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ORIGINAL PAPER

Heteropolyacid catalyzed formation of thioparabanic acid derivatives

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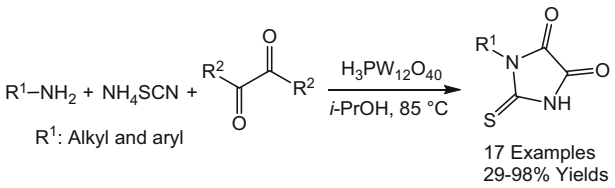
Abstract A heteropoly acid-catalyzed reaction between amines, ammonium thiocyanate, and oxalate esters is reported. This route turned out to be a useful method for the preparation of thioparabanic acid derivatives.
Graphical abstract



Keywords Thioparabanic acid · Heteropoly acid · Oxalate ester · Amine · Catalytic-multicomponent reaction

Introduction

Heterocyclic compounds are ubiquitously found in modern society as pharmaceutical agents and bioactive compounds [1–4]. For this reason, synthetic chemists continue to be interested in the construction and functionalization of heterocyclic cores. Among the various strategies available, multicomponent reactions, has shown increasing popularity [5–8]. Additionally, transition metal-catalyzed multicomponent reactions have served as powerful tools for the rapid and efficient synthesis of heterocyclic compounds [9–12]. These strategies are used to minimize problems with classical multicomponent reactions, such as regioselectivity, low yields, and competing side reactivities. Among the various catalysts, heteropolyacids (HPAs) have been broadly used as acidic catalysts in multicomponent reactions [13]. HPAs are strong bronsted acids and structural characterization of the HPA proton sites is an important step toward understanding the catalytic activity. These studies are very well recapitulated in a review written by Kozhevnikov [14].

2-Thioxo-4,5-imidazolidinedione derivatives (thioparabanic acids) are key scaffold in medicines those broadly used as: antiviral [15], anticancer [16], aldose reductase inhibitors [17], potassium channel openers [18], antibacterial [19], and usefulness in treating atherosclerosis [20]. There are many efficient methods for the synthesis of this important class of heterocycle, but most of the various approaches have certain restrictions regarding the scope and placement of the substitution pattern around the heterocycle core [21–25]. In accordance with our interest at the synthesis of heterocyclic compounds [26–29], we examined the efficiency of heteropolyacids for the synthesis of functionalized thioparabanic acids using oxalate esters, amines, and thiocyanate precursors.

Results and discussion

The reaction was initially examined using *n*-butyl amine (**1a**), ammonium thiocyanate (**2a**), and dimethyl oxalate (**3a**) in the presence of $H_3PW_{12}O_{40}$ as the solid acid.

Electronic supplementary material The online version of this article (doi:10.1007/s00706-016-1774-y) contains supplementary material, which is available to authorized users.

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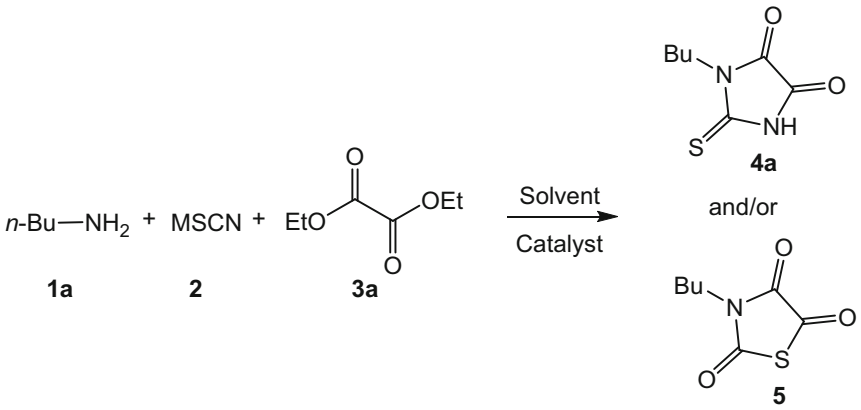
Stirring in MeCN at 85 °C for 8 h afforded 1-butyl-2-thioxoimidazolidine-4,5-dione (**4a**) in 41 % yield together with 3-butylthiazolidine-2,4,5-trione (**5**) in 9 % yield. To develop the reaction conditions a variety of solvents, catalysts, and thiocyanate precursors were examined (Table 1). No desired product formation occurred without the catalyst even at higher temperature (Table 1, entry 1). Additionally, catalyst screen showed that HPA's with of tungsten resulted in higher yields than those composed of molybdenum, most likely due to the greater acidity of tungsten containing HPA (Table 1, entries 2–6) [30]. Reaction conducted with Cs-containing HPA occurred to low conversion (Table 1, entry 7). Supported $H_3PW_{12}O_{40}$ (Fig. 1) on amorphous silica required longer reaction times to afford the desired product in acceptable yield (Table 1, entry 8). Trifluoroacetic acid and trifluoromethanesulfonic acid also promoted the reaction in good yields. However, common bronsted acids like HCl and H_2SO_4 were not

