IONIC LIQUID-ACCELERATED SYNTHESIS OF SOME N-ALKYL DERIVATIVES OF PHTHALIMIDE AND SULFONAMIDES

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ABSTRACT

Ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) efficiently accelerates Michael addition of phthalimide and sulfonamides to α,β -unsaturated esters in the presence of K_2CO_3 under microwave irradiation (MW) to afford *N*-alkyl derivatives of these compounds in high yields and short reaction times.

Keywords: Ionic liquid; *N*-Alkyl phthalimide; *N*-Alkyl sulfonamide; Michael addition; Microwave.

INTRODUCTION

The exploitation of ionic liquids as solvents in organic transformations has been reported extensively during the past decade.¹⁻⁵ The most useful properties of ionic liquids are the ability to dissolve a wide range of substances, very low vapor pressure, high thermal stability, and the fact that they can be stored for long times without decomposition. Moreover, it is often possible to achieve reactions in ionic liquids that otherwise proceed with great difficulty, or even not at all.¹⁻³ Together with the substitution of common molecular solvents, non-conventional activation methods have been applied as powerful tools to decrease reaction times and to enhance reactivity, mainly microwave irradiation.⁶⁻¹³

Michael addition reaction has been used in the carbon-carbon,^{14,15} carbon-oxygen,¹⁶ carbon-sulfur,^{17,18} and carbon-nitrogen bonds formation.¹⁹⁻²³ Aza-Michael addition of phthalimide and sulfonamides to α,β -unsaturated esters provides a direct and appealing route toward synthesis of *N*-alkyl derivatives of these compounds.²⁴⁻²⁷ For *N*-alkyl phthalimides some biological activities, such as antipsychotic,²⁸ anti-inflammatory,^{29,30} hypolipidemic,³¹ and receptor properties have been reported.³² Furthermore, these compounds are very useful intermediate in organic synthesis as they can be easily converted to primary amines (Gabriel synthesis).³³ *N*-Alkylated sulfonamides have also various biological activities, including antidepressant, psychostimulant, analgesic, anti-ulcer, anti-emetic anti-inflammatory properties.³⁴⁻³⁷ Moreover, saccharin as a sulfonamide derivative and its derivatives are very important in medicinal chemistry.^{36,37} To the best of our knowledge, the preparation of *N*-alkyl derivatives of phthalimide and sulfonamides by aza-conjugate addition reaction has been scarcely studied in the literature. Moe et al. have used Na in absolute EtOH to achieve Michael addition of phthalimide to α,β -unsaturated aldehydes.²⁴ Cardillo et al. have carried out the reaction of phthalimide salts to α,β -unsaturated imides in the presence of $AlMe_2Cl$.²⁵ For Michael addition of sulfonamides to α,β -unsaturated compounds, Al_2O_3 ,²⁶ and PBu_3 ²⁷ have been employed. Furthermore, more recently we have performed this transformation using K_2CO_3 /tetrabutylammonium bromide (TBAB). As mentioned, K_2CO_3 accompanied with TBAB has been used previously only for Michael reaction of sulfonamides not phthalimide and saccharin. Moreover, in this report, sulfonamides have been *N*-alkylated with moderate selectivity in the synthesis of *N*-alkyl and *N,N*-dialkyl sulfonamides.³⁸ The mentioned methods are also associated with one or more of the following drawbacks: moderate yields, relatively long reaction times and the use of more reactive Michael acceptors. Because of wide range of biological and synthetic applications of *N*-alkyl phthalimides and sulfonamides, their preparation has received renewed interest processes.

Potassium carbonate (K_2CO_3) is a cheap, commercially available, reusable and green base which has been used frequently in *N*-,³⁹⁻⁴² C-,^{43,44} and O-alkylation reactions.⁴⁵⁻⁴⁷

Having the above aspects in mind and also in continuation of our previous studies on aza-Michael reactions,^{48,49} green organic synthesis,^{39,48-57} as well as applications of K_2CO_3 in *N*-alkylation reactions,³⁹ we report here our results on the synthesis of *N*-alkyl derivatives of phthalimide and sulfonamides via Michael addition of phthalimide and sulfonamides to α,β -unsaturated esters using K_2CO_3 in [bmim]Br under microwave irradiation (Schemes 1 and 2).

