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Catalyst-Free and Selective Synthesis of 2-Aminothiophenes and 2-Amino-4,5-dihydrothiophenes from 4-Thiazolidinones in Water

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Abstract

2-Aminothiophenes and 2-amino-4,5-dihydrothiophenes were selectively and conveniently synthesized from 4-thiazolidinone derivatives. The meaningful product **10m** was efficiently synthesized, which is a commonly-used intermediate for preparing Olanzapine. The present method holds many advantages, such as easy operation, high yields, catalyst-free and using of water as the solvent.

Introduction

Thiophenes are widely used in drug design[1] and can be found in a number of marketed drugs such as Olanzapine **1**, Plavix **2** and Cymbalta **3** (Figure 1).[2] Continuous studies on thiophenes are also involved in dye chemistry,[3] materials science,[4] electronic and optoelectronic devices,[5] biodiagnostics,[6] block copolymer self-assembled superstructures, and conductivity-based sensory devices.[7] As derivatives of thiophenes, dihydrothiophenes are also privileged scaffolds which present in natural products, bioactive molecules and synthetic intermediates.[8] For example, 4,5-dihydrothiophene-3-carbonitrile **4** (Figure 1)[9] exhibit antibacterial and antifungal properties and 2-amino-4,5-dihydrothiophenes (ADHTs) are used as starting materials for the synthesis of partially hydrogenated thieno[2,3-b]pyridines[10] and pyrimidines.[11]

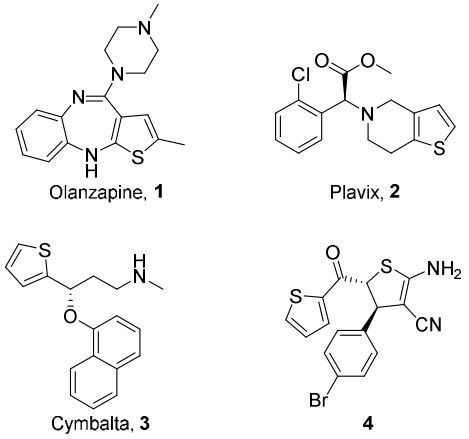

Figure 1. Examples of bioactive thiophenes and dihydrothiophenes.

A variety of synthetic methods have been developed for the preparation of 2-aminothiophenes (ATs), of which the most attractive route is Dieckmann or Thorpe–Ziegler cyclization of thioacetals in basic medium (Scheme 1).[12] In addition, Brandsma explored a one-pot methodology using acetylenes and isothiocyanates for constructions of 5-substituted

