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Concise Access to 2-Aroylbenzothiazoles by Redox Condensation Reaction between *o*-Halonitrobenzenes, Acetophenones, and Elemental Sulfur

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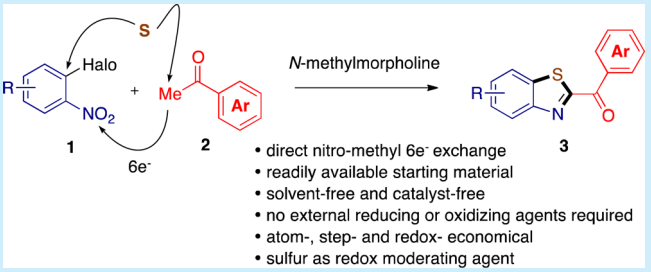
Supporting Information

ABSTRACT: A wide range of 2-aroylbenzothiazoles **3** including some pharmacologically relevant derivatives can be obtained in high yields by simply heating *o*-halonitrobenzenes **1**, acetophenones **2**, elemental sulfur, and *N*-methylmorpholine. This three-component nitro methyl coupling was found to occur in an excellent atom-, step-, and redox-efficient manner in which elemental sulfur played the role of nucleophile building block and redox moderating agent to fulfill electronic requirements of the global reaction.



2-Aroylbenzothiazoles are an important class of benzothiazole heterocycles with various pharmaceutical applications. They exist in a wide range of biologically active molecules such as **4** as antiviral agents,[1] **5** as fatty acid amide hydrolase inhibitors,[2] **6** as effective inhibitors of the antiapoptotic Bcl-2 protein which inhibits cell growth and induces apoptosis in human breast and prostate cancer cell lines,[3] and **7** as potent Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) inhibitors (Figure 1).[4] Moreover, **8** showed a promising profile regarding activity in T47-D cells, selectivity toward ERα and ERβ, inhibition of hepatic CYP enzymes, metabolic stability, and inhibition of marmoset 17β-HSD1 and 17β-HSD2.[5] Additionally, some closely related derivatives of 2-aroylbenzothiazoles were also identified as useful molecules in medicinal chemistry; for example, AC-265347 (**9**) was reported to be a calcium-sensing receptor agonist[6] and lidorestat (**10**) an aldose reductase inhibitor (for treatments for chronic diabetic complications).[7]

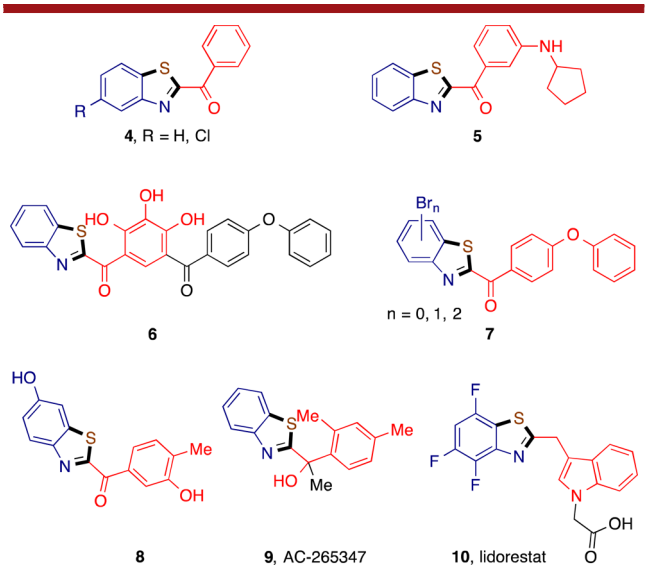


Figure 1. Bioactive 2-aroylbenzothiazoles and derivatives.

The synthesis of these derivatives relies on transformations from anilines (*o*-aminothiophenols[8] or dimers,[9] *o*-iodoanilines[10]) or preformed benzothiazoles (2-unsubstituted,[11] 2-benzyl,[9,12] 2-(α-hydroxybenzyl)benzothiazoles[1]). Although these methods can offer a wide range of structures, they suffer from some intrinsic drawbacks of low atom-, step-, and redox-efficiency. First, aniline and benzothiazole starting materials are not always readily available, and additional steps of preparation of starting material are generally required. Moreover, in the case of anilines,[8,10] reduced derivatives of phenyl glyoxylic acetophenones, phenylacetylenes, phenylglyoxals, etc., have been used as coupling partners. The global transformation required an external oxidizing agent. It should be noted that *o*-halonitrobenzenes are inexpensive, readily available, and stable starting materials for both anilines and benzothiazoles.

