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An Efficient Solventless Method for the Synthesis of *N*,*N*-Dialkyl Sulfonamide Derivatives

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Aza-Michael addition of sulfonamides to α,β-unsaturated esters efficiently proceeds in the presence of catalytic amount of sodium hydroxide (NaOH) and tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst (PTC) under microwave irradiation to afford *N*,*N*-dialkyl sulfonamides as biologically interesting compounds in good to excellent yields and short reaction times.

Keywords: *N*,*N*-Dialkyl sulfonamide, Solvent-free, Michael addition, α,β-Unsaturated ester, NaOH, Microwave

INTRODUCTION

In recent years, there has been a growing interest in the synthesis of bioactive compounds in organic chemistry [1,2]. One important class of these compounds is *N*,*N*-dialkyl sulfonamides. For these compounds various biological activities, such as psychostimulant, analgesic, anti-ulcer, antidepressant, anti-emetic and anti-inflammatory properties have been reported [2]. Therefore, there is a great deal of interest in the synthesis of *N*-alkyl derivatives of sulfonamides. One useful route toward synthesis of these compounds is aza-conjugate addition of sulfonamides to α,β-unsaturated compounds [3]. Indeed, to the best of our knowledge, there are only a few reports of Michael reaction of sulfonamides in the literature. Reagents and catalysts, such as MgO [3a], ZnO [3b], K_2CO_3 [3c] and Al_2O_3 [3d] have been applied to achieve this reaction. However, these methods are efficient for the preparation of *N*-alkyl sulfonamides and not *N*,*N*-dialkylated products. In fact, no efficient procedure for the preparation of *N*,*N*-dialkyl sulfonamides *via* Michael reaction has not been reported so far.

The application of solvent-free protocols in organic synthesis has been explored extensively during the last decade [4]. Solvent-free reactions under microwave or thermal conditions were demonstrated to be as an efficient technique for various organic reactions instead of using harmful organic solvents. Solvent-free conditions often lead to a remarkable decrease in reaction times, increased yields, easier workup, matches with green chemistry protocols, and may enhance the regio- and stereoselectivity of reactions [4].

Considering the above mentioned facts and goals, and in continuation of our previous studies on aza-Michael reactions [3a-3c,5], green organic synthesis [3a-3c,5,6] and synthesis of sulfonamide derivatives [3a-3c], herein we wish to report an efficient method for the preparation of *N*,*N*-dialkyl sulfonamides *via* Michael addition of sulfonamides to α,β-unsaturated esters in the presence of catalytic amount of

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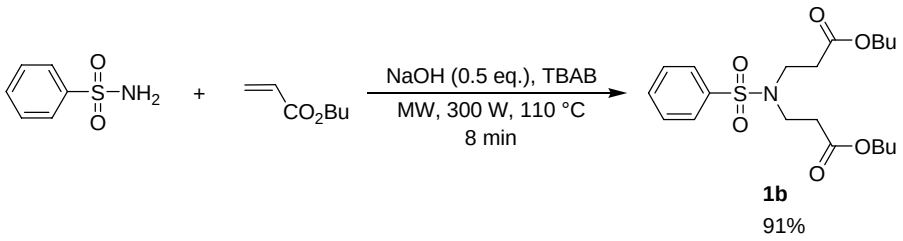

Scheme 1

NaOH and TBAB as a PTC under microwave irradiation (Scheme 1). To the best of our knowledge, this is the first efficient report on the preparation of *N*,*N*-dialkyl sulfonamides *via* Michael addition reaction.

EXPERIMENTAL

Chemicals and Apparatus

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their spectral data with the authentic samples. All reactions were carried out using a laboratory microwave oven (MW 3000, Landgraf Company, Germany). The IR spectra were recorded on a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were recorded on a Bruker Avance DPX-250, FT-NMR spectrometer. The mass spectra were taken on a Shimadzu GC MS-QP 1000 EX apparatus.

