Green Synthesis and Structures of Novel Poly-substituted Double-thiazoles Based on Seven-component Reactions

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Abstract. Poly-substituted double-thiazoles have been synthesized by the reaction of α-thiocyanate ketones, aromatic aldehydes and aminothiourea in H2O, underwenting Michael addition, the SN2 nucleophilic replace and the cyclized dehydration reaction sequently in this article. This seven-component reaction constructs two thiazole cycles, eight σ bonds in one step, maximizing synthetic efficiency and showing the superiority of atom economy, bonding economy and environmentally friendly. The structures of the products were determined by IR, 1H NMR. This reaction achieve green multi-component synthesis of heterocyclic compounds, which would be used in medicinal chemistry and chemical biology research areas.

1. Introduction
Multicomponent reactions(MCRs) [1-3] are one-pot reactions in which the starting material is three or more and the reaction product structure contains all the components. This kind of reaction can effectively avoid the protection and deprotection of functional group, and is convenient for automatic synthesis. Compared with traditional multistep reactions, the advantages of multicomponent reactions in organic synthesis are obvious. MCRs can be used to create large libraries of compounds with the same mother nucleus structure, replacing diversity and complexity, which traditional combinatorial chemistry can not achieve. MCRs become a powerful measure to realize diversity-oriented synthesis. Heterocyclic compounds [4] containing thiazole [5] parent nucleus can be used in the preparation of antibiotics and anti-inflammatory drugs [6], such as sulfamethoxazole, which is an important antimicrobial agent. The mother nucleus of dithiazole is usually antibacterial, anticancer and antiarthritis, which is present in various drugs, such as fungicides or dyes. Therefore, its construction has attracted widespread attention.

In this study, the heterocyclic compounds containing dithiazole parent nucleus have been synthesized by means of microwave-assisted [7,8] multicomponent reaction, in order to obtain lead compounds with good activity. About the synthesis, not only the original material is simple and easy to obtain, but also the product usually contains many active parts, which may become a new drug.

2. Experimental instruments and reagents
Microwave reactions took place in the EmrysTM Creator microwave synthesis instrument produced by the Swedish company Personal Chemist; The NMR spectrum was determined by Bruker DPX400 MHZ type resonance spectrometer, DMSO-D6(or CDCl3) as solvent, and TMS as internal standard; FTIR-Tensor-27 infrared spectrometer(KBr tablets) was used to obtain infrared spectra; Determination of high resolution mass spectrometry was obtained by BRUKER micro TOF-Q II HPLC MS mass spectrometer; X-Ray diffraction analysis was performed on a Siemens P4 type four circular diffraction
instrument. The melting point of the compound was determined by the XT-5 microscopic melting point tester, not calibrated.

The organic reaction was tracked by Thin-Layer Chromatograph (TLC), ultraviolet lamp detection. TLC plate was made with silica gel (Qingdao Ocean Chemical Plant) and sodium carboxymethyl cellulose (CMC) and activated before use. Solvents and reagents used were all commercial.

3. Seven-component assemble—Green synthesis of dithiazole compounds

Aryl aldehyde (3mmol, 1a), aminothiourea (2mmol, 2) and 2 ml H₂O and catalytic HOAc were added into a 10mL EmrysTM special reaction vessel, respectively, which were stirred 5 min at room temperature, then α-thiocyanaryl aryl acetophenone (2mmol, 3a) was added into it.

After being blended homogeneously, the mixture was placed into the EmrysTM microwave synthesis. Specific reaction equation is shown in Scheme 1.

\[
\begin{align*}
\text{CHO} & + 2 \text{H}_2\text{N}^+\text{HNH}_2 + 2 \text{SCN}^- \xrightarrow{\text{HOAc}, \text{MWI}} \text{HN-S-R}_1\text{OR}_2
\end{align*}
\]

Scheme 1. Synthesis of complex mixtures 4 under MWI

This mixture was automatically pre-stirred 20 s in the instrument, which is radiated at 85 °C by microwave, for (initial power of 80W and maximum power of 150W) 15 ~ 25 min (monitored by TLC). After the reaction was completing, the mixture was taken out, cooled and filtered. 21 dithiazole derivatives (Figure1) were obtained by fully washing with 95 % heat ethanol. The molecular structure is shown in Table 1.

