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Bismuth Triflate Catalyzed Friedel-Crafts Acylation of 3-Phenyl- and 3-(2-Carboalkoxyphenyl)sydnones under Microwave Irradiation

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Mesoionic sydnones $(cf. 1)^1$ undergo electrophilic aromatic substitution, including acylation,²⁻⁵ at the C-4 position.⁶⁻¹⁴ In earlier work from our laboratory, we showed that C-4 acetylation of arylsydnones 1 could be effected using acetic anhydride and Montmorillonite K-10 as catalyst¹⁵ and a model study for the acetylation of 3-phenylsydnone (1a) [to form 2a] was conducted using various metal triflates as catalysts.¹⁶ More recently, we have extended this latter study to an exhaustive examination of the acetylation of 1a using lanthanum, gadolinium, scandium, yttrium, indium, or hafnium triflate catalysts.¹⁷ Our preliminary experiments^{16,17} had shown bismuth triflate^{18,19} (with lithium perchlorate as co-catalyst²⁰) to be the most effective catalyst for the acetylations and, accordingly, the study was extended to explore its scope and limitations.¹⁶ In contrast to previous investigations, the sydnone could be acylated utilizing less than stoichiometric amounts of the catalyst and the amount of acetic anhydride as the typical acylating agent was optimized at four molar equivalents (rather than the common practice of using the anhydride as solvent). However, even this improved procedure suffered from drawbacks, in that freshly-prepared bismuth triflate catalyst was required for satisfactory product yields and reaction times were long. Since the synthesis of the catalyst is non-trivial^{24,25} and its effective shelf life is relatively short, it seemed reasonable to expect that the use of microwave irradiation might shorten reaction times and minimize the degradation of the bismuth triflate during the reaction, allowing it to perform optimally. While previous acylation studies with sydnones have been performed using conventional heating there has been no examination of the corresponding reactions under the influence of microwave irradiation.

The present study is a continuation of our previous work with bismuth triflate,¹⁶ but the experiments were conducted under microwave irradiation, and extrapolated to the synthesis of new acyl sydnones from 3-(2-carbalkoxy)phenylsydnones.^{26,27}

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a) R = H, $R' = CH_3$ b) R = H, $R' = CH_3CH_2$ c) R = H, $R' = CH_3(CH_2)_2$ d) R = H, $R' = (CH_3)_2CH$ e) $R = CO_2Me$, $R' = CH_3$ f) $R = CO_2Me$, $R' = CH_3CH_2$ g) $R = CO_2Me$, $R' = CH_3(CH_2)_2$ h) $R = CO_2Me$, $R' = (CH_3)_2CH$ i) $R = CO_2Et$, $R' = CH_3(CH_2)_2$ l) $R = CO_2Et$, $R' = CH_3CH_2$ k) $R = CO_2Et$, $R' = CH_3(CH_2)_2$ l) $R = CO_2Et$, $R' = CH_3CH_2$ k) $R = CO_2Et$, $R' = CH_3(CH_2)_2$ l) $R = CO_2Et$, $R' = (CH_3)_2CH$

Acylation of 1 with Anhydrides Under Microwave Irradiation

The previous protocol¹⁶ for the synthesis of **2a** using conventional heating (100°C, 18 h) was chosen for the initial optimization of the microwave process. Three temperatures (100, 125, and 150°C) were utilized for 15 to 45 min each, with the amounts of catalysts set at 25 mole% of both bismuth triflate and lithium perchlorate in acetonitrile as solvent. The results are displayed in *Table 1*. The first trial (*Entry 1*) was performed at 100°C for 30 minutes and gave a 69% yield of **2a**. Raising the temperature to 125°C for 15 minutes reduced the yield (*Entry 2*) but even higher yields of **2a** were obtained at 125°C for 30 minutes or at 150°C for 15 minutes (*Entries 3 & 4*). The best yield for **2a** was 94% at 125°C for 30 minutes (*Entry 3*). The results of the other experiments are shown in *Table 1*.

The optimum yields of 3-phenyl-4-propanoylsydnone (**2b**) [92%, *Entry* 6], 4-butanoyl-3-phenylsydnone (**2c**) [88%, *Entry* 9] and 4-isobutanoyl-3-phenylsydnone (**2d**) [92%, *Entry* 14] were obtained at 125°C for 30 min, 15 min and 45 min, respectively. These yields greatly surpassed those obtained under conventional heating conditions¹⁶ and took place in a fraction of the time.

