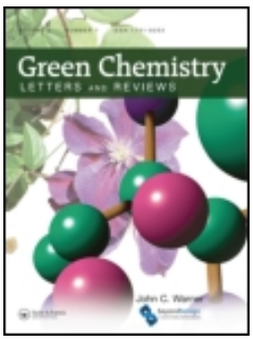

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LETTER

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Organic-salt-mediated highly regioselective *N3*-alkylation of 2-thiophenytoin via Michael reaction under solvent-free conditions

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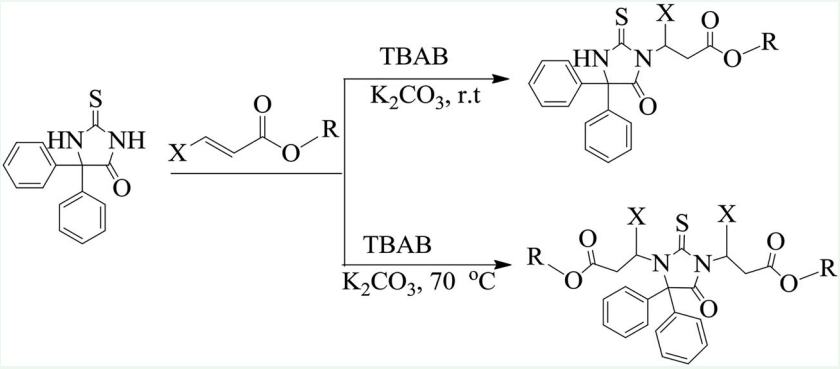
ABSTRACT

A regioselective *N3*-alkylation of 5,5-diphenyl-2-thiohydantoin (2-thiophenytoin) using a very efficient mild base K_2CO_3 and α,β-unsaturated esters in the presence of organic salt TBAB (tetrabutylammonium bromide) at room temperature has been reported (**3b**–**3h**). The selectivity of this reaction is excellent and products have been produced in good yields under solvent-free conditions. The increase of the reaction temperature to 70°C mostly disappeared this selectivity and afforded only the *N1*,*N3*-dialkylated derivatives of 2-thiophenytoin in good yields (**4b**–**4g**). We were unable to selectively *N3*-alkylate 2-thiophenytoin with ethyl acrylate at both room temperature and 70°C under the same conditions (**4a**). Dimethyl and diethyl fumarates cannot work as Michael acceptors and were hydrolyzed to fumaric acid under reaction conditions.



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Solvent-free; regioselective; Michael addition; 2-thiophenytoin; α; β-unsaturated esters

Introduction

Development of solvent-free synthetic methods or the replacement of hazardous volatile solvents with environmentally benign media has become an important and popular research topic in recent years (*1*). In this context, the use of organic salt compounds has received considerable attention. Organic salts are compounds with high polarity, and consequently capable to catalyze or promote the polar organic reactions via creation of strong polar media. Additionally, these compounds can be easily separated from organic products by extraction, using immiscible common organic solvents, and readily reusing them without significant loss of their catalytic activities (*2*–*4*).

Without question, among the known sulfur analogs of hydantoin, 2-thiohydantoin and its derivatives have a superior position due to their wide applications as: antiviral (*5*), anticonvulsant (*6*), antitumor (*7*), hypolipidemic (*8*), antimutagenic (*9*), antithiroidal (*10*), antimicrobial (*11*), anti-ulcer and anti-inflammatory agents (*12*), and pesticides (*13*). 5,5-Diphenyl-2-thiohydantoin (2-thiophenytoin) is a well-known derivative of 2-thiohydantoin that has attracted the attention of medicinal chemists (*14*).

Although, the synthesis of *N3*-alkylated derivatives of this compound from the Biltz reaction between benzil and *N*-monosubstituted of thiourea has been reported as a moderate method (*15*), the preparation of these derivatives from the direct alkylation of 2-thiophenytoin via the Michael reaction has not been investigated, most probably due to its demands for regioselectivity, so far. The achievement of regioselectivity is difficult because of the small difference in acidity of H–N1 and H–N3

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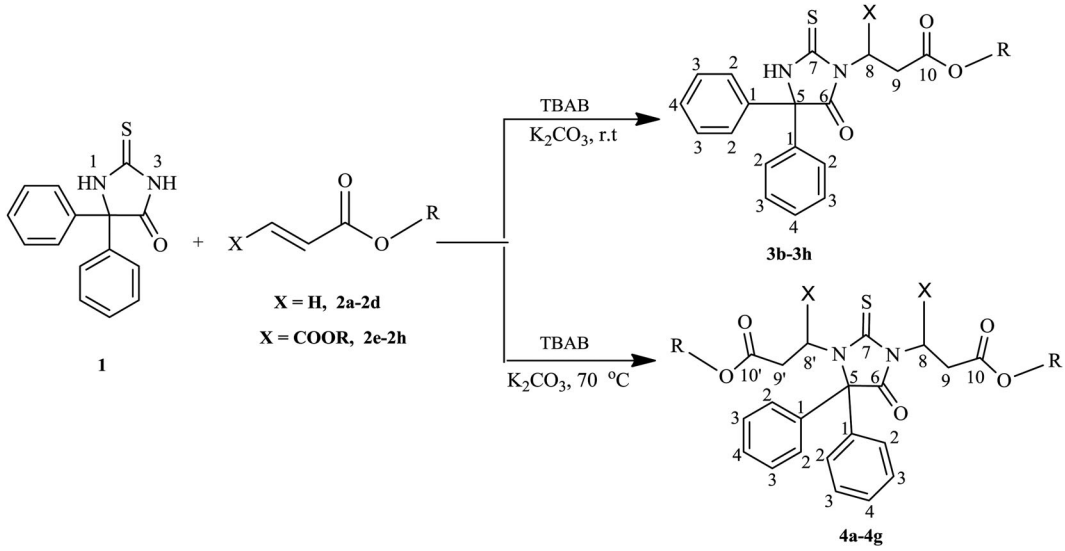

