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A new and efficient method for the facile synthesis of *N*-acyl sulfonamides under Lewis acid catalysis☆

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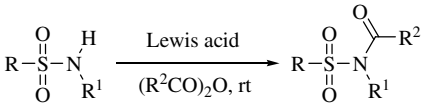
Abstract—The N-acylation of sulfonamides with carboxylic acid anhydrides in the presence of Lewis acids is described. Several Lewis acids such as $BF_3{\cdot}Et_2O$, $ZnCl_2$, $MoCl_5$, $TiCl_4$, $B(C_6F_5)_3$, $Sc(OTf)_3$ and I_2 were found to catalyze the reaction efficiently to furnish the N-acylated products in good yields under solvent-free conditions. The reactions of various sulfonamides were studied with different carboxylic acid anhydrides including the less reactive benzoic and pivalic anhydrides, in the presence of 3 mol % $ZnCl_2$ as the catalyst. Carboxylic acids were also successfully used as acylating agents via the mixed anhydride method.

N-Acylation of sulfonamides is an important transformation since it affords products of significant potential for use in biological applications.[1] This transformation is also a useful tool for lead optimization and lead generation.[2] *N*-Acyl sulfonamides with their acidity makes them suitable carboxylic acid proxies,[3] while their resistance to chemical and enzymatic hydrolysis renders them amenable for use as enzyme inhibitors.[4] In addition, *N*-acyl sulfonamides have diverse pharmacological activities such as precursors of therapeutic agents for Alzheimer's disease,[5] antibacterial inhibitors for tRNA synthetase,[6] antagonists for Angiotensin II,[7] prostaglandin Fla sulfonamides for the treatment of osteoporosis and Luekotriene D_4-receptors.[8]

Historically, the N-acylation of sulfonamides has relied on the reaction of a sulfonamide with anhydrides, esters or acid chlorides in basic reaction media using trialkylamines, pyridine[9] or alkali hydroxides,[10] besides others.[11] Direct condensation of a carboxylic acid with a sulfonamide in the presence of coupling agents such as carbodiimides (EDC·HCl or DCC) or *N*,*N*′-carbonyldiimidazole (CDI) has also been employed, in which the by-product must be removed from the reaction.[12] Recently, *N*-acylbenzotriazoles were used as acylating agents in the presence of NaH as a base.[13] Despite the extensive number of Lewis acid catalyzed acylations of protic nucleophiles such as alcohols, amines and thiols,[14] the N-acylation of less nucleophilic sulfonamides has not received considerable attention. To our knowledge there are only a few reports in the literature describing the N-acylation of sulfonamides under acidic medium.[15] However, strong acidic conditions, namely, concentrated H_2SO_4 (3 mol %) or Fe-exchanged Montmorillonite K-10 and higher temperature (60 °C) are typically needed to achieve conversion. Thus, the investigation of other Lewis acids as efficient catalysts under mild reaction conditions is required for this transformation. Accordingly, a range of Lewis acids were screened for the N-acylation of benzene sulfonamide in the presence of acetic anhydride at room temperature (Scheme 1, Table 1).

Initially, treatment of readily available benzene sulfonamide **1a** with acetic anhydride in the presence of 10 mol % $ZnCl_2$ in dichloromethane furnished the expected *N*-acetyl product **2a** in 15 min in 95% yield (entry 1, Table 1). Interestingly, solvent-free conditions (exclusion of dichloromethane) resulted in a rapid reaction (reaction time was reduced from 15 min to



R= alkyl, aryl; R^1= H, alkyl;
R^2= Me, Et, ^{n}Pr, ^{t}Bu, Ph

Scheme 1.

Keywords: Sulfonamide; Anhydride; N-Acylation; Lewis acid.
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Table 1. Catalytic activity of various Lewis acids in the N-acetylation of benzene sulfonamide[a]

Entry	Lewis acid (mol %)	Time (min)	Yield[b] (%)
1	$ZnCl_2$ (10)	15	95[c]
2	$ZnCl_2$ (10)	2	96
3	$ZnCl_2$ (5)	2	96
4	$ZnCl_2$ (3)	2	97
5	$ZnCl_2$ (1)	10	78
6	—	720	0[d]
7	$BF_3{\cdot}Et_2O$ (3)	3	90
8	$TiCl_4$ (3)	2	88
9	$MoCl_5$ (3)	3	93
10	$B(C_6F_5)_3$ (3)	1	96
11	$Sc(OTf)_3$ (3)	2	92
12	I_2 (3)	300	90

[a] Reaction conditions: Ac_2O (1.5 equiv), no solvent, rt.
[b] Isolated yield after purification.
[c] CH_2Cl_2 was used as solvent.
[d] No reaction.

