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ARTICLE TYPE

Novel Synthesis of Thiazolo/thienoazepine-5,8-diones from Dihalo Cyclic 1,3-Diketones and Mercaptonitrile Salts

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An efficient approach to thiazolo[4,5-*b*]azepine-5,8-diones and thieno[3,2-*b*]azepine-5,8-diones has been developed *via* a domino synthesis of multifunctionalized thiazoles/thiophenes and further intramolecular cyclization. This transformation proceeded rapidly under mild conditions without use of metal catalyst.

Fused azepinediones, such as DGAT1 inhibitor **1**[1] and antitumor agents **2**[2], have drawn much attention due to their various biological activities (Fig 1). Moreover, they are important synthetic intermediates of numerous biologically active fused heterocycles in drug discoveries[3-7], such as αVβ3 antagonists **3**[3], CDK and GSK-3 inhibitors **4** (Paullones)[4]. Thus, tremendous efforts have been devoted to the development of versatile methods for constructing these fused cyclic cores.[8-12] However, very few research focused on the construction of heterocyclic fused azepinediones due to difficulty of synthesis, though they may possess potential biological activities. To the best of our knowledge, there was no report on the preparation of thiazolo[4,5-b]azepine-5,8-diones, while the synthesis of thieno-[3,2-*b*]azepine-5,8-diones were only limited to Kunick's[13] and Kirsch's[14] reports *via* 3-aminothiophene-2-carboxylic acid alkyl esters through many steps. Meanwhile, high reaction temperature, prolonged reaction time and tedious procedures were also required.[13-14] Thus, it is necessary to develop a more mild and straightforward approach to construct novel thiazolo/thieno-azepine-5,8-diones.

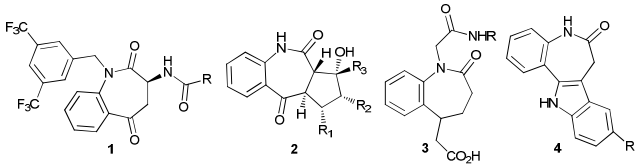
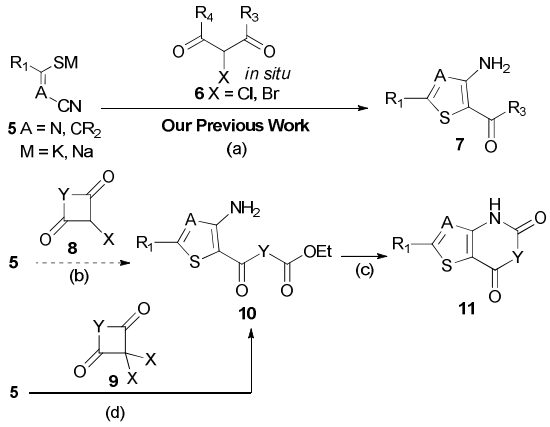


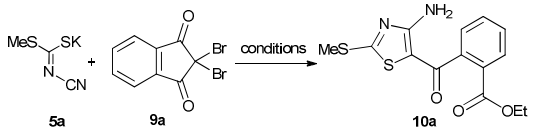
Figure 1. Representative active fused azepinediones and their derivatives.

Recently, we developed a sequential one-pot synthesis of multifunctionalized thiazoles/thiophenes **7** from mercaptonitrile salts **5** and *in situ* generated monohalo acyclic 1,3-dicarbonyl compounds **6**. This transformation involved a regio-selective elimination of a $-COR_4$ group (Scheme 1a).[15] Inspired by this work, we envisaged that keto esters **10** would be obtained if replacing **6** with monohalo cyclic 1,3-diketones **8** (Scheme 1b). In this case, the reaction of salts **5** and cyclic 1,3-diketones **8** would provide valuable intermediates **10**, which could undergo the intramolecular cyclization to form the novel thiazolo/thieno-fused heterocycles **11** (Scheme 1c). However, preliminary experiments disclosed that the reaction of **5** with **8** did not afford the expected thiazoles/thiophenes **10**.[16] Fortunately, when dihalo cyclic 1,3-diketones **9** were used, key intermediates **10** were smoothly isolated (Scheme 1d).



Scheme 1. Synthesis of thiazoles/thiophenes and thiazolo/thieno-fused heterocycles.