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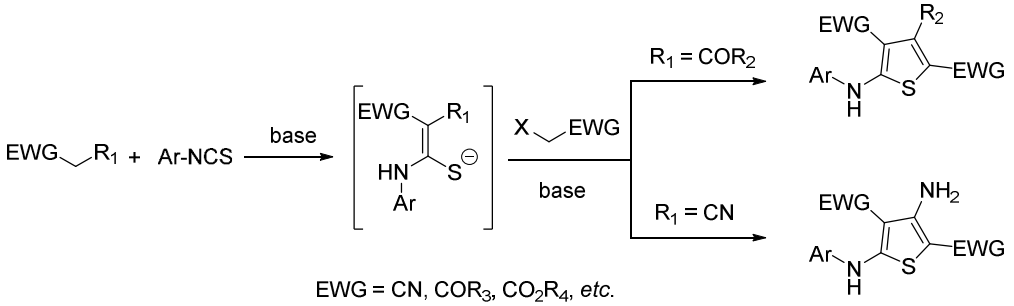
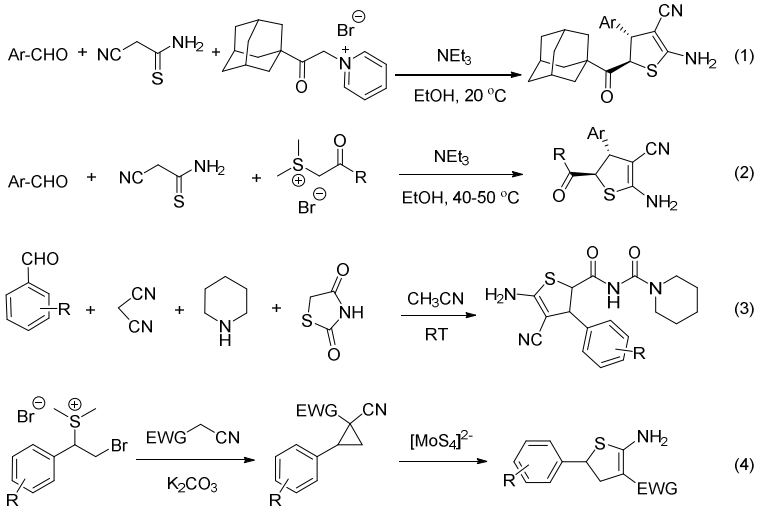
2-aminothiophenes.[13] Wang and co-workers disclosed the efficient synthesis of 3-substituted-2-aminothiophenes from substituted allyl benzotriazoles and isothiocyanates.[14] Then, ATs obtained by treatment of arylaminothieno-oxobutanamides with Lawesson's reagent were reported.[15] Recently, isothiocyanates were reported to react with electron-deficient allenes[16] or Morita–Baylis–Hillman adducts[17] to prepare ATs. In general, these synthetic methods have inherent drawbacks such as narrow substrate scope and the use of strong base n-butyllithium. Therefore, the development of concise and efficient methods for the access of ATs is still in high demand.



Scheme 1. Synthesis of ATs via Dieckmann or Thorpe–Ziegler cyclization of thioacetals.

Although ADHTs have great synthetic value, there are fewer publications on their synthesis in comparison with the detailed study on synthesis of thiophenes. Dotsenko and co-workers reported the synthesis of ADHTs by base-catalyzed condensation of phenacyl thiocyanate with substituted thioamides.[18] Shestopalov *et al.* disclosed a three-component condensation reaction involving aldehydes, cyanothioacetamide and pyridinium or sulfonium ylides for synthesis of ADHTs (Scheme 2, eq 1 and 2).[19] ADHTs could also be synthesized by a domino reaction involving 1,3-thiazolidinedione, malononitrile and aromatic aldehydes (Scheme 2, eq 3).[8g] More recently, ADHTs were synthesized by Chandrasekaran from doubly activated cyclopropanes using tetrathiomolybdate as the sulfur transfer reagent (Scheme 2, eq 4).[20] However, these protocols suffer from one or more drawbacks, such as low yields and the narrow scope of substrates.



Scheme 2. Previous strategies for the preparation of ADHTs.

Here, the synthesis of ATs and ADHTs from 4-thiazolidinone derivatives was reported. At the beginning, we intended to selectively reduce the carboxyl group of 4-thiazolidinone derivatives **9**

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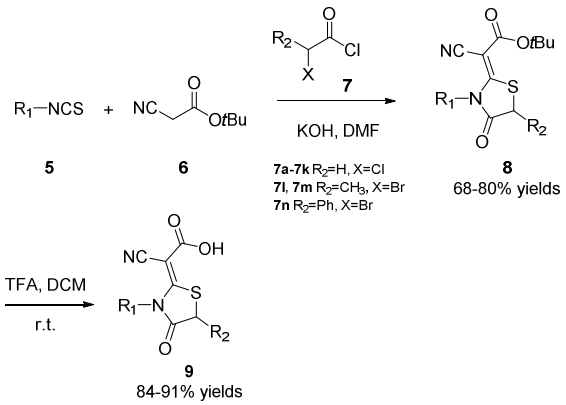
using $NaBH_4$,[21] because 4-thiazolidinones possess broad biological activities.[22] Unfortunately, no target product was obtained after many attempts. To our delight, interesting products ATs and ADHTs were detected. Then, the optimized reaction conditions and the scope of substrates were explored and the possible mechanism was also proposed.

