Accepted Manuscript

Access to thiomorpholin-3-one derivatives: [3 + 3]-cycloadditions of α-chlorohydroxamates and 1,4-dithiane-2,5-diol

Zhao-Lin He, Yi Chen, Xiaohua Wang, Mingwang Ni, Gang Wang

PII: S0040-4020(19)30773-2

DOI: https://doi.org/10.1016/j.tet.2019.07.019

Reference: TET 30461

To appear in: *Tetrahedron*

Received Date: 17 May 2019

Revised Date: 9 July 2019

Accepted Date: 12 July 2019

Please cite this article as: He Z-L, Chen Y, Wang X, Ni M, Wang G, Access to thiomorpholin-3-one derivatives: [3 + 3]-cycloadditions of α-chlorohydroxamates and 1,4-dithiane-2,5-diol, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.07.019.

Graphical Abstract

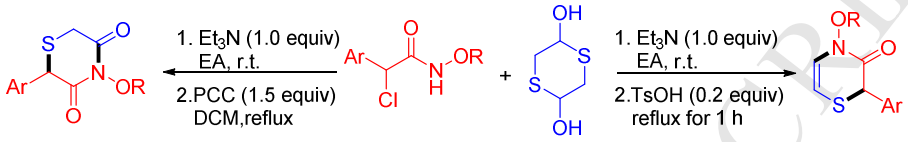
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Access to Thiomorpholin-3-one Derivatives: [3 + 3]-Cycloadditions of α-Chlorohydroxamates and 1,4-Dithiane-2,5-diol

Leave this area blank for abstract info.

He Zhao-Lin[a] , Chen Yi[a], Wang Xiaohua[b], Ni Mingwang[a], and Wang Gang[a,] *

[a] *School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan, 430205, PR China*
[b] *Department of Pharmaceutical Engineering, WuChang University of Technology, Wuhan, 430223, PR China*



- Efficient synthtic route
- Mild condition, simple procedure
- Readily available reagents

Tetrahedron
journal homepage: www.elsevier.com

Access to Thiomorpholin-3-one Derivatives: [3 + 3]-Cycloadditions of α-Chlorohydroxamates and 1,4-dithiane-2,5-diol

He Zhao-Lin[a] , Chen Yi[a], Wang Xiaohua[b], Ni Mingwang[a], and Wang Gang[a,] *

[a] *School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan, 430205, PR China*
[b] *Department of Pharmaceutical Engineering, WuChang University of Technology, Wuhan, 430223, PR China*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
cycloaddition
azaoxyallyl cations
1,4-dithiane-2,5-diol
2*H*-1,4-thiazin-3(4*H*)-ones
thiomorpholine-3,5-diones

ABSTRACT

A protocol of [3 + 3]-cycloaddition was proposed for the synthesis of 2*H*-1,4-thiazin-3(4*H*)-ones and thiomorpholine-3,5-diones from α-chlorohydroxamates and 1,4-dithiane-2,5-diol. This direct and pratical method provides a novel and rapid approach for the synthesis of thiomorpholin-3-one derivatives under mild condition with moderate to good yield and wide functional group tolerance.

1. Introduction

Thiomorpholin-3-ones are unique heterocyclic motifs present in a number of natural products and bioactive molecules with promising activities, such as shermilamine F is a pyridoacridine alkaloids isolated from the Ascidian Cystodytes, bafilomycins F (**1**) isolated from *Streptomyces* sp. is a potent inhibitor of autophagy.[1-2] ML276 was found to be a submicromolar inhibitor of *Pf* G6PD.[3] Fluorescent compound **4**, a transcyclized product of GGT probe NM-GSH, could easily pass through cell-membrane and enrich in lysosomes and selectively lit up the GGT overexpressed cancer cells for easy visualization, possesses the potential for cancer diagnosis and treatment (Figure 1).[4] Due to their bioactivities and medicinal value, the exploration of efficient methods to build thiomorpholin-3-ones' frameworks is of significant importance. Reported methods include: (i) direct condensation of thioglyco-lates with 2-oxazolidinones,[5] (ii) MCR reaction of diaryl 1,2-diones, thiazolium salts and water,[6] (iii) domino reaction from thioglycolates, aldehydes and ammonia catalyzed by L-proline. [7] Despite the accomplishment of the aforementioned methods toward constructing thiomorpholin-3-ones, the development of a more efficient method with facile accessible substrates is still highly desirable.

As a type of transient reactive species, the azaoxyallyl cations which can be generally in situ generated from α-halohydroxamates in the presence of bases, In 2010, this intermediate was first trapped by Jeffrey's group using cyclic dienes in the [4 + 3]-cyloadditon reaction, providing bicyclic lactam derivatives in good yields and diastereoselectivity.[8-11] Later in 2015, Jeffrey and Wu independently reported the first example of dearomative [3 + 2]-cycloaddition reaction of in-situ formed azaoxyallyl cations with substituted indoles, providing rapid access to a variety of functionalized pyrroloindoline derivatives in good yields.[12-13] Since these elegant discoveries,

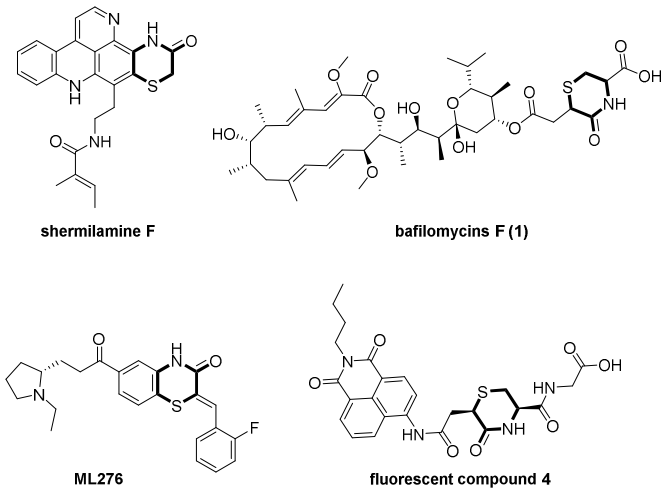


Figure 1. Selected examples of natural products and bioactive compounds containing a thiomorpholin-3-one framework