We have previously shown that access to 2-hetarylbenzothiazoles could be achieved using a three-component nitro-methyl redox condensation between *o*-halonitrobenzene, 2-methylhetarene, and elemental sulfur.[13] Compared to traditional approaches based on non-redox or only oxidizing reactions, this method emerged as an appealing alternative approach from both environmental and economical perspectives with respect to atom-, step-, and redox-economical requirements. In addition, the starting materials for this method are inexpensive and readily available in great structural diversity.

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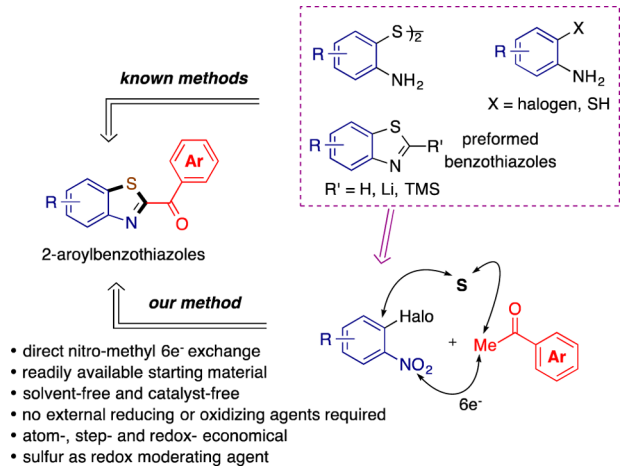
Continuing our efforts on the straightforward access to this heterocycle through three-component nitro-methyl redox condensation, we attempted to use acetophenones as reducing coupling partners (Scheme 1). The objective was also to have

Scheme 1. Access to 2-Aroylbenzothiazoles



available an efficient and flexible method for the preparation of analogs of compounds **4**–**10**. Readily available in a wide range of structures (from acetylation reactions of aromatic compounds, for example), these substrates could furnish six electrons required by the nitro groups, thus avoiding redox redundant transformations and providing a very direct approach to 2-aroylbenzothiazoles.

The use of an additional base can be intuitively envisioned as the result of a removal of one hydrogen chloride molecule. An optimization study focusing on the choice of base and the reaction stoichiometry has been carried out between *o*-chloronitrobenzene **1a**, sulfur, and acetophenone **2a** (Table 1).

Indeed, no product **3aa** was detected in the absence of a base (entry 1). Small nitrogen bases such as pyridine, 3-picoline, *N*-methylpiperidine, and *N*-methylmorpholine were chosen on the basis of their stability to the oxidation reaction with elemental sulfur and the aromatic nucleophilic substitution reaction with *o*-chloronitrobenzene (entries 2–5). Alicyclic bases as *N*-methylmorpholine and *N*-methylpiperidine gave better yields than heteroaromatic bases such as 3-picoline and pyridine, even at lower temperature. The best yield (86%) was achieved with *N*-methylmorpholine at 120 °C (entry 5). Lower molar ratios of either acetophenone or sulfur resulted in lower yields (results not shown). We were pleased to find that the reaction was general for other *o*-halogen substituents with only slight differences in reactivity.