Results and discussions

Starting materials aryl isothiocyanates **5**[23] and key intermediates 4-thiazolidinone derivatives **8**[21e] were easily obtained according to reported procedures. The corresponding carboxylic acids derivatives **9** were prepared by cleavage of *tert*-butyl with TFA in DCM (Scheme 3).



Scheme 3. Preparation of 4-thiazolidinone derivatives **9** from aryl isothiocyanates **5**.

Initially, the reaction conditions were optimized (Table 1) for the direct synthesis of AT using *N*-phenyl 4-thiazolidinone (**9a**) as a model substrate. Various reductants and solvents were screened at room temperature, and the results are presented in Table 1. Among the various reductants tested, $NaBH_4$ was found to be superior in terms of yield of **10a** (Table 1, Entry 1–4). Among the solvents screened, water was found to give the best result (Table 1, Entry 6). Other organic solvents, such as THF, MeOH and EtOH, afforded the product in relatively lower yields (Table 1, Entries 1, 2 and 5). The influence of the amount of reductants was then investigated, and 2.0 equiv. of $NaBH_4$ was the most effective. Moreover, it was found that the yield of AT decreased and ADHT would occur when 3.0 equiv of $NaBH_4$ was used (Table 1, Entry 10). The effect of temperature was also studied. The yield of **10a** increased to a remarkable 87% when the temperature was decreased to 15 °C (Table 1, Entry 11). Further decreasing the temperature to 5 °C led to significant reduction of the yield and extended reaction time (48 h) (Table 1, Entry 12). Therefore, Entry 11 was selected for the optimal reaction conditions. In order to investigate the relationship between the amount of $NaBH_4$ and the products ratio, the amount of $NaBH_4$ was further increased. Gratifyingly, the yield of **11a** increased to 54% when 10.0 equiv. of $NaBH_4$ was employed (Table 1, Entry 15). We next examined the effect of base in water on the reaction. Saturated aqueous $NaHCO_3$, saturated aqueous $KHCO_3$, 1M Na_2CO_3, 1M K_2CO_3, 1M NaOH and 1M KOH were tried, but the yield of **11a** was not improved with AT as the main product (Table 1, Entry 15 vs. Entries 17–22). At 10.0 equiv. of $NaBH_4$, MeOH was investigated again and the result was similar with that of Entry 2. Obvious improved yield and ratio were observed upon using EtOH as solvent (Table 1, Entries 15 vs. Entry 24). The similar yield was obtained when KBH_4 was used in water (Table 1, Entry 27), but the ratio is unsatisfied. To further increase the yield of **11a**, the reactions were carried out at different temperatures (Table 1, Entry 26–31). The

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yield of **11a** increased to 85% when the temperature was increased to 60 °C and 2 mL H_2O was used (Table 1, Entry 30). Further increasing the temperature to 80 °C did not give better results (Table 1, Entry 31). The yield of **11a** decrease to 70% when 5.0 equiv. of KBH_4 was employed (Table 1, Entry 32). Based on the above observation, Entry 30 was selected for the optimal reaction conditions.

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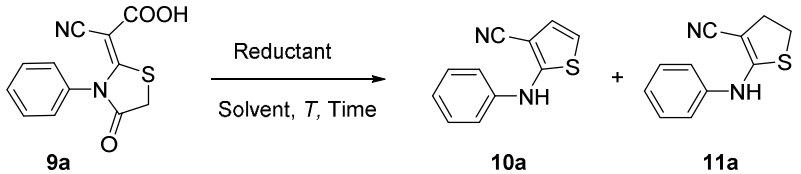
Table 1. Optimization of reaction conditions[a]