General Procedure for the Synthesis of *N*,*N*-Dialkyl Sulfonamides *via* Michael Reaction Under Microwave Irradiation

To a well-ground mixture of compounds consisting of sulfonamide (2 mmol), NaOH (1 mmol) and TBAB (1 mmol) in a microwave vessel was added α,β-unsaturated ester (4.4 mmol) and mixed thoroughly with a glass rod. The resulting mixture was irradiated in a microwave oven at 300 W for the times reported in Table 3. The microwave was programmed to give a maximum internal temperature to 110 °C. Then, the reaction mixture was cooled to room temperature and suspended in CH_2Cl_2 (50 ml), filtered and the filtrate was washed with water (2 × 40 ml) and dried with $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography on silica gel eluted with EtOAc/*n*-hexane (1/3).

Physical and Spectroscopic Data of Isolated Products

(1a). Colorless oil (Lit. [3a] oil); isolated yield: 0.64 g (90%); IR (neat): 3028, 2984, 1733, 1447, 1317 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.22 (t, *J* = 7.1 Hz, 6H, $2CH_3$), 2.59 (t, *J* = 5.0 Hz, 4H, $2O{=}CCH_2$), 3.45 (t, *J* = 5.0 Hz, 4H, $2O{=}CCH_2CH_2$), 4.08 (q, *J* = 7.1 Hz, 4H, $2OCH_2$), 7.46-7.57 (complex, 3H, H_3-H_5 of the aromatic ring), 7.87 (m, 2H, H_2 and H_6 of the aromatic ring); ^{13}C NMR ($CDCl_3$): δ 13.9, 32.8, 44.7, 60.4, 127.2, 129.1, 132.6, 138.9, 170.9; MS (m/z): 357 (M^+).

(1b). Colorless oil (Lit. [3a] oil); isolated yield: 0.75 g (91%); IR (neat): 3036, 2966, 1732, 1447, 1317 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 6.5 Hz, 6H, $2CH_3$), 1.33 (m, 4H, $2CH_3CH_2$),1.56 (m, 4H, $2CH_3CH_2CH_2$), 2.63 (t, *J* = 5.1 Hz, 4H, $2O{=}CCH_2$), 3.45 (t, *J* = 5.1 Hz, 4H, $2O{=}CCH_2CH_2$), 4.06 (t, *J* = 6.9 Hz, 4H, $2OCH_2$), 7.51-7.60 (complex, 3H, H_3-H_5 of the aromatic ring), 7.82 (m, 2H, H_2 and H_6 of the aromatic ring); ^{13}C NMR ($CDCl_3$): δ 13.5, 18.9, 30.5, 34.2, 44.4, 64.2, 126.9, 129.0, 132.4, 138.9, 171.1; MS (m/z): 413 (M^+).

(1c). Colorless oil (Lit. [3b] oil); isolated yield: 0.85 g (90%); IR (neat): 3031, 2974, 1733, 1447, 1316 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, *J* = 6.6 Hz, 6H, $2CH_3$), 1.26-1.32 (complex, 12H, $2CH_3CH_2$, $2CH_3CH_2CH_2$ and $2CH_3(CH_2)_2CH_2$), 1.58 (m, 4H, $2CH_3(CH_2)_3CH_2$), 2.61 (t, *J* = 5.0 Hz, 4H, $2O{=}CCH_2$), 3.41 (t, *J* = 5.0 Hz, 4H, $2O{=}CCH_2CH_2$), 4.05 (t, *J* = 6.9 Hz, 4H, $2OCH_2$), 7.43-7.50 (complex, 3H, H_3-H_5 of the aromatic ring), 7.74 (m, 2H, H_2 and H_6 of the aromatic ring); ^{13}C NMR ($CDCl_3$): δ 13.8, 22.3, 25.5, 28.0, 30.4, 33.9, 44.5, 64.4, 126.4, 128.9, 132.1, 139.4, 171.4; MS (m/z): 392 (M^+-C_6H_5), 368 (M^+-$C_6H_{13}O$), 328 (M^+-$C_6H_5SO_2$).