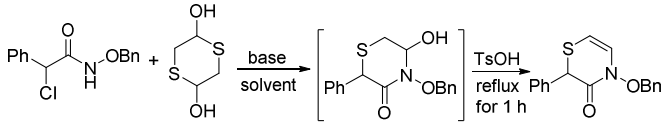
* Corresponding author. Tel.: +86-027-87194560; e-mail: wg@wit.edu.cn

the azaoxyallyl cation species have attracted considerable attention as highly efficient 3-atom units in [3 + m] cycloaddition reactions for the construction of various biologically important nitrogen containing heterocycles.[14] And a series of [3 + 1]-, [3 + 2]-, and [3 + 3]-cycloaddition reactions have been developed with azaoxyallyl cations used as versatile surrogates of "1,3-dipole" to react with sulfur ylides,[15] aldehydes,[16] ketones,[17-18] imines,[19-21] enamines, [22] isothiocyanides,[23] nitrones,[24-25] *N*-oxides,[26] aromatic ethylenes,[27] alkynes,[28] indole derivatives,[29-31] azides and nitriles respectively,[32-33] providing the corresponding cycloaddition products. Some of these new cycloaddition reactions were used for the synthesis of natural products.[29, 30] In addition, the azaoxyallyl cations were also reported as 2-atom units in [2 + 4]-cycloaddition reactions with *N*-(2-chloromethyl)aryl)amides for the construction of 1,4-dihydro-2*H*-benzo[*d*][1,3]oxazines,[34] and the intramolecular cycloaddition involving azaoxyallyl cations for the synthesis of N-Hydroxy Oxindoles by an aza-nazarov-type reaction was reported by Liao group.[35] As a relatively stable sulfur source,[36-38] mercaptoacetaldehyde is an electrophilic-nucleophilic reagent which might function as a cyloadditon partner with 1,3-dipole. Therefore, We envisioned that thiomorpholin-3-one framework might be constructed by the [3 + 3]-cycloaddition of azaoxyallyl cations and mercaptoacetaldehyde. Herein, we wish to report our preliminary result of the protocol to prepare thiomorpholin-3-one derivatives: 2*H*-1,4-thiazin-3(4*H*)-ones and thiomorpholine-3,5-diones.

2. Results and Discussion

To investigate the cyclization between azaoxyallyl cations and mercaptoacetaldehyde, we first examined the reaction between *N*-(benzyloxy)-2-chloro-2-phenylacetamide (**1a**, in situ generated azaoxyallyl cation) and 1,4-dithiane-2,5-diol (**2a**, in situ generated mercaptoacetaldehyde) in the presence of Et_3N in THF, the cycloaddition proceeded smoothly and intermediate **3a'** was observed, after treated with TsOH in one pot, the desired 4-(benzyloxy)-2-phenyl-2*H*-1,4-thiazin-3(4*H*)-one **3a** was isolated in 79% yield. Subsequently, the conditions of the cyclization reaction were screened, a series of bases were explored for this reaction. As shown in **Table 1**, changing Et_3N to DIPEA gave a lower yield in 57%, while secondary amine DIPA exhibited almost comparable activity as Et_3N and the reaction was completed in 8h, giving **3a** in 71% yield (**Table 1, entry 1-3**). The cycloaddition could also be promoted by DMAP, but the reaction rate became quite slow, with substrate **1a** consumed over 96 h and product **3a** isolated in 70% yield. DABCO failed to produce the expected product, giving trace amount of **3a** as indicated by TLC (**Table 1, entry 4-5**). Inorganic bases such as K_2CO_3, Na_2CO_3, EtONa produced **3a** in diminished yields, while NaOH gave no desired product, accompanied by the totally decomposation of **1a** within 12 h (**Table 1, entry 6-9**). Then, a brief solvent survey demonstrated that EA was the best, and the annulation completed in 8h and produced **3a** in 82% yield (**Table 1, entry 10-18**). Intermediate **3a'** was also successfully isolated from the reaction, and the diastereoselectivity was checked by NMR. Unfortunately, all the conditions we tried gave very poor *d.r.* value ranging from 1:1 to 1:1.2 (see supplementary data).

Table 1. Optimization of the annulation towards **3a**[a]



1a **2a** **3a'** **3a**

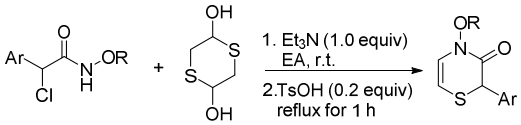
entry	base	solvent	time (h)	yield (%)[b]
1	Et_3N	THF	12	79
2	DIPEA	THF	12	57
3	DIPA	THF	8	71
4	DMAP	THF	96	70
5	DABCO	THF	24	trace
6	Na_2CO_3	THF	72	55
7	K_2CO_3	THF	8	73
8	EtONa	THF	24	61
9	NaOH	THF	12	decomposed
10	Et_3N	DCM	8	46
11	Et_3N	$CHCl_3$	8	76
12	**Et_3N**	**EA**	**8**	**82**
13	Et_3N	Acetone	12	79
14	Et_3N	CH_3CN	8	75
15	Et_3N	Toluene	24	56
16	Et_3N	dioxane	12	80
17	Et_3N	DMF	4	65
18	Et_3N	DMSO	4	42

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.375 mmol), base (0.5 mmol), in solvent (5 mL) were stirred under room temperature.

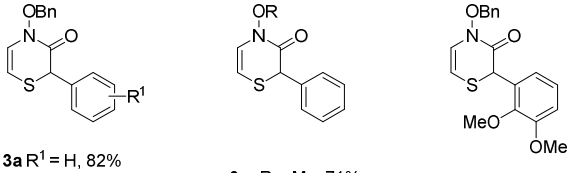
[b] Yield refers to isolated products after chromatography.

With the optimal conditions in hand, we then examined the scope of the cycloaddition reaction, a set of α-halohydroxamates **1** were tested. As shown in **Table 2**, α-halohydroxamate derivatives with various substitution patterns including electron-deficient and electron-donating groups all carried out this reaction smoothly to form the corresponding products **3b-3j** in medium to good yields. The yields of 2*H*-1,4-thiazin-3(4*H*)-ones with electron-donating group substituted aromatic ring (**3d**, **3f**, **3g**) was slightly higher than the products bearing electron-deficient aromatic ring (**3b-3c**, **3e**, **3h-3l**). There was no significant steric effect when the *ortho*-substituted arylacetamides were used as starting materials (**3b-3d**). Replacing the benzyloxy group on the nitrogen atom with methoxy or ethoxy group also gave desired products in good yield (**3m**, **3n**). Disubstituted arylacetamides were also tested to react with **2a**, the corresponding products **3o** and **3p** were isolated in 73% and 84% yield, respectively. Finally, *N*-(benzyloxy)-2-chloro-2-(naphthalen-2-yl)acetamide generated product **3q** in 80% yield. It was noteworthy that alkyl group substituted α-chlorohydroxamate (2-bromo-*N*-ethoxy-2-methylpropanamide) was also tested in the reaction, surprisingly, just the intermediate **3'** was detected in moderate yield, but after reflux by addition of either TsOH or PCC, trace amount of product **3** or **4** was detected by TLC.