From these results, it can be concluded that the best conditions for microwave-induced acylations with 3-phenylsydnone (**1a**) are \sim 30 minutes at 125°C with 25 mole% of both bismuth triflate and lithium perchlorate and 4 eq of the corresponding anhydride in acetonitrile. With this protocol in hand, different sydnones **1b** and **1c** were subjected to analogous microwave conditions. These sydnones were chosen, both because the corresponding acylated products **2e-2l** were needed for another study and to explore the effect (if any) upon acylation due to the steric hindrance presented by an *ortho* substituent on the phenyl ring. These results are tabulated also in *Table 1*. Overall, yields ranged from moderate to poor depending on the sydnone and anhydride employed and, in general, were slightly better with **1b** and slightly worse with **1c** than those obtained using conventional heating (Entries 16–23). For *Entries 22* and *23*, the reaction time was raised to 40 minutes in an unsuccessful attempt to increase the yields.

		Temp.	Time	Yield ^a	mp.	lit. mp.
Entry	Product	(°C)	(min.)	(%)	(°C)	(°C)
1	2a	100	30	69	140–141	143-144 ¹⁵
2	2a	125	15	53		
3	2a	125	30	94		
4	2a	150	15	80		
5	2b	125	15	55	89–91	$92.5 - 94^2$
6	2b	125	30	92		
7	2b	150	15	42		
8	2b	150	30	55		
9	2c	125	15	88	70–72	$72.5 - 74^2$
10	2c	125	30	88		
11	2c	150	15	43		
12	2c	150	30	36		
13	2d	125	30	30	109–111	$113.5 - 115^2$
14	2d	125	45	92		
15	2d	150	15	28		
16	2e	125	30	54 [49] ^a	116–118	$118 - 119^{15}$
17	2f	125	30	58 [31] ^a	107-108	—
18	2g	125	30	36 [17] ^a	85-87	—
19	2h	125	30	21 [3] ^a	121-122	—
20	2i	125	30	22 [47] ^a	123–124	
21	2j	125	30	26 [30] ^a	64–66	—
22	2k	125	40	27 [41] ^a	59–60	—
23	21	125	40	11 [0] ^a	84–86	—

 Table 1

 Microwave-induced Acylation of 3-Phenyl- and 3-(2-Carbalkoxyphenyl)sydnones

^aThe yields in square brackets for the preparation of **2e-2l** (*Entries 16–23*) are those obtained by conventional heating and will be reported elsewhere in due course.

From these results, it is clear that the presence of an electron-withdrawing substituent at the *ortho* position of the aryl ring negatively affects the acylation process, however, without further experimentation, it is unclear which of the two parameters (electronic or steric) has the greater effect.

The identity of 4-acetyl-3-(2-carbomethoxyphenyl)sydnone (**2e**), was confirmed by comparison to an authentic sample previously synthesized in this laboratory.¹⁵ In general, the previously unknown acylated products **2f-2l** exhibited the spectral characteristics expected for such species. Thus, the IR spectra displayed three carbonyl peaks at 1761–1786 cm⁻¹ (sydnone carbonyl), 1717–1736 cm⁻¹ (ester carbonyl), and 1667–1675 cm⁻¹ (ketone carbonyl); the 3150 cm⁻¹ peak of the C-4 hydrogen of the starting sydnone was absent. The ¹H NMR spectra showed the expected aromatic and alkyl signals, as well as the absence of the C-4 proton (δ 6.8), and their ¹³C NMR spectra also

contained the expected peaks, including those for the sydnone C-4 carbon at δ 106–108, the carbonyl of the ester at δ 162–163, the C-5 carbon of the sydnone at δ 165–166 and the carbonyl of the keto group at δ 184–191.

In conclusion, the microwave-induced acylation process offers an attractive alternative to our previous acylation protocols^{15–17} since the former provides the corresponding acyl products in good to excellent yields and takes only minutes in comparison to the many hours required for the reactions under conventional heating conditions.

Experimental Section

General Notes

3-Phenylsydnone (1a),²⁸ 3-(2-carbomethoxyphenyl)sydnone (1b),²⁶ 3-(2-carboethoxyphenyl)sydnone (1c),²⁷ and bismuth triflate¹⁸ were synthesized according to reported procedures. All other starting materials and catalysts (including lithium perchlorate; see **CAUTION** ref. 20) were purchased commercially and used without purification unless otherwise noted. Melting points were determined on a Mel-Temp melting point device and are uncorrected. The infrared spectra were performed as KBr pellets and were taken on a Nicolet 6700 FTIR. NMR spectra were obtained on a Bruker Advance 300 MHz NMR in CDCl₃ and are reported relative to tetramethylsilane as an internal standard. Column chromatography was performed on an Isco CombiFlash Separator System Sg100c. Microwave reactions were conducted in a 300 W, monomode CEM Discover microwave reactor using 10-mL (total volume) sealed reaction vessels. Elemental analyses were carried out by Midwest Microlab LLC, Indianapolis, Indiana 46250.

