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One Pot Regioselective Synthesis of a Small Library of Dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-ones via Smiles Rearrangement

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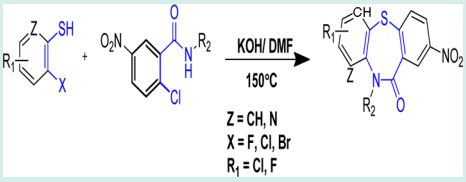
Supporting Information

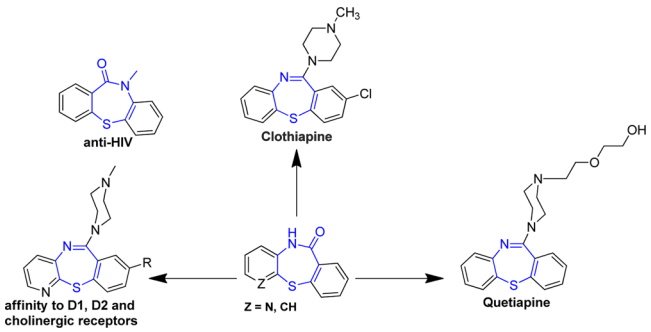
ABSTRACT: A facile and efficient method has been developed for the synthesis of a small library of dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-ones via Smiles rearrangement. Compounds were obtained in excellent isolated yields (70%−92%) under metal-free conditions. More specifically, this transition metal-free process relates to an environmentally friendly, economical, and efficient method for preparing benzoic-fused seven-membered lactams.



KEYWORDS: *metal-free process, benzoic-fused seven-membered lactams, Smiles rearrangement*

INTRODUCTION

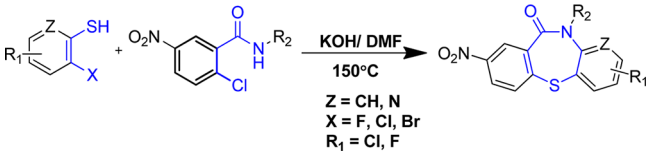
The development of heterocyclic scaffolds is a fast emerging subject in medicinal chemistry. Among these, benzo-fused sulfurated seven-membered lactams are endowed with a large spectrum of biological activities with a wide range of interesting, physiological activities. For example, they were reported as potential Ca-channel blockers,[1] NMDA glycine-site antagonists,[2] anticoagulants,[3] inhibitors of proteases,[4,5] antihypertensive agents,[6−8] and antitumor agents.[9] 6-(4-Methylpiperazin-1-yl)benzo[*f*]pyrido-[2,3-*b*][1,4]thiazepine has good affinity to D_1, D_2 and cholinergic receptors.[10] Additionally, dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-ones and some of their analogues were useful for AIDS prevention and treatment.[11−14] Moreover, they were also used as an intermediate compound for the preparation of quetiapine.[15−17] Additionally, some 3,4-dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-ones have recently been described with anti-TBC activity[18] Because of this, there still remains a need for new benzoazepine-2-one derivatives which exhibit physiological and pharmaceutical activities.



Many methods have been used to synthesize benzoazepine-2-ones, such as multistep cyclization processes,[19] denitrocyclization by intramolecular substitution of the nitro group,[20] photoisomerization via homolytic cleavage of the S−N bond,[21] and click-cyclization via microwave assistance.[22] However, there are still some potential limitations including the demand for substrates which are not readily or commercially available, and inefficiency of the transformations restrain the wider utilization. Therefore, a new and more effective method involving mild, environmentally benign, atom-economical, and metal-free conditions is still highly needed for the combinatorial synthesis of a diversified, small-molecules library to fill the demands for dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-ones.

We have been studying the development of economical syntheses of heterocyclic systems.[23] Herein, we describe a one pot synthesis of dibenzo[*b*,*f*][1,4] thiazepin-11(10*H*)-ones via Smiles rearrangement and without metal catalysts or microwave−assistance. The benzoazepine-2-ones were obtained by the reaction of halobenzenethiol or 3-chloro-5-(trifluoromethyl)pyridine-2-thiol with *N*-substituted nitrobenzamide (Scheme 1).

Scheme 1. Synthesis of Benzoic-Fused Seven-Membered Lactams



RESULTS AND DISCUSSION

Optimized reaction conditions were found by systematically investigating the reaction parameters using 2,3-dichlorobenzenethiol and *N*-benzyl-2-chloro-5-nitro benzamide (Table 1). First, testing different bases like Cs_2CO_3, KOH, NaH, BuOK, Et_3N in dimethylformamide (DMF) at 150 °C proved that KOH was the most suitable base. Then we probed into the

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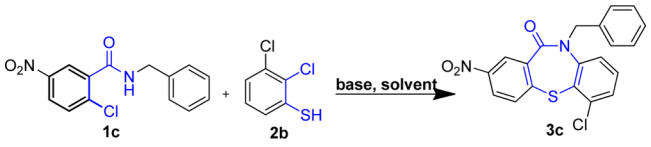
Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	time (h)	yield (%)[b]
1	Cs_2CO_3	DMF	7	43
2	KOH	DMF	5	85
3	BuOK	DMF	5	70
4	NaH	DMF	5	65
5	Et_3N	DMF	8	0
6	KOH	CH_3CN	8	30
7	KOH	DMSO	5	65
8	KOH	NMP	10	0