(1d). Pale yellow oil (Lit. [3b] oil); isolated yield: 0.85 g (88%); IR (neat): 3051, 2965, 1734, 1447, 1316 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.58 (t, *J* = 5.0 Hz, 4H, $2O{=}CCH_2$), 3.36 (t, *J* = 5.0 Hz, 4H, $2O{=}CCH_2CH_2$), 5.00 (s, 4H, $2OCH_2$), 7.22-7.25 (complex, 10H, $2C_6H_5CH_2$), 7.39-7.48 (complex, 3H, H_3-

H_5 of the aromatic ring of sulfonamide moiety), 7.72 (m, 2H, H_2 and H_6 of the aromatic ring of sulfonamide moiety); ^{13}C NMR ($CDCl_3$): δ 33.3, 43.9, 65.5, 126.2, 127.7, 128.1, 128.9, 129.5, 131.8, 134.4, 137.8, 171.4; MS (m/z): 404 (M^+-C_6H_5), 340 (M^+-$C_6H_5SO_2$).

(1e). Pale yellow oil (Lit. [3b] oil); isolated yield: 0.90 g (88%); IR (neat): 3045, 2942, 1733, 1447, 1331 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.51 (t, *J* = 5.2 Hz, 4H, 2O=CCH_2), 2.82 (t, *J* = 6.9 Hz, 4H, 2ArCH_2), 3.30 (t, *J* = 5.2 Hz, 4H, 2O=CCH_2CH_2), 4.19 (t, *J* = 6.9 Hz, 4H, 2OCH_2), 7.10-7.19 (complex, 10H, 2$C_6H_5CH_2$), 7.42-7.45 (complex, 3H, H_3-H_5 of the aromatic ring of sulfonamide moiety), 7.78 (m, 2H, H_2 and H_6 of the aromatic ring of sulfonamide moiety); ^{13}C NMR ($CDCl_3$): δ 34.3, 34.9, 44.9, 65.2, 126.6, 126.7, 126.9, 128.6, 128.8, 129.2, 132.8, 137.5, 171.0; MS (m/z): 432 (M^+-C_6H_5), 388 (M^+-C_8H_9O), 368 (M^+-$C_6H_5SO_2$).

(1f). Pale yellow oil (Lit. [3c] oil); isolated yield: 0.92 g (86%); IR (neat): 3026, 2981, 1732, 1448, 1317 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.51 (t, *J* = 5.1 Hz, 4H, 2O=CCH_2), 3.41 (t, *J* = 5.1 Hz, 4H, 2O=CCH_2CH_2), 4.73 (m, 4H, 2OCH_2), 6.15 (m, 2H, 2PhCH=C*H*), 6.54 (d, 2H, *J* = 15.7 Hz, PhC*H*), 7.28-7.36 (complex, 10H, 2$C_6H_5CH_2$), 7.41-7.47 (complex, 3H, H_3-H_5 of the aromatic ring of sulfonamide moiety), 7.94 (m, 2H, H_2 and H_6 of the aromatic ring of sulfonamide moiety); ^{13}C NMR ($CDCl_3$): δ 33.8, 43.2, 65.4, 122.4, 123.0, 126.7, 126.9, 127.9, 128.5, 129.4, 132.4, 134.1, 139.3, 171.5; MS (m/z): 392 (M^+-$C_6H_5SO_2$).

(1g). Pale yellow oil (Lit. [3c] oil); isolated yield: 0.72 g (84%); IR (neat): 3056, 2975, 1734, 1317 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 6.9 Hz, 6H, 2CH_2CH_3), 1.32 (m, 4H, 2CH_3CH_2), 1.57 (m, 4H, 2CH_3CH_2CH_2), 2.42 (s, 3H, ArCH_3), 2.63 (t, *J* = 5.2 Hz, 4H, 2O=CCH_2), 3.43 (t, *J* = 5.2 Hz, 4H, 2O=CCH_2CH_2), 4.02 (t, *J* = 7.0 Hz, 4H, 2OCH_2), 7.31 (d, *J* = 7.9 Hz, 2H, H_3 and H_5 of the aromatic ring), 7.72 (d, *J* = 7.9 Hz, 2H, H_2 and H_6 of the aromatic ring); ^{13}C NMR ($CDCl_3$): δ 13.6, 19.0, 21.4, 30.4, 33.9, 45.0, 64.5, 126.9, 129.5, 135.9, 143.5, 172.5; MS (m/z): 427 (M^+).