General Procedure for the Acylation of 3-Arylsydnones using Bismuth Triflate and Lithium Perchlorate under Microwave Irradiation (MWI). To the sydnone (1) [0.6 mmol] was added freshly-prepared bismuth triflate (0.106g, 25 mole%),²⁴ lithium perchlorate (0.016g, 25 mole%), acetonitrile (1.5 mL) and the anhydride (4 molar equivalents; acetic anhydride, 0.23 mL; propionic anhydride, 0.31 mL; n-butyric anhydride, 0.39 mL; isobutyric anhydride, 0.39 mL). The reaction mixture was subjected to microwave irradiation at 100°C, 125°C, or 150°C until complete disappearance of the starting material, as determined by TLC (dichloromethane as eluent) on silica. The mixture was neutralized (10% aq. NaHCO₃) and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (MgSO₄), filtered, and evaporated *in vacuo*. The resultant crude material was then separated *via* flash chromatography (12 g silica gel column, gradient of hexanes to dichloromethane to ethyl acetate) to yield the desired material (see Table).

4-Acetyl-3-[2-(carbomethoxy)phenyl]sydnone (2e)

Reaction of **1b** with acetic anhydride according to the general procedure yielded tan crystals (54%) of **2e**, identical (TLC, mp, IR) to an authentic sample.¹⁵

3-[2-Carbomethoxy)phenyl]-4-propanoylsydnone (2f)

Reaction of **1b** with propionic anhydride according to the general procedure yielded light tan crystals (58%) of **2f**, mp. 107–108°C. IR: 2946, 1778 (sydnone C=O), 1722 (C=O), 1667 (C=O) cm⁻¹. ¹H NMR: δ 1.1 (t, 3 H), 2.9 (q, 2 H), 3.8 (s, 3 H), 7.4 (m, 1 H), 7.7 (m,

2 H), 8.25 (m, 1 H). ¹³C NMR: δ 188.24 (C=O), 165.71 (sydnone C=O), 163.13 (C=O), 134.96, 133.47, 132.14, 131.77, 126.93, 126.39, 107.33 (sydnone C-4), 52.79, 33.32, 7.09.

Anal. Calcd. for C₁₃H₁₂N₂O₅: C, 56.52; N, 10.14; H, 4.38. Found: C, 56.78; N, 9.90; H, 4.49.

4-Butanoyl-3-[2-(carbomethoxy)phenyl]sydnone (2g)

Reaction of **1b** with butyric anhydride according to the general procedure yielded **2g** as a pale yellow solid (36%), mp. 85–87°C. IR: 2962, 2934, 1770 (sydnone C=O), 1731 (C=O), 1668 (C=O) cm⁻¹. ¹H NMR: δ 0.93 (t, 3H), 1.60 (m, 2H), 2.86 (s, 3H), 3.82 (s, 3H), 7.41 (m, 1H), 7.78 (m, 2H), 8.25 (m, 1H). ¹³C NMR: δ 187.77 (C=O), 165.68 (sydnone C=O), 163.11 (C=O), 135.00, 133.45, 132.12, 131.77, 126.90, 126.43, 107.47 (sydnone C-4), 52.78, 41.58, 16.86, 13.52.

Anal. Calcd. for C₁₄H₁₄N₂O₅: C, 57.93; N, 9.65; H, 4.86. Found: C, 57.91; N, 9.44; H, 4.92.

3-[2-(Carbomethoxy)phenyl]-4-isobutanoylsydnone (2h)

Reaction of **1b** with isobutyric anhydride according to the general procedure yielded **2h** as a colorless solid (21%), m.p. 121–122°C. IR: 2972, 1776 (sydnone C=O), 1724 (C=O), 1669 (C=O) cm⁻¹. ¹H NMR: δ 1.0 (d, 3H), 3.5 (sept, 1H), 3.7 (s, 3H), 7.9 (m, 3H), 8.2 (m, 1H). ¹³C NMR: δ 191.98 (C=O), 165.24 (sydnone C=O), 163.13 (C=O), 135.08, 133.47, 132.07, 131.75, 126.86, 126.34, 106.99 (sydnone C-4), 52.74, 35.60, 17.66.