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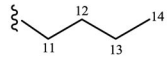
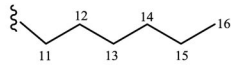
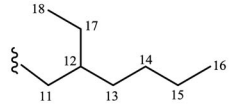
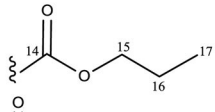
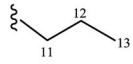
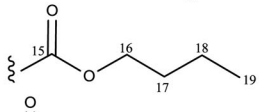
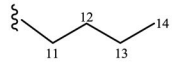
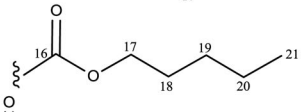
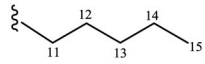
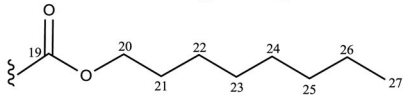
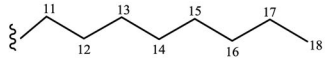
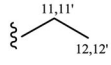
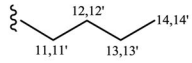
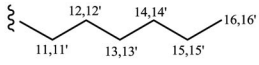
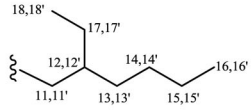
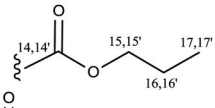
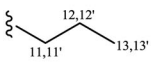
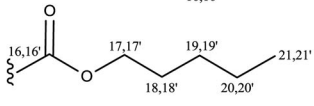
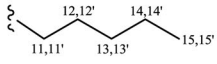
3b	H	
3c	H	
3d	H	
3e		
3f		
3g		
3h		
4a	H	
4b	H	
4c	H	
4d	H	
4e		
4g		

Scheme 1. Michael addition of 2-thiophenytoin to α,β-unsaturated esters under solvent-free conditions.

hydrogens. These results interested us to develop a convenient methodology for direct *N*-alkylation of 2-thiophenytoin. In our research group, an efficient method, in recent years, was reported to the *N*-alkylation of diverse amide and imide groups through the Michael addition reaction (*16–18*). Also, recently, we reported a highly regioselective method for the alkylation of phenytoin under ultrasound irradiation (*19*). In the present study, not only a simple and inexpensive method for *N1,N3*-dialkylation of 2-thiophenytoin is described, the regioselectivity of the method has also been studied (Scheme 1).

Experimental

All acrylic and fumaric esters were synthesized in our laboratory according to the literature procedure (*20*) and their structures were confirmed by IR,^{1}H NMRand^{13}C NMR spectroscopy. 5,5-Diphenyl-2-thiohydantoin (2-thiophenytoin) was purchased from Aldrich and used without further purification. Esters were transferred via a syringe. Organic solvents were removed under reduced pressure by a rotary evaporator. The progress of the reactions was followed by TLC using silica-gel SILIG/UV 254 plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker 400 MHz instrument. FT-IR spectra were recorded on a Perkin-Elmer RX-1 instrument. Elemental analysis for C, H, and N was performed using a Heraeus CHN-O-Rapid analyzer. The melting points were determined in open capillaries with a Stuart Melting Point Apparatus and are uncorrected.

General procedure for alkylation of 2-thiophenytoin

α,β-Unsaturated ester (1.2 mmol for monoalkylation and 2.5 mmol for dialkylation) was added to a well-ground mixture of 2-thiophenytoin (1 mmol), TBAB (1 mmol) and K_2CO_3 (1 mmol) and mixed thoroughly with a glass rod. The resulting mixture was kept in an oil bath at 25°C or 70°C for an appropriate time (Table 3). The progress of the reaction was monitored by TLC. After the completion of the reaction, chloroform (20 mL) was added to the reaction mixture. The solution was stirred to dissolve all the soluble solids. After filtration, TBAB was recovered by the addition of water (3×20 mL) to the filtrate, then collected and dried under vacuum. The chloroform layer was washed with water (3×15 mL). After drying with $MgSO_4$ and removal of the organic solvent, the residue was purified on a short silica-gel column with *n*-hexane/ethyl acetate (9.5:0.5) as the eluent.