9a **10a** **11a**

Entry	Reductant (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (%)[c] **10a**	Yield (%)[c] **11a**
1	$NaBH_4$ (2.0)	THF	25	24	6	Trace
2	$NaBH_4$ (2.0)	MeOH	25	24	20	Trace
3	$NaBH_3CN$ (2.0)	MeOH	25	24	Trace	Trace
4	$LiAlH_4$ (2.0)	THF	25	0.5	8	Trace
5	$NaBH_4$ (2.0)	EtOH	25	8	68	Trace
6	$NaBH_4$ (2.0)	H_2O	25	8	78	Trace
7	$NaBH_4$ (1.0)	H_2O	25	24	8	Trace
8	$NaBH_4$ (1.2)	H_2O	25	24	68	Trace
9	$NaBH_4$ (1.5)	H_2O	25	18	70	Trace
10	$NaBH_4$ (3.0)	H_2O	25	6	62	21
11	**$NaBH_4$ (2.0)**	**H_2O**	**15**	**20**	**87(83[d])**	**Trace**
12	$NaBH_4$ (2.0)	H_2O	5	48	72	Trace
13	$NaBH_4$(5.0)	H_2O	25	6	37	47
14	$NaBH_4$ (7.5)	H_2O	25	6	29	51
15	$NaBH_4$ (10)	H_2O	25	2	25	54
16	$NaBH_4$ (10)	H_2O	15	3	33	52
17	$NaBH_4$ (10)	satd. aqueous $NaHCO_3$	25	3	69	5
18	$NaBH_4$(10)	satd. aqueous $KHCO_3$	25	3	56	Trace
19	$NaBH_4$ (10)	1M Na_2CO_3	25	3	47	26
20	$NaBH_4$ (10)	1M K_2CO_3	25	3	48	15
21	$NaBH_4$ (10)	1M NaOH	25	0.5	Trace	Trace
22	$NaBH_4$ (10)	1M KOH	25	0.5	Trace	Trace
23	$NaBH_4$ (10)	MeOH	25	4	24	Trace
24	$NaBH_4$ (10)	EtOH	25	4	5	62
25	KBH_4 (10)	EtOH	25	4	Trace	Trace
26	KBH_4 (10)	H_2O	15	3	33	58
27	KBH_4(10)	H_2O	25	2	27	63
28	KBH_4(10)	H_2O	40	0.5	18	74
29[b]	KBH_4 (10)	H_2O	40	0.5	16	77
30[b]	**KBH_4 (10)**	**H_2O**	**60**	**0.2**	**6**	**85(81[d])**
31[b]	KBH_4 (10)	H_2O	80	0.2	14	77
32[b]	KBH_4 (5.0)	H_2O	60	0.2	22	70

[a] Reaction conditions: substrate **9a** (0.2 mmol), water (1 mL). [b] Reaction conditions: substrate **9a** (0.2 mmol), water (2 mL). [c] Yield was determined by UPLC (ultra performance liquid

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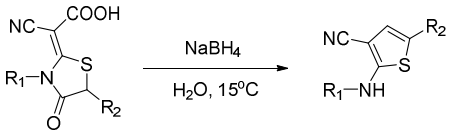
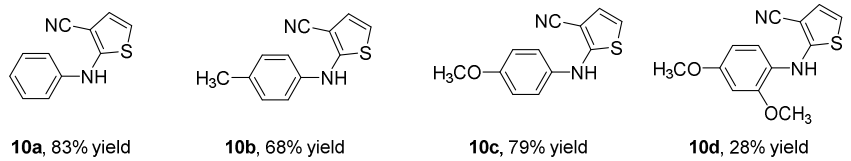
chromatography). [d] Isolated yield.

