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HETEROCYCLES IN FOCUS

1,4-Dithiane-2,5-diol in the synthesis of thiophenes (microreview)

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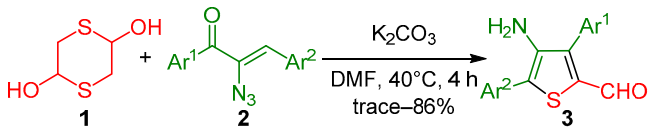
This microreview provides insight on the selected methods of thiophene synthesis starting from 1,4-dithiane-2,5-diol including K_2CO_3- and DABCO-catalyzed reactions, cyclopropane-based reactions, heterocyclization of alkynones, tandem Michael – intramolecular Henry reaction, Gewald reaction and thiophene ring construction as a part of fused and polycyclic structures. Microreview covers literature from 2010 to 2017.

Introduction

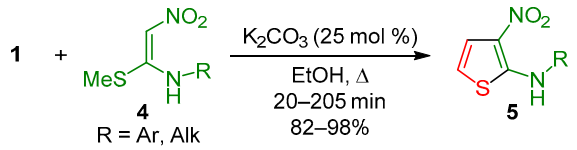
Thiophene and its derivatives have attracted attention due to their wide pharmaceutical and biological activities such as antioxidant, antimicrobial, antihypertensive, antiosteoporosis, anti-inflammatory, antipsychotic, and anticonvulsant.[1] They can also act as HIV inhibitors, glucosidase inhibitors, potential JNK2 and JNK3 kinase inhibitors, adenosine agonists, and mimics of penicillins.[2] Additionally, these heterocycles were reported as key building blocks of compounds with photochromic properties.[3] Therefore, numerous efficient routes have been introduced for the synthesis of thiophene derivatives. Among these methods, the use of 1,4-dithiane-2,5-diol as sulfanylacetaldehyde synthon has received extensive attention.

K_2CO_3-catalyzed reactions

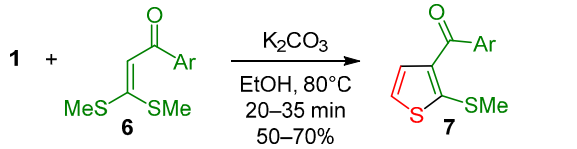
The reaction between 1,4-dithiane-2,5-diol (**1**) and α-azido vinyl ketones **2** catalyzed by K_2CO_3 in DMF gave 3,5-disubstituted 4-aminothiophene-2-carbaldehydes **3** in moderate to high yields.[4]



Kumar et al. described the synthesis of 3-nitrothiophen-2-amines **5** *via* the reaction of 1,4-dithiane-2,5-diol (**1**) and 1-(methylsulfanyl)-2-nitroethenamines **4** in the presence of K_2CO_3 in refluxing EtOH.[5]



Kumara et al. reported another K_2CO_3-catalyzed reaction of compound **1** and α-oxoketene dithioacetals **6** in boiling EtOH for the preparation of 2-(methylsulfanyl)thiophenes **7** in moderate to good yields.[6]



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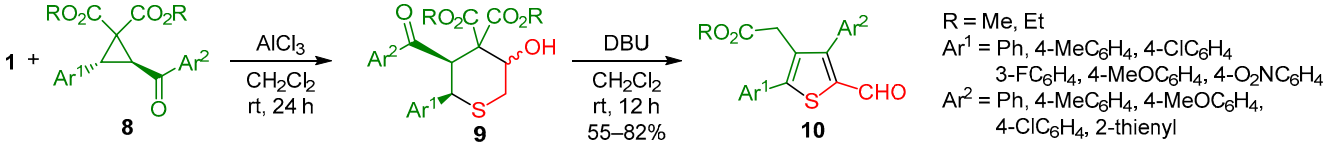
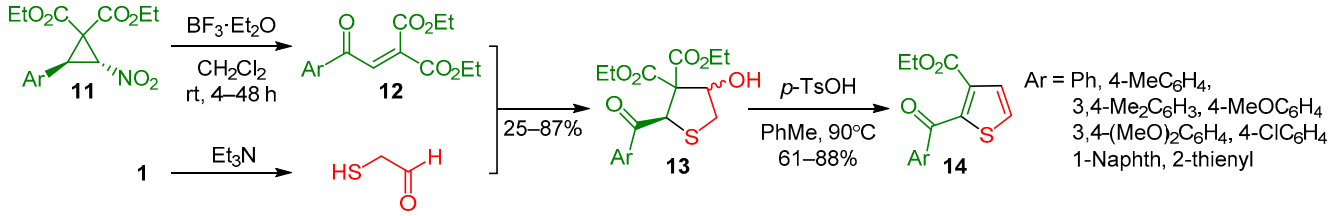
Cyclopropane-based reactions