Diethyl 3,3′-(5-oxo-4,4-diphenyl-2-thioxoimidazolidine-1,3-diyl)dipropanoate (4a)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.11 (t, 3H, J = 7.2 Hz, CH_3), 1.15 (t, 3H, J = 7.2 Hz, CH_3), 1.90–1.94 (m, 2H, CH_2), 2.73 (t, 2H, J = 7.2 Hz, CH_2), 3.97 (q, 2H, J = 7.2 Hz, CH_2), 3.99–4.06 (m, 4H, $2CH_2$), 4.18 (t, 2H, J = 7.2 Hz, CH_2), 7.21–7.39 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.04 (C12), 14.09 (C12′), 30.80 (C9′), 32.39 (C9), 38.00 (C8), 41.11 (C8′), 60.46 (C11), 60.71 (C11′), 76.78 (C5), 127.00 (C2), 128.25 (C4), 128.72 (C3), 135.74 (C1), 170.50 (C10), 170.53 (C10′), 170.58 (C6), 180.52 (C=S); IR (KBr) ν: 3062, 2982, 2935, 1738, 1468, 1445, 1189, 1137, 767, 701 cm^{-1}. Anal. calcd for $C_{25}H_{28}N_2O_5S$: C 64.08, H 6.02, N 5.98; Found C 64.11, H 6.23, N 5.91.

Butyl 3-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)propanoate (3b)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (t, 3H, J = 6.0 Hz, CH_3), 1.32–1.41 (m, 2H, CH_2), 1.54–1.59 (m, 2H, CH_2), 2.78 (t, 2H, J = 7.2 Hz, CH_2), 4.04 (t, 2H, J = 7.0 Hz, CH_2), 4.19 (t, 2H, J = 7.2 Hz, CH_2), 7.29–7.41 (m, 10H, Ar), 9.19 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ: 13.72 (C14), 19.09 (C13), 30.48 (C12), 32.31 (C9), 37.39 (C8), 64.84 (C11), 72.10 (C5), 126.93 (C2), 129.00 (C4), 129.05 (C3), 137.75 (C1), 170.66 (C10), 173.15 (C6), 181.90 (C=S); IR (KBr) υ: 3304, 3064, 2960, 2873, 1736, 1493, 1447, 1169, 758, 698 cm^{-1}; Ms m/z (%): 396 (M^+) (48), 340 (100), 323 (57), 295 (18), 269 (12), 245 (4), 225 (49), 194 (95), 165 (53), 121 (12), 104 (52), 77 (25), 57 (41). Anal. calcd for $C_{22}H_{24}N_2O_3S$: C 66.64, H 6.10, N 7.07; Found C 66.52, H 6.03, N 7.81.

Dibutyl 3,3′-(5-oxo-4,4-diphenyl-2-thioxoimidazolidine-1,3-diyl)dipropanoate (4b)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (t, 3H, J = 7.2 Hz, CH_3), 0.93 (t, 3H, J = 7.2 Hz, CH_3), 1.25–1.41 (m, 4H, $2CH_2$), 1.48–1.61 (m, 4H, $2CH_2$), 1.93–1.97 (m, 2H, CH_2), 2.78 (t, 2H, J = 7.2 Hz, CH_2), 3.95 (t, 2H, J = 7.0 Hz, CH_2), 4.01–4.08 (m, 4H, $2CH_2$), 4.23 (t, 2H, J = 7.0 Hz, CH_2), 7.24–7.46 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.69 (C14), 13.73 (14′), 19.03 (C13′), 19.11 (13), 30.46 (C12), 30.51 (C12′), 30.81 (C9′), 32.40 (C9), 37.97 (C8), 41.17 (C8′), 64.49 (C11), 64.79 (C11′), 76.74 (C5), 128.27 (C2), 129.22 (C4), 129.46 (C3), 135.71 (C1), 170.74 (C10), 170.82 (C10′), 173.74 (C6), 180.61 (C=S); IR (KBr) υ: 3063, 2959, 2934, 1743, 1471, 1445, 1134, 768, 700 cm^{-1}; Anal. calcd for $C_{29}H_{36}N_2O_5S$: C 66.39, H 6.92, N 5.34; Found C 66.23, H 6.83, N 5.42.

Hexyl 3-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)propanoate (3c)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (t, 3H, J = 6.8 Hz, CH_3), 1.30–1.33 (m, 6H, $3CH_2$), 1.63–1.69 (m, 2H, CH_2), 2.77 (t, 2H, J = 7.4 Hz, CH_2), 4.03 (t, 2H, J = 6.8 Hz, CH_2), 4.15 (t, 2H, J = 7.4 Hz, CH_2), 7.29–7.39 (m, 10H, Ar), 8.70 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.05 (C16), 22.55 (C15), 25.54 (C14), 28.42 (C13), 31.42 (C12), 32.34 (C9), 37.33 (C8), 65.15 (C11), 72.16 (C5), 126.96 (C2), 129.02 (C4), 129.08 (C3), 137.78 (C1), 170.70 (C10), 173.21 (C6), 181.83 (C=S); IR (KBr) υ: 3303, 3064, 2957, 2932, 1737, 1492, 1448, 1170, 757, 698 cm^{-1}; Anal. calcd for $C_{24}H_{28}N_2O_3S$: C 67.90, H 6.65, N 6.60; Found C 67.83, H 6.57, N 6.70.

