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NBS-mediated sequential one-pot synthesis of multifunctionalized thiazoles and thiophenes from 1,3-dicarbonyl compounds and mercaptonitrile salts

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ABSTRACT

A NBS-mediated sequential one-pot synthesis of multifunctionalized thiazoles and thiophenes from 1,3-dicarbonyl compounds and mercaptonitrile salts has been developed under mild conditions. This transformation involves sequential bromination/S_N2 alkylation/Thorpe–Ziegler cyclization/regio-selective elimination of a –COR group, affording the desired products in moderate to good yields. The sequence of the leaving reactivity of –COR groups was determined and a possible mechanism was proposed.

Multifunctionalized thiazoles and thiophenes, such as tubulin polymerization inhibitors **1**,[1] CDK inhibitor **2**,[2] anticancer agent **3**,[3] Src/Abl Kinase inhibitors Dasatinib **4**[4] and PI3K inhibitors **5**[5] (Fig. 1), exhibit a broad spectrum of biological activities. In addition, they are common synthetic intermediates in numerous biologically active fused-thiazoles and fused-thiophenes.[6] Accordingly, versatile synthetic protocols have been developed to construct poly-substituted thiazoles and thiophenes.[7–10]

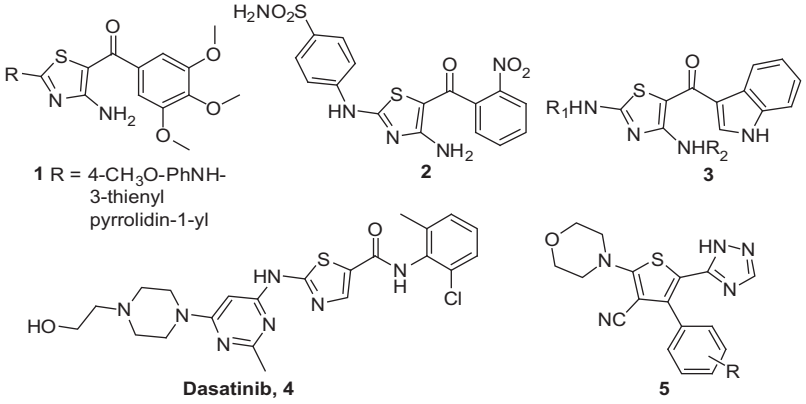

Figure 1. Examples of biologically active multifunctionalized thiazoles and thiophenes.

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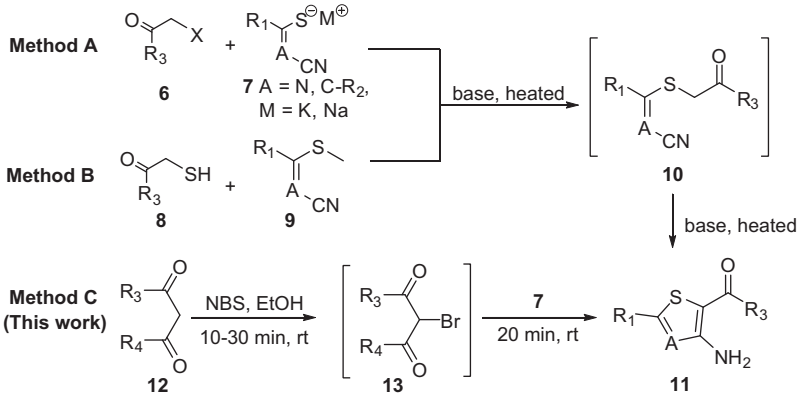
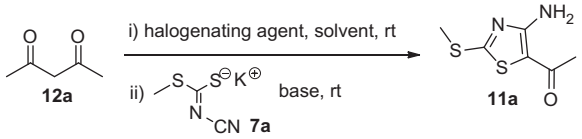


Scheme 1. Synthetic methods for poly-substituted thiazoles and thiophenes via Thorpe–Ziegler cyclization.

Among the known methods for the synthesis of poly-substituted thiazoles and thiophenes,[1–10] Thorpe–Ziegler cyclization is a rather attractive one via intramolecular base-promoted cyclization of nitriles **10** (Scheme 1).[1–3,5,6,8–10] The key intermediate **10** was obtained by two main strategies: (1) introducing a $-CH_2COR$ moiety by alkylation of mercaptonitrile salts **7** with halides **6** (Method A, Scheme 1); and (2) replacing the methylsulfanyl group in compound **9** with thiols **8** (Method B, Scheme 1). However, these procedures suffer from relatively harsh reaction conditions such as high reaction temperature and prolonged reaction time. And the application was also limited due to the use of irritating starting material **6** or odorous thiols **8** and low yields for some substrates.[9,10a] Herein, we report a NBS-mediated sequential one-pot approach to multifunctionalized thiazoles and thiophenes **11** from 1,3-dicarbonyl compounds **12** and mercaptonitrile salts **7** under mild reaction conditions. (Method C, Scheme 1).

