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Regioselective Synthesis of Dihydrothiophene and Thiopyran Frameworks via Catalyst-Controlled Intramolecular C_γ/C_δ–S Fusion of α-Allyl-β'-oxodithioesters

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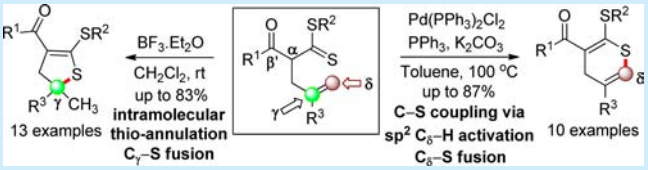
Supporting Information

ABSTRACT: A highly efficient and atom-economic dual reaction manifold has been developed to synthesize 4*H*-thiopyran and 4,5-dihydrothiophene frameworks via regioselective intramolecular C–S fusion of α-allyl-β'-oxodithioesters. The ring size of the sulfur-heterocycles has been efficiently tuned by the use of two different catalytic systems. Palladium activates the C_δ–H of the allyl termini and facilitates the intramolecular C_δ–S coupling to furnish six-membered thiopyran skeletons exclusively. Conversely, the allylic double bond of the same substrate has been activated by $BF_3{\cdot}Et_2O$ to promote the C_γ–S cyclization leading to the formation of a five-membered dihydrothiophene nucleus.

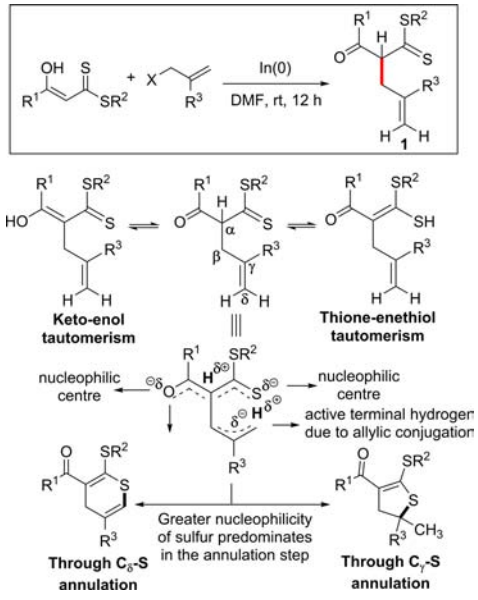


Among the sulfur containing heterocycles thiophene and thiopyran skeletons are the most common and represent the core structures of a wide range of natural and synthetic biological scaffolds.[1−4] Additionally, many of their derivatives also have shown tremendous potential to be utilized as functional materials in the field of applied sciences.[5−8] Therefore, the synthesis of these structural frameworks has drawn considerable attention from synthetic, medicinal, and industrial chemists. To synthesize these classes of sulfur heterocycles, the utmost challenge is to find a suitable precursor, which could be utilized or modified as per need.

For the past few years, the remarkable renovation of a simple synthon α-enolic dithioester has been achieved toward the synthesis of diverse sulfur-heterocycles.[9,10] Recently, the formation and synthetic efficiency of its β-allylated derivative have also been explored by our group.[11] Therefore, encouraged by the success of our continuous efforts, we became interested in developing the synthetic utility of its α-allylated derivatives, i.e. α-allyl-β'-oxodithioesters **1**.

The moiety α-allyl-β'-oxodithioesters **1** has been synthesized from the corresponding α-enolic dithioester by treatment with an allylindium reagent. It involves a regioselective C_{sp^3}–S cross-coupling followed by a [3,3] sigmatropic shift (Scheme 1).[12] Notably, the α-allyl-β'-oxodithioester skeleton **1** contains an α-allylic substitution flanked by carbonyl and thiocarbonyl groups on its two sides, which makes the α-hydrogen of **1** sufficiently labile to undergo keto−enol or thione−enethiol tautomerism (Scheme 1). It indeed increases the charge density of sulfur and oxygen centers and in turn promotes their nucleophilic character. In addition to that, the allylic conjugation into the molecule assists the respective allylic hydrogens to be prone toward C–H activation. Thus, both factors indicate the possibility of α-allyl-β'-oxodithioester **1** to be utilized as an ideal precursor in the construction of five-/six-membered heterocycles.