Table 2. Formation of 2*H*-1,4-thiazin-3(4*H*)-ones 3[a, b]



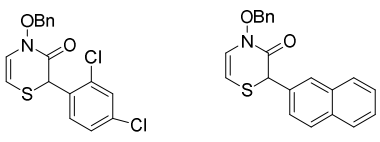
1 **2a** **3**



3a R^1 = H, 82%
3b R^1 = 2-Cl, 66%
3c R^1 = 2-NO_2, 72%
3d R^1 = 2-OMe, 87%
3e R^1 = 3-Cl, 71%
3f R^1 = 3-OMe, 79%
3g R^1 = 4-Me, 86%
3h R^1 = 4-F, 75%
3i R^1 = 4-Cl, 74%
3j R^1 = 4-Br, 68%
3k R^1 = 4-CN, 76%
3l R^1 = 4-NO_2, 72%

3m R = Me, 71%
3n R = Et, 84%

3o, 87%



3p, 73%

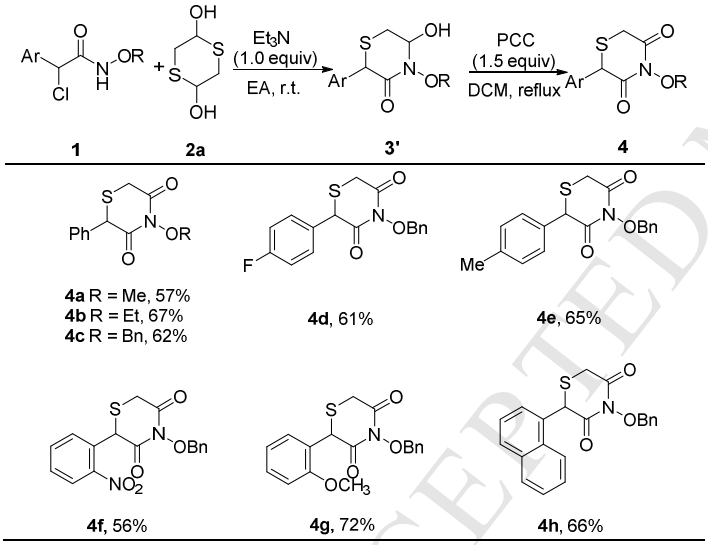
3q, 80%

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.375 mmol), Et_3N (0.5 mmol), in EA (5 mL) were stirred under room temperature for 12h, then TsOH (0.1 mmol) was added and reflux for1h.

[b] Yield refers to isolated products after chromatography.

To augment the application of the methodology, oxidation of the intermediate 4-(benzyloxy)-5-hydroxy-2-phenylthiomorpholin-3-one (**3a'**) was proceeded and 4-(benzyloxy)-2-phenylthiomorpholine-3,5-dione (**4a'**) was isolated as the product to avoid the diastereomer. Then, a variety of thiomorpholine-3,5-diones were synthesized by the oxidation of intermediate 5-hydroxythiomorpholin-3-ones (**3'**) with pyridinium chlorochromate (PCC) in moderate yields. As shown in **Table 3**, a variety of α-halohydroxamate derivatives were checked in this two-steps reaction. Alkoxy groups on the nitrogen atom seemed to influence the yield slightly. Benzyloxy, methoxy and ethoxy group substituted α-halohydroxamate gave desired thiomorpholine-3,5-diones in 57-67% yield (**4a**-**4c**). The substrates bearing various aromatic groups such as *p*-flurophenyl, *p*-tolyl, *o*-nitrophenyl, *o*-methoxyphenyl, naphthyl reacted smoothly and produced the products in 56-72% yield (**4d**-**4h**). The yields of diones with electron-donating group substituted aromatic ring seemed to be slightly higher than the electron-deficient substituted ones (**4e**, **4g** compared to **4d**, **4f**), indicating that the azaoxyallyl cations in situ generated from α-chlorohydroxamates might be stabled by electron-rich aromatic rings.

Table 3. Formation of thiomorpholine-3,5-diones **4** [a, b]



[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.375 mmol), Et_3N (0.5 mmol), in EA (5 mL) were stirred under room temperature for 12h, after a fast flash chromography purification of **3'**, PCC (0.75 mmol) was added to the solution of **3'** in DCM and reflux for1h.

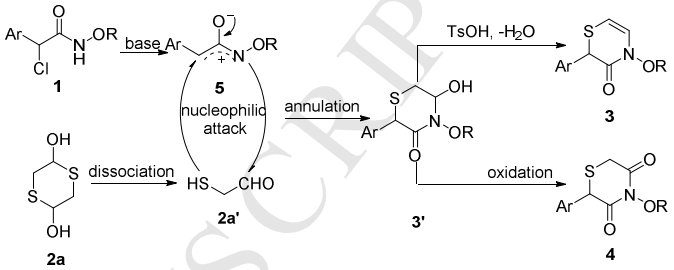
[b] Yield refers to isolated products after chromatography.

A plausible mechanism of the annulation is depicted in **Scheme 1**. Thus, Under weak basic conditions, α-halohydroxamate **1** in situ generates azaoxyallyl cation **5**, and meanwhile mercaptoacetaldehyde **2a'** is generated in situ by the dissociation of 2,5-dihydroxy-1,4-dithiane **2a**. Nucleophilic attack of thiol to azaoxyallyl cation 5 and the following intramolecular nitrogen anion nucleophilic attack to the aldehyde group form the product **3'**, accomplishing the cycloaddition. The final product **3** is obtained by dehydration and the product **4** is obtained by oxidation.

3. Conclusion

In summary, we have described an annulation reaction of α-halohydroxamates with 1,4-dithiane-2,5-diol, giving thiomorpholin-3-one derivatives in moderate to good yields. This procedure provided an efficient route to obtain 2*H*-1,4-thiazin-3(4*H*)-ones and thiomorpholine-3,5-diones under mild condition, exhibiting good functional group tolerance. It is concerned that azaoxyallyl cations is generated in the reaction as a crucial intermediate. Further applications of this methodology in synthetic organic chemistry are currently underway in our laboratory.

Scheme 1. Plausible mechanism



4. Experimental Section

Unless otherwise indicated, all reactions were carried out without N_2/Ar protection with magnetic stirring. Column chromatography was conducted on silica gel (300−400 mesh) using compound-appropriate mixtures of *n*-hexane and EtOAc as eluent. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane (TMS).

A variety of α-chlorohydroxamates **1** were synthesized from the corresponding aldehydes according to the literature.[8, 16] All other chemicals were obtained from commercial sources and used without further purification.