An efficient two-step method was developed for the synthesis of tetrasubstituted thiophenes **10** in the reaction of 1,4-dithiane-2,5-diol (**1**) with *trans*-2-aroyl-3-arylcyclopropane-1,1-dicarboxylates **8**. It involves the [3+3] annulation of cyclopropane **8** with *in situ* generated sulfanylacetaldehyde in the presence of $AlCl_3$, followed by DBU-induced rearrangement of the resulting tetrahydrothiopyranol **9**, producing final products **10**.[7]

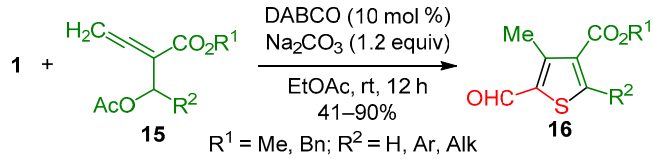


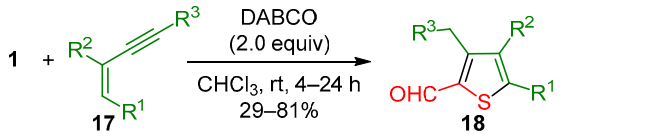
Selvi et al. reported one-pot sequential synthesis of disubstituted thiophenes **14**. First, nitrocyclopropanedicarboxylate **11** is treated with $BF_3{\cdot}Et_2O$ resulting in aroylmethylidene malonate **12**. Next, the mixture of 1,4-dithiane-2,5-diol **1** and triethylamine (to generate sulfanylacetaldehyde *in situ*) is added to compound **12** to give tetrahydrothiophenes **13**, which are converted to thiophenes **14** in the presence of *p*-toluenesulfonic acid in satisfactory yields.[8]



DABCO-catalyzed reactions

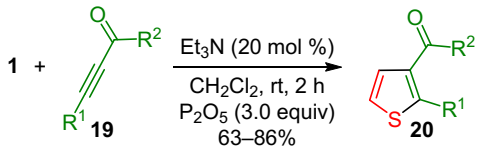
The [3+2] annulations and aromatization sequence between 1,4-dithiane-2,5-diol (**1**) and β'-acetoxy allenoates **15** in the presence of DABCO and Na_2CO_3 gave highly functionalized thiophene-2-carbaldehydes **16**.[9] Another effective route for the synthesis of tetrasubstituted thiophenes **18** was developed in 2016 *via* DABCO-catalyzed reaction of 1,3-enynes **17** and 1,4-dithiane-2,5-diol (**1**) at room temperature.[10]





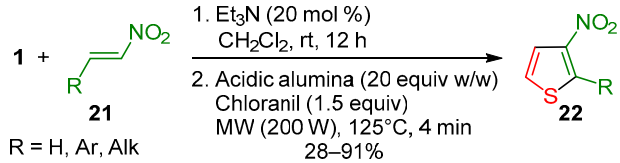
Heterocyclization of alkynones

Shi et al. developed an efficient strategy for the preparation of 2-substituted thiophene-3-carbaldehydes **20** (R^2 = H) through [3+2] cycloaddition of compound **1** and ynals **19** (R^2 = H).[11] In a different recently reported method, 2,3-disubstituted thiophene derivatives **20** were synthesized *via* the reaction of similar starting materials in DMF in the presence of Et_3N followed by treatment with silica gel or HCl in 70–91% overall yields.[12]