Scheme 1. Synthesis and Reactive Sites of α-Allyl-β'-oxodithioesters 1



Based on the preliminary idea about various reactive sites of **1**, we started our synthetic investigation utilizing α-allyl-β'-oxodithioester **1** as the starting substrate. Treatment of the solution of **1** in toluene with $Pd(PPh_3)_2Cl_2$ in the presence of PPh_3 ligand and K_2CO_3 facilitated an intramolecular regioselective C_δ–S coupling of **1** which led to the exclusive formation of 4*H*-thiopyrans **2** (Scheme 2).

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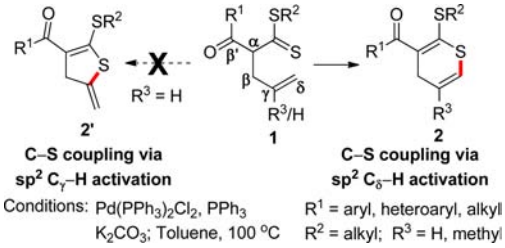
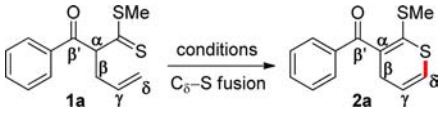
Scheme 2. Regioselective Synthesis of 4*H*-Thiopyrans 2 via Intramolecular C_δ–S Coupling of 1



Initially, we treated a solution of methyl-2-benzoyl-pent-4-enedithioate **1a** (1.0 mmol in 10 mL DMF) with 5 mol % of $Pd(PPh_3)_4$, and the reaction mixture was heated at 100 °C. Unfortunately, it led to a mixture of several overlapping spots after 12 h of heating (Table 1, entry 1). Upon repeating the reaction in toluene, the intramolecular C_δ–S coupling of **1a** was achieved via allylic sp^2 C_δ–H activation leading to the formation of 3-benzoyl-2-(methylthio)-4*H*-thiopyran **2a** in 75% yield (Table 1, entry 2). A further change of the solvent to DCE did not produce a better result (Table 1, entry 3). Subsequently, $Pd(OAc)_2$ and $Pd(PPh_3)_2Cl_2$ individually were tried to check the possibility of Pd(II) catalyzing the reaction, but they did not lead to any product even after 24 h of heating (Table 1, entries 4 and 5). Therefore, we decided to use a ligand and base with Pd(II) to generate Pd(0) in situ that could lead to the formation of the desired product. To our satisfaction, the use of ligand PPh_3 (20 mol %) and base K_2CO_3 (1.0 equiv) with $Pd(OAc)_2$ increased the yield of the desired product **2a** up to 78% (Table 1, entry 6). The change of the catalyst to $Pd(PPh_3)_2Cl_2$ provided us the best result with an 87% yield of the desired thiopyran **2a** (Table 1, entry 7). Further, the catalytic ability of $Ru(PPh_3)_3Cl_2$ and $Rh(PPh_3)_3Cl$ were also evaluated in this case, but they could not trigger the reaction even after 24 h (Table 1, entries 8 and 9). Performing the reaction with PPh_3 in the absence of a Pd catalyst did not result in the formation of the desired product even after 24 h of heating (Table 1, entry 10). In the absence of any catalyst the same scenario was observed (Table 1, entry 11). Finally, the catalyst loading was optimized and 5 mol % of $Pd(PPh_3)_2Cl_2$ was found to be the optimum loading for the reaction (for details see Supporting Information (SI)). Thus, 5 mol % of $Pd(PPh_3)_2Cl_2$ with 20 mol % of PPh_3 and 1.0 equiv of K_2CO_3 were found to be optimal for the C_δ–S coupling protocol.

Table 1. Optimization of the C_δ–S Coupling Protocol[a]