4.1 The Preparation of α-chlorohydroxamates (1)

Aryl aldehyde (10 mmol, 1.0 equiv) and malononitrile (11 mmol, 1.1 equiv) were dissolved in EtOH (10 mL), then piperidine (1 mmol, 0.1 equiv) was added. The mixture was stirred at room temperature for 1 h, and the resulting solid was filtered, washed with cold EtOH, the product 2-arylidenemalononitrile was collected as a white solid and directly used in the next step without further purification. Then 2-arylidenemalononitrile was dissolved in CH_2Cl_2 (15 mL) and *m*CPBA (1.5 equiv) was added in portions, the mixture was stirred at room temperature overnight. Saturated sodium bicarbonate solution was added to adjust PH>7, extracted with CH_2Cl_2 (15 mL ×3), after washing with brine (15 mL), the combined organic phase was dried over anhydrous Na_2SO_4 and concentrate under reduced pressure to give the oxirane-2,2-dicarbonitrile as a brown solid, which could be used directly in the next step without further purification. oxirane-2,2-dicarbonitrile was then dissolved in CH_3CN (15 mL), *O*-alkylhydroxylamine hydrochloride (1.2 equiv) was added and the mixture was heated to reflux for 1 h, H_2O (15 mL) was added, extracted by CH_2Cl_2 (15 mL ×3), after washing with brine (15 mL), the combined organic phase was dried over anhydrous Na_2SO_4 and concentrate under reduced pressure to give the crude product 2-chloroacetamide as a brown oil, which could be further purificated by recrystallization or column chromatography on silica gel (300-400 mesh) to afford the pure product.

*N-(benzyloxy)-2-chloro-2-(3-methoxyphenyl)acetamide (**1d**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 4/1) as a yellow oil (1.41 g, 46% over 3 steps), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 9.33 (s, 1H), 7.36–7.34 (m, 5H), 7.26–7.23 (m, 1H), 6.96–6.94 (m, 2H), 6.89–6.87 (m, 1H), 5.24 (s, 1H), 4.88 (s, 2H), 3.77 ppm (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 165.0, 159.8, 137.2, 134.5, 129.9, 129.5, 129.0, 128.6, 120.0, 115.0, 113.3, 78.3, 58.9, 55.3 ppm.

*N-(benzyloxy)-2-chloro-2-(4-fluorophenyl)acetamide (**1g**).* The title compound was obtained according to the general procedure described above after recrystallization from *n*-hexane/ethyl acetate as white solid (1.53 g, 53% over 3 steps), m.p. 104–106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 9.40 (s, 1H), 7.37–7.32 (m, 7H), 7.01 (t, *J* = 8.4 Hz, 2H), 5.25 (s, 1H), 4.90 ppm (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 164.9, 163.1 (J_{C-F} = 247.3 Hz), 134.5, 131.9 (J_{C-F} = 3.2 Hz), 129.8 (J_{C-F} = 7.5 Hz), 129.4, 129.1, 128.7, 115.9 (J_{C-F} = 22.0 Hz), 78.3, 58.1 ppm.

*N-(benzyloxy)-2-(4-bromophenyl)-2-chloroacetamide (**1i**).* The title compound was obtained according to the general procedure described above after recrystallization from *n*-hexane/ethyl acetate as white solid (1.81 g, 51% over 3 steps), m.p. 116–118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 9.31 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.37–7.35 (m, 5H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.22 (s, 1H), 4.90 ppm (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 164.5, 134.9, 134.4, 132.0, 129.4, 129.1, 128.7, 123.5, 78.3, 58.2 ppm.

*N-(benzyloxy)-2-chloro-2-(2,3-dimethoxyphenyl)acetamide (**1n**).* The title compound was obtained according to the general procedure described above after recrystallization from *n*-hexane/ethyl acetate as white solid (1.31 g, 39% over 3 steps), m.p. 92–94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 9.27 (s, 1H), 7.36–7.34 (m, 5H), 7.06–6.97 (m, 2H), 6.92–6.89 (m, 1H), 5.65 (s, 1H), 4.92 (s, 2H), 3.87 (s, 3H), 3.84 ppm (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 165.3, 152.5, 146.5, 134.8, 130.1, 129.4, 128.8, 128.6, 124.5, 120.6, 113.5, 78.2, 61.1, 55.8, 54.1 ppm.

4.2 General procedure for the synthesis of 2*H*-1,4-thiazin-3(4*H*)-ones (3).

Et_3N (69 μL, 0.2 mmol, 1.0 equiv) was added to the mixture of 2-chloroacetamides **1** (0.5 mmol, 1.0 equiv), 1,4-dithiane-2,5-diol **2a** (57 mg, 0.375 mmol, 0.75 equiv) in EtOAc (5 mL). The mixture was stirred at room temperature until complete consumption of 2-chloroacetamides **1**, TsOH • H_2O (19 mg, 0.1 mmol, 0.2 equiv) was added, and the mixture was heated to reflux for 1 h, H_2O (5 mL) was added after the mixture was cooled to room temperature, extracted with EtOAc (5 mL ×3). After washing with brine (5 mL), the combined organic phase was dried over anhydrous Na_2SO_4 and concentrate under reduced pressure. The residue was purified by column chromatography on silica gel (300−400 mesh) to afford compounds **3**.

*4-(Benzyloxy)-2-phenyl-2H-1,4-thiazin-3(4H)-one (**3a**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow oil (121.9 mg, 82%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.41–7.32 (m, 10H), 6.21 (d, *J* = 7.2 Hz, 1H), 5.44 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 1H), 5.04 (s, 2H), 4.65 ppm (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 159.0, 134.6, 134.2, 130.0, 129.2, 128.7, 128.6, 128.4, 127.8, 127.3, 99.9, 77.9, 47.4 ppm; **HRMS (EI)**: calculated for $C_{17}H_{15}NO_2S$, $[M+H]^+$, 298.0896, found 298.0891.

*4-(Benzyloxy)-2-(2-chlorophenyl)-2H-1,4-thiazin-3(4H)-one (**3b**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a white solid (109.5 mg, 66%), m.p. 104–105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.49–7.47 (m, 2H), 7.43–7.39 (m, 4H), 7.27–7.22 (m, 3H), 6.42 (d, *J* = 7.2 Hz, 1H), 5.46 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 5.16–5.09 ppm (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 158.9, 134.2, 133.9, 132.6, 130.1, 130.0, 129.6, 129.3, 129.1, 128.7, 127.3, 127.1, 100.5, 78.1, 44.1 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}ClNO_2S$, $[M+H]^+$, 332.0507, found 332.0508.