Table 1 Optimization of reaction conditions



Entry	Catalyst	2	M	Solvent	Yield of **4**/%
1	–	**2a**	NH_4	*i*-PrOH	–
2	$H_3PW_{12}O_{40}$	**2a**	NH_4	*i*-PrOH	93
3	$H_4SiW_{12}O_{40}$	**2a**	NH_4	*i*-PrOH	72
4	$H_4PMo_{12}O_{40}$.	**2a**	NH_4	*i*-PrOH	50
5	$H_3PMo_{10}W_2O_{40}$	**2a**	NH_4	*i*-PrOH	69
6	$H_4SiMo_{12}O_{40}$	**2a**	NH_4	*i*-PrOH	26
7	$Cs_2HPW_{12}O_{40}$	**2a**	NH_4	*i*-PrOH	17
8	$H_3PW_{12}O_{40}$-Silica	**2a**	NH_4	*i*-PrOH	89[a]
9	$H_3PW_{12}O_{40}$	**2a**	NH_4	DMSO	54
10	$H_3PW_{12}O_{40}$	**2a**	NH_4	EtOH	78
11	$H_3PW_{12}O_{40}$	**2a**	NH_4	DMF	39
12	$H_3PW_{12}O_{40}$	**2a**	NH_4	Toluene	4
13	$H_3PW_{12}O_{40}$,	**2a**	NH_4	MeCN	41
14	$H_3PW_{12}O_{40}$,	**2a**	NH_4	H_2O	39
15	$H_3PW_{12}O_{40}$	**2b**	K	*i*-PrOH	62
16	$H_3PW_{12}O_{40}$	**2c**	Ag	*i*-PrOH	75
17	$H_3PW_{12}O_{40}$	**2d**	Li	*i*-PrOH	90
18	$H_3PW_{12}O_{40}$	**2e**	Fe(II)	*i*-PrOH	–
19	$H_3PW_{12}O_{40}$	**2a**	K	MeCN	61[b]

For all entries except stated otherwise: **1a** (1.0 mmol), **2** (1.5 mmol), **3a** (1.5 mmol), catalyst (0.1 mmol) in 3 cm^3 solvent at 85 °C for 8 h

[a] Catalyst (60 mg) at 8 °C for 12 h

[b] The yield of **5** at 45 °C for 20 h. 13 % of **4a** was also obtained

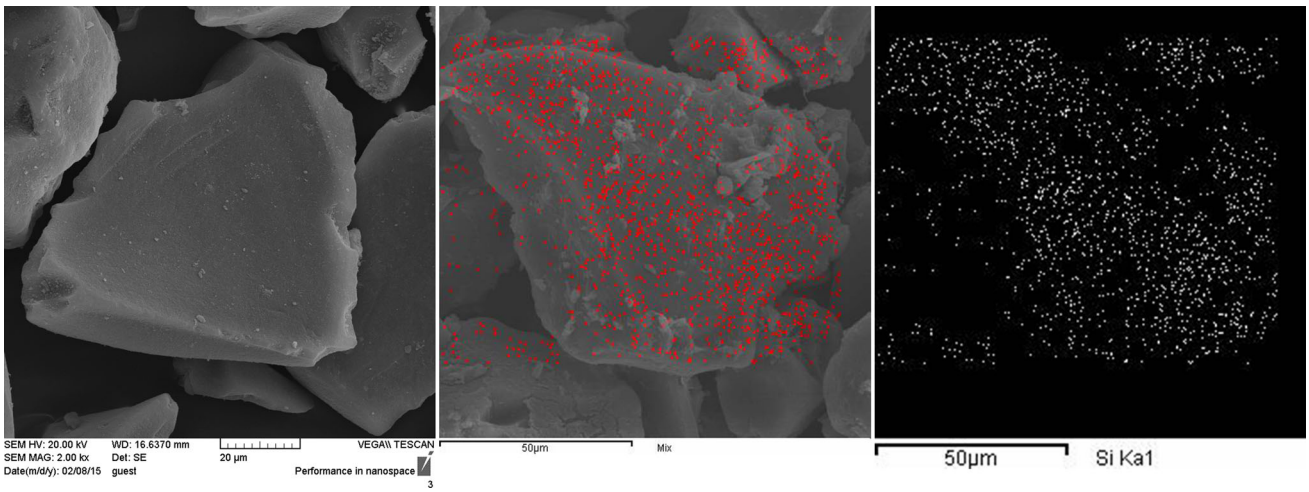


Fig. 1 SEM of silica (*left*) SEM of supported $H_3PW_{12}O_{40}$ on silica (*middle* and *right*)

