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# $TiCl_4$-promoted direct N-acylation of sulfonamide with carboxylic ester

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ABSTRACT

Several Lewis acids were investigated as promoters in the intermolecular or intramolecular direct N-acylation reaction of sulfonamides using carboxylic ester as an acylating agent. $TiCl_4$ was found to possess the highest activity and enhanced efficiently sulfonamide to form *N*-acylsulfonamides under optimized conditions. This method provides a novel approach to make *N*-acylsulfonamides from ester via an easy work-up procedure.

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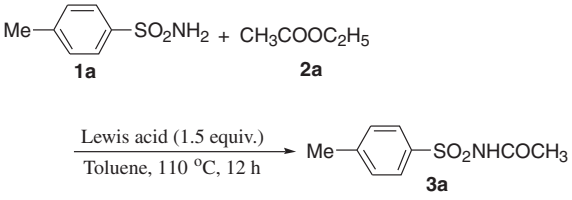
Many bioactive natural products and medical molecules consist of *N*-acylsulfonamide (NAS) structural motifs. For instance, several recently developed drugs, including an inhibitor of human asparagine synthetase,[1] a therapeutic agent for Alzheimer's disease,[2] and a hepatitis C virus NS3 protease inhibitor[3] are all derived from NAS precursors. In addition to being used as carboxylic acid bioisostere because of suitable acidity ($pK_a$ = 4–5),[4] NAS functional group is also incorporated in organocatalysts and plays an important cooperative catalytic role in certain enantioselective asymmetric reactions.[5] Moreover, the family of acylsulfonamides was also employed as a "safety-catch" linker for efficient chemical protein synthesis in solid-phase reaction.[1,6]

Generally, *N*-acylsulfonamide derivatives are prepared via direct condensation of a carboxylic acid with a sulfonamide using carbodiimides (EDC·HCl or DCC) or *N*,*N*′-carbonyldiimidazole (CDI) as coupling agents.[7] Of course, more reactive carboxylic anhydrides and acid chlorides are also used in the presence of a base or an acid.[8] An alternative synthetic approach starting from sulfonyl chloride and carboxylic amides in basic reaction condition can afford *N*-acylsulfonamide product.[9] Recently, sulfonyl isocyanate or *N*-acylbenzotriazoles were used as acylating agents under basic conditions.[10] Moreover, the preparation of acylsulfonamide from aryl halide and sulfonamide catalyzed by Pd (II) and $Mo(CO)_6$ under microwave irradiation was also reported.[11] Recently Chan found Rh (II) could catalyze intermolecular oxidative sulfamidation of aldehyde to form *N*-sulfonylcarboxamide by using $PhI(OCOtBu)_2$ as an oxidant.[12] Although most of the methods provide various approaches to make *N*-acylsulfonamide starting from parent sulfonamide and acylating agents such as acyl chlorides or anhydrides or carboxylic acid, no studies have reported the direct N-acylation

**Table 1**
Catalyst screening for N-acylation from *p*-toluene sulfonamine and ethyl acetate[a]




| Entry | Catalyst | Yield[b] (%) |
|---|---|---|
| 1 | $AlCl_3$ | No reaction |
| 2 | $FeCl_3$ | <5 |
| 3 | $TiCl_4$ | 53 |
| 4 | $Cu(OAc)_2·H_2O$ | No reaction |
| 5 | $Fe_2O_3$ | No reaction |
| 6 | MgO | No reaction |
| 7 | $FeCl_2·4H_2O$ | No reaction |
| 8 | $ZrCl_4$ | No reaction |
| 9 | $MnCl_2·4H_2O$ | No reaction |
| 10 | $ZnCl_2$ | No reaction |
| 11 | CuCl | No reaction |
| 12 | $CdCl_2·2.5H_2O$ | No reaction |
| 13 | $NiCl_2·6H_2O$ | No reaction |

[a] Reaction conditions: *p*-toluene sulfonamide (2 mmol), ethylacetate (4 mmol), Lewis acid (1.5 equiv), toluene, (4.5 mL), the reaction was carried out at 110 °C for 12 h in sealed tube.
[b] Isolated yield after purification.