Dihexyl 3,3′-(5-oxo-4,4-diphenyl-2-thioxoimidazolidine-1,3-diyl)dipropanoate (4c)

Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.82–0.86 (m, 6H, $2CH_3$), 1.22–1.26 (m, 12H, $6CH_2$), 1.47–1.54 (m, 4H, $2CH_2$), 1.91 (t, 2H, J = 7.2 Hz, CH_2), 2.74 (t, 2H, J = 6.9 Hz, CH_2), 3.90 (t, 2H, J = 6.0 Hz, CH_2), 3.95–4.06 (m, 4H, $2CH_2$), 4.18 (t, 2H, J = 6.9 Hz, CH_2), 7.21–7.39 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.99 (C16), 14.02 (C16′), 22.49 (C15), 22.51 (C15′), 25.43 (C14), 25.51 (C14′), 28.35 (C13), 28.42 (C13′), 30.79 (C12), 31.32 (C12′), 31.39 (C9′), 32.36 (C9), 37.96 (C8), 41.14 (C8′), 64.66 (C11), 64.97 (C11′), 76.82 (C5), 128.25 (C2), 129.16 (C4), 129.39 (C3), 135.75 (C1), 170.64 (C10), 170.67 (C10′), 173.63 (C6), 180.56 (C=S); IR (KBr) υ: 3065, 2958, 2932, 1738, 1473, 1446, 1182, 768, 700 cm^{-1}; Ms *m/z* (%): 581 (M^++1) (35), 497 (18), 480 (15), 452 (7), 412 (13), 395 (12), 194 (100), 166 (40), 91 (10), 55 (20); Anal. calcd for $C_{33}H_{44}N_2O_5S$: C 68.25, H 7.64, N 4.82; Found C 68.21, H 7.61, N 4.91.

2-Ethylhexyl 3-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)propanoate (3d)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (t, 3H, J = 7.0 Hz, CH_3), 0.91 (t, 3H, J = 7.0 Hz, CH_3), 1.26–1.39 (m, 8H, $4CH_2$), 1.53–1.58 (m, 1H, CH), 2.76 (t, 2H, J = 7.6 Hz, CH_2), 3.99 (m, 2H, CH_2), 4.18 (t, 2H, J = 7.6 Hz, CH_2), 7.32–7.41 (m, 10H, Ar), 8.96 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 10.99 (C18), 14.11 (C16), 23.00 (C15), 23.70 (C17), 28.90 (C14), 30.31 (C13), 32.31 (C9), 37.23 (C12), 38.59 (C8), 67.44 (C11), 72.25 (C5), 126.97 (C2), 128.92 (C4), 129.01 (C3), 137.77 (C1), 170.81 (C10), 173.24 (C6), 181.76 (C=S); IR (KBr) υ: 3299, 3063, 2957, 2929, 1733, 1489, 1447, 1169, 757, 697 cm^{-1}; Anal. calcd for $C_{26}H_{32}N_2O_3S$: C 69.00, H 7.13, N 6.19; Found: C 68.88, H 7.22, N 6.11.

Di(2-ethylhexyl) 3,3′-(5-oxo-4,4-diphenyl-2-thioxoimidazolidine-1,3-diyl)dipropanoate (4d)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.82–0.90 (m, 12H, $4CH_3$), 1.22–1.38 (m, 16H, $8CH_2$), 1.47 (m, 1H, CH), 1.55–1.57 (m, 1H, CH), 1.93–1.97 (m, 2H, CH_2), 2.78 (t, 2H, J = 7.2 Hz, CH_2), 3.86 (d, 2H, J = 5.6 Hz, CH_2), 3.98 (t, 2H, J = 5.2 Hz, CH_2), 4.04 (t, 2H, J = 8 Hz, CH_2), 4.22 (t, 2H, J = 7.2 Hz, CH_2), 7.24–7.43 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 10.98 (C18,18′), 14.06 (C16), 14.09 (C16′), 22.95 (C15), 22.98 (C15′), 23.71 (C17,17′), 28.84 (C14), 28.89 (C14′), 30.31 (C13,13′), 30.80 (C9′), 32.32 (C9), 37.91 (C12), 38.57 (C12′), 38.61 (C8), 41.17 (C8′), 66.97 (C11), 67.31 (C11′), 76.84 (C5), 128.25 (C2), 129.20 (C4), 129.42 (C3), 135.75 (C1), 170.76 (C10), 170.84 (C10′), 173.69 (C6), 180.57 (C=S); IR (KBr) υ: 3063, 2961, 2929, 1739, 1468, 1445, 1182, 767, 700 cm^{-1}; Anal. calcd for $C_{37}H_{52}N_2O_5S$: C 69.78, H 8.23, N 4.40; Found C 69.65, H 8.13, N 4.52.