*4-(Benzyloxy)-2-(2-nitrophenyl)-2H-1,4-thiazin-3(4H)-one (**3c**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow oil (123.3 mg, 72%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 8.09–8.07 (m, 1H), 7.61–7.59 (m, 1H), 7.52–7.47 (m, 3H), 7.41–7.37 (m, 4H), 6.36 (d, *J* = 7.2 Hz, 1H), 5.54 (s, 1H), 5.51–5.49 (m, 1H), 5.11 ppm (dd, J_1 = 18.0 Hz, J_2 =10.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 158.4, 148.3, 134.1, 133.5, 130.1, 130.0, 129.9, 129.4, 128.7, 127.5, 125.8, 100.7, 78.2, 43.5 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}CN_2O_4S$, $[M+H]^+$, 343.0747, found 343.0750.

*4-(Benzyloxy)-2-(2-methoxyphenyl)-2H-1,4-thiazin-3(4H)-one (**3d**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a yellow oil (142.4 mg, 87%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.49–7.46 (m, 2H), 7.40–7.37 (m, 3H), 7.31–7.27(m, 1H), 7.14–7.12 (m, 1H), 6.92–6.89 (m, 2H), 6.39 (d, *J* = 6.4 Hz, 1H), 5.45 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 5.14–5.08 (m, 3H), 3.85 ppm (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 159.6, 156.5, 134.4, 129.9, 129.7, 129.2, 128.7, 128.3, 126.9, 123.4, 120.6, 110.9, 101.0, 78.0, 55.7, 40.8 ppm; **HRMS (EI)**: calculated for $C_{18}H_{17}NO_3S$, $[M+H]^+$, 328.1002, found 328.1006.

*4-(Benzyloxy)-2-(3-chlorophenyl)-2H-1,4-thiazin-3(4H)-one (**3e**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a yellow oil (117.8 mg, 71%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.40–7.39 (m, 1H), 7.37–7.33 (m, 5H),7.32–7.27 (m, 3H), 6.22 (d, *J* = 7.2 Hz, 1H), 5.45 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 1H), 5.07–5.01 (m, 2H), 4.61–4.60 ppm (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 158.4, 136.6, 134.6, 134.1, 130.0, 129.2, 128.7, 127.9, 127.4, 126.1, 99.6, 77.9, 47.0 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}ClNO_2S$, $[M+H]^+$, 332.0507, found 332.0503.

*4-(Benzyloxy)-2-(3-methoxyphenyl)-2H-1,4-thiazin-3(4H)-one (**3f**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a yellow oil (129.3 mg, 79%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.31 (m, 5H), 7.28–7.24 (m, 1H), 7.00–6.96 (m, 2H), 6.87–6.85 (m, 1H), 6.21 (d, *J* = 7.2 Hz, 1H), 5.44 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 5.03 (s, 2H), 4.62 (d, *J* = 1.6 Hz, 1H), 3.79 ppm (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 159.8, 158.8, 136.1, 134.2, 130.0, 129.7, 129.1, 128.6, 127.3, 120.1, 113.8, 113.5, 99.8, 77.8, 55.3, 47.4 ppm; **HRMS (EI)**: calculated for $C_{18}H_{17}NO_3S$, $[M+H]^+$, 328.1002, found 328.1007.

*4-(Benzyloxy)-2-(p-tolyl)-2H-1,4-thiazin-3(4H)-one (**3g**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow oil (133.9

mg, 86%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.37–7.34 (m, 5H), 7.29–7.25 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.23 (d, *J* = 7.2 Hz, 1H), 5.45 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 5.05 (s, 2H), 4.62 (d, *J* = 0.8 Hz, 1H), 2.34 ppm (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 159.1, 138.3, 134.2, 131.5, 130.0, 129.4, 129.1, 128.6, 127.7, 127.2, 100.0, 77.9, 47.2, 21.2 ppm; **HRMS (EI)**: calculated for $C_{18}H_{17}NO_2S$, $[M+H]^+$, 312.1053, found 312.1051.

*4-(Benzyloxy)-2-(4-fluorophenyl)-2H-1,4-thiazin-3(4H)-one (**3h**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a yellow oil (118.3 mg, 75%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.38–7.35 (m, 7H), 7.06–7.02 (m, 2H), 6.24 (d, *J* = 8.0 Hz, 1H), 5.47 (dd, J_1 = 7.2 Hz, J_2 =1.6 Hz, 1H), 5.07–5.02 (m, 2H), 4.63 ppm (d, *J* = 0.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 162.7 (J_{C-F} = 245.9 Hz), 158.9, 134.1, 130.3 (J_{C-F} = 2.3 Hz), 129.9, 129.7 (J_{C-F} = 7.7 Hz), 129.2, 128.7, 127.3, 115.7 (J_{C-F} = 21.8 Hz), 99.9, 77.9, 46.8 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}FNO_2S$, $[M+H]^+$, 316.0802, found 316.0806.

*4-(Benzyloxy)-2-(4-chlorophenyl)-2H-1,4-thiazin-3(4H)-one (**3i**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a yellow solid (122.8 mg, 74%), m.p. 76–78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.37–7.32 (m, 9H), 6.23 (d, *J* = 7.2 Hz, 1H), 5.44 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 1H), 5.06–5.01 (m, 2H), 4.61 ppm (d, *J* = 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 157.5, 133.3, 133.0, 131.9, 128.8, 128.2, 128.1, 127.8, 127.6, 126.3, 98.6, 76.8, 45.7 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}ClNO_2S$, $[M+H]^+$, 332.0507, found 332.0501.

*4-(Benzyloxy)-2-(4-bromophenyl)-2H-1,4-thiazin-3(4H)-one (**3j**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a yellow solid (127.9 mg, 68%), m.p. 63–65 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.49–7.47 (m, 2H), 7.38–7.32 (m, 5H), 7.28–7.26 (m, 2H), 6.23 (d, *J* = 7.6 Hz, 1H), 5.45 (dd, J_1 = 7.2 Hz, J_2 =1.6 Hz, 1H), 5.07–5.01 (m, 2H), 4.60 ppm (d, *J* = 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 158.5, 134.1, 133.5, 131.8, 130.0, 129.6, 129.2, 128.7, 127.4, 122.6, 99.9, 77.9, 46.9 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}BrNO_2S$, $[M+H]^+$, 376.0001, found 376.0007.

4-(4-(benzyloxy)-3-oxo-3,4-dihydro-2*H*-1,4-thiazin-2-yl)benzonitrile (***3k***). The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a white solid (122.5 mg, 76%), m.p. 130–132 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.65 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.39–7.36 (m, 5H), 6.28 (d, *J* = 7.2 Hz, 1H), 5.47 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 5.07 (dd, J_1 = 14.0 Hz, J_2 = 2.4 Hz, 2H), 4.87 ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 158.0, 139.7, 133.9, 132.4, 129.9, 129.3, 128.7, 128.6, 127.6, 118.4, 112.3, 99.4, 78.0, 47.1 ppm; **HRMS (EI)**: calculated for $C_{18}H_{15}N_2O_2S$, $[M+H]^+$, 323.0849, found 323.0853.