Scheme 1.

Scheme 2.

RESULTS AND DISCUSSION

We have found previously K_2CO_3 acts as an efficient reagent for highly regioselective *N*-alkylation of benzotriazole.³⁹ Moreover, this reagent has been frequently applied in alkylation reactions.⁴⁰⁻⁴⁷ These subjects encouraged us to use this reagent for *N*-alkylation of phthalimide and sulfonamides via Michael reaction. Thus, at first, we used K_2CO_3 to accomplish Michael addition of phthalimide to *n*-butyl acrylate as a model reaction under microwave conditions in [bmim]Br (Scheme 1). Interestingly, the reaction proceeded efficiently at 300 W of microwave power (max. 130 °C) and the desired Michael adduct **1b** was obtained in excellent yield in short reaction time (Table 1). We also studied the influence of different bases to evaluate their capabilities (Table 1). As it is shown in Table 1, the best results were obtained when K_2CO_3 was applied as base. We extended this reaction to benzenesulfonamide as Michael donor that provided compound **2a** in 85% yield within 6 min (Scheme 2). Considering the excellent results obtained from K_2CO_3 , this base was used for all reactions.

Table 1. The effect of various bases on Michael addition of phthalimide (2 mmol) to *n*-butyl acrylate (2.4 mmol) in [bmim]Br (1 g) under microwave conditions (300 W, max. 130 °C)

Entry	Base	Time (min)	Yield ^a (%)
1	K_2CO_3 (0.25 eq.)	15	59
2	K_2CO_3 (0.5 eq.)	10	74
3	K_2CO_3 (1 eq.)	7	96
4	Na_2CO_3 (1 eq.)	12	76
5	<i>t</i> -BuOK (1 eq.)	12	80
6	CaO (1 eq.)	15	47
7	MgO (1 eq.)	15	39
8	NBu ₃ (1 eq.)	12	84

^aIsolated yield.

N-alkylation of phthalimide with *n*-butyl acrylate was also studied in several ionic liquids, such as [bmim]Br, [bmim]Cl, [bmim]BF₄ and [bmim]PF₆ using K₂CO₃ under microwave irradiation. Higher yields and shorter reaction times were observed in [bmim]Br and [bmim]Cl. However, [bmim]Br was applied as solvent for all reactions, because, the preparation of this ionic liquid was easier in comparison with the others.

In order to determine whether ionic liquid was an essential factor to promote the reaction, the model reaction was carried out in several traditional solvents, and the results are depicted in Table 2. As Table 2 indicates, longer reaction times were required in these classical solvents than those in ionic liquid to achieve the reaction. Furthermore, the yields were not so high as those in ionic liquid. It was clear that the ionic liquids accelerated this reaction.

Table 2. Comparative Michael addition of phthalimide (2 mmol) to *n*-butyl acrylate (2.4 mmol) in the presence of K₂CO₃ (2 mmol) in conventional solvents (5 mL) versus [bmim]Br (1 g) in microwave conditions (300 W, max. 130 °C)

Entry	Solvent	Time (min)	Yield ^a (%)
1	-	25	23
2	DMSO	20	63
3	DMF	20	55
4	HMPTA	20	32
5	[bmim]Br	7	96

^aIsolated yield.

To establish the efficiency and applicability of this method, we introduced phthalimide and sulfonamides to different α,β -unsaturated esters. The results are summarized in Tables 3, 4 and 5. As Tables 3, 4 and 5 shows, the reactions proceeded efficiently and the desired Michael adducts were obtained in good to excellent yields and short reaction times.