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**Table 2**
The effect of solvent, reaction time, and temperature on the $TiCl_4$-catalyzed N-acylation of *p*-toluene sulfonamide (**1a**) with ethyl acetate (**2a**)[a]

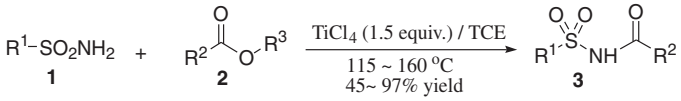
| Entry | Reaction time (h) | Temp (°C) | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 12 | 70 | $CHCl_3$ | 34 |
| 2 | 12 | 110 | Toluene | 53 |
| 3 | 12 | 110 | DCE[e] | 60 |
| 4 | 12 | 110 | TCE[f] | 64 |
| 5 | 18 | 115 | TCE | 76 |
| 6 | 24 | 115 | TCE | 65 |
| 7 | 18 | 90 | TCE | Trace |
| 8 | 18 | 100 | TCE | 62 |
| 9 | 18 | 120 | TCE | 69 |
| 10 | 18 | 140 | TCE | Decomp. |
| 11 | 18 | 115 | TCE | 53[c] |
| 12 | 18 | 115 | TCE | 72[d] |

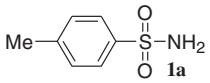
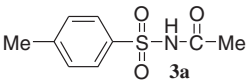
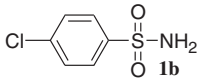
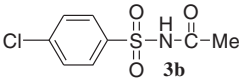
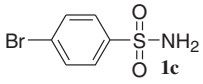
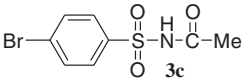
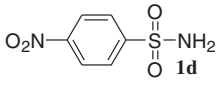
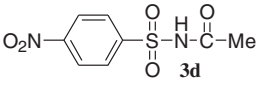
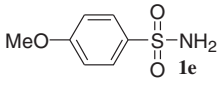
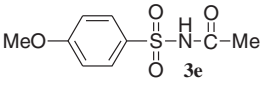
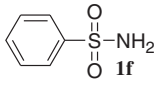
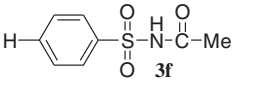
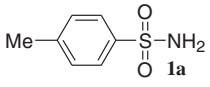
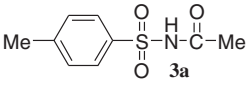
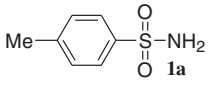
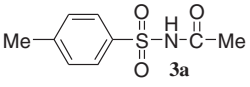
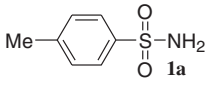
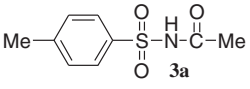
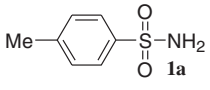
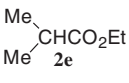
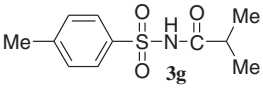
[a] Reaction conditions: *p*-toluene sulfonamide (2 mmol), ethyl acetate (4 mmol), Lewis acid (1.5 equiv), solvent (4.5 mL), the reaction was carried out at the given temperature in a sealed tube.
[b] Isolated yield after purification.
[c] 1.0 equiv of $TiCl_4$ used.
[d] 2.0 equiv of $TiCl_4$ used.
[e] DCE: 1,2-dichloroethane.
[f] TCE: 1,1,2,2-tetrachloroethane.

of sulfonamides with unreactive carboxylic ester. Accordingly, we present here an alternative preparation method for *N*-acylsulfonamide by using carboxylic ester as acylating agents in the presence of Lewis acid catalyst.

Optimal conditions for this transformation were first determined by systematically investigating the Lewis acid catalysts, reaction solvents, reaction time, reaction temperature, and the catalyst/substrate ratio. Initially, the N-acylation reaction of the readily available *p*-toluene sulfonamide **1a** (2 mmol) with ethyl acetate **2a** (4 mmol) was carried out in toluene by using various kinds of Lewis acid promoters (1.5 equiv, 3 mmol) such as $AlCl_3$, $FeCl_3$, $TiCl_4$, $ZrCl_4$, MgO, etc., at 110 °C for 12 h in a sealed tube (Table 1). Gratifyingly, we quickly found $TiCl_4$ was an only promoter for the N-acylation of sulfonamide with ethyl acetate in 53% yield (Table 1, entry 3), and basically other Lewis acids didn't work. Notably, no product was observed when the reaction was carried out in the absence of $TiCl_4$ even after 48 h. Inspired by these positive results, we further investigated other reaction conditions to define the reaction parameters (Table 2). To find the best solvent, the N-acylation of *p*-toluene sulfonamide (**1a**) with ethyl acetate (**2a**) was carried out for 12 h in different solvents such as $CH_3CN$, $CCl_4$, $ClCH_2CH_2Cl$, $Cl_2CHCHCl_2$, toluene, dioxane, etc. We

