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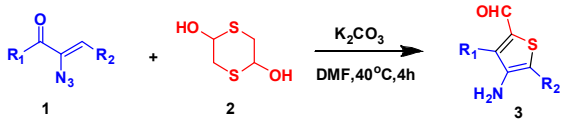

A facile approach to provide 3,5-disubstituted-4-aminothiophene-2-carbaldehyde containing both the amino group and the aldehyde group has been developed.

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Facile preparation of 3,5-disubstituted-4-aminothiophene-2-carbaldehyde from a novel unexpected domino reaction of vinyl azides and 1,4-dithiane-2,5-diol

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A simple and direct synthesis of 3,5-disubstituted-4-aminothiophene-2-carbaldehyde from vinyl azides and 1,4-dithiane-2,5-diol was developed. An attractive feature of this protocol is that the desired products are generated in a highly efficient and eco-friendly manner. A plausible mechanism has been proposed.

Multisubstituted 2- or 3-aminothiophenes are privileged structures which are widely used in the design of biologically active molecules, photo-chromic materials and agrochemicals due to their aromaticity, relative chemical stability and polarizability.[1] The most popular approach to multisubstituted 2-aminothiophenes was Gewald reaction, which involves the multicomponent condensation of ketones or aldehydes, cyanoacetate and elemental sulfur.[2] This reaction was further modificated by the applications of solid support,[3] microwave irradiation,[4] ionic liquid,[5] imidazole,[6] etc. However, there are few reports covering the synthesis of 3-aminothiophenes.[1f, g] The 3-aminothiophenes are mainly prepared by the modified Fiesselmann thiophene synthesis,[1h,7a,b] the Gommper reaction,[7c] and the reaction of β-halogenated or oxygenated acrylonitriles with mercaptans containing an activated methylene group,[7d-g] and one-pot synthesis of 4-substituted-3-amino-2-cyanothiophenes by treating 2-alkyl or aryl substituted acetonitrile with LDA, O-ethyl thioformate and 2-chloroacetonitrile.[7h] Among the above methods, however, only a few describe the direct synthesis of substituted 3-aminothiophenes, in particular 3,5-disubstituted-4-aminothiophene-2-carbaldehyde.

Besides, the above mentioned methods also suffered from unsatisfactory yields, difficult experimental procedures, expensive and detrimental metal precursors as well as harsh reaction conditions.[7a-h] Therefore, the development of improved methods for the synthesis of 3-aminothiophenes has acquired relevance to current research.

Recently much attention has been focused on applying vinyl azides as a pivotal three-atom synthon with the azido group serving as a leaving group for the formation of diverse nitrogen-containing heterocycles including pyrrolo[1,2-α]pyrazine, imidazoles, pyrroles, azaheterocycles, triazole, and oxazolines.[8] Inspired by these results and with the interest of developing a new type of [3+3] cycloaddition of 1,4-dithiane-2,5-diol, we investigated the reaction of vinyl azides and 1,4-dithiane-2,5-diol. Instead of the anticipated [3+3] cycloaddition products, we observed an unexpected domino process leading to 3,5-disubstituted-4-aminothiophene-2-carbaldehyde (Scheme 1). To the best of our knowledge, the preparation of the desired thiophene ring system containing both the amino group and the aldehyde group are rarely reported in the literature.[9]

Scheme 1 A domino process leading to 5-disubstituted-4-aminothiophene-2-carbaldehyde **3**

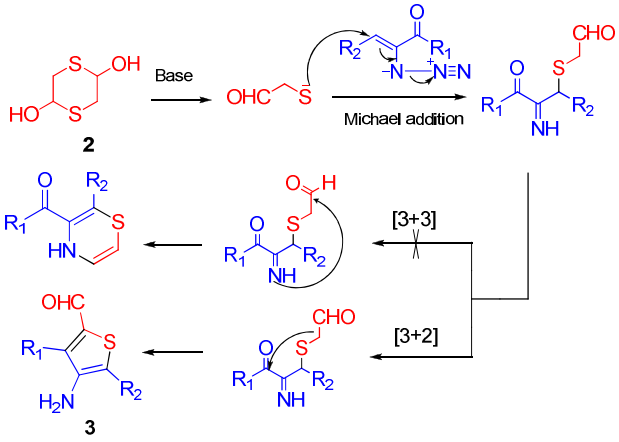
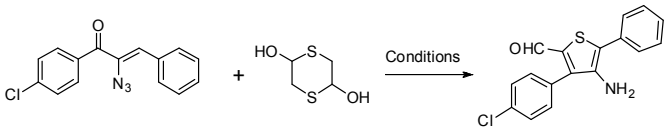