effective in this transformation (not shown in Table 1). Finally, HPA was selected as the acid of choice based on the recycling and efficiency. A solvent screen showed that *i*-PrOH gave best result (Table 1, entry 2). Reaction in apolar solvent like toluene occurred to low conversions (Table 1, entry 12). It is noteworthy that a moderate yield of **4a** was obtained in deionized water (Table 1, entry 14). A variety of thiocyanate precursors were also examined in order to evaluate the influence of the nature of the counter-ion on reaction progress (Table 1, entries 15–18). Among the thiocyanates examined, ammonium and lithium thiocyanates afforded the desired product in higher yield. Finally, NH_4SCN was selected as the reagent of choice based on the cost and efficiency. Note that reaction conducted at lower temperature (45 °C) in MeCN, formed **5** as the main product (Table 1, entry 19). It could be deduced that reaction temperature and solvent control the regioselectivity of SCN anion.

After having defined the optimum reaction conditions, we sought to explore the scope of the reaction (Table 2). Alkyl amines gave higher yields than those of aryl amines which were likely due to the lower nucleophilicity of the aromatic amines (Table 2, entries 1–4 and 11). 2-Chloro- and 4-chlorobenzyl amine (**1g**, **1h**) underwent effective reaction under the optimized catalytic conditions (Table 2, entries 7 and 8). This reaction is sensitive to steric effects as ortho-substituted benzyl amine and aniline afforded the desired products in lower yields (Table 2, entries 6 and 17). Products containing a methoxy group could be obtained in excellent yields (Table 2, entries 9 and 16). The presence of electron withdrawing groups on aromatic ring highly affected the reaction progress as *p*-nitro benzyl amine (**1m**) was not compatible with this reaction (Table 2, entries 12–14). Substrates containing bromide on aromatic ring gave the desired products in acceptable yields (Table 2, entries 10 and 18). Notably, the tolerance for bromide on the aromatic ring offers an opportunity for subsequent cross-coupling, facilitating expedient synthesis of highly complex thioparabanic acids. Varying the oxalate ester structures had little effect on the outcome of the reaction (Table 2, entries 22–25). Oxalic acid gave a competitively lower yield of the desired product than those of oxalic esters (Table 2, entry 26). Besides the oxalate esters and acid, oxalyl chloride (**3g**) was also examined and gave the desired product in nearly quantitative amount in the absence of the catalyst (Table 2, entry 27).

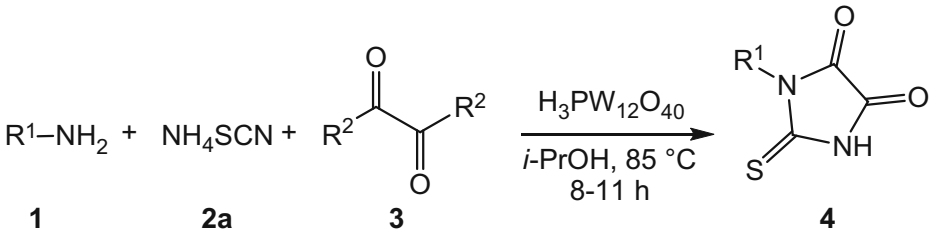
The recycling of the catalyst was then examined using the model reaction (Table 2, entries 19–21). After the completion of the reaction, the catalyst was recovered by filtration, followed by washing with ethanol (5 cm^3 × 3). After drying (80 °C for 8 h in vacuo), the catalyst was reused directly for the next reaction. The catalytic activity remained almost unchanged after two catalytic cycles, indicating that the catalyst is stable and can be regenerated for repeated use. However, the yield decreased as the catalyst was used for the third run.

The structures of products were confirmed by spectroscopic analyses. For example, the ^1H NMR spectrum of **4a** showed all the signals in appropriate regions including characteristic NH and CH_2N signals. The ^{13}C NMR spectrum of **4a** exhibited seven signals in agreement with the proposed structure. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 186$.

A tentative mechanism for this transformation is proposed in Scheme 1. It is conceivable that the initial event is the formation of the substituted 2-oxoacetyl isothiocyanate **6** from the amine, ammonium thiocyanate, and oxalate ester using $H_3PW_{12}O_{40}$. Intermediate **6** undergoes cyclization to produce **7**, which undergoes tautomerization to yield **4**.