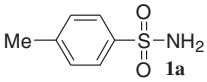
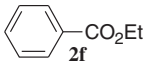
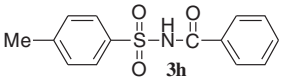
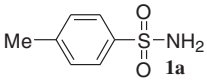
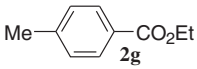
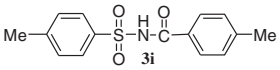
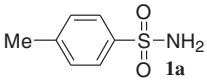
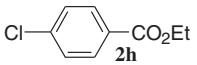
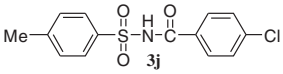
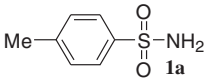
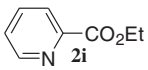
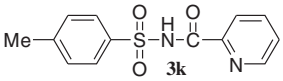
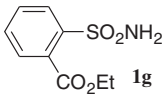
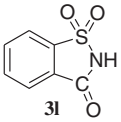
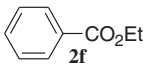
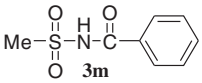
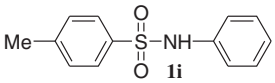
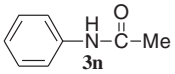
**Table 3**
$TiCl_4$-catalyzed N-acylation of sulfonamines with carboxylic ester[15]




| Entry | Sulfonamide | Carboxylic ester | Time (h) | Product[16] | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  **1a** | $CH_3CO_2Et$ **2a** | 18 |  **3a** | 76 |
| 2 |  **1b** | $CH_3CO_2Et$ **2a** | 30 |  **3b** | 81 |
| 3 |  **1c** | $CH_3CO_2Et$ **2a** | 55 |  **3c** | 77 |
| 4 |  **1d** | $CH_3CO_2Et$ **2a** | 48 |  **3d** | 48 |
| 5 |  **1e** | $CH_3CO_2Et$ **2a** | 36 |  **3e** | 30 (54[b]) |
| 6 |  **1f** | $CH_3CO_2Et$ **2a** | 24 |  **3f** | 70 |
| 7 |  **1a** | $CH_3CO_2Et$ **2b** | 24 |  **3a** | 69 |
| 8 |  **1a** | $CH_3CO_2tBu$ **2c** | 24 |  **3a** | 56 |
| 9 |  **1a** | $CH_3CO_2$ *t*Bu **2d** | 24 |  **3a** | 72 |
| 10 |  **1a** |  **2e** | 24 |  **3g** | 51[c] |

(*continued on next page*)

**Table 3** (*continued*)

| Entry | Sulfonamide | Carboxylic ester | Time (h) | Product[16] | Yield[a] (%) |
|---|---|---|---|---|---|
| 11 |  **1a** |  **2f** | 24 |  **3h** | 97[d] |
| 12 |  **1a** |  **2g** | 24 |  **3i** | 55[d] |
| 13 |  **1a** |  **2h** | 24 |  **3j** | 46[d] |
| 14 |  **1a** |  **2i** | 24 |  **3k** | 45[d] |
| 15 |  **1g** | – | 48 |  **3l** | 82 |
| 16 | $CH_3SO_2NH_2$ **1h** |  **2f** | 24 |  **3m** | 94[d] |
| 17 |  **1i** | $CH_3CO_2Et$ **2a** | 24 |  **3n** | 63 |

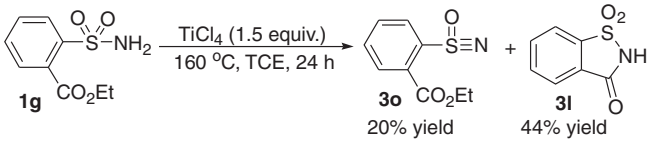
[a] Isolated yields, average of two runs.
[b] 1.5 equiv $N(C_2H_5)_3$ was added, 30% sulfonamine remains unreacted.
[c] 3 equiv ethyl isobutyrate was added.
[d] The reaction was carried out at 160 °C.

found the non-polar solvent $Cl_2CHCHCl_2$ was superior to $CHCl_3$, $ClCH_2CH_2Cl$, and toluene (Table 2, entries 1–4, see Supplementary data for complete details). Based on this results, and we further investigated the effect of the amount of catalysts, reaction temperature, and reaction time on the transformation. After an extended reaction time (from 12 to 18 h), treatment of *p*-toluene sulfonamide and ester in tetrachloroethane at elevated temperature (115 °C) provided the desired N-acylation product in up to 76% yield (Table 2, entry 5). Increasing the amount of catalyst loading from 1.0 to 1.5 equiv. resulted in higher conversion and yield (from 53% to 76%) (Table 2, entries 11 and 5). On the other hand the yield decreased to a certain extent when the catalyst loading is up to 2.0 equiv. (see Table 2, entries 5 and 12). In addition, a longer reaction time (>18 h) and higher reaction temperature (>120 °C) led to tedious work-up and lower yield (Table 2, entries 6, 9, and 10).