(1h). Pale yellow oil; isolated yield: 0.84 g (85%); IR (neat): 3056, 2971, 1734, 1316 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, ArCH_3), 2.60 (t, *J* = 5.2 Hz, 4H, 2O=CCH_2), 3.39 (t, *J* = 5.2 Hz, 4H, 2O=CCH_2CH_2), 5.04 (s, 4H, 2OCH_2), 7.18-7.22 (complex, 10H, 2$C_6H_5CH_2$), 7.34 (d, *J* = 7.9 Hz, 2H, H_3 and H_5 of the aromatic ring of sulfonamide moiety), 7.74 (d, *J* = 7.9 Hz, 2H, H_2 and H_6 of the aromatic ring of sulfonamide moiety); ^{13}C NMR ($CDCl_3$): δ 22.2, 33.7, 44.5, 65.8, 126.3, 127.1, 128.3, 129.0, 129.9, 134.9, 135.6, 143.1, 171.9; MS (m/z): 340 (M^+-$C_7H_7SO_2$).

(1i). Pale yellow oil; isolated yield: 0.83 g (90%); IR (neat): 3046, 2981, 1732, 1448, 1327 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.90 (t, *J* = 6.6 Hz, 6H, 2CH_3), 1.36 (m, 4H, 2CH_3CH_2), 1.57 (m, 4H, 2CH_3CH_2CH_2), 2.52 (t, 4H, *J* = 5.1 Hz, 2O=CCH_2), 3.43 (t, 4H, *J* = 5.1 Hz, 2O=CCH_2CH_2), 4.06 (t, 4H, *J* = 7.0 Hz, 2OCH_2), 7.49-7.55 (complex, 4H), 7.76-7.78 (complex, 3H); ^{13}C NMR ($CDCl_3$): δ 13.7, 19.1, 30.2, 33.6, 44.8, 64.8, 122.1, 128.0, 127.7, 128.0, 128.2, 128.5, 128.9, 129.1, 129.6, 132.3, 171.8; MS (m/z): 390 (M^+-C_4H_9O), 272 (M^+-$C_{10}H_7SO_2$).

(1j). Pale yellow oil (Lit. [3a] oil); isolated yield: 0.64 g (83%); IR (neat): 3042, 2982, 1732, 1447, 1316 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.09-1.19 (complex, 12H, 4CH_3), 2.78 (m, 2H, 2O=CCH), 3.22-3.27 (complex, 4H, 2O=CCH_2CH_2), 4.03 (q, *J* = 7.0 Hz, 4H, 2OCH_2), 7.44-7.53 (complex, 3H, H_3-H_5 of the aromatic ring), 7.75 (m, 2H, H_2 and H_6 of the aromatic ring); ^{13}C NMR ($CDCl_3$): δ 14.1, 15.3, 39.2, 52.4, 60.7, 127.3, 129.1, 132.7, 139.0, 174.7; MS (m/z): 385 (M^+).

(1k). Pale yellow oil; isolated yield: 0.62 g (78%); IR (neat): 3057, 2973, 1733, 1447, 1316 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.12-1.24 (complex, 12H, 4CH_3), 2.44 (s, 3H, ArCH_3), 2.73 (m, 2H, 2O=CCH), 3.25-3.31 (complex, 4H, 2O=CCH_2CH_2), 4.10 (q, *J* = 7.0 Hz, 4H, 2OCH_2), 7.33 (d, *J* = 7.8 Hz, 2H, H_3 and H_5 of the aromatic ring), 7.76 (d, *J* = 7.8 Hz, 2H, H_2 and H_6 of the aromatic ring); ^{13}C NMR ($CDCl_3$): δ 13.9, 15.0, 22.7, 39.4, 51.2, 61.2, 126.6, 129.7, 136.1, 142.95, 172.1; MS (m/z): 399 (M^+).