Having established the optimized the reaction conditions, we studied the scope of the reaction by examining first a series of 2-halonitrobenzenes **1** and acetophenone **2a**. As presented in Figure 2, under the optimized conditions, a wide range of

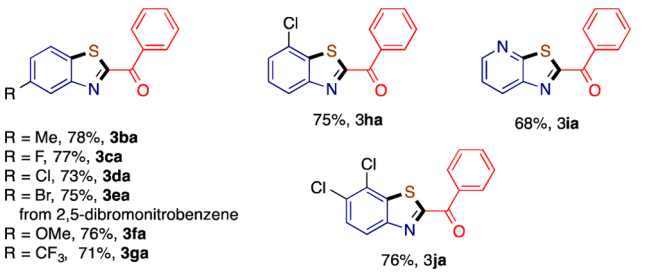


Figure 2. Scope of *o*-chloronitrobenzenes **1a** with acetophenone **2a**.

functional groups in **1** could tolerate the reaction conditions. To our delight, the reaction conditions could be applied to variety of useful functional groups on both organic components, including methyl, fluoro, chloro, bromo, methoxy, and trifluoromethyl substituents (products **3ba**–**ga**). The *o*-chloronitro compound derived from pyridine was also a suitable substrate for this redox condensation, furnishing the desired product in moderate yield (**3ia**). Pleasingly, 2,3,4-trichloronitrobenzene was highly compatible with the reaction conditions and was efficiently converted into the corresponding dichloro product **3ja** in good yield. It should be noted that *o*- and *p*-chloro groups are both strongly activated by the nitro group, but the sulfuration occurred exclusively with the *o*-chloro substituent.

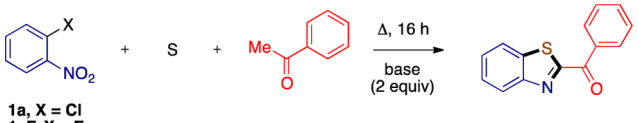
Subsequently, we turned our attention to the use of various methyl ketones **2b**–**n** as reducing coupling partners with **1a** (Scheme 2). Satisfactory yields were obtained when methyl, methoxy, phenoxy, acetamido, or chloro substituents were present in the acetophenone scaffold (**3ab**–**ai**).

Notably, reaction of 2′,4′-dimethylacetophenone and 2′,4′,6′-trimethylacetophenone required a higher temperature to give a yield comparable to that of other substrates (**3ah**), which might be attributed to steric hindrance effects of the *o*-methyl groups.

Interestingly, benzothiazolyl ketones with polyaromatic or heteroaromatic substituents, such as 2-naphthyl, 2-thienyl, pyridyl, furyl, and indolyl groups (**3aj**–**an**), could also be obtained from the corresponding hetaryl methyl ketones. The yields were higher for 2-thiophene-yl **3al** than for its oxygenated analogue **3am**, which could be explained by the higher stability of the thiophene ring. The reaction with sparingly soluble and readily oxidizable 3-indolyl methyl ketone required a higher temperature and DMF solvent to give a satisfactory yield of the desired product **3an** (41%).

For practical reasons, the use of less expensive *o*-chloro derivatives was preferred for most of the above examples. On the contrary, an attractive alternative of this reaction is the possibility of performing it with other *o*-halogen derivatives. For instance, 2,5-difluoronitrobenzene and 2-chloro-5-fluoronitrobenzenes

Table 1. Screening of Reaction Conditions



entry[a]	X	base	*T* (°C)	yield[b] (%)
1	Cl		120	0[c]
2	Cl	pyridine	120	<5[c]
3	Cl	3-picoline	150	51
4	Cl	*N*-methylpiperidine	120	72
5	Cl	*N*-methylmorpholine	120	85
6	F	*N*-methylmorpholine	120	82
7	Br	*N*-methylmorpholine	120	86
8	I	*N*-methylmorpholine	120	81

[a]Reaction condtitions: **1a** (2.5 mmol), **2a** (5 mmol), S (10 mmol, 320 mg), base (5 mmol). [b]Isolated yield. [c]Conversion determined by ^{1}H NMR.