It has been observed that the bulkiness of alkoxy group (-OR) of α,β -unsaturated esters did not affect significantly on the yields and the reaction times (Table 3, Table 4: entries 1 and 2 as well as Table 5). Michael addition of phthalimide and saccharin to substituted α,β -unsaturated esters ethyl methacrylate and ethyl crotonate was not efficient; however, sulfonamides reacted successfully with these esters (Table 4: entries 3 and 4). Lower reaction yield was obtained when 4-methylbenzenesulfonamides instead of benzenesulfonamides was applied in the reaction (Table 4: entry 5). Saccharin afforded lower yields of products in comparison to the other Michael donors (Table 5). We tried to improve the yields of *N*-alkyl derivatives of saccharin; however, our attempt was not successful.

Table 3. Michael addition of phthalimide (2 mmol) to α,β -unsaturated esters (2.4 mmol) using K₂CO₃ (2 mmol) in [bmim]Br (1 g) under microwave irradiation (300 W, max. 130 °C)

Entry	R	Product	Time (min)	Yield ^a (%)
1	CH ₃ CH ₂	1a	7	94
2	CH ₃ (CH ₂) ₂ CH ₂	1b	7	96
3	CH ₃ (CH ₂) ₄ CH ₂	1c	7	95
4	C ₆ H ₅ CH ₂	1d	7	95
5	C ₆ H ₅ CH ₂ CH ₂	1e	8	94
6	C ₆ H ₅ CH=CHCH ₂	1f	8	93
7	<i>o</i> -CH ₃ O-C ₆ H ₄ OCH ₂ CH(OH)CH ₂	1g	10	90
8	C ₆ H ₅	1h	5	91

^aIsolated yield.

Table 4. Michael addition of sulfonamides (2 mmol) to α,β -unsaturated esters (2.2 mmol) using K₂CO₃ (2 mmol) in [bmim]Br (1g) under microwave irradiation (300 W, max. 110 °C)

Entry	Ar	R ¹	R ²	R ³	Product ^b	Time (min)	Yield ^a (%)
1	C ₆ H ₅	H	H	CH ₃ (CH ₂) ₂ CH ₂	2a	6	85
2	C ₆ H ₅	H	H	C ₆ H ₅ CH=CHCH ₂	2b	7	83
3	C ₆ H ₅	H	CH ₃	CH ₃ CH ₂	2c	10	79
4	C ₆ H ₅	CH ₃	H	CH ₃ CH ₂	2d	14	74
5	<i>p</i> -CH ₃ C ₆ H ₄	H	H	CH ₃ (CH ₂) ₂ CH ₂	2e	8	78

^aIsolated yield. ^bIn this method, the selectivity was high and *N,N*-dialkylated sulfonamides were produced beside *N*-alkylated products in low yields (7-14%).

Table 5. Michael addition of saccharin (as a sulfonamide derivative) (2 mmol) to α,β -unsaturated esters (3 mmol) using K₂CO₃ (2 mmol) in [bmim]Br (1 g) under microwave irradiation (200 W, max. 100 °C)

Entry	R	Product	Time (min)	Yield ^a (%)
1	CH ₃ (CH ₂) ₂ CH ₂	3a	2	42
2	CH ₃ (CH ₂) ₄ CH ₂	3b	2	41
3	C ₆ H ₅ CH ₂	3c	2	43
4	C ₆ H ₅ CH=CHCH ₂	3d	2	40
5	<i>o</i> -CH ₃ O-C ₆ H ₄ OCH ₂ CH(OH)CH ₂	3e	2	37
6	(CH ₃) ₂ CH	3f	2	41
7	Cyclohexyl	3g	2	39

^aIsolated yield.

Ease of recycling of the reagent is one of the most advantages of our method. For the reaction of phthalimide with *n*-butyl acrylate no significant loss of the product yield was observed when K₂CO₃/[bmim]Br was used after five times recycling.