RESULTS AND DISCUSSION

In our previous studies on Michael addition of sulfonamides to α,β-unsaturated esters, we have found that NaOH acts as efficient catalyst for the synthesis of *N*,*N*-dialkyl derivatives of sulfonamides *via* Michael reaction under solvent-free conditions. For the similar reactions under microwave irradiation, we used NaOH (1 mmol) in the presence of TBAB (1 mmol) for Michael addition of benzenesulfonamide (2 mmol) to *n*-butyl acrylate (4.4 mmol) as a model reaction in the absence of any organic solvents

Table 1. Effect of Different Basic Catalysts (1 mmol) on Michael Addition of Benzenesulfonamide (2 mmol) to *n*-Butyl Acrylate (4.4 mmol) in the Presence of TBAB (1 mmol) Under Microwave Irradiation (300 W, max. 110 °C)

Entry	Solvent	Time (min)	Yield (%)[a]
1	NaOH	8	91
2	*t*-BuOK	12	69
3	Cs_2CO_3	15	62
4	Na_2CO_3	20	39
5	NBu_3	20	21
6	DABCO	20	28

[a]Isolated yield.

Table 2. Michael Addition of Benzenesulfonamide (2 mmol) to *n*-Butyl Acrylate (4.4 mmol) in the Presence of NaOH (1 mmol) and TBAB (1 mmol) at Different Microwave Powers

Entry	MW Power (W)	Time (min)	Yield (%)[a]
1	100	20	45
2	200	12	76
3	300	8	91
4	400	6	85
5	500	5	77
6	600	3	74

[a]Isolated yield.

(Scheme 1). We found that, at 300 W of microwave power (max. 110 °C), the reaction proceeded efficiently and the desired Michael adduct **1b** was obtained in 91% yield after 8 min. When using 1 equivalent of *n*-butyl acrylate in the presence of 0.5 equivalent of NaOH only *N*,*N*-dialkyl sulfonamide **1b** was isolated as the sole product of the reaction and the formation of *N*-alkylated product was not observed. We also studied the effect of other basic catalysts in the presence of TBAB upon the reaction. The results are summarized in Table 1. As Table 1 indicates, higher yields and shorter reaction times were observed when NaOH was used. Then we applied this optimized condition for the preparation of structurally diverse important *N*,*N*-dialkyl sulfonamides in good to excellent yields (Table 5).

Table 3. Comparative Michael Addition of Benzenesulfonamide (2 mmol) to *n*-Butyl Acrylate (4.4 mmol) in the Presence of NaOH (1 mmol) in Conventional Solvents (10 ml) *vs*. the Solvent-free Method under Microwave (MW, 300 W, max. 110 °C) and Thermal (Δ, 110 °C) Conditions

Entry	Solvent	Time (min)		Yield (%)[a]	
		MW	Δ	MW	Δ
1	DMSO	20	360	67	46
2	DMF	20	360	60	34
3	HMPTA	20	360	41	21
4	o-Xylene	20	360	23	<10
5[b]	-	20	360	17	<5
6[c]	Solvent-free	8	180	91	49

[a]Isolated yield. [b]Without solvent in the absence of PTC (TBAB). [c]Our Solvent-free method in the presence of TBAB.

The reaction of benzenesulfonamide with *n*-butyl acrylate in the presence of NaOH and TBAB was examined at different microwave powers (100-600 W) with controlled temperature (max. 110 °C) (Table 2). As Table 2 shows, the best results were obtained at 300 W of microwave power.