In conclusion, we have described an efficient procedure for the synthesis of thioparabanic acids. To our knowledge,

Table 2 Synthesis of functionalized thioparabanic acids



Entry	Amine	R^1	Malonate	R^2	Yield/%
1	**1a**	*n*-Bu	**3a**	EtO	**4a**, 93
2	**1b**	*t*-Bu	**3a**	EtO	**4b**, 92
3	**1c**	Ph	**3a**	EtO	**4c**, 85
4	**1d**	Bn	**3a**	EtO	**4d**, 94
5	**1e**	4-CH_3-Bn	**3a**	EtO	**4e**, 93
6	**1f**	2-CH_3-Bn	**3a**	EtO	**4f**, 87
7	**1g**	2-Cl-Bn	**3a**	EtO	**4g**, 89
8	**1h**	4-Cl-Bn	**3a**	EtO	**4h**, 87
9	**1i**	4-OMe-Bn	**3a**	EtO	**4i**, 98
10	**1j**	4-Br-Bn	**3a**	EtO	**4j**, 87
11	**1k**	Naphthyl-CH_2	**3a**	EtO	**4k**, 94
12	**1l**	4-*i*-PrOCO-Bn	**3a**	EtO	**4l**, 69
13	**1m**	4-NO_2- Bn	**3a**	EtO	–
14	**1n**	3-CF_3-C_6H_4	**3a**	EtO	**4m**, 29
15	**1o**	3-Me-C_6H_4	**3a**	EtO	**4n**, 89
16	**1p**	4-OMe-C_6H_4	**3a**	EtO	**4o**, 89
17	**1q**	2-Me-C_6H_4	**3a**	EtO	**4p**, 69
18	**1r**	4-Br-C_6H_4	**3a**	EtO	**4q**, 76
19	**1a**	*n*-Bu	**3a**	EtO	**4d**, 89[a]
20	**1a**	*n*-Bu	**3a**	EtO	**4d**, 80
21	**1a**	*n*-Bu	**3a**	EtO	**4d**, 65
22	**1a**	*n*-Bu	**3b**	MeO	**4d**, 91
23	**1a**	*n*-Bu	**3c**	BnO	**4d**, 90
24	**1a**	*n*-Bu	**3d**	*i*-PrO	**4d**, 84
25	**1a**	*n*-Bu	**3e**	*t*-BuO	**4d**, 95
26	**1a**	*n*-Bu	**3f**	OH	**4d**, 61
27	**1a**	*n*-Bu	**3g**	Cl	**4d**, 99[b]

For all entries except stated otherwise: **1** (1.0 mmol), **2a** (1.5 mmol), **3** (1.5 mmol), $H_3PW_{12}O_{40}$ (0.1 mmol), in 3 cm^3 *i*-PrOH at 85 °C for 8 h

[a] Entries 19–21 indicate the yield of the product in recycling tests, second through fourth runs

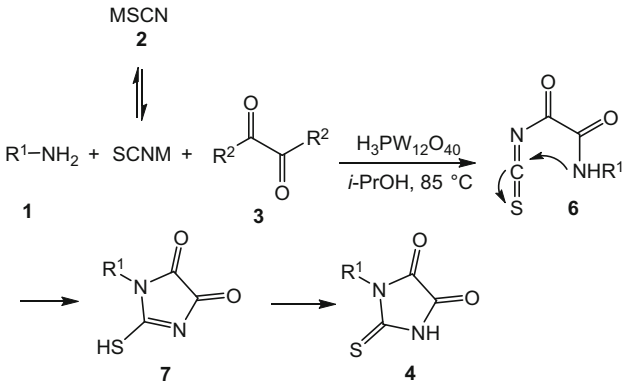
[b] The yield was obtained in the absence of the catalyst

this work was the first example of the utilizing HPA for the preparation of thioparabanic acid using amines, thiocyanates, and dialkyl oxalates. Using this procedure, a simple recrystalization from CH_2Cl_2/acetone would suffice to isolate the pure titled product. The optimized reaction conditions reported herein are compatible with the presence of functional groups such as CO_2, OMe, Cl, Br, and CF_3.

Experimental

All reagents were purchased from the Merck chemical companies and used without further purification. Products were characterized by different spectroscopic methods (FT-IR, GC-Mass, and NMR spectra), elemental analysis (CHN), and melting points. The NMR spectra were

Scheme 1



recorded in acetone-d_6. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 500 MHz instrument. The chemical shifts (δ) are reported in ppm relative to the TMS as internal standard. J values are given in Hz. IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus. The elemental analysis was performed using Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel poly-gram SIL G/UV 254 plates. Morphology and particle dispersion was investigated by scanning electron microscopy (SEM) (Cam scan MV2300). All known compounds (**4b**, **4d**, **4e**, **4g**–**4i**, and **4k**) gave satisfactory spectroscopic data and were consistent with that reported in the literature [25] (see ESI for characterization data for all products).