Anal. Calcd. for C₁₄H₁₄N₂O₅: C, 57.93; N, 9.65; H, 4.86. Found: C, 57.65; N, 9.64; H, 5.15.

4-Acetyl-3-[2-(carboethoxy)phenyl]sydnone (2i)

Reaction of **1c** with acetic anhydride according to the general procedure yielded light tan crystals (22%) of **2i**, mp 123–124°C. IR: 1770 (sydnone C=O), 1717 (C=O), 1674 (C=O) cm⁻¹. ¹H NMR: δ 1.28 (t, 3H), 2.48 (s, 3H), 4.26 (q, 2H), 7.40 (m, 1H), 7.77 (m, 2H), 8.27 (m, 1H). ¹³C NMR: δ 184.50 (C=O), 165.87 (sydnone C=O), 162.69 (C=O), 134.73, 133.29, 132.15, 131.93, 126.84, 126.80, 108.05 (sydnone C-4), 62.05, 29.67, 27.49.

Anal. Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; N, 10.14; H, 4.38. Found: C, 56.64; N, 10.08; H, 4.40.

3-[2-(Carboethoxy)phenyl]-4-propanoylsydnone (2j)

Reaction of **1c** with propionic anhydride according to the general procedure yielded light tan crystals (26%) of **2j**, mp. 64–66°C. IR: 2982, 1774 (sydnone C=O), 1723 (C=O), 1673 (C=O) cm⁻¹. ¹H NMR: δ 0.94 (t, 3H), 1.16 (t, 3H), 2.77 (q, 2H), 4.02 (q, 2H), 7.82-7.97 (m, 3H), 8.01 (m, 1H). ¹³C NMR: δ 188.09 (C=O), 165.70 (sydnone C=O), 162.69 (C=O), 134.80, 133.30, 132.09, 131.89, 129.83, 126.81, 107.40 (sydnone C-4), 62.02, 33.32, 13.89, 7.07.

Anal. Calcd. for C₁₄H₁₄N₂O₅: C, 57.93; N, 9.65; H, 4.86. Found: C, 57.71; N, 9.38; H, 4.81.

4-Butanoyl-3-[2-(carboethoxy)phenyl]sydnone (2k)

Reaction of **1c** with butyric anhydride for 40 minutes according to the general procedure yielded light tan crystals (27%) of **2k**, mp. 59–60°C. IR: 2966, 2935, 2876, 1770 (sydnone C=O), 1731 (C=O), 1667 (C=O) cm⁻¹. ¹H NMR: δ 0.92 (t, 3H), 1.27 (t, 3H), 1.60 (sextet, 2H), 2.85 (t, 2H), 4.25 (q, 2H), 7.40 (m, 1H), 7.77 (m, 2H), 8.27 (m, 1H). ¹³C NMR: δ 187.64 (C=O), 165.69 (sydnone C=O), 162.71 (C=O), 134.85, 133.30, 132.08, 131.92, 126.83, 126.80, 107.54 (sydnone C-4), 62.02, 41.59, 16.80, 13.91, 13.54.

Anal. Calcd. for C₁₅H₁₆N₂O₅: C, 59.21; N, 9.21; H, 5.30. Found: C, 59.22; N, 9.11; H, 5.34.

3-[2-(Carboethoxy)phenyl]-4-isobutanoylsydnone (21)

Reaction of **1c** with isobutyric anhydride for 40 minutes according to the general procedure yielded light tan crystals (11%) of **2l**, mp. 84–86°C. IR: 1761 (sydnone C=O), 1720 (C=O), 1668 (C=O) cm⁻¹. ¹H NMR: δ 1.10 (d, 6H), 1.28 (t, 3H), 3.51 (septet, 1H), 4.25 (q, 2H), 7.41 (m, 1H), 7.77 (m, 2H), 8.27 (m, 1H). ¹³C NMR: δ 191.94 (C=O), 165.26 (sydnone C=O), 162.70 (C=O), 134.99, 133.31, 132.03, 131.91, 126.76, 107.05 (sydnone C-4), 62.01, 36.70, 17.69, 13.93.

Anal. Calcd. for C₁₅H₁₆N₂O₅: C, 55.90; N, 8.69; H, 5.63. Found: C, 56.03; N, 8.91; H, 5.77.

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