CONCLUSIONS

In summary, we have developed an efficient method for Michael addition of phthalimide and sulfonamides to α,β -unsaturated esters. This new strategy for the synthesis of *N*-Alkyl phthalimides and sulfonamides as biologically interesting compounds has some advantages, including high yield, short reaction time, ease of product isolation, low cost, potential for recycling of ionic liquid as well as reagent and compliance with green chemistry protocols

EXPERIMENTAL

All chemicals were purchased from Merck or Fluka chemical companies. All reactions were carried out using laboratory microwave oven (MW 3000, Landgraf Company, Germany). IR spectra were run on a Shimadzu FTIR-8300

spectrophotometer. The ^1H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Bruker Avanced DPX-250, FT-NMR spectrometer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for Michael addition of phthalimide and sulfonamides to α,β -unsaturated esters

To a mixture of compounds consisting of phthalimide or sulfonamide (2 mmol), well-ground K_2CO_3 (2 mmol) and α,β -unsaturated ester (2.2 to 3 mmol, Tables 3, 4 and 5) in a microwave vessel was added [bmim]Br (1 g) and mixed carefully. The resulting mixture was irradiated in a microwave oven for the powers, the temperatures and the times reported in Tables 3, 4 and 5. Afterward, the reaction mixture was cooled to room temperature and was extracted with Et_2O (3×50 mL). The organic extracts were then combined. After removal of the solvent, the crude product was purified by column chromatography on silica gel eluted with EtOAc/n -hexane (1/5 for *N*-alkyl phthalimides and saccharins and 1/3 for *N*-alkyl sulfonamides). After isolation of the products and evaporating of the remainder Et_2O in ionic liquid, the ionic liquid containing reagent K_2CO_3 (K_2CO_3 /[bmim]Br) was used for next run under identical reaction conditions.

Ethyl 3-phthalimido propanoate (1a)

Colorless solid; mp 60-61 °C; IR (KBr): 3051, 2968, 1774, 1716 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.11 (3H, t, $J = 7.1$ Hz, CH_3), 2.57 (2H, t, $J = 7.2$ Hz, $\text{O}=\text{CCH}_2$), 3.86 (2H, t, $J = 7.2$ Hz, NCH_2), 4.06 (2H, q, $J = 7.1$ Hz, OCH_2), 7.57-7.70 (4H, m); ^{13}C NMR (CDCl_3): δ 13.8, 32.7, 33.5, 64.3, 122.9 (two carbons), 131.7 (two carbons), 133.8 (two carbons), 167.5 (two carbons), 170.6; MS (m/z): 247 (M^+).

Butyl 3-phthalimido propanoate (1b)

Colorless solid; mp 51-52 °C; IR (KBr): 3069, 2960, 1774, 1716 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.90 (3H, t, $J = 6.8$ Hz, CH_3), 1.28 (2H, m, CH_2CH_2), 1.59 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.58 (2H, t, $J = 7.2$ Hz, $\text{O}=\text{CCH}_2$), 3.91 (2H, t, $J = 7.2$ Hz, NCH_2), 4.08 (2H, t, $J = 6.9$ Hz, OCH_2), 7.64-7.76 (4H, m); ^{13}C NMR (CDCl_3): δ 13.3, 18.5, 30.2, 32.5, 33.4, 64.1, 122.8 (two carbons), 131.7 (two carbons), 133.6 (two carbons), 167.3 (two carbons), 170.3; MS (m/z): 275 (M^+).

Hexyl 3-phthalimido propanoate (1c)

Colorless solid; mp 40-41 °C; IR (KBr): 3055, 2970, 1774, 1716 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.89 (3H, t, $J = 6.7$ Hz, CH_3), 1.29-1.36 (6H, m), 1.60 (2H, m, $\text{CH}_2(\text{CH}_2)_3\text{CH}_2$), 2.59 (2H, t, $J = 7.0$ Hz, $\text{O}=\text{CCH}_2$), 3.95 (2H, t, $J = 7.0$ Hz, NCH_2), 4.09 (2H, t, $J = 6.9$ Hz, OCH_2), 7.68-7.83 (4H, m); ^{13}C NMR (CDCl_3): δ 13.7, 22.1, 25.4, 28.1, 30.2, 32.4, 33.4, 64.3, 122.7 (two carbons), 132.1 (two carbons), 133.6 (two carbons), 167.2 (two carbons), 170.2; MS (m/z): 303 (M^+).