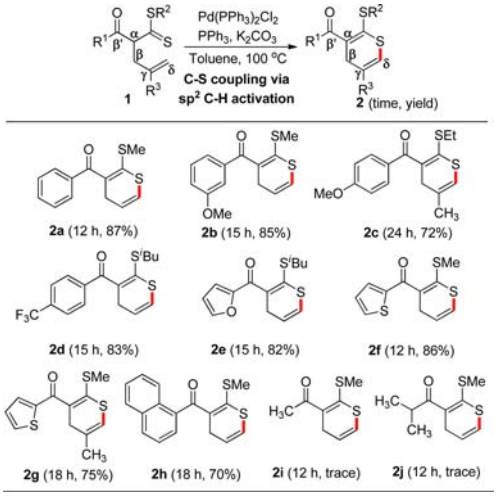


entry	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Pd(PPh_3)_4$ (5)	DMF	100	12	–[c]
2	$Pd(PPh_3)_4$ (5)	toluene	100	12	75
3	$Pd(PPh_3)_4$ (5)	DCE	reflux	12	20
4	$Pd(OAc)_2$ (5)	toluene	100	24	–[d]
5	$Pd(PPh_3)_2Cl_2$ (5)	toluene	100	24	–[d]
6	$Pd(OAc)_2$ (5), PPh_3 (20) and K_2CO_3[e]	toluene	100	12	78
7	**$Pd(PPh_3)_2Cl_2$ (5), PPh_3 (20) and K_2CO_3**[e]	toluene	100	12	87
8	$Ru(PPh_3)_3Cl_2$ (5)	toluene	100	24	–[d]
9	$Rh(PPh_3)_3Cl$ (5)	toluene	100	24	–[d]
10	PPh_3 (50)	toluene	100	24	–[d]
11	none	toluene	100	24	–[d]

[a]Reaction of methyl-2-benzoyl-pent-4-enedithioate **1a** (1.0 mmol) under different conditions. [b]Isolated pure yields. [c]Complex TLC pattern with a mixture of several overlapping spots. [d]No reaction. [e]1.0 mmol of K_2CO_3 was used.

Using the optimized reaction conditions, we evaluated the substrate scope of the protocol, and the results are summarized in Scheme 3. A number of α-allyl-β'-oxodithioesters were well-tolerated under the optimized conditions to furnish the corresponding 4*H*-thiopyrans in good to excellent yields. In the case of α-allyl-β'-oxodithioesters **1** with substituted allylic groups, the reaction required a comparatively longer time with a decreased yield of the corresponding products (Scheme 3, entries **2c** and **2g**). The α-allyl-β'-oxodithioester with methyl and isopropyl groups at R^1 (Scheme 3, entries **2i** and **2j**) gave a mixture of spots in TLC with a trace amount of desired products probably due to the decomposition of the corresponding starting synthon during the prolonged heating.

Scheme 3. Substrate Scope of the C_δ–S Coupling Protocol for the Synthesis of 2



Next, we directed our attention toward the preparation of five-membered heterocycles. Realizing that the coupling approach is not useful in this perspective, we applied an intramolecular nucleophilic attack strategy to prepare the five-membered skeleton. We postulated that if the allylic double bond can be activated by making it electron deficient, a C_γ–X (X = O, S) annulation of the precursor **1** can be achieved via an intramolecular nucleophilic attack of X to the allylic double bond. Therefore, we treated α-allyl-β'-oxodithioesters **1** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at rt leading to the C_γ–S annulation to furnish 4,5-dihydrothiophenes **3** in moderate to excellent yields (Scheme 4).

Directed toward the activation of the allylic double bond to behave as an electrophile, we used different Lewis acids. Initially, a solution of methyl-2-benzoyl-pent-4-enedithioate **1a** (1.0 mmol in 10 mL dry CH_2Cl_2) was treated with 0.5 equiv of $BF_3{\cdot}Et_2O$ and the mixture was stirred for 12 h until the full consumption of starting material. To our delight, it resulted in the C_γ–S annulation of **1a** leading to the formation of 3-benzoyl-5-methyl-2-methylthio-4,5-dihydrothiophene **3a** in 83% yield (Table 2, entry 1). To check the solvent effect on the reaction,[11b]

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Scheme 4. Regioselective Synthesis of 4,5-Dihydrothiophene 3 via Intramolecular C_γ–S Annulation of 1

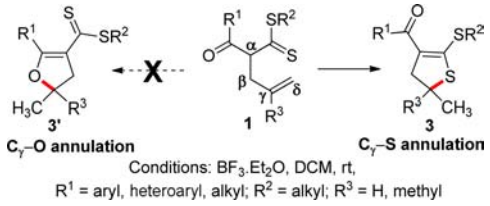
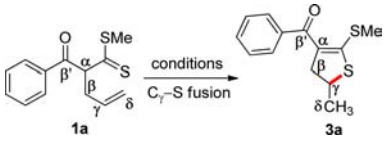


Table 2. Optimization of Intramolecular C_γ–S Annulation Reaction[a]