Table 1. Optimization of reaction conditions[a]

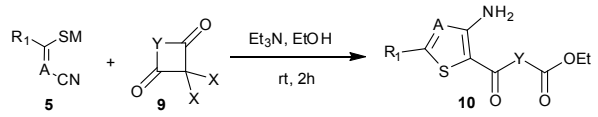


5a 9a 10a

Entry	**5a** (equiv.)	Base	**10a** Yield(%)[b]
1	1	Et_3N	35
2	1.5	Et_3N	52
3	**2**	**Et_3N**	**75**
4	2.5	Et_3N	74
5	2	–	39
6	2	K_2CO_3	52
7	2	$NaHCO_3$	55
8	2	NaOAc	65
9	2	NaOEt	67
10	2	DBU	71
11	2	Et_3N	68[c]
12	2	Et_3N	58[d]
13	2	Et_3N	54[e]
14	2	Et_3N	69[f]
15	2	Et_3N	71[g]

[a] Reaction conditions: **9a** (0.5 mmol, 1.0 equiv.), **5a**, base (0.5 mmol, 1.0 equiv.) in EtOH (2 mL) at rt for 2 h. [b] Isolated yields. [c] 0.5 equiv. of Et_3N was used. [d] 2.0 equiv. of Et_3N was used. [e] Reaction occurred at 0 °C. [f] Reaction occurred at 50 °C. [g] 2,2-Dichloroindane-1,3-dione **9a'** was used instead of **9a**.

Table 2. Domino synthesis of multifunctionalized thiazoles and thiophenes **10** from **9** and **5**[a]



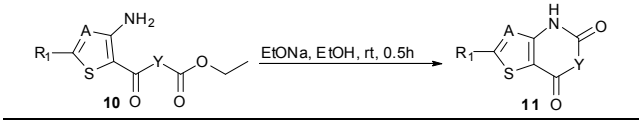
Entry	5	9	Product 10	Yield (%)[b]
1	5a	9a	10a	75
2	5a	9b	10b / 10b'	70 (10b/10b' = 1:1)
3	5a	9c	10c	65
4	5a	9d	10d	68
5	5a	9e	10e	59
6	5a	9f	10f	52
7	5b	9a	10g	43
8	5c	9a	10h	82
9	5c	9c	10i	64
10	5c	9d	10j	71
11	5c	9e	10k	55
12	5c	9f	10l	57

[a] Reaction conditions: **5** (1 mmol, 2.0 equiv.), **9** (0.5 mmol, 1.0 equiv.), Et_3N (0.5 mmol, 1.0 equiv.) in EtOH (2 mL) at rt for 2 h. [b] Isolated yields.

Encouraged by above results, we selected the reaction of potassium methyl N-cyanodithioimidocarbonate **5a** with 2,2-dibromoindane-1,3-dione **9a** as model to optimize the reaction conditions. An equimolar mixture of **5a** and **9a** was stirred for 2 hours at room temperature in the presence of Et_3N in ethanol, affording **10a** in 35% yield (entry 1, Table 1). Increasing the amount of **5a** from 1.0 equiv. to 2.0 equiv., the yield was significantly increased up to 75% (entry 2 *vs.* entry 3, Table 1). However, more than 2.0 equiv. of **5a** did not improve the yield further (entry 3 *vs.* entry 4, Table 1). Among the screened bases, including no base, inorganic and organic bases (entries 3 and 5–10, Table 1), Et_3N was the best one (entry 3, Table 1). Increasing or decreasing the amount of Et_3N slightly influenced the yield (entries 11–12, Table 1). When the reaction was conducted at 0 °C or 50 °C, the yield was not improved either (entries 14–15, Table 1). Finally, 2,2-dichloroindene-1,3-dione **9a'** was used instead of **9a**, leading to a slightly lower yield (entry 3 *vs.* entry 15, Table 1).

Subsequently, the reaction scope was explored under the optimized reaction conditions (entry 3, Table 1). Various dihalo cyclic 1,3-diketones, including five-membered rings **9a–c** and six-membered rings **9d–f**, were reacted with **5a** affording the corresponding thiazole derivatives **10a–f** in moderate to good yields (entries 1–6, Table 2). Dihalo cyclic 1,3-diketones fused aromatic ring **9a–b** led to superior yields compared to **9c–f**. As expected, asymmetric substrate **9b** formed two isomers (**10b** and **10b'**) without significant selectivity (entry 2, Table 2). Considering the significance of 2-aminothiazoles in drug design, **10g** containing a phenylamino group was also prepared from **5b** and **9a** in 43% yield (entry 7, Table 2). Furthermore, the reaction was expanded to the synthesis of poly-substituted thiophenes. Reactions of potassium (2,2-dicyano-1-methylthioethen-1-yl)-thiolate **5c** with **9a** and **9c–f** provided the corresponding thiophene derivatives **10h–l** in 55-82% yields, respectively.