With the optimal conditions established, we explored the substrates scope for synthesis of ATs. The results were summarized in Table 2 and it demonstrated broad substrates scope. The reactions of substrates bearing electron-donating groups on the aromatic ring of 4-thiazolidinones, such as methyl (**9b**) and methoxy (**9c**) groups, afforded the corresponding products in good yields. But for the substrate containing an 2,4-dimethoxy group, the yield of **10d** decreased rapidly. Meanwhile, the reactions of substrates bearing electron-withdrawing groups on the aromatic ring of 4-thiazolidinones, such as fluoro (**9f**), chloro (**9e**), cyano (**9i**) and nitro (**9j**) groups, also afforded the corresponding products in good yields. In the case of substrate containing an ortho-nitro (**9h**) group, only 39% yield was obtained. Heteroaromatic substrate (**9k**) provided a lower yield. Upon the introducing methyl or phenyl into thiophene ring, the reactions also occurred smoothly to generate corresponding products **10l-10n** in moderate to good yields. Most important, the meaningful product **10m** could be provided conveniently, which is the commonly-used intermediate of typical antipsychotics Olanzapine.[24]

Table 2. Synthesis of ATs.[a]



9a-9n **10a-10n**

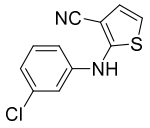


10a, 83% yield

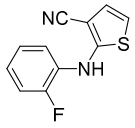
10b, 68% yield

10c, 79% yield

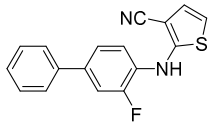
10d, 28% yield



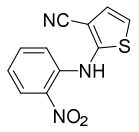
10e, 72% yield



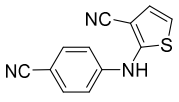
10f, 82% yield



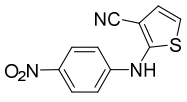
10g, 80% yield



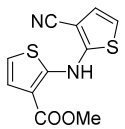
10h, 39% yield[b]



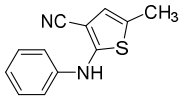
10i, 61% yield[b]



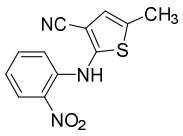
10j, 77% yield



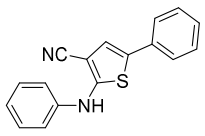
10k, 36% yield



10l, 45% yield



10m, 81% yield[b]



10n, 45% yield

[a] Reaction conditions: 4-thiazolidinone derivative **9** (0.5 mmol) and $NaBH_4$ (1.0 mmol) were

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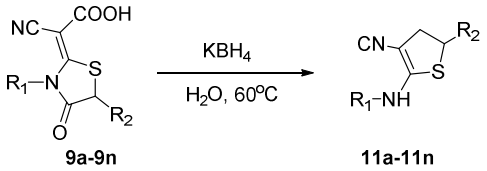
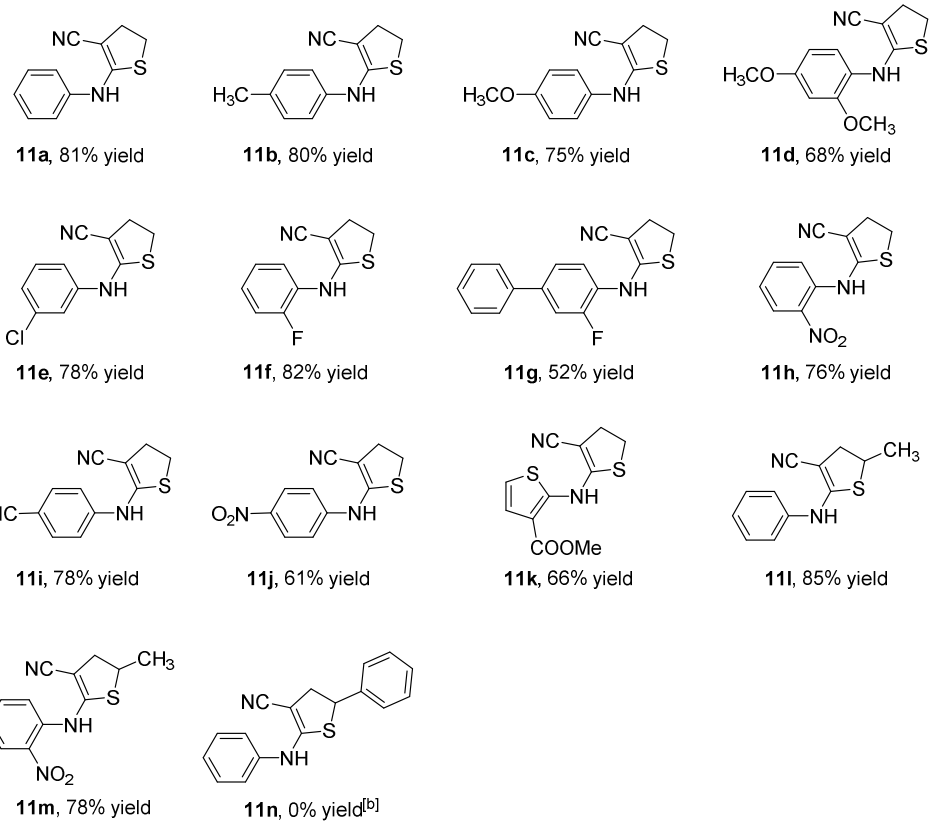
stirred in water (2.5 mL) at 15 °C for 0.5–24 h. [b] Reaction conditions: 4-thiazolidinone derivative **9** (0.5 mmol) and $NaBH_4$ (0.5 mmol) were stirred in water (2.5 mL) at 15 °C for 0.5 h.