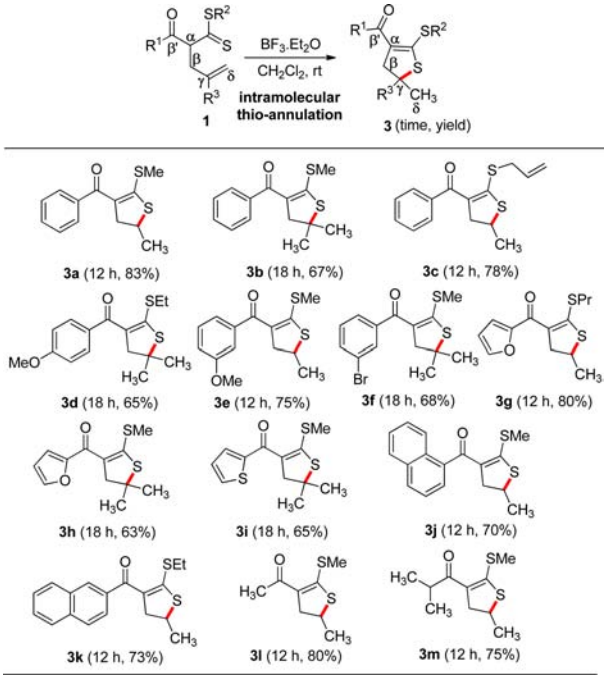
entry	catalyst	loading (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	$BF_3{\cdot}Et_2O$	0.5	CH_2Cl_2	rt	12	83
2	$BF_3{\cdot}Et_2O$	0.5	$CHCl_3$	rt	12	74
3	$BF_3{\cdot}Et_2O$	0.5	DCE	rt	12	70
4	$BF_3{\cdot}Et_2O$	0.5	CH_3CN	rt	12	–[c]
5	$BF_3{\cdot}Et_2O$	0.5	THF	rt	12	–[c]
6	$AlCl_3$	0.5	CH_2Cl_2	rt	12	50
7	$InCl_3$	0.5	CH_2Cl_2	rt	12	–[c]
8	$Y(OTf)_3$	0.5	CH_2Cl_2	rt	12	–[c]
9	$Sc(OTf)_3$	0.5	CH_2Cl_2	rt	12	–[c]
10	DMAP	0.5	CH_2Cl_2	rt	12	–[c]
11	DBU	0.5	CH_2Cl_2	rt	12	–[d]
12	piperidine	0.5	CH_2Cl_2	rt	12	–[c]
13	CH_3CO_2H	0.5	CH_2Cl_2	rt	12	–[c]
14	HCl	0.5	CH_2Cl_2	rt	12	–[c]

[a]Reaction of adduct methyl-2-benzoyl-pent-4-enedithioate **1a** (1.0 mmol) under different conditions. [b]Isolated pure yields. [c]No reaction. [d]Complex TLC pattern with a mixture of overlapping spots.

we performed the reaction in different solvents such as $CHCl_3$, DCE, CH_3CN, and THF. The reaction proceeded in $CHCl_3$ and DCE albeit with lower yields, but surprisingly CH_3CN and THF did not lead to any product even after 12 h of stirring (Table 2, entries 2–5). Next, a series of other Lewis acids such as $AlCl_3$, $InCl_3$, $Y(OTf)_3$, $Sc(OTf)_3$ and bases such as DMAP, DBU, piperidine were tried, but none of them could improve the initial result (Table 2, entries 6–12). Brønsted acids such as CH_3CO_2H and HCl also could not trigger the reaction (Table 2, entries 13 and 14). Thus, $BF_3{\cdot}Et_2O$ was found to be most suitable catalyst for the reaction. Finally, the loading of $BF_3{\cdot}Et_2O$ was optimized and 0.5 equiv of the catalyst was found to be optimum. A blank reaction did not lead to any product after 24 h (see SI). Thus, 0.5 equiv of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at rt was identified as the optimized conditions for the C_γ–S annulation.

With the optimized reaction conditions in hand, we explored the substrate scope for the C_γ–S intramolecular annulation protocol. As can be seen from Scheme 5, the protocol tolerated a number of α-allyl-β'-oxodithioesters with a wide range of substituent variations at R^1, R^2, and R^3 furnishing corresponding thiophenes **3** in moderate to good yields. R^1 and R^2 have no prominent influence on the outcome of the reaction. But, in the case of α-allyl-β'-oxodithioesters **1** with substituted allylic groups, the reaction rate became sluggish with a decreased yield of the corresponding products probably due to the

Scheme 5. Substrate Scope of the C_γ–S Annulation Protocol for the Synthesis of 3



decreased electrophilicity of the methyl substituted allylic groups (Scheme 5, entries **3b**, **3d**, **3f**, **3h**, and **3i**).