Table 3. Synthesis of thiazolo/thienoazepine-5,8-diones **11**[a,b]



[a] Reaction conditions: **10** (0.2 mmol, 1.0 equiv.), NaOEt (0.4 mmol, 2.0 equiv.) in EtOH (2 mL) at rt for 0.5 h. [b] Isolated yields.

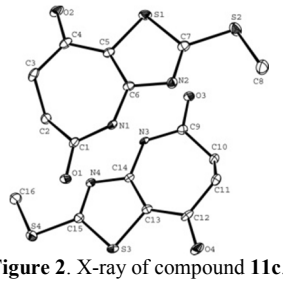
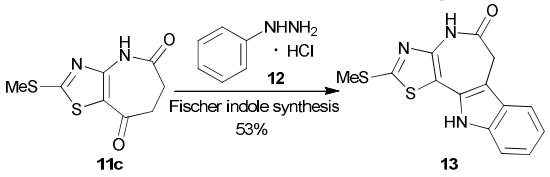


Figure 2. X-ray of compound **11c**.

With a series of functionazed thiazoles and thiophenes **10** in hand, we turned our attention to their intramolecular cyclizations. Optimization studies[17] revealed that the cyclization of **10c** could proceed efficiently in the presence of NaOEt in ethanol for 0.5 h at room temperature. Under above conditions, a series of thiazolo[4,5-*b*]azepine-5,8-diones (**11a–d**) and thieno[3,2-*b*]azepine-5,8-diones (**11e–f**) were prepared from precursors **10** in

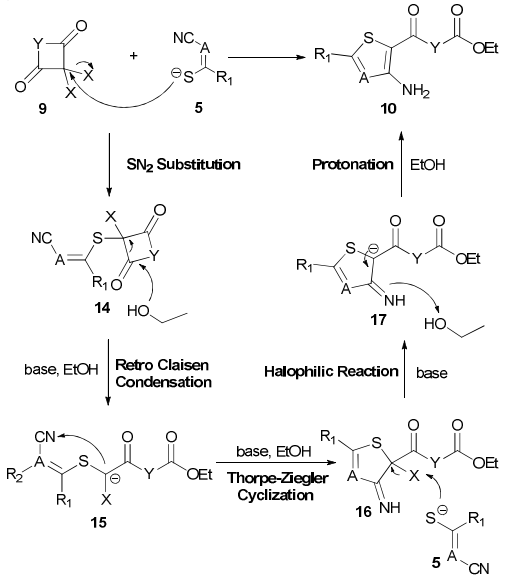
excellent yields (Table 3). And the structure of compound **11c** was unambiguously confirmed by X-ray diffraction study (Fig 2). However, the cyclization of **10d–f** and **10j–k** failed to afford fused eight-membered lactam rings, which could be attributed to the instability of the products in the presence of nucleophiles.[18]

In order to demonstrate the synthetic utility of this novel synthetic method, **11c** was treated with phenylhydrazine hydrochloride under Fischer indole synthetic conditions[12], affording thiazoloazepino-indol-5-one **13** in 53% yield (Scheme 2). Compound **13** is under research for potential biological activities due to its structural similarity to Paullones **4**, which are potent CDK and GSK-3 inhibitors as showed in Fig 1.



Scheme 2. Synthesis of thiazole analogue of Paullone **13**.

A possible domino reaction pathway for the construction of thiazoles/thiophenes was proposed and illustrated in Scheme 3. Dihalo cyclic 1,3-diketone **9** was first attacked by **5** affording intermediate **14**, which was converted to **15** *via* retro Claisen condensation[19] in the presence of base. Then anion **15** underwent Thorpe–Ziegler cyclization to furnish intermediate **16**. Subsequently, the halogen of **16** was attacked by thiolate anion **5** *via* halophilic reaction[20], followed by proton transfer from the alcohol, affording the desired product **10**. This accounted for the fact that the reaction required two equivalents of **5** (entries 1–4, Table 1).



Scheme 3. Possible domino reaction pathway.

Conclusions

In summary, we have developed a mild and efficient strategy for the synthesis of thiazolo[4,5-*b*]azepine-5,8-diones and thieno-[3,2-*b*]azepine-5,8-diones from dihalo cyclic 1,3-diketones and mercaptonitrile salts *via* domino S_N2 substitution/retro Claisen condensation/Thorpe–Ziegler cyclization/halophilic reaction and further cyclization. This method has been successfully applied in the rapid synthesis of a thiazole analogue of Paullone and the further extention will be disclosed in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Detailed experimental procedures and spectral data for all new compounds; crystallographic data of **11c** in CIF format]. See DOI: 10.1039/b000000x/

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