2 min) without loss of chemical yield (entry 2, Table 1). Lowering the concentration of catalyst to 5 mol % and 3 mol % led to similar results, while decreasing it to 1 mol % extended the reaction time and decreased the yield (Table 1, entries 3–5). Notably, no product was observed when the reaction was carried out in the absence of $ZnCl_2$ even after 12 h (Table 1, entry 6). We then tested various other Lewis acids such as $BF_3{\cdot}Et_2O$, $TiCl_4$, $MoCl_5$, $B(C_6F_5)_3$ and $Sc(OTf)_3$ and obtained similar results as observed in the case of $ZnCl_2$ (Table 1, entries 7–11). However, the use of I_2 as a catalyst required a longer reaction time (Table 1, entry 12). Although most of these Lewis acids provided good yields of the product, zinc(II) chloride, for obvious reasons (being cheapest, milder conditions and easy to handle) was chosen for further experiments.

To determine the reactivity of various carboxylic acid anhydrides, a series of acid anhydrides were reacted with benzene sulfonamide **1a** in the presence of 3 mol % $ZnCl_2$ under solvent-free reaction conditions. Besides acetic anhydride, the reaction conditions tolerated a diverse array of aliphatic and aromatic anhydrides, Table 2. In general, the more hindered the anhydride, the slower the acylation rate. Acylation with benzoic anhydride (Table 2, entry 6) was up to 20 times slower than those with aliphatic anhydrides. With a suitable set of reaction conditions (3 mol % $ZnCl_2$, 1.5 equiv of anhydride) in hand,[16] N-acylations of sterically and electronically different sulfonamides were examined. Toluene sulfonamide **1b** was converted to its *N*-acetyl and *N*-trifluoroacetyl derivatives **2g** and **2h** in 97% and 93% yields, respectively (Table 2, entries 7 and 8). The presence of a nitro functionality on the aromatic ring did not affect the course of N-acylation with acetic and butyric anhydrides (Table 2, entries 9 and 10). Changing the substrate from an aryl sulfonamide to an alkyl sulfonamide such as methanesulfonamide **1d** also gave the desired acylated products (Table 2, entries 11 and 12). To explore the generality and scope further, several N-substituted sulfonamides (secondary), namely, *N*-benzyl toluene sulfonamide **1e** and *N*-alkylmethanesulfonamides **1f** and **1g** were also examined for the N-acylation reactions with acetic and propionic anhydrides under the present reaction conditions (Table 2, entries 13–17).

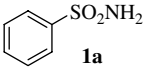
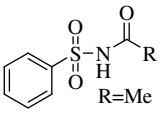
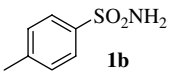
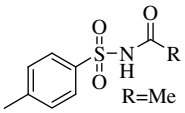
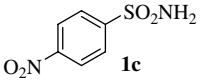
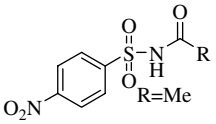
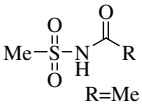
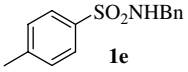
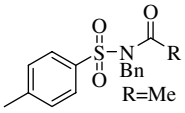
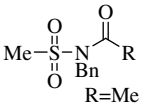
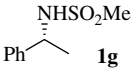
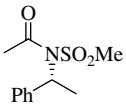
Having obtained these results, it was of interest to determine whether carboxylic acids were capable of undergoing acylation to give the corresponding *N*-acyl sulfonamides under the reaction conditions described. Hence, we have studied the N-acylation reactions using various carboxylic acids as acylating agents in acidic medium for the first time. Since, benzoic anhydride is the least reactive anhydride, we planned to carry out the acylation directly with the carboxylic acid in the presence of benzoic anhydride by adopting the mixed anhydride method.[14d] Thus, the aliphatic carboxylic acid, 5-hexynoic acid **3a** was treated with benzene sulfonamide in the presence of benzoic anhydride in CH_2Cl_2 with 5 mol % of $ZnCl_2$ for 1 h to afford the corresponding acyl sulfonamide **4a** in 85% yield (Scheme 2). *trans*-Cinnamic acid **3b** was treated with benzene sulfonamide and also with toluene sulfonamide to give the products **4b** and **4c** in 80% and 84% yields, respectively (Table 3, entries 1 and 2). Satisfactory results were also achieved with other carboxylic acid substrates including 3,4-dimethoxyphenylacetic acid **3c** and levulinic acid **3d** on reaction with benzene sulfonamide to give the corresponding acyl sulfonamides **4d** and **4e** (Table 3, entries 3 and 4). The N-acylation of benzene sulfonamide **1a** and methane sulfonamide **1d** with 2-(4-isobutylphenyl)propionic acid **3e** [(±)-Ibuprofen] furnished the desired *N*-acyl sulfonamides **4f** and **4g** (Table 3, entries 5 and 6), which possess insignificant biological activity, in enantiomerically pure form.[17]