| Entry | Products | R₁ | R₂ | Time/min | Yield/% |
|-------|----------|----|----|----------|---------|
| 1     | 4a       | 4-Cl | H  | 15       | 89      |
| 2     | 4b       | 4-CH₃| H  | 15       | 90      |
| 3     | 4c       | 4-OCH₃| H  | 17       | 87      |
| 4     | 4d       | 4-(H₃C)₂N| H  | 18       | 95      |
| 5     | 4e       | H  | H  | 14       | 89      |
| 6     | 4f       | 4-Br | H  | 13       | 95      |
| 7     | 4g       | 2,4-Cl₂| H  | 14       | 79      |
| 8     | 4h       | 3,4-Cl₂| H  | 13       | 89      |
| 9     | 4i       | 4-NO₂| H  | 12       | 84      |
| 10    | 4j       | 4-Br | 4-OCH₃| 19       | 83      |
| 11    | 4k       | 4-NO₂| 4-OCH₃| 18       | 82      |
| 12    | 4l       | 4-CH₃| 4-OCH₃| 19       | 93      |
| 13    | 4m       | 4-OCH₃| 4-OCH₃| 20       | 93      |
| 14    | 4n       | 4-Cl | 4-OCH₃| 16       | 95      |
| 15    | 4o       | 4-CH₃| 3-Cl| 15       | 91      |
| 16    | 4p       | 4-OCH₃| 3-Cl| 16       | 89      |
| 17    | 4q       | 4-Cl | 3-Cl| 15       | 88      |
| 18    | 4r       | 4-(H₃C)₂N| 3-Cl| 17       | 88      |
| 19    | 4s       | 3-OCH₃-4-CN| 3-Cl| 18       | 89      |
| 20    | 4t       | 4-CH₃| 3-NO₂| 17       | 89      |
| 21    | 4u       | H  | 4-HO| 16       | 79      |
This reaction involves a series of cascade reactions seven components and has the following advantages:

1. Water is used as a reaction solvent and no other organic solvent is needed during the reaction;
2. The final treatment is simple and the filtration is only needed. After the completion of the reaction, the target product is directly precipitated. And the reaction substrates especially aminothiourea all have hydrophilic group, easy to dissolve in water;
3. Cheap and easily available starting materials (such as aryl aldehyde, amino thiourea and α-thiocyanacetophenone) are used and there is high stereoscopic configuration in the product;
4. The reaction time is short, only 12-19 min;
5. The reaction has good atomic economy and bonding efficiency;
6. There are a large number of bonds, that’s eight, constructed in one-step reaction;
7. The reaction was complex: the carbon-oxygen double bond (C = O) of three formyl groups and the single bond (C-S) of two-thionyl acetophenone were broken, meanwhile two carbon-sulfur bonds (C-S), four carbon nitrogen bonds (C-N) and two carbon bonds (C-C) were newly formed.

4. Confirmation of the structures of title compounds
The structures of all products were confirmed by 1H NMR, HRMS and IR. Restricted to length, only 4b is used as an example to illustrate the structural detection of the products.

Name of 4B: (2Z,2’Z)-5,5’-(p-tolylmethylene)bis(2-((E)-(4-methyl-benzylidene)hydrazono)-4-phenyl-2,3-dihydrothiazole), Orangered solid. Mp: 221-223 °C
IR (KBr, v, cm⁻¹): 3444, 2917, 1606, 1572, 1510, 1434, 1361, 1270, 1092, 791, 698, 513. ¹H NMR (400 MHz, DMSO-d₆) (δ ppm): 12.09 (s, 2H, NH), 7.99 (s, 2H, =CH), 7.51 (d, J = 8.0 Hz, 5H, ArH), 7.30-7.24 (m, 4H, ArH), 7.24-7.17 (m, 13H, ArH), 5.81 (s, 1H, CH), 2.32 (s, 3H, CH₃), 2.31 (s, 6H, CH₃). HRMS (ESI): m/z Calcd. for: C₄₂H₃₅N₆S₂: 687.2365, found: 687.2369.

In the nuclear magnetic resonance hydrogen spectrum of product 4b, one peak and three hydrogen were the absorption peaks of CH₃ linked to benzene ring in the range δ = 2.32; One peak, six hydrogen, at δ = 2.31 for the other two CH₃ associated with the benzene ring; In δ = 5.81, a monopole, 1 hydrogen, is the submethyl C-H absorption peak.

The number of other hydrogen atoms matches its structure.
In order to confirm the structure of the product, 4b single crystal was cultured and X-Ray diffraction was analyzed. Figure 2 shows the molecular structure of compound 4b.

![Fig. 2 X-ray Crystallography Structure of Compound 4b](image-url)
5. Conclusions

(1) As a result, a series of novel dithiazole parent nuclea derivatives were synthesized, with the orderly-resemble of dithiazole compounds. The multicomponent reaction was under microwave radiation, with water as a solvent, and α-thionyl ketone containing multi activation centers of reaction as reaction template, and introducing substituted aryl aldehyde and aminothiourea.

(2) This study provides not only a new response template for the seven-component reaction, which is an effective synthesis strategy and a green synthesis method for the construction of a specific bithiazole skeleton, but also a theoretical reference for exploring the effectiveness and diversity of the multi-component reaction and the development of the synthesis methodology.

The structures of the products are determined by 1H NMR, IR. Furthermore, the structures of some products are confirmed X-ray analysis. The microwave-assisted reactions mentioned above have advantages of shorter reaction time, higher yields and easier work-up as well as environmentally friendly. Therefore, a new and environmentally friendly method for the synthesis of these important compounds is provided.

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