Dipropyl 2-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)succinate (3e)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.72 (t, 3H, J = 7.0 Hz, CH_3), 0.78 (t, 3H, J = 7.0 Hz, CH_3), 1.40–1.47 (m, 4H, $2CH_2$), 3.06 (dd, 1H, J_1 = 8.4 Hz, J_2 = 16.0 Hz, CH), 3.32 (dd, 1H, J_1 = 7.0 Hz, J_2 = 16.0 Hz), 3.87 (t, 2H, J = 7.0 Hz, CH_2), 3.96–4.02 (m, 2H, CH_2), 5.72 (m, 1H, CH), 7.13–7.19 (m, 10H, Ar), 8.01 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 9.22 (C17), 9.24 (C13), 20.63 (C12), 20.74 (C16), 32.67 (C9), 50.61 (C8), 65.65 (C11), 66.89 (C15), 75.68 (C5), 126.05 (C2), 127.93 (C4), 127.98 (C3), 136.55 (C1), 166.66 (C10), 168.81 (C14), 171.94 (C6), 180.22 (C=S); IR (KBr) υ: 3303, 3062, 2968, 2937, 1742, 1493, 1447, 1180, 758, 698 cm^{-1}; Anal. calcd for $C_{25}H_{28}N_2O_5S$: C 64.08, H 6.02, N 5.98; Found C 64.14, H 5.98, N 5.93.

Tetrapropyl 2,2′-(5-oxo-4,4-diphenyl-2-thioxoimidazolidine-1,3-diyl)disuccinate (4e)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.67 (t, 3H, J = 7.2 Hz, CH_3), 0.77 (t, 3H, J = 7.2 Hz, CH_3), 0.84 (t, 3H, J = 7.2 Hz, CH_3), 0.98 (t, 3H, J = 7.2 Hz, CH_3), 1.34–1.47 (m, 6H, $3CH_2$), 1.62–1.79 (m, 2H, CH_2), 2.95 (dd, 2H, J_1 = 7.6 Hz, J_2 = 16.8 Hz, CH_2), 3.21–3.30 (m, 4H, $2CH_2$), 3.75–3.79 (m, 2H, CH_2), 3.86–3.90 (m, 2H, CH_2), 3.93–3.99 (m, 2H, CH_2), 4.99 (m, 2H, 2CH), 7.19–7.47 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 9.11 (C13′), 9.20 (C17′), 10.08 (C13), 12.35 (C17), 19.99 (C12′), 20.54 (C16′), 20.73 (C16), 21.46 (C12), 37.12 (C9′), 42.21 (C9), 50.39 (C8′), 58.50 (C8), 65.72 (C11′), 65.85 (C15′), 66.89 (C11), 66.92 (C15), 75.68 (C5), 125.84 (C2), 127.88 (C4), 127.99 (C3), 139.15 (C1), 159.01 (C14′), 166.94 (C10′), 168.99 (C10), 172.51 (C14), 179.50 (C6), 181.69 (C=S); IR (KBr) υ: 3165, 3065, 2968, 2936, 1745, 1588, 1572, 1510, 756, 698

cm^{-1}; Anal. calcd for $C_{35}H_{44}N_2O_9S$: C 62.86, H 6.63, N 4.19; Found C 62.76, H 6.81, N 4.21.

Dibutyl 2-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)succinate (3f)

Colorless oil; ^1H NMR ($CDCl_3$, 400 MHz,) δ: 0.85–0.99 (m, 6H, $2CH_3$), 1.23–1.45 (m, 4H, $2CH_2$), 1.50–1.59 (m, 4H, $2CH_2$), 3.15 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 16.6$ Hz, CH), 3.41 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 16.6$ Hz, CH), 4.02 (t, 2H, $J = 6.8$ Hz, CH_2), 4.06–4.20 (m, 2H, CH_2), 5.80 (m, 1H, CH), 7.32–7.45 (m, 10H, Ar), 7.82 (s, 1H, NH); IR (KBr) υ: 3305, 3063, 2960, 2934, 1739, 1491, 1448, 1182, 758, 697 cm^{-1}; Anal. calcd for $C_{27}H_{32}N_2O_5S$: C 65.30, H 6.49, N 5.64; Found C 65.31, H 6.43, N 5.69.

Dipentyl 2-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)succinate (3g)

Colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.74 (t, 3H, $J =$ 6.8 Hz, CH_3), 0.78 (t, 3H, $J = 6.8$ Hz, CH_3), 1.08–1.19 (m, 8H, $4CH_2$), 1.33–1.45 (m, 4H, $2CH_2$), 2.99 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 17.2$ Hz, CH), 3.28 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 17.2$ Hz, CH), 3.87 (t, 2H, $J = 6.4$ Hz, CH_2), 3.95–4.01 (m, 2H, CH_2), 5.68 (m, 1H, CH), 7.17–7.43 (m, 10H, Ar), 9.03 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.92 (C15), 13.97 (C21), 22.20 (C14), 22.27 (C20), 27.72 (C12), 27.92 (C18), 28.07 (C13,19), 33.81 (C9), 51.50 (C8), 65.31 (C11), 66.48 (C17), 72.18 (C5), 127.12 (C2), 128.90 (C4), 128.96 (C3), 137.64 (C1), 167.77 (C10), 169.94 (C16), 173.02 (C6), 181.09 (C=S); IR (KBr) υ: 3308, 3063, 2958, 2932, 1746, 1495, 1447, 1181, 758, 697 cm^{-1}; Anal. calcd for $C_{29}H_{36}N_2O_5S$: C 66.39, H 6.92, N 5.34; Found C 66.43, H 6.78, N 5.29.