In conclusion, we have demonstrated a Lewis acid catalyzed N-acylation of sulfonamides with acid anhydrides. The $ZnCl_2$ catalyst used was general for N-acylation with a variety of anhydrides and was also effective in benzoylation and pivalation of sulfonamides. Importantly, the method was extended to the use of carboxylic acids as acylating agents. The advantages of this method include high yields, short reaction times, the use of a commercially available catalyst and solvent-free and mild reaction conditions making this method attractive for potential applications in organic synthesis.

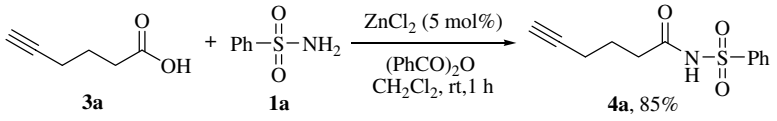
General experimental procedure for N-acylation of sulfonamides with anhydrides: To a mixture of sulfonamide (1.0 mmol) and anhydride (1.5 mmol), 3 mol % of anhydrous $ZnCl_2$ was added and the reaction stirred for the given time (see Tables 1 and 2). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with dichloromethane and washed with water and brine solution. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The crude compound was purified by column chromatography (hexanes and ethyl acetate) to afford the corresponding N-acylated product.[18]

General experimental procedure for N-acylation of sulfonamides with carboxylic acids: To a stirred solution of 5 mol % anhydrous $ZnCl_2$ in anhydrous dichloromethane, carboxylic acid (1.2 mmol) was added followed by

Table 2. N-Acylation of sulfonamides with anhydrides

Entry	Sulfonamide	Anhydride	Time (min)	Product[a]		Yield[b] (%)
1	 **1a**	$(RCO)_2O$ R = Me	2	 R=Me	**2a**	97
2	**1a**	R = Et	4	R = Et	**2b**	96
3	**1a**	R = ^{n}Pr	7	R = ^{n}Pr	**2c**	95
4	**1a**	R = ^{t}Bu	60	R = ^{t}Bu	**2d**	90
5	**1a**	R = CF_3	10	R = CF_3	**2e**	94
6	**1a**	R = Ph	240	R = Ph	**2f**	88[c]
7	 **1b**	$(RCO)_2O$ R = Me	2	 R=Me	**2g**	97
8	**1b**	R = CF_3	10	R = CF_3	**2h**	93
9	 **1c**	$(RCO)_2O$ R = Me	3	 R=Me	**2i**	95
10	**1c**	R = ^{n}Pr	5	R = ^{n}Pr	**2j**	94
11	$MeSO_2NH_2$ **1d**	$(RCO)_2O$ R = Me	2	 R=Me	**2k**	98
12	**1d**	R = ^{n}Pr	3	R = ^{n}Pr	**2l**	96
13	 **1e**	$(RCO)_2O$ R = Me	5	 R=Me	**2m**	94
14	**1e**	R = Et	8	R = Et	**2n**	93
15	$MeSO_2NHBn$ **1f**	$(RCO)_2O$ R = Me	5	 R=Me	**2o**	95
16	**1f**	R = Et	7	R = Et	**2p**	92
17	 **1g**	$(MeCO)_2O$	2		**2q**	96

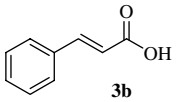
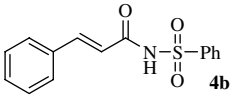
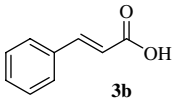
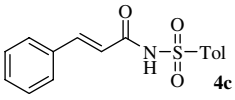
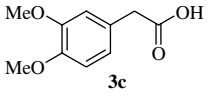
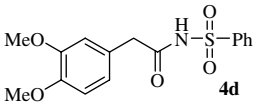
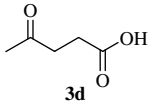
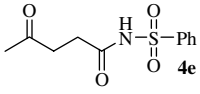
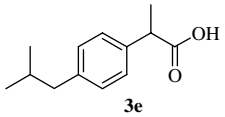
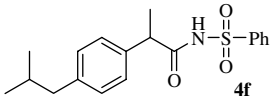
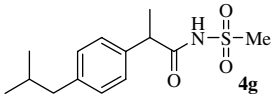
[a] All the products were characterized by ^1H NMR, mass and IR spectroscopy.
[b] Isolated yields.
[c] CH_2Cl_2 was used as solvent since the two substrates are solids.