Benzyl 3-phthalimido propanoate (1d)

Colorless solid; mp 57-59 °C; IR (KBr): 3061, 2958, 1774, 1716 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.59 (2H, t, $J = 7.1$ Hz, $\text{O}=\text{CCH}_2$), 3.86 (2H, t, $J = 7.1$ Hz, NCH_2), 4.94 (2H, s, OCH_2), 7.08-7.17 (5H, m), 7.52 (2H, m), 7.63 (2H, m); ^{13}C NMR (CDCl_3): δ 32.9, 33.7, 66.6, 122.6 (two carbons), 128.2 (two carbons), 128.5, 129.4 (two carbons), 131.9 (two carbons), 133.9 (two carbons), 135.6, 167.8 (two carbons), 170.6; MS (m/z): 309 (M^+).

Phenethyl 3-phthalimido propanoate (1e)

Colorless solid; mp 53-55 °C; IR (KBr): 3052, 2933, 1774, 1716 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.69 (2H, t, $J = 7.2$ Hz, $\text{O}=\text{CCH}_2$), 2.87 (2H, t, $J = 7.1$ Hz, ArCH_2), 3.93 (2H, t, $J = 7.2$ Hz, NCH_2), 4.26 (2H, t, $J = 7.1$ Hz, OCH_2), 7.13-7.26 (5H, m), 7.64 (2H, m), 7.77 (2H, m); ^{13}C NMR (CDCl_3): δ 32.8, 33.6, 34.9, 65.2, 123.1 (two carbons), 126.4, 128.3 (two carbons), 128.9 (two carbons), 132.7 (two carbons), 133.9 (two carbons), 137.6, 167.8 (two carbons), 170.7; MS (m/z): 323 (M^+).

Cinnamyl 3-phthalimido propanoate (1f)

Pale yellow oil; IR (neat): 3061, 2954, 1774, 1716, 1497 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.68 (2H, t, $J = 7.1$ Hz, $\text{O}=\text{CCH}_2$), 3.92 (2H, t, $J = 7.1$ Hz, NCH_2), 4.64 (2H, m, OCH_2), 6.12 (1H, m, $\text{ArCH}=\text{CH}$), 6.49 (1H, d, $J = 15.8$ Hz, ArCH), 7.17-7.26 (5H, m), 7.57 (2H, m), 7.72 (2H, m); ^{13}C NMR (CDCl_3): δ 32.9, 33.7, 65.4, 122.8 (two carbons), 123.2, 126.6 (two carbons), 128.0, 128.5 (two carbons), 131.9 (two carbons), 133.9 (two carbons), 134.4, 136.1, 167.9 (two carbons), 170.6; MS (m/z): 335 (M^+).

2-Hydroxy-3-(2-methoxyphenoxy)propyl 3-phthalimido propanoate (1g)

Pale yellow oil; IR (neat): 3480, 3049, 2948, 1770, 1715 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.63 (2H, t, $J = 7.0$ Hz, $\text{O}=\text{CCH}_2$), 3.67 (3H, s, CH_3), 3.80-3.90 (5H, m), 4.11-4.19 (3H, m), 6.71-6.79 (4H, m), 7.54 (2H, m), 7.68 (2H, m); ^{13}C NMR (CDCl_3): δ 32.8, 33.6, 55.7, 65.7, 67.9, 70.5, 111.9, 114.2, 120.9, 121.8 (two carbons), 123.2, 131.7 (two carbons), 134.0 (two carbons), 147.8, 149.3, 168.0 (two carbons), 170.8; MS (m/z): 399 (M^+).