Then, the scope of substrates to give ADHTs was explored (Table 3). The reactions of substrates bearing electron-donating or electron-withdrawing groups proceeded smoothly to give the expected products **11a–11j** in moderate to good yields. In case of the substrates containing 2,4-dimethoxy and 4-nitro groups, the yields of products **11d** and **11i** decreased slightly, which were different to the reactions of ATs. When benzene ring was replaced with biphenyl, the yield of **11g** was only 52%. The decreased water solubility of substrate **9g** might cause the lower yield. Heteroaromatic substrate (**9k**) also performed smoothly to afford product **11k** in moderate yield. The yield still remained high when the R_2 was the methyl group. But upon changing R_2 to phenyl, no desired product was obtained and the major product was the AT **10n** in yield of 56%.

Table 3. Synthesis of ADHTs.[a]



9a-9n **11a-11n**



11a, 81% yield **11b**, 80% yield **11c**, 75% yield **11d**, 68% yield

11e, 78% yield **11f**, 82% yield **11g**, 52% yield **11h**, 76% yield

11i, 78% yield **11j**, 61% yield **11k**, 66% yield **11l**, 85% yield

11m, 78% yield **11n**, 0% yield[b]

[a] Reaction conditions: 4-thiazolidinone derivative **9** (0.5 mmol) and KBH_4 (5.0 mmol) were stirred in water (5.0 mL) at 60 °C for 0.5 h. [b] The major product is **10n** in yield of 56%.

Besides ^1H, ^{13}C and ^{19}F NMR spectroscopy, the structures of **10g** and **11a** were confirmed by

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X-ray diffraction analysis (Figure 2). The results confirmed that the ADHTs were obtained instead of 2-amino-2,3-dihydrothiophenes. In addition, ADHTs **11** exists amino–imino automerism due to prototropic tautomerism (Scheme 4). This tautomerism can be seen in both ^{1}H, ^{13}C and ^{19}F NMR spectra. X-ray single crystal analysis of **11a** revealed that it only exist amino form (Figure 2). The similar tautomerism was previously studied in the 2-amino-1,3-thiazolidin-4-one derivatives.[25]