3a **1a** **4a**, 85%

Scheme 2.

Table 3. N-Acylation of sulfonamides using carboxylic acids[a]

Entry	Carboxylic acid	Sulfonamide	Time (h)	Product[b]	Yield[c] (%)
1	 **3b**	**1a**	2	 **4b**	80
2	 **3b**	**1b**	2	 **4c**	84
3	 **3c**	**1a**	0.75	 **4d**	82
4	 **3d**	**1a**	1	 **4e**	80
5	 **3e**	**1a**	1.5	 **4f**	85
6	**3e**	**1d**	1.5	 **4g**	82

[a] Reaction conditions: 5 mol % $ZnCl_2$, 1.2 equiv $(PhCO)_2O$, CH_2Cl_2, rt.
[b] All the products were characterized by ^1H NMR, mass and IR spectroscopy.
[c] Isolated yields.

the addition of benzoic anhydride (1.2 mmol) under a nitrogen atmosphere at room temperature. After 10 min, a solution of sulfonamide in CH_2Cl_2 was added and the resulting reaction mixture was stirred for the given time (see Table 3). After completion, the reaction mixture was washed with water then brine and the combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The crude compound was purified by column chromatography (hexanes and ethyl acetate) to afford the corresponding N-acylated product.[18]

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16. In order to check the efficiency of the method, a large scale (3 g) acylation of benzene sulfonamide was also carried out using 3 mol % of $ZnCl_2$ and the reaction proceeded in 8 minutes to give the product **2a** in 96% yield.
17. The enantiomers of compound **4g** show activity in reperfusion injury treatment and one of the enantiomers (*R*-enantiomer, repertaxin) was selected as a clinical candidate that is now in phase II clinical studies for the prevention of reperfusion injury; see Ref. 2b.
18. Spectral data for new products: *N-(4-Nitrophenylsulfonyl)acetamide* (**2i**): Pale yellow solid, mp 197–199 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40–8.32 (m, 2H), 8.28–8.20 (m, 2H), 3.23–2.31 (br s, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 150.2, 144.5, 129.2, 124.4, 23.2; IR(KBr): ν 3109, 2922, 1717, 1693, 1533, 1465, 1351, 609 cm^{-1}; HRMS-ESI: calcd for $C_8H_8N_2O_5NaS$, 267.0051; found, 267.0055. *N-(4-Nitrophenylsulfonyl)-butyramide* (**2j**): Semi solid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40–8.32 (m, 2H), 8.28–8.20 (m, 2H), 2.23 (t, $J = 7.3$ Hz, 2H), 1.66–1.46 (m, 2H), 0.86 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 150.2, 144.7, 129.2, 124.4, 37.2, 17.4, 13.1; IR(neat): ν 3426, 1715, 1651, 1531, 1351, 1026 cm^{-1}; HRMS-ESI: calcd for $C_{10}H_{12}N_2O_5NaS$, 295.0364; found, 295.0377. *N-(Methylsulfonyl)butyramide* (**2l**): White solid, mp 72–74 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.23–8.66 (br s, 1H), 3.36 (s, 3H), 2.33 (t, $J = 7.3$ Hz, 2H), 1.80–1.60 (m, 2H), 0.99 (t, $J = 14.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 41.5, 38.2, 18.0, 13.5; IR(KBr): ν 3198, 2968, 1692, 1460, 1334, 1144, 848 cm^{-1}; HRMS-ESI: calcd for $C_5H_{11}NO_3$-NaS, 188.0357; found, 188.0349. *N-Benzyl-N-tosylpropionamide* (**2n**): White solid, mp 159–160 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69–7.61 (m, 2H), 7.41–7.22 (m, 7H), 5.11 (s, 2H), 2.56 (q, $J = 7.0$ Hz, 2H), 2.43 (s, 3H), 1.01 (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 144.9, 137.0, 136.9, 129.8, 128.8, 128.0, 127.9, 127.8, 49.6, 