With the optimized reaction conditions in hand, a variety of substrates were surveyed to explore the scope of the reaction (Table 3). It was observed that electronic effects from aromatic ring substituents play a key role in N-acylation of sulfonamides, benzenesulfamide with electron withdrawing group such as chloro, bromo and nitro at the para position requires longer reaction time (30–55 h) for the best yield (Table 3, entries 2–4), and total conversion of substrate with electron donating group such as Me- was achieved in a shorter reaction time of 18–24 h (monitored by TLC) (Table 3, entries 1 and 6). But for the substrate **1e**, Sulfonamide with a methoxy substituent gave poor yield (30%) at first, then we think the formation of oxonium salt from anisole segment of benzenesulfamide and HCl[13] might lead to low reactivity, so 1.5 equiv. of N $(C_2H_5)_3$ was introduced to the reaction system for neutralizing HCl, and the corresponding yield raised from 30% to 54% (Table 3, entry 5). Increasing the steric hindrance of substitute group ($R^2$) from carboxylic ester led to a substantial decrease in product yield (Table 3, entries 1 and 10), while decreasing the steric hindrance of alkoxyl group ($R^3$) from carboxylic ester led to improved N-acylation yield (Table 3, entries 8 and 9).

Moreover, several examples illustrated that aromatic and aromatic heterocyclic carboxylic ester with electron-withdrawing or electron-donating group could react smoothly with sulfamide to afford the corresponding *N*-acylsulfonamides in 45–97% yields (Table 3, entries 11–14), and changing the substrate from an aryl sulfonamide to an alkyl sulfonamide such as methanesulfonamide also gave the desired acylated product (Table 3, entry 16). Also, the N-acylation reaction of N-substituted *p*-toluene sulfonamide and ethyl acetate gave a 63% yield of *N*-phenylacetamide instead of the desired *N*,*N*-disubstituted sulfonamide (Table 3, entry 17). Moreover, $TiCl_4$ can also efficiently catalyze 2-sulfamoyl-benzoic acid ethyl ester to form saccharin (**3l**) (Table 3, entry 15) via intramolecular N-acylation in 82% yield at 115 °C (see Supplementary data about the single-crystal X-ray diffraction data of **3l**), and unexpected dehydration reaction proceeded to afford 20% yield of dehydrated compound (**3o**) except saccharin (44% yield) at higher reaction temperature (160 °C, Scheme 1).[14]

In conclusion, we have demonstrated $TiCl_4$-catalyzed direct intermolecular or intramolecular N-acylation of sulfonamide with carboxylic ester for the first time. Importantly, the transformation was extended to the use of carboxylic ester as an acylating agent. Our current efforts are centred on $TiCl_4$-catalyzed dehydration of sulfonamides, and we will report our studies in due course.




**Scheme 1.** $TiCl_4$-promoted dehydration of 2-sulfamoyl-benzoic acid ethyl ester.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.092.

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14. For this substrate, an unexpected dehydration reaction proceeded to afford 20% yield of 2-(ethoxycarbonyl) benzenesulfanenitrile (**3o**) at higher reaction temperature (160 °C) (see Scheme 1).
15. *General experimental procedure for N-acylation of sulfonamide with carboxylic ester*: sulfonamide (2 mmol), carboxylic ester (4 mmol), and $Cl_2CHCHCl_2$ (4.5 mL) were combined in a pressure tube equipped with a stir bar. The mixture was stirred at 50 °C for about 10 min, then $TiCl_4$ (3.0 mmol) was added and the reaction mixture was heated to 115 °C for the given time (see Table 3). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with 10 mL of $H_2O$ to remove the excess $TiCl_4$, then filtered, and extracted with EtOAc (3 × 15 mL), the combined organic layers were dried over anhydrous $Na_2SO_4$, then the solvent was evaporated in vacuo, and the crude compound was purified by flash column chromatography (silica gel, petroleum/ethyl acetate, 2:1) to afford the corresponding *N*-acyl sulfonamine.
16. All the products except compound **3o** are known compounds and are also identified using $^1H$ NMR, LRMS, IR, and mp by comparison with previously reported data (see Supplementary data for complete details).