Table 1 Optimization of reaction conditions[a]



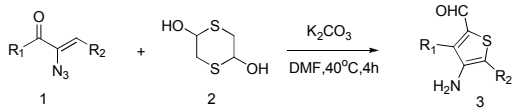
Entry	Base (equiv)	Solvent	T (°C)	t (h)	Conversion (%)[b]
1	—	DMF	40	4	Trace
2	**K_2CO_3(3)**	**DMF**	**40**	**4**	**88(86)[c]**
3	C_2H_5ONa(3)	DMF	40	4	43
4	KOH(3)	DMF	40	4	36
5	DBU(3)	DMF	40	4	13
6	Et_3N(3)	DMF	40	4	56
7	K_2CO_3(3)	C_2H_5OH	40	4	68
8	K_2CO_3(3)	THF	40	4	49
9	K_2CO_3(3)	CH_2Cl_2	40	4	37
10	K_2CO_3(3)	Toluene	40	4	22
11	K_2CO_3(3)	DMF	20	4	82
12	K_2CO_3(3)	DMF	60	4	79
13	K_2CO_3(1)	DMF	40	4	72
14	K_2CO_3(2)	DMF	40	4	75
15	K_2CO_3(5)	DMF	40	4	86

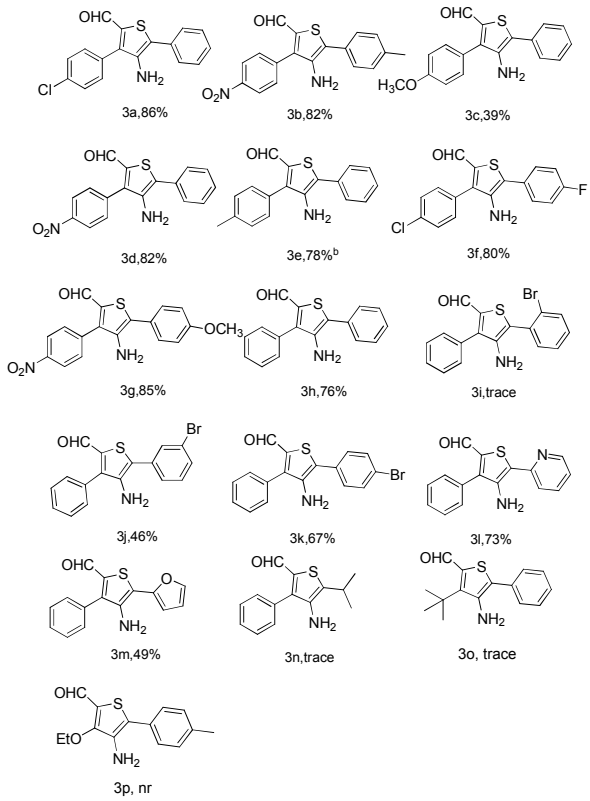
[a]Reaction conditions: (Z)-2-azido-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (0.4mmol, 1.0equiv), 1,4-dithiane-2,5-diol (0.4mmol, 1.0equiv), base (1.2mmol, 3.0 equiv) 2mL of solvent, 4h. The most efficient entry is highlighted in bold. [b]Determined by LC-MS, based on the disappearance of the starting α-azidovinylketones. [c] Isolated yields.

Initially, the coupling of (Z)-2-azido-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one and 1,4-dithiane-2,5-diol were selected as the reagents to optimize the reaction condition. Firstly, a range of bases were screened (Table 1, entries 1-6). There was almost no reaction without any base (Table 1, entry 1), which showed that bases may be needed for the deprotonation of 2-mercaptoacetaldehyde. But strong bases such as KOH and C_2H_5ONa (Table 1, entries 3-4) seemed destructive to the reaction. And some organic bases such as DBU and Et_3N (Table 1, entries 5-6) showed no improvement to the reaction. In order to investigate the effects of solvents on this reaction, a range of solvents including a polar protic solvent (Table 1, entry 7), polar aprotic solvents (Table 1, entry 8-9) and nonpolar solvent (Table 1, entry 10) were tested. But none of them showed better effects than DMF. The reaction was also assessed at different temperatures (Table 1, entries 11-12) with a slight decrease in the yield. Besides, we also conducted the reaction with different equivalents of K_2CO_3 (Table 1, entries 13-15). However, there was no significant improvement in yield with excessive K_2CO_3 (Table 1, entry 15) while the conversion decreased with less equivalents of K_2CO_3 (Table 1, entries 13-14). On the basis of this initial study, the most efficient reaction condition occurred when (Z)-2-azido-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (1 equiv), 1,4-dithiane-2,5-diol (1 equiv) and K_2CO_3 (3 equiv) were mixed in DMF at 40°C for 4h (Table 1, entry 2).