During our research efforts aimed at the development of convenient syntheses of various heterocycles[11], we found that 4-amino-5-acetyl-2-(methylthio)thiazole **11a** could be rapidly formed from the reaction of 3-chloropentane-2,4-dione **13a** and mercaptonitrile salt **7a** at room temperature. Considering the sequential one-pot synthesis showed many advantages in organic synthesis[12] and that **13** could be easily prepared from the α-halogenation of 1,3-dicarbonyl compounds **12**[13], we envisaged that **11** might be achieved by a sequential one-pot procedure via bromination/S_N2 alkylation/Thorpe–Ziegler cyclization/regio-selective elimination of a –COR group.

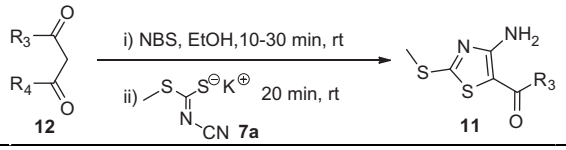
Table 1
Optimization of reaction conditions[a]

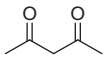
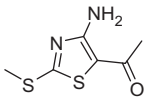
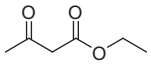
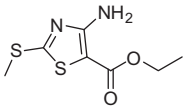
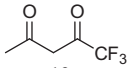
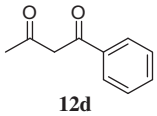
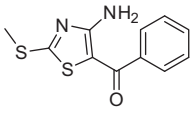
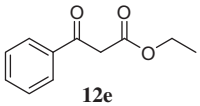
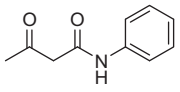
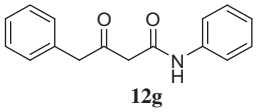
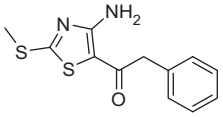
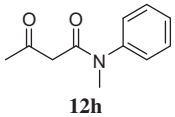
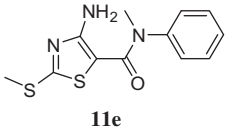


Entry	Halogenating agent (equiv)	Solvent	Yield[b] (%)
1	NCS (1.0)	C_2H_5OH	74
2	NBS (1.0)	C_2H_5OH	81
3	I_2 (1.0)	C_2H_5OH	25
4	NBS (0.9)	C_2H_5OH	73
5	NBS (1.1)	C_2H_5OH	79
6	NBS (1.0)	H_2O	39
7	NBS (1.0)	DMSO	67
8	NBS (1.0)	CH_3COCH_3	59
9	NBS (1.0)	CH_2Cl_2	54
10	**NBS (1.0)**	**C_2H_5OH**	**82**[c]

[a] Reaction conditions: **12a** (1 mmol), halogenating agent (1 mmol), 3 mL of solvent, rt, 10 min; then **7a** (1 mmol) and Et_3N (1 mmol), rt, 20 min.
[b] Isolated yields.
[c] The reaction was conducted under base-free condition.

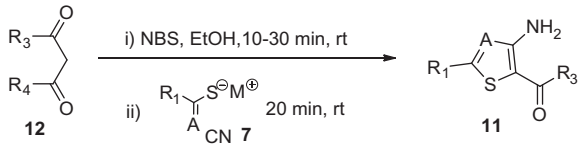
Table 2
Synthesis of multifunctionalized thiazoles and thiophenes **11** from 1,3-dicarbonyl compounds **12** and **7a**[a]