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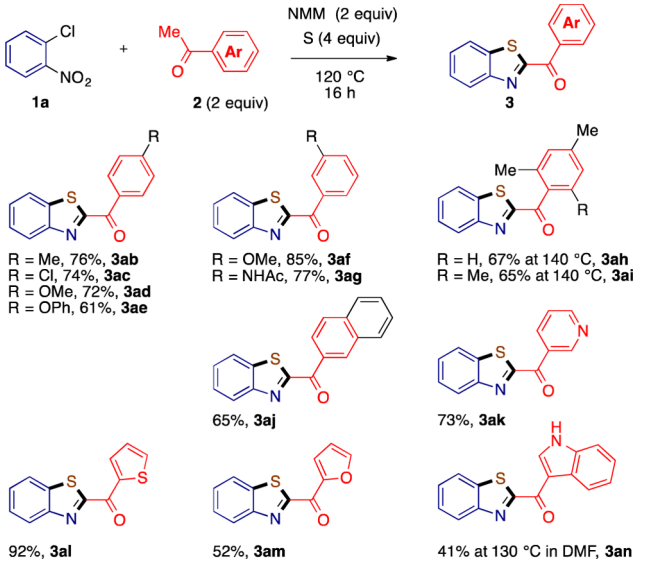
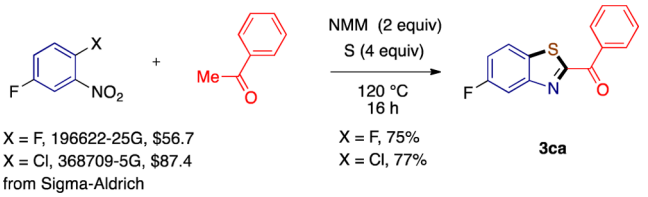
Scheme 2. Scope of Aryl Methyl Ketones 2 with *o*-Chloronitrobenzene 1a



both provided the same condensed products in comparable yields, but the difluoro derivative is less expensive (Scheme 3).[14]

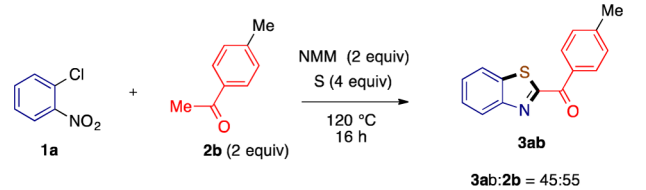
Scheme 3. Formation of 3ca Using Different *o*-Halonitrobenzenes 1



Interestingly, it should be noted that benzothiazoles **3aa** and **3da** have been reported to have potent antiviral activity,[1] whereas molecules **3ae**, **3ag**, and **3ah** could serve as precusors for the construction of a fatty acid amide hydrolase inhibitor **5**, CaMKII inhibitor **7**, and calcium-sensing receptor agonist AC-265347 (**9**), respectively.

Although the mechanism is far from well understood, some control experiments were performed to gain further insights into the nature of this transformation. First, the reaction stoichiometry was investigated for organic components. The reaction between *o*-chloronitrobenzene **1a** (1 equiv) and 4′-methylacetophenone **2b** (2 equiv) performed in a sealed tube was chosen for this purpose (Scheme 4). Under standard conditions, the reaction proceeded smoothly without any formation of gaseous byproducts. ^{1}H NMR analysis of the crude mixture based on methyl signals of the *p*-tolyl ring[15] showed a clean 45:55 mixture

Scheme 4. Control Experiment with 1a and 2b

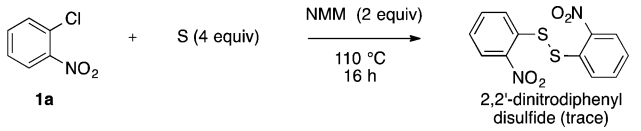


of 4′-methylacetophenone **2b** and the desired condensed product **3ab** (see the Supporting Information).

This observation suggested that only one molecule of acetophenone was required and sulfur should play a dual role as the redox-moderating agent by compensating for the electron gap of the global process.