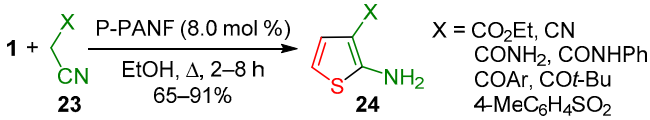
Tandem Michael – intramolecular Henry reaction

Recently, Southern et al. described a new approach for the construction of 2-substituted 3-nitrothiophenes **22** by the reaction of 1,4-dithiane-2,5-diol (**1**) and nitroalkenes **21**. First, in the presence of Et_3N as a result of tandem Michael – intramolecular Henry reaction, tetrahydrothiophene is formed. Subsequent microwave irradiation under solvent-free conditions gives the desired 3-nitrothiophenes **22**.[13]



Gewald reaction

The Gewald reaction between 1,4-dithiane-2,5-diol (**1**) and activated nitriles **23** was recently carried out using a reusable fiber catalyst (P-PANF) in refluxing EtOH to produce 2-aminothiophenes **24** in good to excellent yields.[14]



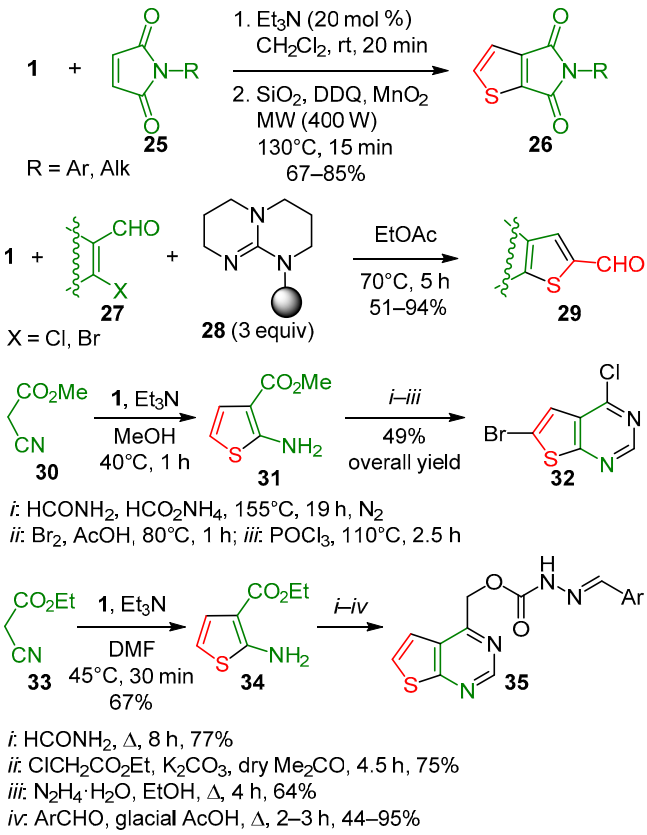
Fused and polycyclic structures

One-pot [3+2] annulation reaction of 1,4-dithiane-2,5-diol (**1**) and *N*-substituted 1*H*-pyrrole-2,5-diones **25** gave a series of 2,3-thienoimides **26**. The reaction was performed in the presence of Et_3N followed by a subsequent dehydration and aromatization.[15]

Novel type of polycyclic thiophene-2-carbaldehydes **29** was synthesized *via* a metal-free cascade reaction of compound **1** and cyclic β-halo-α,β-unsaturated aldehydes **27** using a polymer-supported organic base **28** in EtOAc at 70°C. Base **28** was recycled up to 4 times without significant yield decrease.[16]

Bugge et al. demonstrated a practical and scalable four-step synthesis of 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine **32** in 49% overall yield. The reaction steps include Gewald reaction giving thiophene **31**, then pyrimidone formation, bromination, and chlorination.[17]

Rashmi et al. reported a multistep method for transformation of the Gewald reaction product thiophene **34** to 5,6-unsubstituted thieno[2,3-*d*]pyrimidines **35** in good yields. The obtained products **35** were tested for growth inhibition of *Mycobacterium tuberculosis* H37Rv, showing good antimycobacterial activity.[18]



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