Phenyl 3-phthalimido propanoate (1h)

Colorless solid; mp 70-72 °C; IR (KBr): 3076, 2970, 1775, 1713 cm^{-1} ; ^1H

NMR (CDCl_3): δ 2.74 (2H, t, $J = 7.1$ Hz, $\text{O}=\text{CCH}_2$), 3.95 (2H, t, $J = 7.1$ Hz, NCH_2), 6.98 (2H, d, $J = 8.0$ Hz), 7.09 (1H, d, $J = 6.9$), 7.24 (2H, dd, $J = 6.9$, 8.0 Hz), 7.61-7.73 (4H, m); ^{13}C NMR (CDCl_3): δ 32.9, 33.5, 121.4 (two carbons), 122.9 (two carbons), 125.7, 129.2 (two carbons), 131.6 (two carbons), 133.9 (two carbons), 150.3, 167.5 (two carbons), 170.3; MS (m/z): 295 (M^+).

Butyl 3-(phenylsulfonamido)propanoate (2a)

Colorless oil (Lit.³⁸ oil); IR (neat): 3271, 3048, 2960, 1733, 1447, 1330 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.90 (3H, t, $J = 6.5$ Hz, CH_3), 1.34 (2H, m, CH_2CH_2), 1.56 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.51 (2H, t, $J = 5.0$ Hz, $\text{O}=\text{CCH}_2$), 3.19 (t, 2H, $J = 5.0$ Hz, $\text{O}=\text{CCH}_2\text{CH}_2$), 4.03 (t, 2H, $J = 7.0$ Hz, OCH_2), 5.68 (1H, s, NH , exchangeable with D_2O), 7.48-7.57 (3H, complex, H_2 - H_6 of aromatic ring), 7.79 (2H, m, H_2 and H_6 of aromatic ring); ^{13}C NMR (CDCl_3): δ 13.5, 18.9, 30.4, 34.1, 38.7, 64.6, 126.8, 129.0 (two carbons), 132.5 (two carbons), 139.9, 172.7; MS (m/z): 285 (M^+).

Cinnamyl 3-(phenylsulfonamido)propanoate (2b)

Pale yellow oil (Lit.³⁸ oil); IR (neat): 3287, 3059, 2964, 1732, 1447, 132 9 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.55 (2H, t, $J = 5.2$ Hz, $\text{O}=\text{CCH}_2$), 3.19 (2H, t, $J = 5.2$ Hz, $\text{O}=\text{CCH}_2\text{CH}_2$), 4.69 (2H, m, OCH_2), 5.50 (1H, s, NH), 6.23 (1H, m, $\text{PhCH}=\text{CH}$), 6.63 (1H, d, $J = 15.7$ Hz, PhCH), 7.29-7.35 (5H, complex, H_2 - H_6 of aromatic ring of alkoxy group), 7.45-7.50 (3H, complex, H_2 - H_6 of aromatic ring of sulfonamide), 7.95 (2H, m, H_2 and H_6 of aromatic ring of sulfonamide); ^{13}C NMR (CDCl_3): δ 34.2, 38.8, 65.8, 122.6, 122.9, 126.6 (two carbons), 126.9, 128.1, 128.6 (two carbons), 129.0 (two carbons), 132.7 (two carbons), 134.6, 139.9, 171.7; MS (m/z): 345 (M^+).

Ethyl 2-methyl-3-(phenylsulfonamido)propanoate (2c)

Pale yellow oil (Lit.³⁸ oil); IR (neat): 3283, 3034, 2966, 1732, 1447, 1328 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.17-1.26 (6H, complex, 2CH_3), 2.73 (1H, m, $\text{O}=\text{CCH}$), 3.14-3.20 (2H, complex, $\text{O}=\text{CCH}(\text{CH}_3)\text{CH}_2$), 4.12 (2H, q, $J = 7.0$ Hz, OCH_2), 5.65 (1H, s, NH), 7.55-7.64 (3H, complex, H_2 - H_6 of aromatic ring), 7.93 (2H, m, H_2 and H_6 of aromatic ring); ^{13}C NMR (CDCl_3): δ 14.0, 14.7, 39.6, 45.4, 60.8, 126.8, 129.1 (two carbons), 132.5 (two carbons), 139.9, 174.7; MS (m/z): 271 (M^+).