The structure of all the isolated products **2** and **3** were identified by their satisfactory spectral data (IR, ^{1}H, ^{13}C NMR, and HRMS) (see SI). In the ^{1}H NMR of compound **2** (Scheme 3), the β-CH_2 (δ ~3.3 ppm) and δ-CH (δ ~6.0 ppm) appeared as a doublet and the γ-CH appeared as a multiplet (δ ~5.5–5.6 ppm). For thiopyrans with a substituted methyl group at the γ-position (**2c** and **2g**), both the β- and δ-CH appeared as a singlet in their respective spectrum. In the ^{1}H NMR of **3** (Scheme 5) the β-CH_2 appeared as two distinct multiplets (δ ~2.9–3.0 and 3.3–3.4 ppm) for diastereotopic protons. The δ-CH_3 was split as a doublet (δ ~1.4 ppm) by the adjacent γ-CH. A multiplet around 3.8–3.9 ppm assigns the γ-CH of the 3,4-dihydrothiopyran **3**.

Observing the regioselective formation of the five- and six-membered sulfur-heterocycles, two entirely different mechanistic pathways are believed to be operating in two catalytic systems. According to the observed trend,[9a,12] at the initial step **1** is proposed to take up thioenol form **1b** rather than **1a** in the reaction medium. Thus, the **1b** form of **1** governs its entire reaction scenario. In the case of C_δ–S fusion of α-allyl-β'-oxodithioester **1**, the in situ generated Pd(0) is proposed to participate in the catalytic cycle as the active catalyst. The hypothesis is also supported by the reaction of Pd(0), i.e. $Pd(PPh_3)_4$ with **1** which also furnished the thiopyran product **2** in good yield (Table 1, entry 2). Therefore, the in situ generated Pd(0) undergoes an oxidative addition to the thioenol form **1b** to form **1c**.[10a] The intermediate **1c** can activate both the sp^2 C_δ–H and C_γ–H (in case of R^3 = H) of the allyl group. Thus, it can lead to the formation of six- or seven-membered intermediate **A** or **A′**. But during the reaction course the sp^2 C_δ–H of the allyl termini, being more labile (Scheme 1), becomes activated by palladium, which leads to the formation of the comparatively rarer seven-membered Pd complex **A** rather than the more familiar six-membered Pd complex **A′**.[13] Consequently, complex **A** suffers C_δ–S coupling followed by a reductive elimination to form 4*H*-

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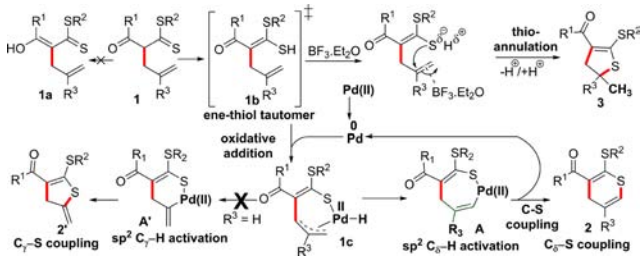
thiopyran framework **2**. The reductive elimination step eventually regenerates Pd(0) to complete the proposed Pd(0)−Pd(II)−Pd(0) palladacycle.

During C_γ−S annulation of **1**, $BF_3{\cdot}Et_2O$ being a strong Lewis acid drifts the π electron density of the allylic double bond toward itself making the allylic double bond sufficiently electrophilic for intramolecular nucleophilic attack. Ultimately, the greater nucleophilicity of sulfur compared to oxygen facilitates the regioselective thio-annulation of **1** via its thioenol form **1b** to generate the corresponding 4,5-dihydrothiophene nucleus **3** (Scheme 6).

Scheme 6. Plausible Mechanism for the Formation of 2 and 3



In summary, we successfully synthesized 4*H*-thiopyran and 4,5-dihydrothiophene frameworks utilizing the newly generated α-allyl-β'-oxodithioesters with excellent results regarding step and atom economy, cost, and waste generation. Two entirely different pathways were operated on the same substrate due to the variation of the catalytic systems. Palladium selectively activates the sp^2 C_δ−H of the allyl termini leading to the intramolecular C_δ−S coupling to furnish 4*H*-thiopyrans. Conversely, the allylic double bond of the precursor becomes activated by $BF_3{\cdot}Et_2O$ to promote the intramolecular thio-annulation resulting in the formation of 4,5-dihydrothiophenes at rt via C_γ−S fusion. Thus, the architectural strategy demonstrates an entirely new approach for the synthesis of two different moieties, thiopyran and thiophene, from a common substrate with a wide scope of substituent diversity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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