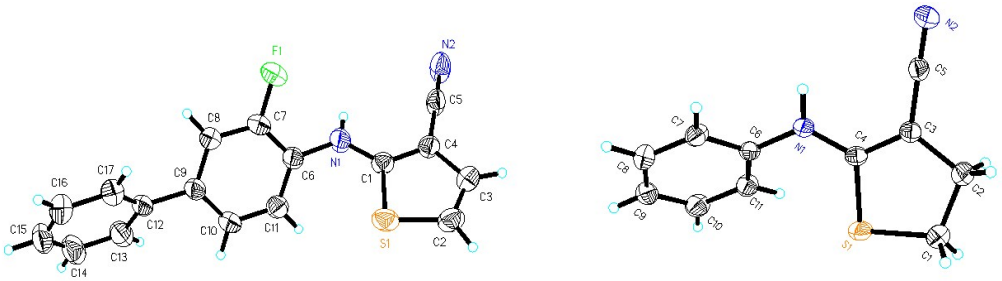
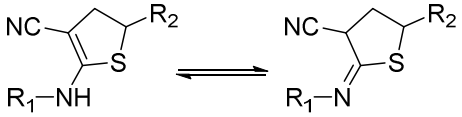


Figure 2. Single-crystal X-ray diffraction structures of **10g** and **11a**.



Scheme 4. Tautomers of **11**.

A possible reaction mechanism was proposed in Scheme 5. Initially, reduction and deprotonation of 4-thiazolidinone derivatives **9** led to formation of carboxylates A. The followed C−N bond cleavage formed aldehydes **B**, which underwent intramolecular cyclization to form tetrahydrothiophenes **C**. Subsequently, tetrahydrothiophenes **C** were consumed in two paths: **a** and **b**. Tetrahydrothiophenes **C** released CO_2 to give hydroxyl compounds **D** in path **a**. Finally, hydroxyl compounds **D** underwent a dehydration process to give ATs **10**. In path **b,** the C=N bond was reduced first to form carboxylates **E**, the second step was decarboxylation of carboxylates **E** with the followed release of hydroxyl ion, and 2,5-dihydrothiophenes **G** were given. 2,5-dihydrothiophenes **G** can be easily converted to more stable 4,5-dihydrothiophenes **11**.

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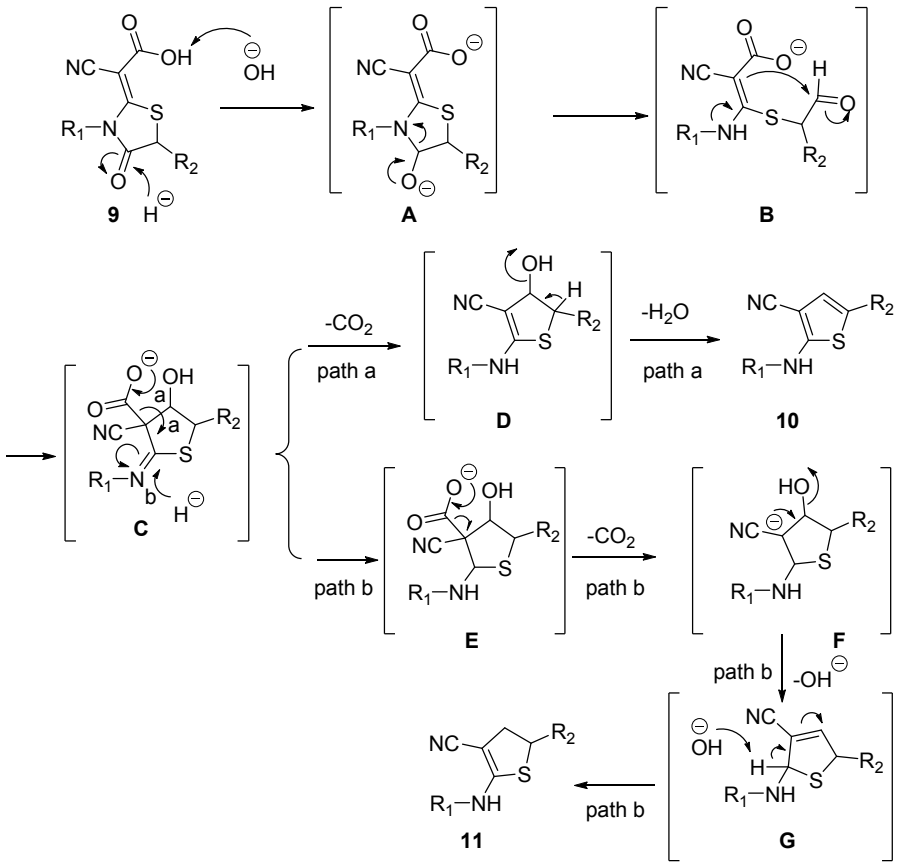

Scheme 5. Proposed mechanism for the formation of **10** and **11**.