Ethyl 3-(phenylsulfonamido)butanoate (2d)

Pale yellow solid; mp 60-62 °C (Lit.³⁸ mp 60-62 °C); IR (KBr): 3285, 3044, 2953, 1732, 1447, 1329 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.14-1.23 (6H, complex, 2CH_3), 2.38-2.43 (2H, complex, $\text{O}=\text{CCH}_2$), 3.68 (1H, m, $\text{O}=\text{CCH}_2\text{CH}$), 4.04 (2H, q, $J = 7.1$ Hz, OCH_2), 5.39 (1H, s, NH), 7.49-7.59 (3H, complex, H_2 - H_6 of aromatic ring), 7.89 (2H, m, H_2 and H_6 of aromatic ring); ^{13}C NMR (CDCl_3): δ 14.0, 21.0, 40.7, 46.6, 60.7, 126.9, 129.0 (two carbons), 132.5 (two carbons), 140.9, 171.1; MS (m/z): 271 (M^+).

Butyl 3-(4-methylphenylsulfonamido)propanoate (2e)

Pale yellow oil (Lit.³⁸ oil); IR (neat): 3286, 3044, 2960, 1732, 1330 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.89 (3H, t, $J = 6.8$ Hz, $\text{CH}_2(\text{CH}_3)\text{CH}_2$), 1.33 (2H, m, CH_2CH_2), 1.56 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.40 (3H, s, ArCH_3), 2.51 (2H, t, $J = 5.3$ Hz, $\text{O}=\text{CCH}_2$), 3.16 (2H, t, $J = 5.3$ Hz, $\text{O}=\text{CCH}_2\text{CH}_2$), 4.04 (2H, t, $J = 7.0$ Hz, OCH_2), 5.76 (1H, s, NH), 7.33 (2H, d, $J = 7.9$ Hz, H_2 and H_6 of aromatic ring), 7.72 (2H, d, $J = 7.9$ Hz, H_2 and H_6 of aromatic ring); ^{13}C NMR (CDCl_3): δ 13.5, 18.9, 21.3, 30.3, 34.1, 38.7, 64.5, 126.9, 129.6 (two carbons), 135.8 (two carbons), 143.2, 172.7; MS (m/z): 299 (M^+).

Butyl 3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl) propanoate (3a)

Yellow oil; IR (neat): 3039, 2938, 1733, 1455, 1333 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.84 (3H, t, $J = 7.4$ Hz, CH_3), 1.25 (2H, m, CH_2CH_2), 1.51 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.80 (2H, t, $J = 6.8$ Hz, $\text{O}=\text{CCH}_2$), 4.00-4.08 (4H, m, NCH_2 and OCH_2), 7.81-7.97 (4H, m); ^{13}C NMR (CDCl_3): δ 12.6, 18.0, 29.4, 32.0, 33.6, 63.9, 119.9, 124.2, 126.2, 133.3, 133.8, 136.4, 157.6, 169.3; MS (m/z): 311 (M^+).

Hexyl 3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)propanoate (3b)

Pale yellow oil; IR (neat): 3051, 2931, 1734, 1457, 1339 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.78 (3H, t, $J = 7.0$ Hz, CH_3), 1.16-1.25 (6H, m), 1.53 (2H, m, $\text{CH}_2(\text{CH}_2)_3\text{CH}_2$), 2.81 (2H, t, $J = 6.7$ Hz, $\text{O}=\text{CCH}_2$), 3.95-4.04 (4H, m, NCH_2 and OCH_2), 7.78-7.92 (4H, m); ^{13}C NMR (CDCl_3): δ 12.9, 21.4, 24.4, 27.4, 30.3, 32.0, 33.6, 64.1, 119.9, 124.1, 126.1, 133.4, 133.9, 136.6, 157.6, 169.2; MS (m/z): 339 (M^+).