General procedure for the preparation of catalyst and 4

The heteropolyacids were prepared by a hydrothermal synthesis method [31]. As an example $H_4PMo_{12}O_{40}$ was prepared according to the following procedure: a mixture of 0.98 g phosphoric acid and 14.4 g molybdenum trioxide was suspended in 150 cm^3 distilled H_2O and the mixture stirred for 6 h at 80 °C. After cooling to 25 °C and removal of insoluble molybdates, the heteropolyacid solution was evaporated and dried at 85 °C for 24 h to give orange crystals. Silica-supported HPA was prepared by the standard literature procedure [32]. A mixture of silica (Davisil^{TM}, 200–425 mesh, 150 Å) and HPA in H_2O-*i*-PrOH or MeCN was stirred at 25 °C for 24 h. The catalyst was washed with deionized H_2O and dried at 110 °C for 12 h. The supported catalyst was then calcinated at 200 °C for 3 h.

A mixture of ammonium thiocyanate (1.5 mmol), HPA (0.1 mmol), and oxalate source (1.5 mmol) in 2 cm^3 *i*-PrOH was stirred at 85 °C for 30 min. A solution of amine (1.0 mmol) in 1 cm^3 *i*-PrOH was then added to initial mixture in one portion. The resulting mixture was heated for an additional 8–11 h. After completion of reaction, the mixture was diluted with 5 cm^3 EtOAc and subsequently 5 cm^3 sat. NH_4Cl solution was added. The mixture was stirred for additional 30 min, and two layers were separated. The aqueous layer was extracted with EtOAc (7 cm^3 × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was washed with ether and then recrystallized from CH_2Cl_2/acetone to give the pure desired product.

1-Butyl-2-thioxoimidazolidine-4,5-dione (**4a**, $C_7H_{10}N_2O_2S$)

The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.17 g (93 %) **4a**. Pale yellow powder; m.p.: 71–74 °C; IR (KBr): $\bar{\nu}$ = 3271, 1753, 1737, 1659, 1441, 1314, 1124 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 0.92 (3H, t, ^3J = 7.3 Hz, CH_3), 1.35 (2H, m, CH_2), 1.66 (2H, m, CH_2), 3.91 (2H, t, ^3J = 7.4 Hz, CH_2), 10.23 (1H, br s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): δ = 13.5 (CH_3), 19.9 (CH_2), 29.6 (CH_2), 41.5 (CH_2), 155.6 (C=O), 156.3 (C=O), 171.6 (C=S) ppm; EI-MS (70 eV): *m*/*z* (%) = 186 (M$^+$, 8), 144 (37), 115 (100), 99 (28), 71 (67).

1-(tert-Butyl)-2-thioxoimidazolidine-4,5-dione (**4b**) [25]

The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.17 g (92 %) **4b**. Pale yellow powder; m.p.: 93–96 °C.

1-Phenyl-2-thioxoimidazolidine-4,5-dione (**4c**, $C_9H_6N_2O_2S$)

The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.17 g (85 %) **4c**. Yellow powder; m.p.: 135–137 °C; IR (KBr): $\bar{\nu}$ = 3273, 1754, 1735, 1652, 1427, 1318, 1124 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.29 (2H, d, ^3J = 6.8 Hz, 2 CH), 7.47–7.54 (3H, m, 3 CH), 9.52 (1H, br s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): δ = 129.2 (CH), 130.6 (2 CH), 133.6 (2 CH), 139.4 (C), 161.5 (C=O), 162.3 (C=O), 174.7 (C=S) ppm; EI-MS (70 eV): *m*/*z* (%) = 206 (M$^+$, 7), 164 (32), 135 (43), 119 (24), 92 (47), 77 (100).

1-Benzyl-2-thioxoimidazolidine-4,5-dione (**4d**) [25]

The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.21 g (94 %) **4d**. Pale yellow powder; m.p.: 152–154 °C (Ref. [25] 151–153 °C).

1-(4-Methylbenzyl)-2-thioxoimidazolidine-4,5-dione (**4e**) [25]

The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.22 g (93 %) **4e**. Pale yellow powder; m.p.: 167–169 °C.

1-(2-Methylbenzyl)-2-thioxoimidazolidine-4,5-dione (**4f**, $C_{11}H_{10}N_2O_2S$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.20 g (87 %) **4f**. Pale yellow powder; m.p.: 159–162 °C; IR (KBr): $\bar{\nu} = 3283, 1760, 1738, 1658, 1460, 1323, 1128$ cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 2.21$ (3H, s, CH_3), 5.21 (2H, s, CH_2), 7.10 (1H, d, $^3J = 7.5$ Hz, CH), 7.20–7.29 (2H, m, 2 CH), 7.36 (1H, d, $^3J = 7.7$ Hz, CH), 9.57 (1H, s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 22.7$ (CH_3), 46.4 (CH_2), 126.3 (CH), 127.1 (CH), 129.6 (CH), 131.5 (CH), 136.2 (C), 139.6 (C), 156.3 (C=O), 157.1 (C=O), 173.6 (C=S) ppm; EI-MS (70 eV): *m/z* (%) = 234 (M^+, 6), 192 (14), 163 (68), 147 (24), 121 (36), 106 (100).