[a]Reaction conditions: *N*-benzyl-2-chloro-5-nitrobenzamide **1c** (0.6 mmol), 2,3-dichlorobenzenethiol **2b** (0.5 mmol), and base (1.5 mmol) in solvent (15.0 mL) under N_2 at 150 °C (entries 1−5, 7−8)/80 °C (entries 5 and 6). [b]Isolated yield.

influence of different solvents on the reaction. DMF was found to be superior to CH_3CN, DMSO, and NMP.

The optimized reaction conditions were used to explore the scope and limitations for synthesizing dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-ones (Tables 2, 3 and 4). The desired dibenzo[*b*,*f*]-[1,4]thiazepin-11(10*H*)-ones were obtained in 70% to 92% yield (Tables 2 and 3). Besides, we used DMSO as solvent when R_2 was aryl (Table 2, entries 5−10) because of its better solubilizing power for the *N*-aryl compounds. Varying R_2 from aryl to alkyl afforded no significant differences in yield (Table 2) with this solvent change. We also found that neither the *N*-aryl substrates with an electron-donating group (Table 2, entries 8−10) nor substrates with an electron-withdrawing group (Table 2, entries 5−7) affected the experimental results. According to the experimental results, when the *N*-substituent of **1** was isopropyl or cyclohexyl, the reaction did not afford the expected product in spite of trying higher temperature and reaction times. We believe steric hindrance is responsible for the results. Additionally, from Table 3, it is interesting to note that neither the variation of halogen type nor the variation of the halogens' position did interfere with the outcome of the reaction. Besides, a short series of

Scheme 2. Plausible Reaction Mechanism

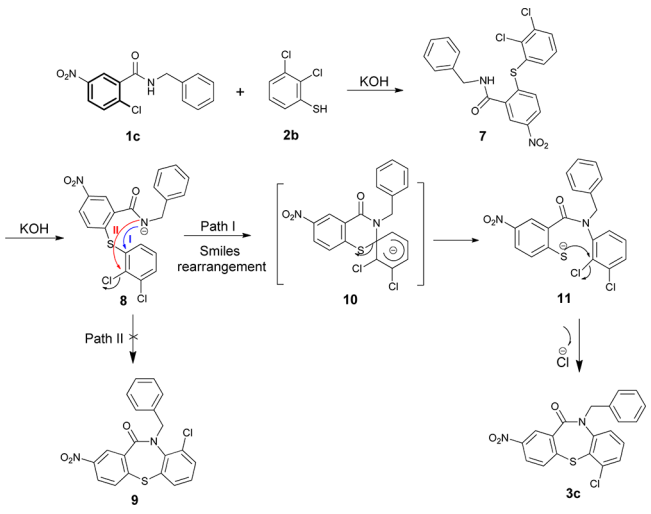
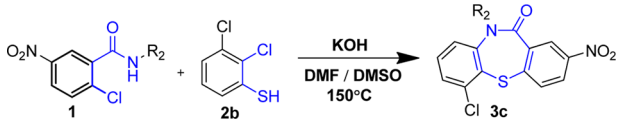


Table 2. Synthesis of Dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-ones 3



entry	R_2	product[a]	yield (%)[b]
1	**1a**	**3a**	72
2	**1b**	**3b**	70
3	**1c**	**3c (4b)**	88
4	**1d**	**3d**	75
5	**1e**	**3e**	80
6	**1f**	**3f**	89
7	**1g**	**3g**	90
8	**1h**	**3h**	82
9	**1i**	**3i**	92
10	**1j**	**3j**	88

[a]Reaction conditions: 2,3-dichlorobenzenethiol **2b** (0.5 mmol), *N*-substituted nitrobenzamide **1a** and analogues **1b**−**1j** (0.6 mmol) and KOH (1.5 mmol) in DMF (15.0 mL, **1a**−**1d**)/DMSO (15.0 mL, **1e**−**1j**) under N_2 at 150 °C for 4 h. [b]Isolated yield.

pyridobenthiazepine derivatives were also obtained with high yields (Table 4).

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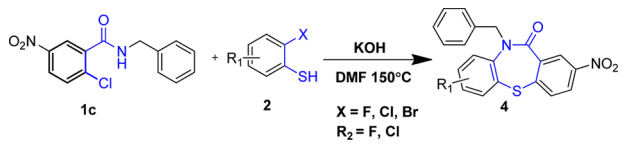
Table 3. Synthesis of Dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-ones 4



entry	2	product[a]	yield (%)[b]
1	**2a**	**4a**	72
2	**2b**	**4b (3c)**	88
3	**2c**	**4c**	82
4	**2d**	**4d**	85
5	**2e**	**4e**	75

[a]Reaction conditions: *N*-benzyl-2-chloro-5-nitrobenzamide **1c** (0.6 mmol), halogenous benzenethiol **2a** and analogues **2c**−**2e** (0.5 mmol) and KOH (1.5 mmol) in DMF (15.0 mL) under N_2 at 150 °C for 4 h. [b]Isolated yield.