4-(benzyloxy)-2-(4-nitrophenyl)-2*H*-1,4-thiazin-3(4*H*)-one (**3l**). The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a yellow solid (123.3 mg, 72%), m.p. 138–140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 8.20 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.39–7.34 (m, 5H), 6.30 (d, *J* = 7.2 Hz, 1H), 5.49 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 5.07 (dd, J_1 = 13.6 Hz, J_2 = 10.4 Hz, 2H), 4.72 ppm (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 158.0, 147.7, 141.6, 133.9, 129.9, 129.3, 129.0, 128.6, 127.6, 123.8, 99.5, 78.1, 46.8 ppm; **HRMS (EI)**: calculated for $C_{17}H_{15}N_2O_4S$, $[M+H]^+$, 343.0747, found 343.0745.

*4-Methoxy-2-phenyl-2H-1,4-thiazin-3(4H)-one (**3m**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow oil (78.6 mg, 71%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.42–7.31 (m, 5H), 6.48 (d, *J* = 7.2 Hz, 1H), 5.63 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 4.65 (d, *J* = 1.6 Hz, 1H), 3.10 ppm (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 158.7, 134.6, 128.7, 128.4, 127.7, 126.1, 101.0, 63.4, 47.3 ppm; **HRMS (EI)**: calculated for $C_{11}H_{11}NO_2S$, $[M+H]^+$, 222.0583, found 222.0585.

*4-Ethoxy-2-phenyl-2H-1,4-thiazin-3(4H)-one (**3n**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow oil (98.8 mg, 84%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.41–7.28 (m, 5H), 6.48 (d, *J* = 7.2 Hz, 1H), 5.58 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 4.64 (d, *J* = 1.6 Hz, 1H), 4.20–4.09 (m, 2H), 1.31 ppm (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 159.1, 134.7, 128.7, 128.3, 127.7, 127.0, 100.2, 71.7, 47.3, 13.5 ppm; **HRMS (EI)**: calculated for $C_{11}H_{11}NO_2S$, $[M+H]^+$, 236.0740, found 236.0745.

*4-(Benzyloxy)-2-(2,4-dichlorophenyl)-2H-1,4-thiazin-3(4H)-one (**3o**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a white solid (133.3 mg, 73%), m.p. 118–120 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.48–7.44 (m, 3H), 7.41–7.39 (m, 3H), 7.23 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.42 (d, *J* = 7.2 Hz, 1H), 5.47 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 5.11 (dd, J_1 = 12.0 Hz, J_2 = 6.4 Hz, 2H), 5.04 pm (d, *J* = 1.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 158.5, 134.9, 134.6, 134.0, 131.1, 130.0, 129.9, 129.8, 129.3, 128.7, 127.3, 100.4, 78.1, 43.5 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}Cl_2NO_2S$, $[M+H]^+$, 366.0117, found 366.0119.

*4-(Benzyloxy)-2-(2,3-dimethoxyphenyl)-2H-1,4-thiazin-3(4H)-one (**3p**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow oil (155.5 mg, 87%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.48–7.46 (m, 2H), 7.40–7.37 (m, 3H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.91–6.88 (m, 1H), 6.86–6.83 (m, 1H), 6.38 (d, *J* = 6.8 Hz, 1H), 5.50 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 5.11 (d, *J* = 1.2 Hz, 1H), 5.10 (s, 2H), 3.90 (s, 3H), 3.86 ppm (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 159.9, 152.6, 146.8, 134.4, 130.0, 129.2, 128.6, 127.0, 124.1, 120.5, 112.8, 100.9, 78.0, 61.2, 55.8, 41.1 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}Cl_2NO_2S$, $[M+H]^+$, 358.1108, found 358.1123.

*4-(Benzyloxy)-2-(naphthalen-1-yl)-2H-1,4-thiazin-3(4H)-one (**3q**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a white solid (139.0 mg, 80%), m.p. 140–141 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 8.07 (d, *J* = 8.4 Hz, 1H), 7.88–7.80 (m, 2H), 7.59–7.48 (m, 2H), 7.44–7.24 (m, 7H), 6.41 (d, *J* = 7.6 Hz, 1H), 5.47 (dd, J_1 = 7.2 Hz, J_2 =1.6 Hz, 1H), 5.38 (s, 1H), 5.12 ppm (dd, J_1 = 18.0 Hz, J_2 =10.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 159.4, 134.3, 134.2, 130.6, 130.1, 130.0, 129.4, 129.2, 128.7, 127.1, 126.7, 126.0, 125.8, 125.0, 123.4, 100.7, 78.1, 44.2 ppm; **HRMS (EI)**: calculated for $C_{21}H_{17}NO_2S$, $[M+H]^+$, 348.1053, found 348.1050.

4.3 General procedure for the synthesis of thiomorpholine-3,5-diones (4).

Et_3N (69 μL, 0.2 mmol, 1.0 equiv) was added to the mixture of 2-chloroacetamides **1** (0.5 mmol, 1.0 equiv), 1,4-dithiane-2,5-diol **2a** (57 mg, 0.375 mmol, 0.75 equiv) in EtOAc (5 mL). The mixture was stirred at room temperature until complete consumption of 2-chloroacetamides **1,** solvent was removed under reduced pressure. The residue was quickly purified by a short column chromatography on silica gel (300−400 mesh, eluting with DCM/ EtOAc 5/1) to afford compounds **3'**. Then PCC (162 mg, 0.75 mmol, 1.5 equiv) was added to the solution of **3'** in DCM (5 ml) and the mixture was heated to reflux until complete consumption of **3'**, H_2O (5 mL) was added after the mixture was cooled to room temperature, extracted with DCM (5 mL ×3). After washing with brine (5 mL), the combined organic phase was dried over anhydrous Na_2SO_4 and concentrate under reduced pressure. The residue was purified by column chromatography on silica gel (300−400 mesh) to afford compounds **4**.

*4-Methoxy-2-phenylthiomorpholine-3,5-dione (**4a**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow solid (67.6 mg, 57%), m.p. 104–106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.43–7.26 (m, 5H), 4.87 (s, 1H), 3.94 (s, 3H), 3.55–3.49 ppm (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 166.0, 164.9, 133.1, 129.2, 128.9, 127.8, 64.1, 48.8, 30.7 ppm; **HRMS (EI)**: calculated for $C_{11}H_{11}NO_3S$, $[M+H]^+$, 238.0532, found 238.0538.