With the optimized reaction conditions in hand, the scope of the reaction was studied using a set of vinyl azides **1** and 1,4-dithiane-2,5-diol (Table 2).The α-azidovinylketones and α-azidovinylesters were readily prepared from the corresponding olefins by successive reaction with bromine and then with sodium azide.[10]

Table 2 Scope of the reaction of vinyl azides and 1,4-dithiane-2,5-diol under optimal conditions[a]



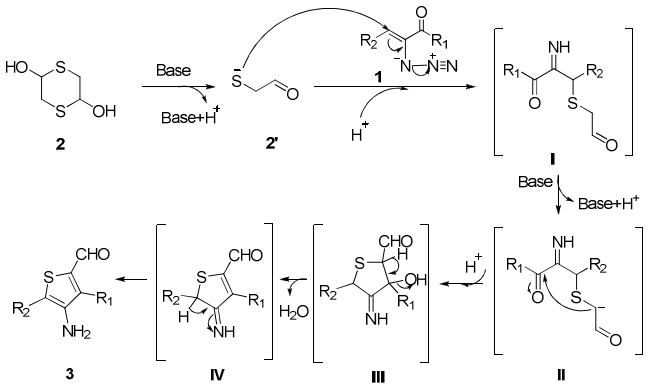


[a]Reaction conditions: vinyl azides (0.4mmol, 1.0equiv), 1,4-dithiane-2,5-diol (0.4mmol, 1.0equiv), K_2CO_3 (1.2mmol, 3.0 equiv) 2mL of DMF, 4h, 40°C. Isolated yield. [b]The reaction was conducted with 3.0 equiv of KOH

The result reveals that various substituted vinyl azides bearing several functional groups worked well with 1,4-dithiane-2,5-diol to provide the desired products. In general, α-azidovinylketones with electron-withdrawing groups at the $\mathbf{R^1}$ position performed better (**3a, 3d** compared to **3c, 3h**). However, substitutes at the $\mathbf{R^2}$ position with different electronic property affected little on the yields of the products (**3a** compared to **3f**; **3k** compared to **3h**; **3g, 3b** compared to **3d**). Interestingly, when the $\mathbf{R^2}$ position was substituted with bromobenzene, there was a distinct decrease in yields when the bromine was substituted at the 2- or 3- position (**3i, 3j** compared to **3k**), which indicated that steric hindrance at the $\mathbf{R^2}$

position may block the binding of α-azidovinylketones and 2-mercaptoacetaldehyde. Not surprisingly, the furan and pyridine group at the $\mathbf{R^2}$ position were also utilized in this approach (**3l, 3m**). Meanwhile, there was almost no reaction when the alkyl group was substituted at the $\mathbf{R^2}$ position (**3n**) or at the $\mathbf{R^1}$ position (**3o**). And (Z)-ethyl 2-azido-3-p-tolylacrylate was also experimented with 1,4-dithiane-2,5-diol at the same conditions (**3p**), but there was totally no reaction probably due to the low activity of ester group.

Scheme 2 Proposed reaction mechanism



The structures of the 3,5-disubstituted-4-aminothiophene-2-carbaldehyde **3** were characterized by IR, ^{1}H NMR, ^{13}C NMR, HRMS and HSQC(**3a**). On the basis of the results above, we proposed the following possible mechanism for this reaction, as shown in Scheme **2**.[11] First, it is expected to involve Michael addition-elimination of the mercaptoacetaldehyde **2'** to the vinyl azides **1** affording an active intermediate **I**, driven by the excellent leaving-group ability of nitrogen. Subsequently, the deprotonation of methylene of intermediate **I** by the base caused an intramolecular condensation to give the desired product **3.**

Conclusions

In conclusion, we have developed a facile approach to provide the structurally novel units, 3,5-disubstituted-4-aminothiophene-2-carbaldehyde, which are ubiquitous structural units in a number of biologically active compounds. The synthesis is economical both in lost atom count and the reaction materials. This novel reaction can be realized in good yields via a domino process involving sequential cyclization and intramolecular rearrangement. Eco-friendly reaction conditions, short reaction time, and facile substituent variation are all notable aspects of this methodology. This simple synthesis with the ability to incorporate multiple functional groups into a desired thiophene ring system provides an attractive strategy for pharmaceutical building blocks and medicinal chemistry applications.

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Notes and references

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