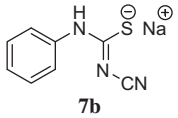
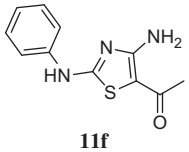
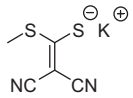
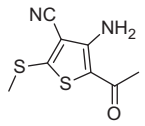
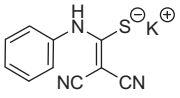
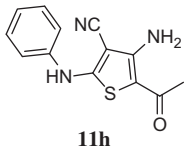
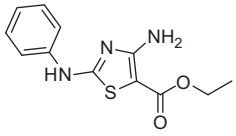
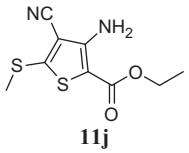
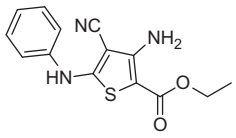
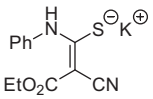
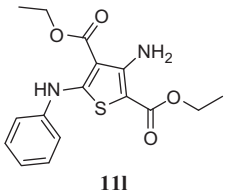
Entry	Reactant **12**	Product **11**	Yields[b] (%)
1	 **12a**	 **11a**	82
2	 **12b**	 **11b**	75
3	 **12c**	**11a**	71
4	 **12d**	 **11c**	68
5	 **12e**	**11b**	63
6	 **12f**	**11a**	75
7	 **12g**	 **11d**	81
8	 **12h**	 **11e**	64

[a] Reaction conditions: **12** (1 mmol), NBS (1 mmol), 3 mL EtOH, rt, 10 min (30 min for **12b** and **12e**); then **7** (1 mmol), rt, 20 min.
[b] Isolated yields.

Table 3
Synthesis of multifunctionalized thiazoles and thiophenes **11** from 1,3-dicarbonyl compounds **12** and **7**[a]

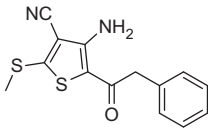
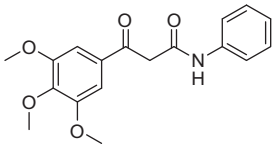
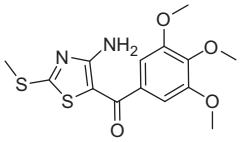


12 **7** **11**

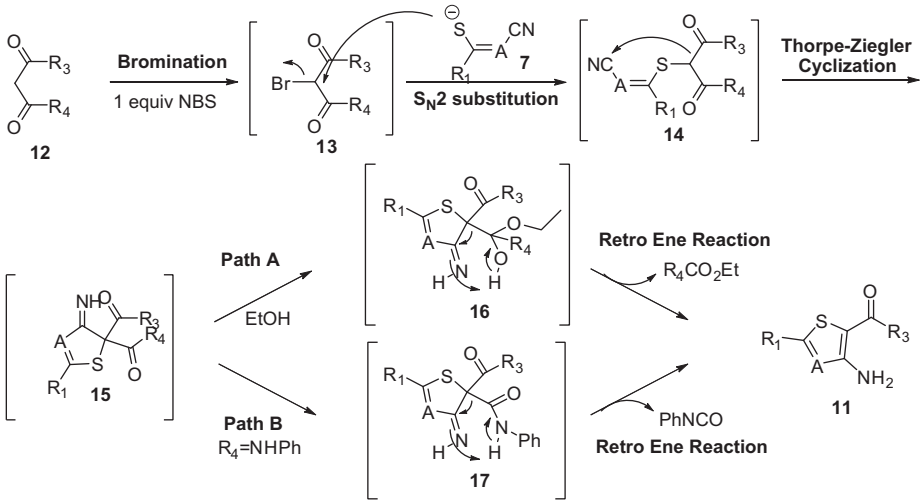
Entry	Reactant **12**	Reactant **7**	Product **11**	Yields[b] (%)
1	**12a**	 **7b**	 **11f**	77
2	**12a**	 **7c**	 **11g**	86
3	**12a**	 **7d**	 **11h**	79
4	**12b**	**7b**	 **11i**	72
5	**12b**	**7c**	 **11j**	81
6	**12b**	**7d**	 **11k**	74
7	**12b**	 **7e**	 **11l**	53

(*continued on next page*)

Table 3 (*continued*)

Entry	Reactant **12**	Reactant **7**	Product **11**	Yields[b] (%)
8	**12g**	**7c**	 **11m**	85
9	 **12i**	**7a**	 **11n**	76

[a] Reaction conditions: **12** (1 mmol), NBS (1 mmol), 3 mL EtOH, rt, 10 min (30 min for **12b**); then **7** (1 mmol), rt, 20 min.
[b] Isolated yields.



Scheme 2. Proposed mechanisms for tandem reaction.