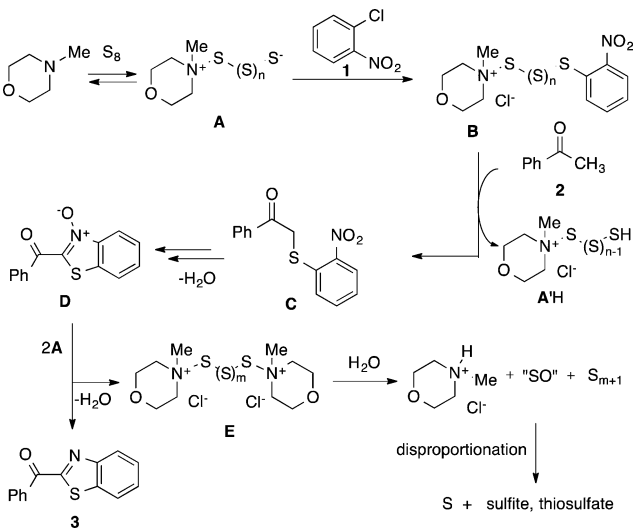
Next, starting materials were heated with *N*-methylmorpholine at 120 °C for 16 h. The ^{1}H NMR analyses of the crude mixtures showed that all of the organic molecules remained unchanged except that a trace amount of 2,2′-dinitrodiphenyl disulfide was formed when *o*-chloronitrobenzene, sulfur, and *N*-methylmorpholine were heated together (Scheme 5). This result indicated that the transformation involved a cascade pathway via highly reactive intermediates.

Scheme 5. Control Experiment without Acetophenone



On the basis of these observations as well as related reactions, we propose the mechanism shown in Scheme 6.

Scheme 6. Proposed Mechanism



The process could be initiated by the reaction of sulfur with *N*-methylmorpholine to reversibly generate ammonium polysulfide zwitterion **A**. Subsequent nucleophilic aromatic substitution of zwitterion **A** on **1a** would lead to **B**. Thanks to the electron-withdrawing effect of the aromatic nitro group, the S−S bond next to the aromatic ring of **B** is fragile, and **B** would be capable of attacking acetophenone **2**[16] to provide sulfide **C** and a homologue of zwitterion **A**. Activated by both a benzoyl group and aryl sulfide group, the methylene group of sulfide **C** could condense readily with the aromatic nitro group leading to nitrone **D**. Reduction of **D** with **A** or homologues would provide **3** along with double-zwitterion **E**. Hydrolysis of **E** by water (byproduct of the steps **C** → **D** and **D** → **E**) would regenerate partially elemental sulfur[16] and lead to oxygenated sulfur compounds ("SO") and *N*-methylmorpholinium hydrochloride. Obviously, it should be pointed out that the presence of morpholinium

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hydrochloride could accelerate the tautomerization of acetophenone, thus facilitating the **D** → **E** step.

In summary, we have developed a three-component redox condensation of a variety of *o*-nitrohalobenzenes and acetophenone with elemental sulfur, enabling a direct, inexpensive, and easy synthesis of 2-benzoylbenzothiazoles. The choice of base is of vital importance to the success of the transformation, and *N*-methylmorpholine was found to be particularly suitable for this role. Elemental sulfur was found to play dual roles as nucleophilic building block and redox moderating agent to fulfill electronic requirement of the global process. The process involves the formation of three new bonds (two C−S and one C═N) in a highly efficient and atom-, step-, and redox-economical manner without addition of oxidizing or reducing agents or coupling catalyst.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01182.

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Notes

The authors declare no competing financial interest.

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(14) At the time of manuscript preparation, 2-chloro-5-fluoronitrobenzene and 2,5-difluoronitrobenzene were commercially available from Sigma-Aldrich for $87.40/25 g (196622-5G) and $56.70/25 g (368709-5G), respectively.
(15) Only three ^{1}H NMR singlet signals which correspond to one methyl signal of the product **3ab** and two methyl signals of the starting ketone **2b** were observed between 2.0 and 2.8 ppm. If other products derived from **2b** were formed, other singlet signals should be observed in this zone.
(16) For the single example of related bis(DABCO)disulfide dichloride salt, see: (a) Konstantinova, L. S.; Rakitin, O. A.; Rees, C. W.; Amelichev, S. A. *Mendeleev Commun.* **2004**, *14*, 9. (b) Konstantinova, L. S.; Amelichev, S. A.; Rakitin, O. A. *Russ. Chem. Bull.* **2006**, *55*, 2081. (c) Konstantinova, L. S.; Lysov, K. A.; Souvorova, L. I.; Rakitin, O. A. *Beilstein J. Org. Chem.* **2013**, *9*, 577. This compound was found to be unstable and readily hydrolyzed to yield elemental sulfur, DABCO hydrochloride, and other sulfur compounds with positive oxidation states of sulfur.

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