Tetrapentyl 2,2′-(5-oxo-4,4-diphenyl-2-thioxoimidazolidine-1,3-diyl)disuccinate (4g)

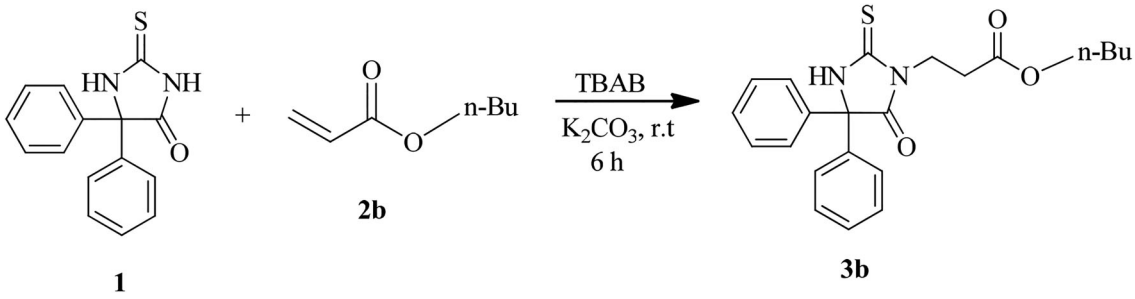
Colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.74–0.85 (m, 12H, $4CH_3$), 1.06–1.45 (m, 22H, $10CH_2$), 1.60–1.75 (m, 2H, CH_2), 2.93 (dd, 2H, $J_1 = 7.6$ Hz, $J_2 = 16.8$ Hz, CH_2), 3.20–3.29 (m, 4H, CH_2), 3.79 (t, 2H, $J = 7.2$ Hz, CH_2), 3.89–3.94 (m, 2H, CH_2), 3.96–4.01 (m, 2H, CH_2), 4.98 (m, 2H, 2CH), 7.18–7.42 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.87 (C15′), 12.91 (C21′), 21.13 (C14′), 21.18 (C21), 21.22 (C15), 26.21 (C14), 26.68 (C19′), 26.80 (C18), 26.86 (C20), 27.03 (C13,19), 27.72 (C13′), 29.92 (C12′), 30.03 (C18′), 33.27 (C12,20′), 37.83 (C9), 40.73 (C9′), 50.34 (C8), 58.50 (C8′), 64.32 (C11′), 65.50 (C17′), 65.72 (C11), 66.92 (C17), 75.67 (C5), 125.84 (C2), 127.29 (C4), 127.90 (C3), 139.17 (C1), 159.01 (C10), 166.64 (C16), 168.99 (C16′), 172.51 (C10′), 179.50 (C6), 181.69 (C=S); IR (KBr) υ: 3063, 2957, 2932, 1739, 1588, 1571, 1294, 1259, 758, 697 cm^{-1}; Anal. calcd for $C_{43}H_{60}N_2O_9S$: C 66.13, H 7.74, N 3.59; Found C 66.21, H 7.81, N 3.61.

Dioctyl 2-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)succinate (3h)

Colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.80 (t, 6H, $J =$ 6.8 Hz, $2CH_3$), 1.13–1.17 (m, 20H, $10CH_2$), 1.36–1.44 (m, 4H, $2CH_2$), 3.00 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 16.2$ Hz, CH), 3.29 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 16.2$ Hz, CH), 3.89 (t, 2H, J = 6.8 Hz, CH_2), 3.98–4.03 (m, 2H, CH_2), 5.69 (m, 1H, CH), 7.18–7.29 (m, 10H, Ar), 8.53 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.12 (C18,27), 22.65 (C17), 25.62 (C16), 25.74 (C25), 25.80 (C26), 28.24 (C15), 28.40 (C24), 29.12 (C13,22), 29.18 (C23,14), 29.28 (C12), 31.79 (C21), 33.77 (C9), 51.56 (C8), 65.31 (C11), 66.50 (C20), 72.10 (C5), 127.11 (C2), 128.93 (C4), 128.98 (C3), 137.62 (C1), 167.71 (C10), 169.88 (C19), 172.97 (C6), 181.16 (C=S); IR (KBr) υ: 3309, 3063, 2955, 2927, 1746, 1493, 1447, 1180, 758, 697 cm^{-1}; Anal. calcd for $C_{35}H_{48}N_2O_5S$: C 69.05, H 7.95, N 4.60; Found C 69.09, H 7.91, N 4.73.

Results and discussion

We have found that highly regioselective *N3*-alkylation of 2-thiophenytoin could be achieved using K_2CO_3 and Michael acceptors in the presence of organic salt TBAB at room temperature (Scheme 1). We carried out a model Michael addition reaction in which *n*-butyl acrylate **2b** (1.2 mmol) used as a model substrate reacted with 2-thiophenytoin (1 mmol) in the presence of K_2CO_3 (1 mmol) and TBAB (1 mmol) at room temperature (Scheme 2). Surprisingly, mono-Michael adduct was the



Scheme 2. Michael addition of 2-thiophenytoin to *n*-butyl acrylate (model reaction) at room temperature.

Table 1. Optimization of reaction conditions.