*4-Ethoxy-2-phenylthiomorpholine-3,5-dione (**4b**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow oil (84.2 mg, 67%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.32–7.28 (m, 5H), 4.80 (s, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.51–3.40 (m, 2H), 1.30 ppm (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 165.3, 164.2, 132.2, 128.1, 127.8, 126.7, 76.4, 76.0, 75.7, 71.3, 47.8, 29.7, 12.3 ppm; **HRMS (EI)**: calculated for $C_{12}H_{13}NO_3S$, $[M+H]^+$, 252.0689, found 252.0683.

*4-(Benzyloxy)-2-phenylthiomorpholine-3,5-dione (**4c**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow oil (97.2 mg, 62%), **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.56–7.54 (m, 2H), 7.40–7.34 (m, 6H), 7.28–7.25 (m, 2H), 5.07 (s, 2H), 4.84 (s, 1H), 3.56–3.45 ppm (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 166.4, 165.3, 133.7, 133.3, 130.2, 129.3, 129.2, 128.8, 128.6, 127.9, 78.4, 49.1, 30.9 ppm; **HRMS (EI)**: calculated for $C_{17}H_{15}NO_3S$, $[M+H]^+$, 252.0689, found 252.0683.

*4-(Benzyloxy)-2-(4-fluorophenyl)thiomorpholine-3,5-dione (**4d**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a white solid (101.1 mg, 61%), m.p. 122–124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.56–7.53 (m, 2H), 7.40–7.38 (m, 3H), 7.26–7.22 (m, 2H), 7.07–7.03 (m, 2H), 5.07 (s, 2H), 4.81 (s, 1H), 3.62–3.47 ppm (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 166.3, 165.0, 162.7 (J_{C-F} = 247.2 Hz), 133.5, 130.2, 129.8 (J_{C-F} = 8.8 Hz), 129.3, 129.0 (J_{C-F} = 3.9 Hz), 128.5, 116.1 (J_{C-F} = 22.1 Hz), 78.3, 48.5, 31.2 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}FNO_3S$, $[M+H]^+$, 332.0751, found 332.0755.

*4-(Benzyloxy)-2-(p-tolyl)thiomorpholine-3,5-dione (**4e**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a white solid (106.4 mg, 65%), m.p. 112–114 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.57–7.54 (m, 2H), 7.40–7.38 (m, 3H), 7.21–7.11 (m, 4H), 5.07 (s, 2H), 4.81 (s, 1H), 3.56–3.47 (m, 2H), 2.35 ppm (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 166.5, 165.2, 138.8, 133.6, 130.1, 129.8, 129.3, 128.5, 127.7, 78.3, 48.8, 30.9, 21.1 ppm; **HRMS (EI)**: calculated for $C_{18}H_{17}NO_3S$, $[M+H]^+$, 328.1002, found 328.1004.

*4-(Benzyloxy)-2-(2-nitrophenyl)thiomorpholine-3,5-dione (**4f**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a white solid (100.4 mg, 56%), m.p. 114–116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 8.13 (d, *J* = 8.0 Hz, 1H), 7.61–7.53 (m, 4H), 7.41–7.38 (m, 3H), 7.24 (d, *J* = 7.6 Hz, 1H), 5.76 (s, 1H), 5.08 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 2H), 3.81–3.52 ppm (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 165.7, 164.6, 148.1, 133.8, 133.5, 130.5, 130.2, 130.0, 129.3, 129.2, 128.5, 126.2, 78.5, 46.2, 32.2 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}N_2O_5S$, $[M+H]^+$, 359.0696, found 359.0691.

*4-(Benzyloxy)-2-(2-methoxyphenyl)thiomorpholine-3,5-dione (**4g**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale yellow solid (123.6 mg, 72%), m.p. 170–172 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.58–7.55 (m, 2H), 7.40–7.38 (m, 3H), 7.36–7.31 (m, 1H), 7.01–7.00 (m, 1H), 6.95–6.90 (m, 2H), 5.18 (s, 1H), 5.08 (s, 2H), 3.85 (s, 3H), 3.65–3.56 ppm (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 166.8, 165.6, 156.7, 133.8, 130.3, 130.2, 129.2, 128.8, 128.5, 123.0, 120.8, 111.5, 78.3, 55.8, 44.2, 31.6 ppm; **HRMS (EI)**: calculated for $C_{17}H_{14}N_2O_5S$, $[M+H]^+$, 344.0951, found 344.0950.

*4-(Benzyloxy)-2-(naphthalen-1-yl)thiomorpholine-3,5-dione (**4h**).* The title compound was obtained according to the general procedure described above after column chromatography on silica gel (eluting with *n*-hexane/ EtOAc 5/1) as a pale pink solid (119.9 mg, 66%), m.p. 151–153 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, TMS): δ = 7.91–7.84 (m, 3H), 7.60–7.51 (m, 4H), 7.42–7.38 (m, 3H), 7.36–7.32 (m, 1H), 7.12 (d, *J* = 6.8 Hz, 1H), 5.54 (s, 1H), 5.15 (s, 2H), 3.61–3.50 ppm (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$, TMS): δ = 166.6, 165.2, 134.4, 133.6, 130.4, 130.2, 130.0, 129.4, 129.3, 128.5, 126.8, 126.3, 125.7, 124.7, 123.2, 78.4, 46.8, 31.2 ppm; **HRMS (EI)**: calculated for $C_{21}H_{17}NO_3S$, $[M+H]^+$, 364.1002, found 364.1003.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (Nos. 21702155) and the Natural Science Foundation of Hubei Province (No. 2016CFB168) for financial support.

Supplementary data

† Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.tet.XXXX.XX.XXXX

References and notes

1. Bontemps, N.; Gattacceca, F.; Long, C.; Thomas, O. P.; Banaigs, B. *J. Nat. Prod.* **2013**, *76*, 1801− 1805.
2. Carr, G.; Williams, D. E.; Díaz-Marrero, A. R.; Patrick, B. O.; Bottriell, H.; Balgi, A. D.; Donohue, E.; Roberge, M.; Andersen, R. J. *J. Nat. Prod.* **2010,** *73*, 422–427.
3. Preuss, J.; Maloney, P.; Peddibhotla, S.; Hedrick, M. P.; Hershberger, P.; Gosalia, P.; Milewski, M.; Li, Y. L.; Sugarman,

E.; Hood, B.; Suyama, E.; Nguyen, K.; Vasile, S.; Sergienko, E.; Mangravita-Novo, A.; Vicchiarelli, M.; McAnally, D.; Smith, L. H.; Roth, G. P.; Diwan, J.; Chung, T. D. Y.; Jortzik, E.; Rahlfs, S.; Becker, K.; Pinkerton, A. B.; Bode, L. *J. Med. Chem.* **2012**, *55*, 7262−7272..