To test our hypothesis, we selected reagent **7a** and pentane-2,4-dione **12a** for the model reaction. To our delight, α-halogenation of **12a** with NCS was rapidly completed in ethanol at room temperature within 10 min. After addition of **7a** and Et_3N, the mixture was stirred for 20 min, affording the desired product **11a** in 74% yield (Table 1, entry 1). Encouraged by this success, the reaction was further optimized by changing halogenating agent, solvent, temperature, and base (Table 1, entries 2–10). When NBS was used instead of NCS, the yield was improved (81%, Table 1, entry 2). And using I_2 as the halogenating agent led to a poor yield (25%, entry 3, Table 1). Thus, NBS is a more suitable halogenating agent for this transformation. However, changing the amount of NBS did not improve the yields (Table 1, entries 4–5). Then the solvents were screened and ethanol was found to be superior to others (Table 1, entries 6–9). It was worth noting that the product was obtained in similar good yield under base-free condition (Table 1, entry 10).

With the optimized conditions in hand (Table 1, entry 10), we next investigated the substrate scope of 1,3-dicarbonyl compounds. As shown in Table 2, **7a** reacted smoothly with various 1,3-dicarbonyl compounds **12**, including β-diketones **12a** and **12c-d**, β-ketoesters **12b** and **12e**, and β-ketoamides **12f–h**, affording 2-methylthio-4-aminothiazoles **11a–e** in 63–82% yields. Usually, the stronger electronic withdrawing group in 1,3-dicarbonyl compounds **12** was preferentially removed. For example, CH_3CO– was easier to be eliminated than C_2H_5OCO– and PhCO– (Table 2, entries 2 and 4). However, C_6H_5NHCO– was unexpectedly easier to leave than CH_3CO– and BnCO–(entries 6–7, Table 2). And the presence of active hydrogen in the amide was essential for the high leaving reactivity of C_6H_5NHCO– (Table 2, entry 6 vs entry 8). According to the experimental results, the order of the leaving reactivity of –COR groups was determined as: C_6H_5NHCO– > CH_3CO– > C_6H_5CO– > C_2H_5OCO–, $C_6H_5N(CH_3)CO$–.

Subsequently, the scope of the transformation was further expanded with different mercaptonitriles **7** and typical 1,3-dicarbonyl compounds, such as β-diketones **12a**, β-ketoester **12b**, and β-ketoamides **12g** and **12i**, respectively (Table 3).[14] **7a-b** reacted with **12** affording the thiazole derivatives, while using **7c–e** as reactants led to the thiophene derivatives. All the reactions were performed smoothly affording the desired products in good yields (72–86%) except **11l** (53%) within 1 h at room temperature. Among them, **11j** (81%, Table 3, entry 5) and **11n** (76%, Table 3, entry 9) were regarded as key intermediates of PI3K inhibitors **5** and tubulin polymerization inhibitor **1**, respectively. According to the literature, **11j** was prepared in 67% yield from odorous ethyl

2-mercaptoacetate after stirring for 12 h at room temperature (Method B)[5b], while **11n** was achieved from corresponding costly halide **6** in 53% yields after heating for 5 h (Method A).[1c] Hence, this novel procedure was more efficient and environment-friendly than conventional methods.

Finally, a plausible mechanism for this transformation was proposed and illustrated in Scheme 2. 1,3-Dicarbonyl compounds **12** were brominated by NBS and the in situ generated monobromo 1,3-dicarbonyl compounds **13** were subsequently attacked by **7**, affording intermediates **14**. Then Thorpe–Ziegler cyclization occurred leading to intermediates **15**. When intermediates **16** were generated via the addition of ethanol to the carbonyl group in **15**, a retro ene reaction would happen furnishing the product **11** (Path A, Scheme 2).[15] Whereas R_4 represented C_6H_5NHCO–, the retro ene reaction would take place directly in intermediates **17**.[15,16] As a result, the C_6H_5NHCO– group was preferentially removed, affording products **11** (Path B, Scheme 2).

In summary, we have developed a NBS mediated sequential one-pot approach to multifunctionalized thiazoles and thiophenes from 1,3-dicarbonyl compounds and mercaptonitrile salts. The advantages of this method include mild reaction conditions, accessible starting materials, short reaction time, simple operation, broad substrate scope, and satisfactory yields. Thus, this method is of practical value in organic and medicinal chemistry.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.014.

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14. *General procedure for the synthesis of multifunctionalized thiazoles and thiophenes* **11**: To a solution of 1,3-dicarbonyl compounds **12** (1.0 mmol) in EtOH (3.0 mL) was added NBS (178 mg, 1 mmol). The reaction mixture was stirred for 10 min (30 min for **12b** and **12e**) at room temperature. Afterwards **7** (1 mmol) was added and the reaction mixture was stirred for another 20 min at room temperature. After that, the solvent was evaporated under reduced pressure, and the residue was purified via a short silica gel column to afford the desired product **11**.
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