Entry	Base[a]	Reaction time (h)	Additive	Yield[b] **3b** (%)
1	K_2CO_3	2	–	–
2	K_2CO_3	6	–	–
3	K_2CO_3	2	TBAB	30
4	K_2CO_3	6	TBAB	70
5	DABCO	6	–	–
6	DABCO	6	–	–
7	DABCO	6	TBAB	5
8	DABCO	6	TBAB	7
9	Na_2CO_3	6	–	–
10	Na_2CO_3	6	TBAB	–
11	Na_2CO_3	6	TBAB	–
12	$N(Et)_3$	6	–	–
13	$N(Et)_3$	6	TBAB	5
14	$N(Et)_3$	0	TBAB	15
15	Pyr	6	–	–
16	Pyr	6	TBAB	–
17	Pyr	6	TBAB	–

[a]The reactions were performed with 2-thiophenytoin (1.0 mmol), base (1.0 mmol) and *n*-butyl acrylate (1.2 mmol) in tetrabutylammonium bromide (1.0 mmol) at room temperature under solvent-free conditions.
[b]Isolated yield.

Table 2. Regioselectively *N3*-alkylation of 2-thiophenytoin (1) with *n*-butyl acrylate (**2b**) mediated by different solvents.

Entry[a]	Solvent	Time (h)	Yield **3b** (%)[b]
1	DMSO	6	17
2	Ethanol	6	11
3	TBAB	6	70
4	DMF	6	63
5	Water	6	–
6	Solvent-free	6	–

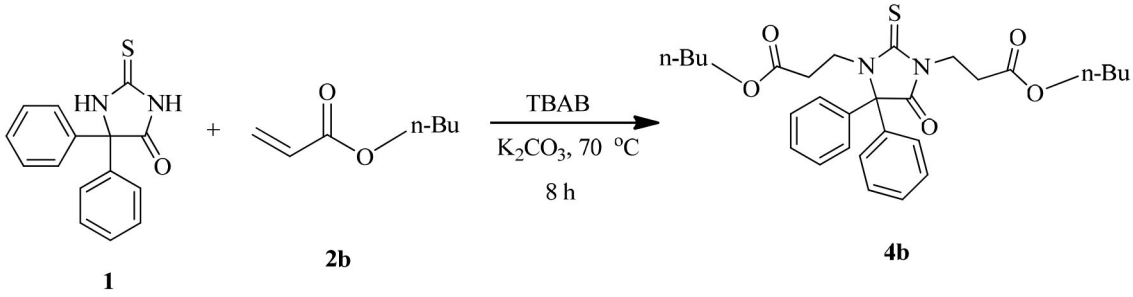
[a]The reactions were carried out with 2-thiophenytoin (1 mmol), potassium carbonate (1 mmol) and *n*-butyl acrylate (1.2 mmol) in tetrabutylammonium bromide (1 mmol) or 5 mL solvent at room temperature.
[b]Isolated yield.

only product of model reaction and the related bis-Michael adduct was not produced at all. Different mild bases such as K_2CO_3, Na_2CO_3, DABCO and pyridine were tested in this model reaction among which K_2CO_3 was found to be the most efficient in terms of yield for model reaction (Table 1, entry 4). Due to this advantage, base K_2CO_3 was chosen for our model reaction.

In continuation of our research to optimize the reaction conditions, we examined the model reaction in the presence of an optimized molar ratio of K_2CO_3 (1 mmol), *n*-butyl acrylate (1.2 mmol) and 2-thiophenytoin (1 mmol) in 5 mL of different solvents such as DMSO, ethanol, DMF, TBAB (1 mmol), and solvent-free conditions at room temperature (Table 2). All the reactions produced *N3*-mono-Michael adduct **3b** as the only product and the *N1,N3*-bis-Michael adduct was not obtained at all. Low yields of the products were obtained when DMSO or ethanol was used as the solvent (Table 2, entries 1, 2). The model reaction was unsuccessful in water or under solvent-free condition (Table 2, entries 5, 6). The desired product was isolated in 70% yield within 6 h in the presence of TBAB (Table 2, entry 3). A further optimization revealed that better results were obtained with 1 equiv of TBAB. The same reaction in DMF produced 63% of the related Michael adduct in 6 h (Table 2, entry 4). Therefore, the organic salt TBAB was a suitable media for this transformation. In our reaction, this organic salt provides a strong polar media and accelerates the reaction by dissolving all organic reactants (ester and 2-thiophenytoin) and the inorganic salt catalyst (K_2CO_3).

With this established optimum conditions, we were keen to explore the scope of regioselectivity of the reaction with respect to various other α,β-unsaturated esters and 2-thiophenytoin, the results of which are given in Table 3.

In all cases the reaction proceeded smoothly to give the corresponding *N3*-monoalkylated of 2-thiophenytoin, as the mono-Michael adduct, in good yields (Table 3, entries 2, 4, 6, 10, 12, 13, 15). Interestingly, for ethyl acrylate (Table 3, entry 1) the formation of the bis-Michael adduct (*N1,N3*-dialkylated 2-thiophenytoin) is preferred over the mono-Michael adduct (*N3*-monoalkylated 2-thiophenytoin). We were not able to perform selective monoalkylation even when less than one equivalent of ethyl acrylate was used. One can argue that the ethyl group steric hindrance is less than other alkyl groups and this might be an explanation for the ease of 2-thiophenytoin dialkylation. The formation of *N1,N3*-dialkylated 2-thiophenytoin with Michael acceptor ethyl acrylate prompted us to investigate the model reaction with excess amount of *n*-butyl acrylate at room temperature. However, only



Scheme 3. Michael addition of 2-thiophenytoin to *n*-butyl acrylate (model reaction) at 70°C.