1-(2-Chlorobenzyl)-2-thioxoimidazolidine-4,5-dione (**4g**) [25]
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.23 g (89 %) **4g**. Pale yellow powder; m.p.: 164–167 °C.

1-(4-Chlorobenzyl)-2-thioxoimidazolidine-4,5-dione (**4h**) [25]
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.22 g (87 %) **4h**. Pale yellow powder; m.p.: 170–172 °C.

1-(4-Methoxybenzyl)-2-thioxoimidazolidine-4,5-dione (**4i**) [25]
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.24 g (98 %) **4i**. Pale yellow powder; m.p.: 173–176 °C.

1-(4-Bromobenzyl)-2-thioxoimidazolidine-4,5-dione (**4j**, $C_{10}H_7BrN_2O_2S$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.26 g (87 %) **4j**. Pale yellow powder; m.p.: 182–184 °C; IR (KBr): $\bar{\nu} = 3292, 1763, 1737, 1652, 1424, 1336, 1128$ cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 4.92$ (2H, s, CH_2), 7.27 (2H, d, $^3J = 8.1$ Hz, 2 CH), 7.78 (2H, d, $^3J = 8.1$ Hz, 2 CH), 9.45 (1H, s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 50.2$ (CH_2), 123.4 (C), 127.1 (2 CH), 129.4 (2 CH), 134.1 (C), 154.7 (C=O), 157.0 (C=O), 174.3 (C=S) ppm; EI-MS (70 eV): *m/z* (%) = 299 (M^+, 3), 255 (127), 227 (69), 211 (18), 185 (57), 169 (100).

1-(Naphthalen-1-yl)-2-thioxoimidazolidine-4,5-dione (**4k**) [25]
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.24 g (94 %) **4k**. Pale yellow powder; m.p.: 182–185 °C.

Isopropyl 4-[(4,5-dioxo-2-thioxoimidazolidin-1-yl)methyl] benzoate (**4l**, $C_{14}H_{14}N_2O_4S$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.21 g (69 %) **4l**. Pale yellow powder; m.p.: 108–118 °C; IR (KBr): $\bar{\nu} = 3278, 1758, 1742, 1731, 1647, 1446, 1327, 1126$ cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 1.22$ (6H, d, $^3J = 6.7$ Hz, 2 CH_3), 5.04 (2H, s, CH_2), 5.36 (1H, m, CH), 7.57–7.69 (4H, m, 4 CH), 9.36 (H, br s, NH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 22.7$ (2 CH_3), 47.7 (CH_2), 69.2 (CH), 127.2 (2 CH), 129.6 (C), 132.3 (2 CH), 138.9 (C), 155.9 (C=O), 157.2 (C=O), 167.1 (C=O), 176.8 (C=S) ppm; EI-MS (70 eV): *m/z* (%) = 306 (M^+, 5), 263 (14), 221 (20), 192 (69), 176 (28), 150 (36), 135 (17), 91 (100).

2-Thioxo-1-[3-(trifluoromethyl)phenyl]imidazolidine-4,5-dione (**4m**, $C_{10}H_5F_3N_2O_2S$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.08 g (29 %) **4m**. Yellow powder; m.p.: 119–121 °C; IR (KBr): $\bar{\nu} = 3278, 1764, 1738, 1651, 1437, 1326, 1125$ cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 7.20$ (1H, m, CH), 7.48 (1H, d, $^3J = 6.8$ Hz, CH), 7.68 (1H, t, $^3J = 6.8$ Hz, CH), 7.76 (1H, s, CH), 9.74 (1H, br s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 124.2$ (CH, q, $^3J = 3.8$ Hz), 126.5 (CH, q, $^3J = 3.8$ Hz), 129.8 (CH), 131.0 (CF_3, q, $^1J = 270.2$ Hz), 133.5 (CH), 135.2 (C, q, $^2J = 32.2$ Hz), 139.3 (C), 155.7 (C=O), 156.2 (C=O), 176.4 (C=S) ppm; EI-MS (70 eV): *m/z* (%) = 274 (M^+, 3), 232 (15), 203 (67), 187 (18), 161 (100).