Conclusions

A new and efficient method for the synthesis of ATs and ADHTs derivatives was developed using inexpensive and readily available starting materials and reagents. Many advantages, such as easy operation, high yields, using of water as a solvent, catalyst-free and broad substrates scope, make this method absorb more attention.

Experimental Section

General Procedure for the Synthesis of tert-butyl 2-cyano-2-(4-oxo-3-arylthiazolidin-2-ylidene)acetates (8a–8n)

Tert-butyl cyanoacetate (10 mmol) followed by a solution of aryl isothiocyanate **5** (10 mmol) in anhydrous DMF (10 mL) were added to a cold suspension of powdered KOH (20 mmol) in dry DMF (10 mL). The mixture was stirred at room temperature for 0.5 h, then cooled again to 0°C, treated with a solution of appropriate 2-halogen acyl chloride **7** (15 mmol) in anhydrous DMF (10 mL) and stirred at room temperature overnight. The mixture was poured into ice-cold water, and the resulting precipitate was filtered off, dried, and crystallized from DCM-EtOH to give compounds **8a–8n** in yield of 68%–80%.

General Procedure for the Synthesis of 2-cyano-2-(4-oxo-3-arylthiazolidin-2-ylidene)acetic acid (9a–9n)

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To a solution of tert-butyl acetate derivative **8** (5 mmol) in DCM (50 mL) was added a mixture of TFA (7.5 mL) and DCM (75 mL). The mixture was stirred at room temperature until the reaction was complete as indicated by TLC (typically 24 h). The solvent was evaporated under reduced pressure. The residual solid was further crystallized from DCM-MeOH to afford the compounds **9a**–**9n** in yield of 84%–91%.

General Procedure for the Synthesis of ATs (10a–10n)

Carboxylic acid compound **9** (0.5 mmol) was added to a solution of $NaBH_4$ (1 mmol) in water (2.5 mL) at 15 °C. The reaction mixture was stirred at 15 °C until the reaction was complete as determined by TLC analysis (typically 0.5–24 h). The reaction mixture was quenched with 1 M HCl, and the product precipitated was filtered. The solid was purified by silica gel column chromatography (PE : EA = 5:1) to afford the compounds **10a–10n**.

General Procedure for the Synthesis of ADHTs **(11a–11m)**

Carboxylic acid compound **9** (0.5 mmol) was added to a solution of KBH_4 (5 mmol) in water (5 mL) at 60 °C. The reaction mixture was stirred at 60 °C for 0.5 h. The reaction mixture was cooled to room temperature and quenched with 1 M HCl. The aqueous layer was extracted with EtOAc (3×2 mL). The combined organic phases were washed once with brine, dried with anhydrous Na_2SO_4, vacuum-filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE : EA = 3:1) to afford the corresponding ADHTs **11a–11m**.

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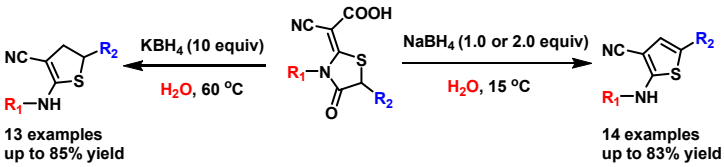

The image of selectively synthesis of 2-aminothiophenes and 2-amino-4,5-dihydrothiophenes from 4-thiazolidinones in water.