Additionally, the molecular structure of the representative product **3c** was determined by X-ray crystallography analysis (Figure 1). Thus, a plausible mechanism was presented in

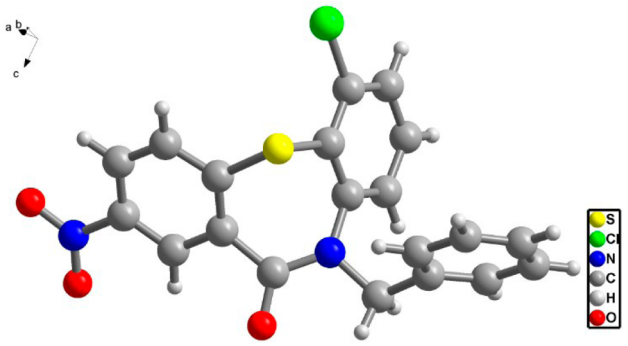
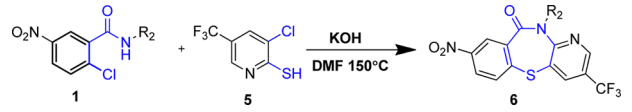


Figure 1. X-ray structure of compound **3c**.

Scheme 2, on the basis of our results combined with the reported papers.[22] The reaction of **1c** with **2b** yielded compound **7**. Compound **7** could proceed via two paths (I and II). Path II could afford the direct intramolecular nucleophilic substitution product **9**. By contrast, path I could lead to the compound **3c** via Smiles rearrangement. We only obtained compound **3c**. Imido nitrogen in compound **8** underwent intramolecular nucleophilic attack on the carbonium ion **10**. Migration of the spiro-sulfur, proceeding through the "Meisenheimer Complex" **10**, with intramolecular nucleophilic displacement of chlorine anion by a sulfur anion of compound **11** yielded the desired cyclic product **3c** (Scheme 2).

Table 4. Synthesis of Benzo[1,4]thiazin-3(4*H*)-ones 6



entry	R_2	product[a]	yield (%)[b]
1	**1b**	**6a**	70
2	**1c**	**6b**	83
3	**1d**	**6c**	72
4	**1f**	**6d**	81
5	**1h**	**6e**	80
6	**1i**	**6f**	86
7	**1j**	**6g**	85

[a]Reaction conditions: 3-chloro-5-(trifluoromethyl)pyridine-2-thiol **5** (0.5 mmol), N-substituted nitrobenzamide analogues **1b**−**1d** and **1f**, **1h**, **1i**, **1k** (0.6 mmol) and KOH (1.5 mmol) in DMF (15.0 mL, **1b**−**1d**) / DMSO (15.0 mL, **1f**, **1h**, **1i**, **1j**) under NRR2 RRat 150 °C for 4 h. [b]Isolated yield.

Moreover, we recently did a theoretical study of this S−N type Smiles rearrangement process to rationalize the experimental observations.[23a] By performing quantum chemistry calculations, we show the molecular mechanism for the S−N type Smiles rearrangement. And the theoretical results show that the Smiles rearrangement pathway is energetically more favorable than the direct nucleophilic substitution pathway.

CONCLUSION

We have developed an operationally simple and economic synthesis of a great number of benzo-fused sulfurated seven-membered lactams in high yields. This metal-free method accords with the developing of the current organic synthesis trend toward cleaner and greener chemical processes because of the pressing environmental and energy problems. Therefore, this transition metal-free process has potential applications in the synthesis of biologically and medicinally relevant compounds.

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EXPERIMENTAL PROCEDURES

General Experimental Procedures for the Synthesis of TTdibenzo[*b,f*][1,4]thiazepin-11(10*H*)-ones or benzo[*b*]-pyrido[2,3-*f*][1,4]thiazepin-11(10*H*)-ones. A 25 mL Schlenk tube equipped with a magnetic stirring bar was charged with halogenous benzenethiol (**2a**−**2e**) or 3-chloro-5-(trifluoromethyl)pyridine-2-thiol (**5**) (0.5 mmol, 1.0 equiv), *N*-substituted nitrobenzamides (**1a**−**1j**) (0.6 mmol, 1.2 equiv), KOH (84 mg, 1.5 mmol, 3.0 equiv), and then 15 mL of DMF or DMSO was added via syringe at room temperature, and the mixture was prestirred for about 15 min. Then the reaction was stirred at 150 °C. After the reaction was completed, the mixture was diluted with brine (40 mL) and extracted with ethyl acetate twice (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo to afford a residue. The crude product was then purified by column chromatography on silica gel to give the pure product.

ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures, copies of ^1H NMR and ^{13}C NMR spectra of all compounds and X-ray data of **3c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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