2-Thioxo-1-(m-tolyl)imidazolidine-4,5-dione (**4n**, $C_{10}H_8N_2O_2S$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.20 g (89 %) **4n**. Yellow powder; m.p.: 130–132 °C; IR (KBr): $\bar{\nu} = 3281, 1769, 1735, 1662, 1438, 1336, 1125$ cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 2.34$ (3H, s, CH_3), 6.93–6.96 (2H, m, 2 CH), 7.24 (1H, d, $^3J = 7.5$ Hz, CH), 7.37 (1H, s, CH), 9.68 (1H, s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 22.7$ (CH_3), 123.5 (CH), 124.8 (CH), 129.0 (CH), 130.6 (CH), 134.1 (C), 137.3 (C), 157.1 (C=O), 157.4 (C=O), 176.8 (C=S) ppm; EI-MS (70 eV): *m/z* (%) = 220 (M^+, 6), 178 (12), 149 (72), 106 (100), 91 (51).

1-(4-Methoxyphenyl)-2-thioxoimidazolidine-4,5-dione (**4o**, $C_{10}H_8N_2O_3S$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.21 g (89 %) **4o**. Yellow powder; m.p.: 153–155 °C; IR (KBr): $\bar{\nu} = 3282, 1767, 1738, 1668, 1442, 1342, 1125$ cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 3.86$ (3H, s, OCH_3), 7.09 (2H, d, $^3J = 7.6$ Hz, 2 CH), 7.25 (2H, d, $^3J = 7.5$ Hz, 2 CH), 9.72 (1H, br s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 56.8$ (OCH_3), 116.3 (2 CH), 129.7 (2 CH), 132.4 (C), 156.3 (C=O), 157.1 (C=O), 159.1 (C), 176.2 (C=S) ppm; EI-MS (70 eV): *m/z* (%) = 236 (M^+, 8), 194 (17), 165 (71), 149 (21), 123 (58), 106 (100).

2-Thioxo-1-(o-tolyl)imidazolidine-4,5-dione
(**4p,** $C_{10}H_8N_2O_2S$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.21 g (69 %) **4p**. Yellow powder; m.p.: 121–124 °C; IR (KBr): $\bar{\nu} = 3282, 1758, 1730, 1651, 1449, 1342, 1125\ cm^{-1}$; ^1H NMR (500 MHz, acetone-d_6): $\delta = 2.20$ (3H, s, CH_3), 7.21–7.35 (3H, m, 3 CH), 7.53 (1H, t, $^3J = 7.9$ Hz, CH), 9.75 (1H, s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 21.4$ (CH_3), 124.8 (CH), 129.4 (CH), 129.6 (CH), 131.1 (CH), 133.9 (C), 136.2 (C), 155.9 (C=O), 156.3 (C=O), 177.2 (C=S) ppm; EI-MS (70 eV): *m/z* (%) = 220 (M^+, 2), 176 (17), 149 (67), 133 (26), 106 (100), 91 (78).

1-(4-Bromophenyl)-2-thioxoimidazolidine-4,5-dione
(**4q**, $C_{10}H_8N_2O_2S$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.22 g (76 %) **4q**. Yellow powder; m.p.: 167–169 °C; IR (KBr): $\bar{\nu} = 3284, 1767, 1738, 1652, 1436, 1334, 1126\ cm^{-1}$; ^1H NMR (500 MHz, acetone-d_6): $\delta = 7.47$ (2H, d, $^3J = 8.2$ Hz, 2 CH), 7.74 (2H, d, $^3J = 8.2$ Hz, 2 CH), 9.85 (H, br s, NH) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 124.7$ (C), 127.2 (2 CH), 131.8 (2 CH), 136.1 (C), 156.1 (C=O), 158.2 (C=O), 177.2 (C=S) ppm; EI-MS (70 eV): *m/z* (%) = 285 (M^+, 5), 241 (12), 213 (69), 197 (17), 170 (100), 155 (47).

3-Butylthiazolidine-2,4,5-trione (**5**, $C_7H_9NO_3$)
The crude product was purified by recrystallization from CH_2Cl_2/acetone affording 0.11 g (61 %) **5**. Yellow oily solid; IR (KBr): $\bar{\nu} = 3205, 1762, 1748, 1736, 1445, 1312, 1136\ cm^{-1}$; ^1H NMR (500 MHz, acetone-d_6): $\delta = 0.87$ (3H, t, $^3J = 7.8$ Hz, CH_3), 1.28 (2H, m, CH_2), 1.61 (2H, m, CH_2), 3.73 (2H, t, $^3J = 7.2$ Hz, CH_2) ppm; ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 14.8$ (CH_3), 21.3 (CH_2), 30.8 (CH_2), 47.5 (CH_2), 159.8 (C=O), 174.1 (C=O), 192.9 (C=O) ppm; EI-MS (70 eV): *m/z* (%) = 187 (M^+, 3), 159 (25), 133 (46), 99 (73), 73 (100).