In order to show the importance of microwave irradiation to promote Michael addition of sulfonamides to α,β-unsaturated esters, a mixture of benzenesulfonamide (2 mmol), NaOH (1 mmol), TBAB (1 mmol) and *n*-butyl acrylate (4.4 mmol) was heated in an oil-bath at 110 °C for 3 h. However, these conditions afforded **1b** in only 49% yield. Elongation of the reaction time or elevating the temperature did not improve the reaction yield. This result shows the positive effect of microwave irradiation upon the yield and efficiency of this Michael reaction.

We have also studied similar reaction in the absence of solvent under microwave irradiation *vs*. similar reaction in solution. In order to show the merit of microwave irradiation in solvent-free conditions on the reaction of benzenesulfonamide with *n*-butyl acrylate, we also investigated the effect of microwave irradiation and conventional heating in solution. The results of these studies are summarized in Table 3. As it is shown in Table 3, higher yields and shorter reaction times were observed in the solvent-free conditions promoted

Table 4. Comparative Synthesis of Michael Adduct **1b** Using the Reported Method *vs*. our Method

Entry	Reagent	Time (min)	Yield (%)[a]	Ref.
1[b]	NaOH	8	91	-
2	MgO	5	9	[3a]
3	ZnO	5	7	[3b]
4	K_2CO_3	5	16	[3c]

[a]Isolated yield. [b]Our method.

by microwave irradiation.

To assess the efficiency and potential of the presented method in comparison to the other reported methods for the synthesis of *N*,*N*-dialkyl sulfonamides *via* Michael reaction, the preparation of compound **1b** was also examined by these methods (Table 4). As it is evident from the results given in Table 4, the presented method is an improvement for the preparation of these compounds.

CONCLUSIONS

In summary, we have developed a new method for the synthesis of *N*,*N*-dialkyl sulfonamides *via* Michael addition of sulfonamides to various α,β-unsaturated esters promoted by microwave irradiation in the absence of any solvents. In comparison to the other methods, this protocol is more advantageous with respect to generality, high yields, short reaction times and ease of product isolation.

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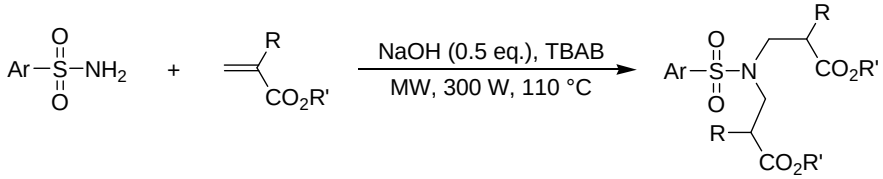
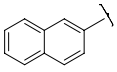
Table 5. Synthesis of *N*,*N*-Dialkyl Sulfonamides Under Solvent-Free Conditions Promoted by Microwave Irradiation



R = H, Me R' = Alkyl **1a-1j**

Entry	Ar	R	R'	Product	Time (min)	Yield (%)[a]
1[b]	C_6H_5	H	CH_3CH_2	**1a**	8	90
2	C_6H_5	H	$CH_3(CH_2)_2CH_2$	**1b**	8	91
3	C_6H_5	H	$CH_3(CH_2)_4CH_2$	**1c**	8	90
4	C_6H_5	H	$C_6H_5CH_2$	**1d**	8	88
5	C_6H_5	H	$C_6H_5CH_2CH_2$	**1e**	10	88
6	C_6H_5	H	$C_6H_5CH{=}CHCH_2$	**1f**	10	86
7	*p*-$CH_3C_6H_4$	H	$CH_3(CH_2)_2CH_2$	**1g**	10	84
8	*p*-$CH_3C_6H_4$	H	$C_6H_5CH_2$	**1h**	10	85
9		H	$CH_3(CH_2)_2CH_2$	**1i**	8	90
10	C_6H_5	CH_3	CH_3CH_2	**1j**	10	83
11	*p*-$CH_3C_6H_4$	CH_3	CH_3CH_2	**1k**	12	78

[a]Isolated yield. [b]In this reaction, the α,β-unsaturated ester/sulfonamide (mol/mol) ratio was 2.5/1.

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