29.8, 21.8, 8.8; IR(KBr): ν 3396, 2977, 1706, 1354, 1158, 1011, 729, 585 cm^{-1}; HRMS-ESI: calcd for $C_{17}H_{19}NO_3NaS$, 340.0983; found: 340.0991. *N-Benzyl-N-(methylsulfonyl)acetamide* (**2o**): White solid, mp 73–75 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43–7.29 (m, 5H), 5.02 (m, 2H), 3.13 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 136.2, 128.9, 128.0, 127.4, 49.3, 42.7, 24.8; IR (KBr): ν 3386, 2933, 1707, 1450, 1338, 1161, 960, 832, 511 cm^{-1}; HRMS-ESI: calcd for $C_{10}H_{13}NO_3NaS$, 250.0513; found, 250.0520. *N-Benzyl-N-(methylsulfonyl)propionamide* (**2p**): Viscous liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43–7.29 (m, 5H), 5.02 (m, 2H), 3.20 (s, 3H), 2.59 (q, $J = 7.3$ Hz, 2H), 1.15 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 136.4, 129.0, 127.9, 127.1, 48.9, 42.7, 29.6, 8.7; IR(Neat): ν 2984, 2940, 1701, 1454, 1351, 1159, 956, 779, 515 cm^{-1}; HRMS-ESI: calcd for $C_{11}H_{15}NO_3NaS$, 264.0670; found, 264.0661. *(R)-N-(Methylsulfonyl)-N-(1-phenylethyl)acetamide* (**2q**): Viscous liquid; $[\alpha]_D^{25}$ −59.4 (*c* 1 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59–7.18 (m, 5H), 5.85 (q, $J = 7.0$ Hz, 1H), 3.10 (s, 3H), 2.23 (s, 3H), 1.86 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 139.5, 128.6, 127.7, 127.1, 55.6, 43.2, 25.9, 18.4; IR (KBr): ν 3028, 2938, 1694, 1349, 1238, 1163, 949, 770, 550 cm^{-1}; HRMS-ESI: $(M+H)^+$ calcd for $C_{11}H_{15}NO_3NaS$, 264.0670; found: 264.0672. *N-(Phenylsulfonyl)hex-5-ynamide* (**4a**): White solid, mp 73–75 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.12–8.80 (br s, 1H), 8.17–8.02 (m, 2H), 7.75–7.49 (m, 3H), 2.44 (t, $J = 6.8$ Hz, 2H), 2.25–2.10 (m, 2H), 1.96–1.69 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 139.6, 134.3, 129.2, 128.4, 83.0, 69.8, 34.8, 22.8, 17.6; IR(neat): ν 3272, 3129, 1683, 1458, 1166, 686 cm^{-1}; HRMS-ESI: $(M+H)^+$ calcd for $C_{12}H_{14}NO_3S$, 252.0694; found, 252.0704. *N-(Phenylsulfonyl)cinnamamide* (**4b**): White solid, mp 152–154 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.40–9.10 (br s, 1H), 8.22–8.08 (m, 1H), 7.80–7.27 (m, 10H), 6.48 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 146.4, 138.7, 134.2, 133.8, 131.1, 129.2, 129.1, 128.6, 128.5, 117.5; IR(KBr): ν 3289, 1697, 1626, 1426, 1085 cm^{-1}; HRMS-ESI: calcd for $C_{15}H_{13}NO_3NaS$, 310.0513; found, 310.0515. *2-(3,4-Dimethoxyphenyl)-N-(phenylsulfonyl)acetamide* (**4d**): Semi solid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06–7.94 (m, 1H), 7.74–7.43 (m, 3H), 6.88–6.57 (m, 4H), 3.87 (s, 3H), 3.79 (s, 3H), 3.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 169.0, 149.6, 149.0, 138.5, 134.2, 128.8, 128.5, 124.7, 121.8, 112.3, 112.0, 56.0, 43.5; IR(KBr): ν 3425, 2924, 1696, 1454, 1166 cm^{-1}; EIMS: *m*/*z* 358.1 (M+Na). *N-(Phenyl sulfonyl)-4-oxopentanamide* (**4e**): Semi solid, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.71–7.60 (m, 2H), 7.51–7.32 (m, 3H), 2.48 (t, $J = 6.2$ Hz, 2H), 2.20 (t, $J = 6.2$ Hz, 2H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 207.2, 173.9, 144.2, 132.0, 129.0, 125.6, 37.6, 29.7, 27.7; IR(KBr): ν 3349, 3256, 1714, 1695, 1448, 1334 cm^{-1}; EIMS: *m*/*z* 278.0 (M+Na).