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References

1. Ward SE, Harrington FP, Gordon LJ, Hopley SC, Scott CM, Watson JM (2005) J Med Chem 48:3478
2. Massari S, Daelemans D, Barreca ML, Knezevich A, Sabatini S, Cecchetti V, Marcello A, Pannecouque C, Tabarrini O (2010) J Med Chem 53:641
3. Soneda T, Takeshita H, Kagoshima Y, Yamamoto Y, Hosokawa T, Konosu T, Masuda N, Uchida T, Achiwa I, Kuroyanagi J, Fujisawa T, Yokomizo A, Noguchi T (2009) Preparation of imidazolecarboxamide derivatives as antibacterial agents. Chem Abstr 151:148320 **(WO 2009084614, Jul 9, 2009)**
4. Murugana R, Anbazhaganb S, Narayanan S (2009) Eur J Med Chem 44:3272
5. Tu SJ, Zhang XH, Han ZG, Cao XD, Wu SS, Yan S, Hao WJ, Zhang G, Ma N (2009) J Comb Chem 11:428
6. Evdokimov NM, Kireev AS, Yakovenko AA, Antipin MY, Magedov IV, Kornienko A (2007) J Org Chem 72:3443
7. Allais C, Grassot JM, Rodriguez J, Constantieux T (2014) Chem Rev 114:10829
8. Yavari I, Ghazanfarpour-Darjani M, Sabbaghan M, Hossaini Z (2007) Tetrahedron Lett 48:3749
9. Ghazanfarpour-Darjani M, Babapour-Kooshalshahi M, Mousavi-Safavi SM, Akbari J, Khalaj M (2015) Synlett 27:259
10. Ma D, Lu X, Shi L, Zhang H, Jiang Y, Liu X (2011) Angew Chem Int Ed 50:1118
11. Yavari I, Ghazanfarpour-Darjani M, Nematpour M (2015) Tetrahedron Lett 56:2416
12. Yavari I, Ghazanfarpour-Darjani M, Bayat MJ, Malekafzali A (2014) Synlett 25:959
13. Heravi MM, Sadjadi S (2009) J Iran Chem Soc 6:1
14. Kozhevnikov IV (1998) Chem Rev 98:171
15. Gulliya KS, Franck B, Schneider U, Sharma R, Arnold L, Matthews JL (1994) Photooxidation products and derivatives thereof of merocyanine-540, their preparation and uses as anticancer and antiviral agents. Chem Abstr 121:108825 **(US Patent 5,312,919, May 17, 1994)**
16. Gulliya KS, Sharam R, Liu HW, Arnold L, Matthews JL (1995) Anticancer Drugs 6:545
17. Kotani T, Nagaki Y, Ishii A, Konishi Y, Yago H, Suehiro S, Okukado N, Okamoto K (1997) J Med Chem 40:684
18. Butera JA, Elokdah HM, Sulkowski TS, Primeau JL, Lennox JR, Graceffa RF (2006) Preparation of 1,3-disubstituted-2-thioxoimidazolidine-4,5-diones as potassium channel openers. Chem Abstr 139:69265 **(US Patent 7,115,620, October 3, 2006; (2003))**
19. Sunduru N, Srivastava K, Rajakumar S, Puri SK, Saxena JK, Chauhan PM (2009) Bioorg Med Chem Lett 19:2570
20. Elokdah H, Sulkowski TS, Gharbia MA, Butera JA, Chai SY, Mcfarlane GR, Mckean ML, Babiak JL, Adelman SJ, Quine EM (2004) J Med Chem 47:681
21. Fahmy HH, Soliman GA (2001) Arch Pharm Res 24:180
22. Elokdah H, Sulkowski TS (2003) Preparation of 1,3-disubstituted-2-thioxoimidazolidine-4,5-diones for the treatment of atherosclerosis. Chem Abstr 139:69264 **(US Patent 20030119889, Jun 26, 2003)**
23. Schmeyers J, Kaupp G (2002) Tetrahedron 58:7241
24. Aragoni MC, Arca M, Devillanova FA, Hursthouse MB, Huth SL, Isaia F, Lippolis V, Mancini A, Ogilvie HR, Verani G (2005) J Organomet Chem 690:1923
25. Yavari I, Souri S, Sirouspour M (2008) Synlett 19:1633
26. Samzadeh-Kermani A (2014) Monatsh Chem 145:611
27. Samzadeh-Kermani A (2014) Synlett 25:1839
28. Samzadeh-Kermani A (2015) Synlett 26:643
29. Samzadeh-Kermani A (2016) Monatsh Chem 147:761
30. Bardin BB, Bordawekar SV, Neurock M, Davis RJ (1998) J Phys Chem B 102:10819
31. Tsigdinos GA, Hallada C (1968) J Inorg Chem 7:437
32. Izumi Y, Hasebe R, Urabe K (1983) J Catal 84:402