4. Tong, H.-J.; Zheng, Y.-J.; Zhou, L.; Li, X.-M.; Qian, R.; Wang, R.; Zhao, J.-H.; Lou, K.-Y.; Wang, W. *Anal. Chem*. **2016**, *88*, 10816−10820.
5. Ishibashi, H.; Uegaki, M.; Sakai, M.; Takeda, Y. *Tetrahedron* **2001**, *57*, 2115−2120.
6. Bertolasi, V.; Bortolini, O.; Donvito, A.; Fantin, G.; Fogagnolo, M.; Giovannini, P. P.; Massi, A.; Pacifico, S. *Org. Biomol. Chem.* **2012**, *10*, 6579−6586.
7. Xu, L.-J.; Wang, H.-Y.; Zheng, C.-W.; Zhao, G. *Tetrahedron* **2017**, *73*, 6057−6066.
8. Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc*. **2011**, *133*, 7688−7691.
9. Acharya, A.; Eickhoff, J. A.; Jeffrey, C. S. *Synthesis* **2013**, *45*, 1825−1836.
10. Barnes, K. L.; Koster, A. K.; Jeffrey, C. S. *Tetrahedron Lett*. **2014**, *55*, 4690−4696.
11. Acharya, A.; Eickhoff, J. A.; Chen, K.; Catalano, V. J.; Jeffrey, C. S. *Org. Chem. Front*. **2016**, *3*, 330−334.
12. Acharya, A.; Anumandla, D.; Jeffrey, C. S. *J. Am. Chem. Soc*. **2015**, *137*, 14858−14860.
13. DiPoto, M. C.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc*. **2015**, *137*, 14861−14864.
14. Xuan, J.; Cao, X.; Cheng, X. *Chem. Commun*. **2018**, *54*, 5154−5163.
15. Li, C.; Jiang, K.; Ouyang, Q.; Liu, T.-Y.; Chen, Y.-C. *Org. Lett*. **2016**, *18*, 2738−2741.
16. Zhang, K.-F.; Yang, C.; Yao, H.-Q.; Lin, A.-J. *Org. Lett*. **2016**, *18*, 4618−4621.
17. Acharya, A.; Montes, K.; Jeffrey, C. S. *Org. Lett.* **2016**, *18*, 6082–6085.
18. Shao, P.-L.; Li, Z.-R.; Wang, Z.-P.; Zhou, M.-H.; Wu, Q.; Hu, P.; He, Y. *J. Org. Chem.* **2017**, *82*, 10680−10686.
19. Eyilcim, O.; Issever, S.; Ocal, N.; Gronert , S.; Erden, I. *Tetrahedron Lett.* **2018**, *59*, 3674−3677.
20. Zhao, H.-W.; Zhao, Y.-D.; Liu, Y.-Y.; Zhao, L.-J.; Song, X.-Q.; Chen, X.-Q.; Pang, H.-L.; Du, J.; Feng, N.-N. *RSC Adv*. **2017**, *7*, 55106–55109.
21. Cheng, X.; Cao, X.; Zhou, S.-J.; Cai, B.-G.; He, X.-K.; Xuan, J. *Adv. Synth. Catal.* **2018**, doi.org/10.1002/adsc.201801181.
22. Baldé, B.; Force, G.; Marin, L.; Guillot, R.; Schulz, E.; Gandon, V.; Lebœuf, D. *Org. Lett.* **2018**, *20*, 7405–7409.
23. Zhao, H.-W.; Zhao, Y.-D.; Liu, Y.-Y.; Du, J.; Pang, H.-L.; Chen, X.-Q.; Song, X.-Q.; Feng, N.-N. *Eur. J. Org. Chem*. **2017**, 3466−3472.
24. Zhao, H.-W.; Zhao, Y.-D.; Liu, Y.-Y.; Zhao, L.-J.; Feng, N.-N.; Pang, H.-L.; Chen, X.-Q.; Song, X.-Q.; Du, J. *RSC Adv*. **2017**, *7*, 12916–12922.
25. Xuan, J.; Cheng, X.; Cao, X. *ChemistrySelect* **2017**, *2*, 4364−4367.
26. An, Y.-Y.; Xia, H.-G.; Wu, J. *Chem. Commun.* **2016**, *52*, 10415−10418.
27. Zhang, Y.-X.; Ma, H.-J.; Liu, X.-X.; Cui, X.-F.; Wang, S.-H.; Zhan, Z.-Z.; Pu, J.-H.; Huang, G.-S. *Org. Biomol. Chem*. **2018**, *16*, 4439–4442.
28. Wang, G.-Q.; Chen, R.-X.; Wu, M.-H.; Sun, S.-F.; Luo, X.; Chen, Z.; Guo, H.-B.; Chong, C.; Xing, Y.-L. *Tetrahedron Lett.* **2017**, *58*, 847–850.
29. Zhang, C.; Ji, W.-Z.; Liu, Y. A.; Song, C.; Liao, X.-B. *J. Nat. Prod*. **2018**, *81*, 1065−1069.
30. Ji, W.-Z.; Yao, L.-C.; Liao, X.-B. *Org. Lett*. **2016**, *18*, 628−630.
31. Zhang, K.-F.; Xu, X.-Y.; Zheng, J.-A.; Yao, H.-Q.; Huang, Y.; Lin, A.-J. *Org. Lett.* **2017**, *19*, 2596−2599.
32. DiPoto, M. C.; Wu, J. *Org. Lett*. **2018**, *20*, 499−501.
33. Xu, X.-Y.; Zhang, K.-F.; Li, P.-P.; Yao, H.-Q.; Lin, A.-J. *Org. Lett*. **2018**, *20*, 1781−1784.
34. Jin, Q.-M.; Gao, M.; Zhang, D.-J.; Jiang, C.-H.; Yao, N.; Zhang, J. *Org. Biomol. Chem.* **2018**, *16*, 7336−7339.
35. Ji, W.-Z.; Liu, Y.-H.; Liao, X.-B. *Angew. Chem. Int. Ed*. 2016, 55, 13286−13289.
36. Sajadikhah, S. S.; Maghsoodlou, M. T. *Chem Heterocycl Comp*, **2018**, *54*, 581-583.
37. Cheng, Y.; Peng, H.-Y.; Dong, Z.-B. *Tetrahedron Lett*. **2019**, *60*, 617−620.
38. Zamberlan, F.; Fantinati, A.; Trapella, C. *Eur. J. Org. Chem.* **2018**, 3248–3264.

- An efficient and practical process for the synthesis of 2*H*-1,4-thiazin-3(4*H*)-ones and thiomorpholine-3,5-diones.
- This method has the feathers of mild condition (common solvents, without N_2/Ar protection), good yield, simple procedure and wide functional group tolerance.