Table 3. Michael addition of 2-thiophenytoin to diverse α,β-unsaturated esters at room temperature or 70°C under solvent-free conditions.

Entry	X	R	Ester	Time (h)	Mono-Michael adduct (yield %)[c]	Bis-Michael adduct (yield %)[d]
1[a,b]	H	CH_3CH_2	**2a**	6	–	**4a** (65)
2[a]	H	$CH_3(CH_2)_3$	**2b**	6	**3b** (70)	–
3[b]	H	$CH_3(CH_2)_3$	**2b**	8	–	**4b** (60)
4[a]	H	$CH_3(CH_2)_5$	**2c**	12	**3c** (60)	–
5[b]	H	$CH_3(CH_2)_5$	**2c**	14	–	**4c** (62)
6[a]	H	$CH_3(CH_2)_3CH(CH_2CH_3)CH_2$	**2d**	18	**3d** (55)	–
7[b]	H	$CH_3(CH_2)_3CH(CH_2CH_3)CH_2$	**2d**	21	–	**4d** (60)
8[a,b]	COOR	CH_3	–	24	–	–
9[a,b]	COOR	CH_3CH_2	–	48	–	–
10[a]	COOR	$CH_3CH_2CH_2$	**2e**	23	**3e** (55)	–
11[b]	COOR	$CH_3CH_2CH_2$	**2e**	23	–	**4e** (57)
12[a,b]	COOR	$CH_3(CH_2)_3$	**2f**	30	**3f** (55, 60)	–
13[a]	COOR	$CH_3(CH_2)_4$	**2g**	45	**3g** (55)	–
14[b]	COOR	$CH_3(CH_2)_4$	**2g**	45	–	**4g** (50)
15[a,b]	COOR	$CH_3(CH_2)_7$	**2h**	48	**3h** (60, 62)	–
16[a,b]	COOR	$CH_3(CH_2)_3CHPh$	–	48	–	–
17[a,b]	COOR	$CH_3(CH_2)_3CHCH_3$	–	48	–	–
18[a,b]	COOR	$PhCH_2$	–	48	–	–

[a]Reaction conditions: 2-Thiophenytoin (1.0 mmol), α,β-unsaturated esters (1.2 mmol), TBAB (1.0 mmol), K_2CO_3 (1.0 mmol), at room temperature.
[b]The reaction was performed with 2-thiophenytoin (1.0 mmol), α,β-unsaturated esters (2.5 mmol), TBAB (1.0 mmol), K_2CO_3 (1 mmol), at 70°C.
[c]Isolated yield of mono-Michael adduct.
[d]Isolated yield of bis-Michael adduct.

the *N3*-monoalkylated 2-thiophenytoin was isolated and the reaction did not produce any dialkylated 2-thiophenytoin, even with prolonged reaction time up to two days. To eliminate this problem, we decided to heat the reaction vessel. When the temperature was elevated to 70°C, based on the TLC test, the starting material 2-thiophenytoin spot immediately disappeared, and two new spots, stronger and weaker related to *N3*-monoalkylated and *N1,N3*-dialkylated products, respectively, appeared. Further keeping the reaction mixture at 70°C, the monoalkylated product completely converted to the dialkylated product (Scheme 3). The reason for this selectivity could be that at room temperature the steric effect of two phenyl groups at C5 in 2-thiophenytoin prevents the nucleophilic attack of the N1-position.

Encouraged by these results, we next focused our study on the synthesis of other *N1,N3*-dialkylated derivatives of 2-thiophenytoin with diverse α,β-unsaturated esters, under the same conditions (Table 3, entries 3, 5, 7, 11, 14). The reaction was not successful with 1-phenylpentyl fumarate, 1-methylpentyl fumarate and benzyl fumarate (Table 3, entries 16, 17, 18). When we used dimethyl as well as diethyl fumarates as Michael acceptors, fumaric acid and 2-thiophenytoin were obtained instead of the desired Michael adducts at both room temperature and 70°C (Table 3, entries 8, 9). This can be attributed to the fact that these esters are susceptible to hydrolysis, due to their smaller alkoxy groups (–OMe and –OEt) under the reaction alkaline media conditions. Surprisingly, the reaction of *n*-butyl fumarate and also *n*-octyl fumarate with 2-thiophenytoin produced only the corresponding *N3*-mono-Michael adducts at both room temperature and 70°C (Table 3, entries 12, 15). The yields of these adducts were 55% and 60%, respectively, at room temperature, and the increase in reaction temperature to 70°C had no significant effect on the yields obtained (60% and 62%).

Conclusions

We have developed a versatile regioselective Michael addition reaction of 2-thiophenytoin to α,β-unsaturated esters. The present procedure has notable advantages that include a simple operation procedure, environmentally benign reaction conditions, inexpensive and availability of the employed base catalyst. The method as reported herein will find applications in other areas of research.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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