Benzyl 3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)propanoate(3c)

Pale yellow oil; IR (neat): 3059, 2947, 1733, 1339 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.78 (2H, t, $J = 6.8$ Hz, $\text{O}=\text{CCH}_2$), 3.99 (2H, t, $J = 6.8$ Hz, NCH_2), 5.02 (2H, s, OCH_2), 7.11-7.21 (5H, m), 7.79-7.94 (4H, m); ^{13}C NMR (CDCl_3): δ 32.6, 33.9, 66.9, 119.6, 123.9, 126.6, 128.0 (two carbons), 128.4, 129.7 (two carbons), 133.2, 133.7, 135.8, 136.2, 157.4, 169.1; MS (m/z): 345 (M^+).

Cinnamyl 3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl) propanoate (3d)

Yellow oil; IR (neat): 3061, 2954, 1733, 1338 cm^{-1} ; ^1H NMR (CDCl_3): δ

2.85 (2H, t, $J = 6.9$ Hz, $\text{O}=\text{CCH}_2$), 4.03 (2H, t, $J = 6.9$ Hz, NCH_2), 4.70 (2H, m, OCH_2), 6.23 (1H, m, $\text{ArCH}=\text{CH}$), 6.54 (1H, d, $J = 15.7$ Hz, ArCH), 7.19-7.30 (5H, m), 7.76-7.93 (4H, m); ^{13}C NMR (CDCl_3): δ 32.1, 33.6, 64.5, 119.9, 121.7, 124.2, 125.6, 126.1, 126.7 (two carbons), 127.0, 127.5 (two carbons), 133.3, 133.5, 133.8, 136.8, 157.5, 168.5; MS m/z (%): 307 (M^+-SO_2).

2-Hydroxy-3-(2-methoxyphenoxy)propyl 3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)propanoate (3e)

Pale yellow oil; IR (neat): 3475, 3059, 2953, 1734, 1339 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.80 (2H, t, $J = 6.8$ Hz, $\text{O}=\text{CCH}_2$), 3.61 (3H, s, CH_3), 3.87-3.99 (5H, m), 4.14-4.23 (3H, m), 6.68-6.83 (4H, m), 7.80-7.94 (4H, m); ^{13}C NMR (CDCl_3): δ 32.5, 33.8, 56.2, 65.5, 67.4, 71.1, 112.2, 114.5, 120.0, 121.1, 122.9, 124.4, 126.0, 133.4, 133.6, 136.2, 147.5, 149.2, 157.8, 168.3; MS (m/z): 371 (M^+-SO_2).

Isopropyl 3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)yl)propanoate (3f)

Pale yellow oil; IR (neat): 3033, 2982, 1734, 1457, 1340 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.18 (6H, d, $J = 6.6$ Hz, 2CH_3), 2.77 (2H, t, $J = 6.7$, $\text{O}=\text{CCH}_2$), 4.01 (2H, t, $J = 6.7$ Hz, NCH_2), 4.97 (1H, q, $J = 6.6$, OCH), 7.79-7.95 (4H, m); ^{13}C NMR (CDCl_3): δ 20.7 (two carbons), 32.2, 33.6, 67.5, 119.9, 124.2, 126.2, 133.3, 133.8, 136.6, 157.6, 168.7; MS (m/z): 297 (M^+).

Cyclohexyl 3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H) yl) propanoate (3g)

Colorless solid; mp 62-64 $^\circ\text{C}$; IR (neat): 2938, 1733, 1339 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.19-1.36 (6H, m), 1.65-1.81 (4H, m), 2.81 (2H, t, $J = 6.8$ Hz, $\text{O}=\text{CCH}_2$), 4.04 (2H, t, $J = 6.8$ Hz, NCH_2), 4.76 (1H, m, OCH), 7.81-8.00 (4H, m); ^{13}C NMR (CDCl_3): δ 23.6 (two carbons), 25.2, 31.4, 33.2, 34.6 (two carbons), 73.3, 120.9, 125.1, 127.1, 134.3, 134.8, 137.5, 158.6, 169.6; MS (m/z): 273 (M^+-SO_2).

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