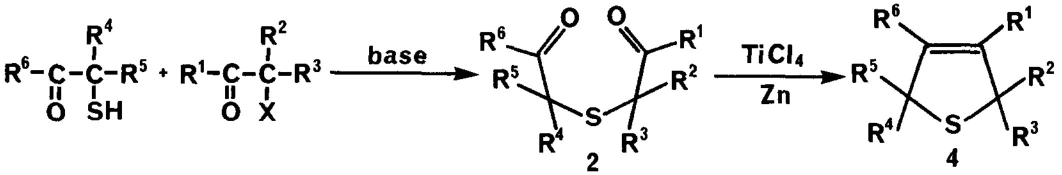
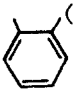


Table 2 Preparation of Unsymmetrically Substituted 2,5-Dihydrothiophenes (**4**)

run	R^1	R^2	R^3	R^4	R^5	R^6	yield (%) of **4**[a)]
1	C_6H_5	H	H	H	CH_3	CH_3	82
2	C_6H_5	H	H	CH_3	CH_3	CH_3	81
3	C_6H_5	C_6H_5	H	H	CH_3	CH_3	76[b,c)]
4	C_6H_5	CH_3	H	H	CH_3	CH_3	63[b)]
5	 $(CH_2)_2$-		H	H	CH_3	CH_3	44[b,d)]

a) THF was used as the solvent. b) The starting diketo sulfides are mixtures of erythro- and threo-isomers and therefore the resulting 2,5-disubstituted-2,5-dihydrothiophenes are mixtures of cis- and trans-isomers. c) Oxidation of this compound with DDQ affords 2,3-dimethyl-4,5-diphenylthiophene. d) Oxidation of this compound by DDQ (2 mol. equiv) leads to 1,2-dimethylnaphtho[2,1-*b*]thiophene.

Symmetrically substituted diketo sulfides (**1**) are readily prepared in high yields by reaction of α-haloketones with sodium sulfide. Unsymmetrically substituted diketo sulfides (**2**) are obtained in excellent yields by reaction of α-haloketones with α-mercaptoketones. We now found that a low-valent titanium reagent, prepared from titanium(IV) chloride and zinc powder in situ,[2] brings about the intramolecular coupling reaction of **1** and **2** to provide an efficient synthesis of 2,5-dihydrothiophenes (**3** and **4**).

Tables 1 and 2 summarize preparation of symmetrically substituted 2,5-dihydrothiophenes **3** from **1** and unsymmetrically substituted 2,5-dihydrothiophenes **4** from **2**, respectively. These results show that the reaction is general and especially useful for the preparation of highly substituted 2,5-dihydrothiophenes which are otherwise difficult to prepare. Neither products arising from an intermolecular coupling reaction nor isomeric 2,3-dihydrothiophenes were formed.[3,4]

References and Notes

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2. T. Mukaiyama, T. Sato, and J. Hanna, Chem. Lett., 1041 (1973).
3. Some by-products were occasionally isolated in low yields; for example, in run 3 in Table 1, 2,3-diphenyl-1,3-butadiene (trace), 3,4-diphenylthiophene (11%), and 3,4-dihydroxy-3,4-diphenylthiolane (trace) were isolated.
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